

Maria Caulfield: Thank you Dr. Ponesse, for bearing with us. We're on our second day of our enquiry, and lots of interesting evidence coming through. I was just wondering if you could just give...start...and thank you very much for giving up your time, but could you start just by outlining a bit of background of your experience and your particular area of expertise for this inquiry?

Dr. Ponesse: Sure. And can I just ask are you guys seeing me on screen or anything on screen presently? Like my presentation or PowerPoint?

Lord Alton: We have hard copies of your presentation.

Dr. Ponesse: Oh okay you do. Okay okay so that's fine. Just we'll just use that. So, so my background, I'm a developmental pediatric neurologist here in Canada. I'm a clinical neurologist not a regular -- although I do some research, it's not in this field. I'm not a basic science researcher as well so my, my interest in this is purely, well it's purely interest. I have presented on it before in several capacities, you know grand rounds and in other venues, but again it's simply as a, an interested, but, like I have a...part of my research program's in bioethics, so that's partly why I guess I've come round to this in some ways.

Maria Caulfield: ...And do you want to go through your presentation with us, because we do have hard copies, so we could,...we would be delighted if you could talk us through your presentation.

Dr. Ponesse: Sure. Okay, so yeah. And I, and as a clinical neurologist I don't have any commercial interests. Again I mentioned my, my ...I guess my academic interest from a research

standpoint. But basically I'm going to walk all of you through, I, I guess the important questions that you have to ask in this area. There's a lot of unknowns just as there are unknowns in the area

of adult pain. That's hard enough what with a lot of subjectivity, the effect of one's emotional state on the feeling or perceptual pain. You know we use analog scales in order to to quantify pain. So in the human fetus this is even a more I guess vexing question in terms of trying to get at the status of pain in the human fetus. So also how do we know and how do we measure pain in

any way? Or how do we measure responses to being given lack of a fetus's ability to verbalize like we do, to, maybe to some extent, express effect on the face etc..

So we're going to talk a little bit about that as well. I will be using dates in terms of weeks gestation in order just to give some context as to when these capacities or structures in the body

structures in the brain might come online based on the research that I've followed. So just to keep in mind the length, the duration of pregnancy is roughly 40 weeks give or take. So I'm going to be talking in weeks gestation with your ground zero being conception and then delivery at roughly 40 weeks. So I'm also going to be talking about a little bit of neuroanatomy and neurophysiology so I understand obviously not everyone shares that background so I'm going to try and make it as interesting as I can. Given that, given that I as a neurologist, in my medical school days was still a little bit...I found neuroanatomy dry so I'm going to try to make it somewhat more easy to swallow. So basically the whole the way the whole field of research into whether or not the fetus could feel pain or in other words have nociceptive capacity was simply as a result of both our technological improvements in the NICU, the N I C U...The first slide

after the questions is basically just showing the same age fetus one within and one...one within the womb and one outside. So that was certainly one area, and I'm going to touch on a particular group that was instrumental in getting that going, and the other avenue has been the fetal surgery areas where we approximately have 8 to 10 different procedures we can, now do perform in, you know, a mother who was probably along between 18/19 and 26 weeks. And in many ways the timing is all important. For example, spina bifida surgery -- repairing the, basically the opening in the lower part of the spine and putting back the various neural contents -- that has to be done at a certain point in order to get the best outcome. So there's only so long we can go in gestation before these types of surgeries can be done and to get an effective result. So there's been a lot of research from an anesthetic standpoint into realizing not only do we have to care for the mother's pain needs but also the fetus's. So basically Anand started the first group looking at premature babies because even in the 80s, the mid 80s, we didn't know too much about the pain responses of premature babies born, and, you know, who were having surgeries, you know, in, while they were, while they were outside the womb in the NICU -- various surgeries having to do with gut closures, etc. So he looked into hormones -- endocrine and autonomic, that is fight or flight type responses that were noted to be activated during the surgery and alleviated by pain management by opiates, giving of morphine, fentanyl, etc... And so by about this time in the mid 80s people started reading this research through high impact journals like The Lancet, The New England Journal of Medicine and then actual anesthesiologists had to be on board for these surgeries.

So I do want to get at two concepts that I think are quite difficult.

And that is the idea of, how to characterize and define pain, and then what this term I use previously "nociception" actually is, because you know, there's a lot to pain that falls inside of just our basic consideration of the nervous system, you know, although it is mediated by the nervous system, we tend to think of, many aspects of pain as sort of involving our conscious perception, our emotional states, our learning and memory, what we, what we've been through in

the past. All of that plays into our subjective experience. So this obviously would be a very difficult thing to pin down in the fetus, although there are interesting ways of trying to get at this question, but the main thing I want to start with is, is nociception with, which is basically, the actual sensation, if the sensation, the nervous impulse that starts with an actual threat to a bodily integrity or threatened to structure or tissue in our body.

And my next slide on this is just, I'm just, I don't want you to focus too much on the details, but you can see under the slide "nociception," there's obviously there's the cortex, the higher brain we can call it. And then there's the more peripheral or spinal level and nociception is because basically everything up until the cortex, up until the thalamus, that is, it's the relay of the pain transmission, starting from a basic receptor that is a little tiny point on the skin, for example, that will start the ball rolling, traveling through the spinal cord, through the spinal cord and up to be

processed by various, what we call sub-cortical structures. And finally what is thought to mediate

conscious experience, the cortex itself. So there's a lot of details obviously that I'm not going to touch on for the sake of simplicity, but I, I just wanted you to have a basic, sort of a diagram of the pathway because it's all of the pathways in neurology.

And as well I'm going to present the evidence that I know of, in a format that I came about by virtue of my interactions with my addled neurology colleagues, because when I've talked about fetal pain to them, it's interesting, as inquisitive, academic...academics are, they, you know, they would bring up very reasonable objections. So I'm going to present on many of the objections that I had heard over time and my responses to them. And I think this way it's a bit more interesting for everyone involved. So first objection that I explore is the fact that the fetus being immature or having an immature nervous system means that the nociceptive pain pathway is really not functional or only partially functional. And I think that this assumes that pain perception or nociception to fetal life, you know, we, we engage, the fetus engages the same sorts of structures as those used by the adult and that's actually not borne out by the literature. So the response to that objection is the fact that the fetus has unique neuroanatomy. This is a big

time. It actually, this neuroanatomy does double duty or triple...a variety of different nervous system impulses. So for example, there are cutaneous touch receptors that might in an adult, just

feel pressure sensation in the fetus, both, by, by virtue of a post-mortem studies on fetus, fetuses

looking at these receptors, as well as animal research in fetuses of primates. They note that the cutaneous touch receptors are present in much more, much more approximate or close to the skin

as they would be in an adult. That's being, in some ways thought to provide much more sensitivity. And secondly, a distribution of the receptors is much more densely configured than in an adult human being, and primarily located in areas of face and hands and that these are present

by 20 weeks everywhere.

A second objection that I've had is the fact that if you're, if you, if you know how, for example, electricity flows through wires, one of the structures within the nervous system that helps with conduction of nerve impulses is something called myelin, which is like, the insulation on a copper wire. And we do know that many, that the fetus, the immature nervous system is in many ways immature because of immature or, or lack of myelination at early ages. But the objection though fails to consider the fact that in adults our nervous, our nerves do not carry pain on using the myelinated nerves. We actually have very slowly conducted nerve impulses, we use unmyelinated or very thinly myelinated fibers for carrying nervous impulses. So surprisingly, adults have slower conduction velocity. The other thing is that, that that's a, a response to this objection is the fact that the fetus is so much smaller, that the distance needed to travel is so much smaller. So there's no reason to think that nociception would be slower, diminished. And then finally there is myelination that occurs, at least in this more, sub spinal, or sorry, spinal and peripheral nerve related nervous system. And this myelination happens actually in the middle of the second trimester to the third trimester.

Another objection would be that because of immaturity, nociceptive input, is, is diminished. Um, overall or in an absolute sense. And one thing that we have as adults is, I mentioned previously, in previous slides, how the nerves, the nerve impulse or the pain impulse travels up the spine through the spinal cord and up through the spine to the brain stem, and, eventually, up to the thalamus and cortex. But what a fetus does not have, and something that adults have is on descending inhibition, and this is actually a more recent discovery, and it's being taken advantage

of by various pharmacologists using, for example, serotonin, serotonergic uptake inhibitors, other medications that have been added to the arsenal of pain treatment in adults.

So what I'm mentioning here is a part of the brain stem that once pain is, proceeds, it actually sends down an impulse. It's almost like a motor response, but, but not that, sends an impulse of, almost like cascading serotonin and noradrenaline, in order to inhibit any pain sensation. So once

that sensation is perceived, there's actually a counteracting response. And, we don't see periaqueductal gray matter, that's well formed in the fetus at this point. So we have reason to think that there's lack of inhibition of pain that we otherwise would have as adults.

My fourth objection, and I only have maybe five, I think five objections and then I can wrap up, but my fourth objection, or what, what has been mentioned to me is that the chemistry in general

in, in the fetus, the neurochemistry that is to say neurotransmitter function is a not mature. And this particular picture is simply a basic or simplistic neuron showing that at the end of the neuron there's little, they're called vesicles, little sort of balloons carrying the chemicals like serotonin as I said, or noradrenaline or dopamine and we think about neurotransmission as sort of a lock and key, but what's been noted on post-mortem studies in, in the fetus is that, that receptors for basically opiates I'll use the broad term of opiates has been found between 12 and 16 weeks of age. So they're not present before, but they are starting to be present at that point. And we know

from primate studies that there's really a, you know, we don't take on new structures without there being sort of a functional need for them. So we have reason to believe that the opiate receptors that have been found are only there, in order to basically a start the fetus readying itself

for times where it may be threatened, into eventually transmit pain impulse. My fourth objection has to do just overall just how do we get out the question, how do we get at basically evidence for pain in the fetus? You know, as I mentioned, we have a, we have a variety of behaviors in adults that can easily tell us a little bit about, not completely about the, subjective experience, but

we know a colleague who might be in pain. But this obviously is, is not the case for the fetus, so what do we have to go on? Well in 23 week old, a 22 week old prem, premature babies we do have reminiscent facial expressions, that's mediated by subcortical motor system. We do have withdrawal reflexes that at least show that what we call called nociception is intact with pain transmission that can go from receptor to spinal cord and then a result in a withdrawal reflex. And we have a variety of other, reflexes that if you, if you transmit pain impulse or induce a noxious stimuli, you can reduce the dimensions of the reflex using fentanyl or opiates. So that is to say we have sort of a one to one relationship between inducing a...noxia, or a pain impulse

and the amount of, basically the threshold, how intense the reflex is by virtue of, the amount of opiate we are, we're able to give, the fetus. So, and these are studies done in...

Maria Caulfield: ...Can I just, just interrupt you for a minute, just to, just say we've only got a couple of minutes left so I don't want to rush you too much, but we're keen to, to get your key points in. So I was just wondering if you could, in the rest of your presentation, just highlight some of the key points that we need to focus on for the inquiry. Dr. Ponesse: Ok. So, you know, one of the ways, I mentioned pain, but there's also stress responses and other physiologic, physiologic response that again, are, produce pain, or hormone

responses proportional to the stimulus. So that's another avenue of evidence for pain mediation in

the fetus. That is to say again hormonal and autonomic responses that are responsive to opiates

like fentanyl. And then lastly it's simply just about the conscious perception. This is the hardest question we have in the fetus. You know, obviously, there's reason to believe that, that conscious

perception, if at all present, is significantly limited. What we're noticing though, that pain responses are seen in children and adults who are lacking or have had a cortical destruction who

in babies that don't have part of the cortex or all of their cortex there are pain responses. And we

know through EEG that everything to do with wakefulness state, sleep states, that is to say the integrity of the cortex and the thalamic connections are present from 20 to 21 weeks. So basically I've covered all the objections that I've wanted to, and tried to provide some indication of structural integrity at very early times. And rightly, and I hope my thesis has really been to show that many things are online by 20 weeks gestational age. And I'm pretty much done. I Just that, just some of the summary slides there you can read on your own.

Maria Caulfield: Yeah. Well thank you very much. That, the evidence there is quite impressive. Just to turn to my colleagues. Are there any particular questions that you wanted to ask?

Lord Alton: Can I just ask Dr Ponesse of something that arises out of his presentation? You said in fact towards the very end of your remarks there that where a baby is perhaps missing a bulk of

cerebral cortex -- so I guess in cases like anencephaly and hydranencephaly-- nevertheless you say they experience pain and I think, that, I think is really new and interesting thing that you said to us. And I wonder in the follow-up correspondence that you have ... to the committee of inquiry whether you be good enough to develop that for us because I've not seen that anywhere else. And you also said, sorry, and you also said there may be no age limit at which one can be sure the noxious stimuli are not harmless. Again that's in stark contrast with the Royal College of

Gynecology, and indeed from other witnesses that we've heard from. So can you just put that on the record for us because I saw that in the slides, but you didn't actually, weren't able to say it because of the time constraints, that there's, maybe no age limit at all at which one can be sure that noxious stimuli are not harmless. Thank you.

Dr Ponesse: Yeah. So sorry. I, there was a lot there that, that broke up and I couldn't hear. So I'm

hopefully, hopefully characterizing your question accurately. So I think I heard two things, one of which I'll just take the latter part though. I think you had a question as to a summary slide stating about, you know, that we can't be sure that noxious stimuli are not harmless. I guess what

I meant there is simply that when studies are done on fetuses who have had either surgery, particular procedures done at early ages, what's been noted is that by virtue of a hormonal and autonomic responses, there are follow up studies looking at certain aspects of neuro developmental. It's one of my references, so neurodevelopmental outcomes, certain other outcomes in terms of cognitive and emotional states showing that, there, there may be, there may be impairment that is somewhat more long standing than we think.

o although I guess what I mean to say is, do we know even at very early ages under gestational age 10 that a fetus can or cannot feel pain? What I, what I think of, it is alluded to in research, in the research referenced, is that there may be long-term outcomes. So that is to say there's no free

lunch. Whatever we do, if we're not careful and we don't mediate with, with pain relief, there may be long-term outcomes. So I hope I'm addressing that latter part because again, I couldn't hear everything. And I guess, you mentioned something could you repeat the first part of your question please?

Lord Alton: It was about the evidence that you gave towards the end of your remarks about what happens where a baby is missing a bulk of cerebral cortex, but nevertheless they could experience pain. It's not something I heard before. I presume it refers to babies with conditions like anencephaly and hydranencephaly, but perhaps if you could, if you can't do it now, I'd be really appreciative if you could elaborate on that in some correspondence.

Dr Ponesse Sure. If you want, I can elaborate on that. All I mean to say is again, procedures, painful procedures done in those children lacking cortex is, has, has again a sort of a proportional

on correspondence effect of, you know, particular pain induction and the amount of, of anesthesia required to say like reduce the grimacing response. Again, it's sub-cortical, but it's, it's

being induced, it is responsive to opiates. So I guess it could be a question of semantics. What are we going to call that in a, in a fetus that or sorry a premature baby or a term baby with anencephaly or hydranencephaly. Well what we're having is, is a response, a grimace response, and that response is attenuated by by opiates being given. So, you know, again, what do we call that? But it is being addressed by pain relief. Anyway, I can, I can send more on that.

Maria Caulfield: Well thank you very much for that. And we may well send you some, some further questions if you'd be happy to, by email if you'd be happy to reply to them.

Dr Ponesse: Sure. More than, more than happy. Yep.

Fiona Bruce: Thank you. Thank you so much. It's been helpful.

Dr Ponesse: You're welcome

