

## Faraday Institute Lecture/Discussion

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**Denis Alexander:** I am sorry to interrupt your dessert but time is moving on and we are running a little bit behind schedule, so we ought to start moving into the discussion period of this evening. Perhaps I should introduce myself: I'm Denis Alexander, the Director of the Faraday Institute, and so want to welcome you once again on behalf of the college here and also, of course, on behalf of the Faraday Institute. I am delighted that so many people could come.

There are a few apologies that I should just mention: Austin Smith was unfortunately unable to be here; Martin Johnson also is indisposed; Roger Barker was going to come but sadly had a family tragedy as one of his family members was killed last week so can't be here with us – but we are delighted that you can all be here. I think Bob mentioned earlier that we record this discussion – don't feel inhibited in any way by that. The most important thing is you can edit your comments, so if you feel they're not exactly as you might have wanted you can alter them after they are transcribed and circulated; so please feel free to contribute and eventually what you say will go on the website, edited and checked.

We are very thankful to our chair persons and also to our speakers this evening and we want to give them every opportunity to contribute. The way we normally run these discussions, and we have them each term, is to have some contributions from various people and then we give an opportunity to the speaker, or speakers this evening, to come back on those points. We try to avoid a "question and answer" session as we like this to be a discussion where there is a common contribution from around the table.

I am a biologist, but not a stem cell biologist, and I want to be just a catalyst for this evening's discussion. I thought perhaps the way we might start is to give the stem cell community, as I would like to call them, an opportunity to come back and reflect and contribute to the

discussion that we've had so far earlier on in the lecture. I know there are a number of cell stem people around the table here and so perhaps I could throw it open and give them priority. I think possibly Ann McLaren might offer some comments to start us off.

**Ann McLaren:** I am impressed by the case that our main speaker put forward today but one point that occurred to me that I feel quite strongly about is the ethics of oocytedonation. It seems to me that this scheme of providing what are essentially "crippled" embryos – OK we're not allowed perhaps to call them embryos, but they can't implant so they are, as it were, ethically "safe" to make stem cell lines from – will need a lot of human eggs to work out the technology of it and to make sure that it's safe and doing what it's supposed to do.

In this country, the UK, there are long, long waiting lists of infertile women who can't get eggs to have babies and in the States you can buy eggs, if you have enough dollars, though these are quite expensive. But there must be many infertile women who are not rich enough to be able to buy eggs to have babies. To me, there's an ethical problem about using human eggs for this particular way of getting round the use of frozen IVF embryos, which are not going to survive ever to make babies if they are not wanted by the original parental project. These are just going to be allowed to die and I would rather *they* were used for making human embryonic stem cells rather than using human eggs which could be used for clinical purposes. So that's one question.

**Denis Alexander:** Before we ask Brian and Bill to come back, because I'm sure that they have comments on that, there may be others who would like to reflect on it.

**Bob Moore:** I have been slightly saddened by the negative tone in some cases of cell stem work where we talk about killing embryos and about what we are not allowed to do, rather than hold a more positive view. I just wonder – and we discussed this briefly before supper – what the ethical position would be if one were, say, to take an embryo and simply extract from it two or three cells which would be used for stem cells, and the embryo would then be implanted and develop normally. Would that be an ethical and positive position to encourage people to work, for

example, towards that position rather than talking always about the destruction and the negative view of stem cell manipulation?

**Denis Alexander:** Does anyone want to pick up also on the issues of the ethics of egg donation, on the particular point that Anne mentioned.

**Onora O'Neill:** I would just add that it seems to me that if one is dubious about egg donation, like Anne and I are, I'm much more dubious about commerce in human eggs.

**Brian Heap:** Would you like to expand on that?

**Onora O'Neill:** As I understand it on some of the Ivy League campuses there are small ads in student newspapers asking these intelligent girls, who may have very little knowledge about these matters, to sell their eggs for sums that are quite considerable – one episode of egg donation to cover two years of college fees – and I think that though one might criticise HFEA for getting laxer in certain ways, they have held the line on not creating a trade in human gametes and in forbidding trade in human gametes.

**Bill Hurlbut:** Someone has recently suggested that we rank colleges by how much people are willing to pay for the eggs of their students---and Stanford is way ahead! This is an advert from seven years ago for, I think, 50,000 dollars, but now we have one in the Stanford Daily for 150,000 dollars.

**Derek Burke:** It also specifies the SAT scores

**Bill Hurlbut:** Yes, 1400, which is the top three per cent.

**Brian Heap:** So we're back to American eugenics.

**Bill Hurlbut:** And 5 foot 10 inches.

**Denis Alexander:** Is this a spoof?

**Bill Hurlbut:** No, everything I have said is true. In this case I know it was not a spoof, because one of my students who followed up on the ad was the runner up. She went back to Harvard, where, of course, the other 'qualified' donor was, and she was put up in a fancy hotel, given a thirty-page questionnaire to fill out including questions like "Did your grandfather freckle when he

tanned.” She was asked about food preferences and hobbies and so forth, and after all this she was deemed ‘acceptable’. In the meantime I had been on a television program where the audience asked the broker from the law firm why they wanted such a tall, intelligent, athletic egg donor and he said “obviously because they are a tall intelligent athletic family”. When my student actually was introduced to the parents-to-be, it turned out the mother was 5 foot 1 inch! I suspect the father didn’t want to have a short son.

**Brian Heap:** Well, just picking up on Bob’s point about the idea of using single cells from the pre-implantation embryo, of course that has been pursued and there have been some interesting experiments reported of looking at whether that would be feasible. The particular study, as Bill will no doubt enlarge, fell into disrepute because unfortunately although it was demonstrated that you could take a single cell or two from the pre-implantation embryo and you could use that for the development of embryonic stem cells, what happened to the embryos thereafter? The embryos thereafter were killed and that, of course, took you back to square one; so whereas on the one hand it was demonstrating yes, this is feasible, on the other hand it was showing, I suppose because there was a question of the risk that was associated with that in terms of the surviving embryos, that embryo was subsequently killed, so it rather spoiled the study.

**Anne McLaren:** If I could just comment from the point of view of a woman, this *is* done of course with pre-implantation diagnosis. One knows that there is a certain risk but one does it for a particular reason, for benefit. I think most women would prefer not to have one or two cells removed from their embryos before they were put into the uterus if they could have a totally intact one.

**Bob Moor:** Now I completely accept that but you were the one who was making the point of how limited the numbers of oocytes in embryos actually are ..

**Anne McLaren:** I didn’t say the number of embryos was limited. The number of frozen embryos that could be used is very large indeed; it’s the number of oocytes that is limited.

**Bob Moor:** Yes but even with the numbers of frozen embryos, if one were to take a cell or two from those and then freeze them down. All I want to do is to move away from this idea that the only way to get a cell is to kill it. (**Anne McLaren:** Yes, I see the point) Say that NIH said we will support approaches which will lead to that kind of technology, then I suspect we might get a much better technology in the future that would not kill embryos.

**Denis Alexander:** Martin, would you like to comment?

**Martin Evans:** Maybe at this stage in the discussion we should introduce this idea of using animal oocytes. What does that do ethically?

**Denis Alexander:** It does a lot of science, apparently.

**Brian Heap:** I think Martin should tell us.

**Martin Evans:** Well, I think there's a lot more to be done in this area in looking at it, but my present feeling is that it may be a very exceptional way forward. One has to discount the huge "yuk" factor but when you think about what is the likely outcome of such experiments – these are transplanting a human cell or a human cell nucleus into an animal egg, probably a cow egg, maybe a mouse egg, it doesn't really matter – we think that this will give a reprogramming of the nucleus and an early development of an embryo, but it would be a hybrid embryo from whence it may be possible (it may not, we don't yet know) to derive stem cells.

Now the imbalance with the embryo and the nucleus is going to be twofold. First of all there's going to be an imbalance possibly of cytoplasmic factors in the egg but secondly there's going to be an imbalance because the mitochondria that come from the egg could not be matched with the nucleus. With somatic cell hybridization experiments, largely between man and mouse or man and hamster, it's been shown that the resulting hybrid cell tends to select for the mitochondria that match the major chromosomal components. Now I suspect – but of course these experiments need to be done and they haven't yet been done, or they've only been done in China and we have a rather insufficient report of the outcome – that it may well be that a human nucleus in the, shall we say, cow cytoplasm will become reprogrammed, the cow mitochondria will

be sufficient for a short-term support but that in order to get a cell line out you will have to have the human mitochondria taking over. If that's the case and of course that depends upon these types of experiments being allowed and done and evaluated, but if that's the case, we may well find that we get a fully human cell line from this type of experiment.

Now at the moment, certainly publicly, there's a huge "yuk" factor involved and in this country at least we have a white paper that is looking to outlaw such experiments. I don't know if anybody round this table knows what the latest is, but I suspect that the particular paragraphs in the white paper *are* going to be altered – but we have to wait and see. But once again we have here something which on the face of it looks like a very undesirable or even immoral type of experiment which, when you look at it in detail, may well be one of the best ways forward.

**Denis Alexander:** Thank you. Does anyone want to comment on that?

**Bob Moor:** Yes, two comments. One is I believe that the Chinese people have had a very large chromosomal abnormalities in their eggs but I very much like the idea that we don't talk about doing nuclear transplantation of a human nucleus into an animal egg, but we actually do it by cell fusion. I believe that if we talked about cell fusion instead of nuclear transplantation that would take away just one small aspect of the unacceptability. It would also provide an egg that had a large percentage of human support which would actually drive perhaps the cell cycle. I have this horrendous view of a cell cycle being driven by proteins which are not in synchrony with the length of the cell cycle and I think by cell fusion, instead of by nuclear transplantation, one might well overcome that problem very greatly.

**Martin Evans:** I think these experiments need to be done because we don't really know.

**Brian Heap:** Can you just clarify for those who are not expert in the area what you mean by cell fusion?

**Bob Moore:** There are two possibilities: one is to take the nucleus out of one cell and simply put a different nucleus back from another species. You then do that by essentially between the genetics of the nucleus that you had transplanted and the cytoplasm that surrounds it. Whereas if

you did cell fusion, which is just to take two cells and just chemically fuse them together, you would then be providing the animal nucleus or the human nucleus with a lot of the cytoplasm that it might otherwise have been denied by nuclear transplantation.

**Denis Alexander:** Thank you. I think that Derek has something to say.

**Derek Burke:** Well, I just wanted to make a point from my background in the GM food and crop debate and that is to advise people not to take the “yuk” factor lightly. We thought that genetic modification of plants would be seen as in fact a refinement of the crude processes that were going on in nutrigenesis followed by selective crop breeding. That argument was never accepted so what seems rational and logical to us, and I thought the last few minutes we were busy trying to invent ways of justifying what we wanted to do, does not persuade the public. The big thing you’ve got going for you is the need in human medicine, but don’t overplay it because it will not come as quickly as we think and then you’ll be in trouble. So be very cautious please about “yuk” factors.

**Brian Heap:** Yes, just to follow on from that I think the area that I find disappointing in this discussion about hybrids, fusing cells from different species, is that the government’s gone down the line of going to a public consultation. I think it’s a much more complicated issue and you can hear some of the elements in the discussion we’ve just had. There are some very important scientific questions to address and I think it’s a great pity that they didn’t go down the line which they did in 2000 of having an expert group consisting of scientists, philosophers, theologians, ethicists and so on, to look at this whole issue before going to a public consultation. I don’t think our public are sufficiently – I don’t want to underestimate this because I think we often do underestimate what the public awareness is of some of these issues but I think that this is a topic on which the government should have taken a different stance. Unfortunately, it’s probably too late to reverse that.

**Derek Burke:** I'm afraid the GM-nation debate has happened and it will never go back to the advice of an expert committee. Somehow we have to find ways of interacting with the public so that we're not railroaded by the single issue pressure groups.

**Brian Heap:** I don't agree with that actually because the expert group on cloning and stem cells in 2000 was actually set up and had an impact through various channels that subsequently led to legislation which was accepted, and voted by a large majority in both houses as you know. I think that was an example to me of where an expert group can actually play a rather important role.

**Denis Alexander:** I think Roger wanted to come in here.

**Roger Pedersen:** Really it was a comment and feedback on Martin's suggestions which I think actually touches all the issues involved in the possible success of using animal eggs for somatic cell nuclear transfer, cell fusion. I think a lot is said and a lot is staked on this process. It's become iconic of the stem cell field and of the embryo research field, and of course your proposal for altered nuclear transfer depends completely on the potential of success for that approach. But the fact is that nobody in the world to this moment has succeeded in doing somatic cell nuclear transfer with a human egg. Every single attempt has failed, including thousands of eggs being used in the hands of the Koreans and whatever you say about their ethics, they actually were relatively competent technologists because they succeeded in cloning a dog which was probably the most difficult species to clone other than a human.

So I think we shouldn't underestimate the difficulty of this procedure and the potential of animal eggs circumventing this obstacle, whatever it is, this biological obstacle the human egg, makes them interesting. Given the "yuk" factor of using, of creating an animal, of generating an animal-human hybrid, cybrid accurately speaking, I think that scientific justification for doing so has to be made very thoroughly to the public and it is probably mainly to understand a) reprogramming of human cells and b) potentially generate immune-matched tissues.

**Denis Alexander:** Is there anything more than – we talk about the "yuk" factor which is clear and out there in the public domain – are there real ethical issues here?

**Wolf Reik:** Two scientific points: one sort of relates to what Roger just mentioned, so the first one is not related to Roger. What Roger said was what Bill was talking about, the fact that an embryo may be pre-patterned at a very early stage. Now this is a contentious issue and I thought you were courageous to mention the Roberts paper, which is under investigation for scientific fraud.

**Bill Hurlbut:** Yes I mentioned that too.

**Wolf Reik:** No, you didn't mention that directly. However, you did say that you had evidence that the paper was correct so I would challenge you to tell us what that evidence is, that this paper is correct; so that's one issue. This is a big contentious issue: you cannot put this in front of us and say this is an established fact, which you did.

**Denis Alexander:** OK, I want us to talk about that but just before we leave cybrids – we might never see cybrids again this evening if we left it now – then we'll come back to Wolf's important point. Are there really serious significant ethical issues to do with cybrids or are we simply talking about a "yuk" factor here and that's it.

**Martin Evans:** I would like to ask the assembled company who I think really provide quite a good ethical forum. These are going to be *in vitro*, in other words in laboratory experiments. They are not going towards any reproductive end. Is there any reason whatsoever why we should even be considering controlling them?

**Wolf Reik:** Only scientific issues like the mitochondria thing, maybe reprogramming issues – we want to find out.

**Derek Burke:** Well, I think from a public-political point of view you have to justify this as the only way that these aims can be achieved and we have to have clear medical opportunities to offer. My guess will be that there is a deep-seated repugnance at the very idea of hybrid animals, hybrid creatures.

**Martin Evans:** But these are hybrids between oocytes and human cells. We already have plenty of hybrids between human cells and other cells. Now, what is the difference? Why shouldn't we just get on with it quietly in the lab, why bother with ..

**Derek Burke:** Well, we were moving one gene out of a soil bacterium into a ...**(M.E .absolutely)** and those became Frankenstein plants and they are still called Frankenstein plants. We lost the whole debate and the whole technology because they were so lazy.

**Martin Evans:** But in that case you wanted to make this Frankenstein plant, you wanted to use it as a crop plant. In the first place, we are not wanting to use these as anything at all.

**Derek Burke:** Well, maybe you're right.

**Denis Alexander:** I'm keeping on the same topics for the minute, so we're still on cybrids.

**Patrick Richmond:** I just wanted to throw into the discussion that there may well be a rôle for biological and psychological elements in the human personality that affect the way we hear these debates. I have heard it said, and this applies to sermons as much as to scientific presentations, that when you get to a certain level of complexity your audience will tend to glaze over and adopt certain heuristic devices to short cut them to whether they are going to agree with you. If you are able to come across as a credible person it may not depend on the particular argument you give, it may depend on the bells that you are able to ring or the buttons you are able to press, so if you set off too many "yuk" factors people will be alienated from you and they won't go into the details. It's then possible to lose a political debate simply by being associated with something like Frankenstein's food. Most people listening are not able, and not willing, and haven't got the time to engage at the level of sophistication required but will adopt a short cut so if you have pressed too many negative buttons, you will lose the debate on that.

Likewise, it may well be true that when people are engaged in a moral debate they have certain intuitive responses to positions. Interesting research (which I think was by Hauser in the *New Scientist*) recently suggests that most people are hard-wired to respond in certain ways to certain ethical dilemmas very quickly, and they will rationalize afterwards. In other words we are hard-wired to respond to certain positions and when we are faced with new ones, we try and work from the precedent we've got which picks up on something like that. So if the scientists come out with too many "yuk" factors, or present the case in such a way that it requires a sophisticated

understanding of it and may at first sight appear to trip over some hard-wired ethical responses we've got like interfering with people, then the debate will be lost – not because the reasons were no good, not because this was bad philosophy, but because this was bad politics and bad group psychology, bad communications psychology.

**Denis Alexander:** I think that's very interesting. We're not hearing any ethical objections to cybrids around the table, I haven't heard anything ethical. I have heard "yuk" things and public policy but I haven't heard any ethical things – I think that's true, isn't it?

**Roger Pedersen:** I would raise a point – I don't know if this qualifies as your standard ethics but I think that scientists and people who represent science to the public may be guilty of misrepresentation about the necessity of nuclear transfer and the practicability of nuclear transfer, for matching within this match.

For one thing, it's completely impractical: not only is it impossible so far, it's completely impractical because you cannot match every person's need for a customized transplant. The NHS certainly couldn't afford it and I don't know who could, otherwise. And there are other ways potentially of matching in requirements. We've modeled some of these but one very interesting one, parthanogenic ...because they're nearly homozygous and it's the homozygosity that makes them very good donors. So I don't think that we're being honest with the public if we tell them that they have to accept nuclear transfer as the path to the clinic. That may be unethical.

**Anne McLaren:** Just on that particular point, I agree with Roger for clinical use of nuclear transfer stem cells but there are other very good reasons why people want to do cybrid experiments of human nuclei into empty animal eggs at the moment, which is to find out more about the biochemical and physiological basis of diseases like motor neurone disease. For that you need eggs, but animal eggs might well do. I think that the public respond to that actually, I find.

**Hill Gaston:** It seems to be that there is a point where "yuk" suddenly becomes ethics and I think the ethics for the experiment that Martin wants to do don't seem to me to be troublesome; but in fact whether it's presented or not, the public are going to extrapolate and they'll say when these

hybrids are made and kept past sixteen days, something terrible is happening. Now I can see that you don't want to do that, none of us wants to do that, but someone will argue that some crazy person somewhere *will* do this and that therefore you get from something which is, perhaps, an ethically not too difficult a challenge to something which clearly raises anxieties.

**Anne McClaren:** They'd be put in prison.

**Martin Evans:** But in that case you wanted to make this Frankenstein plant, you wanted to use it as a crop plant. In the first place, we are not wanting to use these as anything at all.

**Bill Hurlbut:** It's a little ironic to some people in America – we both think our countries are a little off – that people in Britain would worry about putting a human nucleus in an animal egg--which creates something, maybe a human embryo but maybe not--whereas they would not worry about instrumentally using human embryos. In other words, if the highest concern is *human* life, then what is created using an animal egg might be of lower concern since it is likely to be biologically something less than a fully natural human embryo. I personally think it raises interesting and important questions as to what exactly *is* produced, and it could well be something morally equivalent to what I am suggesting with altered nuclear transfer. Also, by the way, I talked about this recently with Hans Scholer. Providing an abundant source of eggs is clearly a very important part of the future of this science, yet I agree with you Anne about the ethical concerns. I am on the record in the President's Council saying I would not favour a single incident of superovulation to get the eggs for my project because I personally am ethically uncomfortable with it, at least at the level Roger says where SCNT is scientifically speculative and of no direct benefit to the egg donor. Maybe if it was curing one's own child you could justify the dangers of superovulation, but at this stage in the development of our science I am uncomfortable with it. I recognize that the project I have proposed will require eggs, and I am very sympathetic to the concerns you raise, but I think that with creative scientific research we can find morally acceptable ways to go forward, and eventually obtain abundant sources of human eggs if needed. Hans Scholer and I talked about the possibility of doing the preliminary research on Altered Nuclear Transfer by ramping up

through primate studies and looking at nuclear transfer where CDX2 is knocked down, silenced in the cow egg for example. Maybe that would be an interesting way to go about all this.

I want to ask Dr Moor though – before dinner we were talking about hopeful projects for finding abundant sources of eggs. Everything I read suggests to me, and there is a lot of talk about this in scientific circles, that there will eventually be ways to get eggs without superovulating human patients. These might include in vitro maturation of immature eggs deemed unsuitable for clinical IVF, Hans Scholer's project using stem cells to generate oocytes, using ovaries from oophorectomies or from cadavers, or maybe even just taking a cortical biopsy from the ovary of a living patient---and there are a variety of other possibilities too. Would you comment on that? You are probably the expert in the room on that.

**Bob Moor:** I certainly believe that if we were willing to put considerable funds towards it, there would be a strong likelihood that we would have success. We really know we can take eggs at a fairly grown stage and mature them through. The next stage is to grow them up and this has been done in the lab, so I can see no biological reason why we shouldn't be able to do that in humans. This is why I started off by saying I was looking for positive rather than negative views. If we were to put forward all these as positive views look at what we might be able to do if we had the funds; then I believe that we would achieve much more than we are achieving at the moment.

**Bill Hurlbut:** Now whether we're getting good at it is another question, but are you feeling that no primate cloning, no primate SCNT projects will work or do you think it's just a matter of time?

**Roger Pedersen:** To my knowledge, nobody has made a primate embryonic stem cell line from a nuclear transfer. There are parthenogenetic primate lines and there's a parthenogenetic human line that was made by the Koreans who falsified it to look like a...

**Bill Hurlbut:** I think you are going to find that primate stem cells can be made using nuclear transfer, in which case SCNT would theoretically be perfectable with human cells. If they succeed with a primate like a rhesus macaque would you think it would be likely to succeed with a human or – I am of course advocating Altered Nuclear Transfer but I am speaking of SCNT.

**Roger Pedersen:** I would say primates are probably in a group, so what works for one would probably work for another. If I may be allowed to comment on the altered nuclear transfer proposal: I think everyone would agree that it's a laudable effort to find a middle ground, to find a compromise that would enable human embryonic stem cell work to go forward in the US with the constraints that are imposed there. Why it seems a foreign idea here is that we've already had that debate and embryo research is a legitimate, lawful, agreed-upon activity using surplus embryos and in some instances generating those embryos for research. It's the law of the land and it is funded by the government, so it sounds regressive to try and circumvent something that's already agreed.

**Bill Hurlbut:** Let me make a comment to that. First of all you have noticed I haven't been stomping through Britain trying to change the law. I didn't think I would change anybody's opinion coming here and yet I think I can make a point on this that we all ought to take seriously. First, it would be very good if we had international co-operation with research on the same stem cell lines. After all, the controversy doesn't just limit collaboration with the U.S., there is disagreement even within the European Union. Second, I think ANT would provide a good tool for a range of studies. Most of my colleagues at Stanford and elsewhere in America are hoping SCNT or direct reprogramming will work since they want genotypically specified lines, and I can certainly see the scientific advantages that such lines would allow. So I am just trying to provide the optimal functional tool, that is the best balance of scientific value and political realism. But in the process of perfecting Altered Nuclear Transfer we might also establish an ethical principle that would allow a lot of other useful studies in early developmental biology. As I said in my talk, once an accepted method is perfected it would open up other types of research. For example, suppose ANT with the silencing of CDX2 allows the reprogramming necessary to obtain embryonic stem cell lines. That process would then qualify for NIH funding for further studies. You could now knock down one more gene at a time to see what factors are necessary for reprogramming. As long as you have something that is not an embryo you could do studies of imprinting and studies of cell signaling,

etc. during the cleavage stages. So it establishes a fundamental platform that opens up a much broader range of scientific research.

In the United States sometime in the next couple of months there is going to be a Senate debate and a vote on the use of the IVF embryos and, by the way, probably another bill that would fund Altered Nuclear Transfer. Last summer a bill to fund ANT and similar alternative sources of pluripotent stem cells passed a hundred to nothing in the Senate but then was rejected by the House to keep the President from having anything positive to sign as he vetoed the IVF embryos bill – politics! But the interesting thing is that almost nobody is addressing the question of well, if you can't use left-over IVF embryos to get embryonic stem cells, what else should you reasonably be allowed to do with them? In your country you don't seem to worry about that, you just do what you consider reasonable in a measured sort of way as needed for a range of scientific goals. But in America, the debate over the use of embryos is limited to the issue of embryonic stem cell research. Yet there are many other scientific studies that could be argued for, including research that would help perfect IVF. If we have a tool like Altered Nuclear Transfer we could theoretically do a lot of studies in developmental biology. I think you can tell from my comments today that I am very excited by developmental biology and I think we ought to seek a way forward.

Just one further comment on this: Anne has said she has used the words I didn't want to hear, namely a "crippled" embryo. Altered Nuclear Transfer, according to the ethical analysis of the moral philosophers and scientists involved in this project, involves a *pre-emptive* alteration that precludes the creation of an embryo. That is the whole point of the project, it creates a biological artefact with an 'insufficiency' in its starting ingredients such that it is inadequately constituted to rise to the level of a living being. It's really much more fundamental than simply an inability to undergo implantation. It is no more an organism than a teratoma. I never made that argument by the way, even though it's one always quoted from the New York Times to Time Magazine to everywhere, saying that ANT creates an embryo that only lives long enough to get stem cells and then dies, or can't implant or something. I never made that argument. I made the argument that

it's possible to leave a fundamental ingredient *out* of the equation so that you don't have what constitutes a living system, and yet create a sub-system, a partial trajectory or organic growth that can produce embryonic-type stem cells. It's a crucial distinction morally, and if we're going to solve this problem we can't create embryos that die. That will not work. I know there's a little bit of an ambiguity in what counts as an embryo. That term is used very loosely in medical science. Some would use the term for every product of fertilization or nuclear transfer, no matter what potential for organized, integrated growth is present. Some might even use it when referring to hydatiform moles and teratomas. I would say these are not rightly designated embryos, but that's a debate we might have to have. If we could define with clarity and precision the exact moral boundaries, we could, perhaps, open up wonderful science that is currently now controversial or even constrained by law.

**Wolf Reik:** So the point put to you by Brian really is why do you not take on board the recent advances by the Yamanaka Lab in actually being able to reprogram somatic cells directly with all the caveats that apply to that?

**Martin Evans:** Complete with programming etc etc

**Wolf Reik:** But ethically you guys should jump to that.

**Bill Hurlbut:** We are.

**Wolf Reik:** But you didn't in your response today, you didn't.

**Bill Hurlbut:** When did I not? I have always been in favour of direct reprogramming. If you go back and read everything I have written on it you can see that I'm in favour of that.

**Wolf Reik:** I haven't read that but today in the debate you didn't pick up on that point when it was put to you.

**Bill Hurlbut:** It was put to me that it creates an embryo. I was responding to a different...

**Wolf Reik:** No, it doesn't create an embryo it creates an embryonic stem cell-like cell, it doesn't create an embryo at all. It doesn't involve nuclear transfer, you said it referred to the fact that it might involve nuclear transfer. It doesn't.

**Bill Hurlbut:** Well then let me clarify my position on it. I certainly favour that if it works.

However, I will say this. It leaves you with no way to go backwards from the fourth or fifth day, so therefore it leaves you no tool for NIH funding for studies of early developmental biology, and that's a disadvantage of direct reprogramming when compared with ANT.

Second, some of you would have much better judgment on this than I do, but I'm personally not convinced that you will get the same cell. It may be the same by some criteria, but the Yanamaka cells did not form fully functional tetraploid complementation mice. I just wonder if you don't need to go to kindergarten before you go to fifth grade. It's a theory of soup versus sequence. Do you need the layers growing out like in a tree? Are things happening that have to build on each other, or is it possible to mix and stir and get an embryonic stem cell from an adult cell simply by adding four factors?

**Martin Evans:** There may be other genetic programming.

**Bill Hurlbut:** All the way from the bottom.

**Denis Alexander:** Wolf, do you want to comment on epigenetic programming?

**Wolf Reik:** Well, I am going to shoot myself in the foot now! What's likely from looking at the results of what these cells are is that – and I think Anne commented on it – there are aspects of reprogramming that are very, very good, very exciting: put all these transcriptor factors into the cell stem, force them to adopt a new cell faith; but there are other aspects there, the genetic ones, which are not perfectly reprogrammed. I think that there's more work needed to identify additional factors and new cocktails that alter achievement – I don't think there's any reason to think that that's not possible.

**Anne McLaren:** And it hasn't yet been completed.

**Wolf Reik:** It's a short period of time since the paper!

**Anne McLaren:** I'm sure it will be.

**Brian Heap:** To rephrase Wolf's question I was going to ask you supposing the Kyoto work does show that there is a way forward for reprogramming, it seems to me that there are so many

options with that so rather than put this huge investment into hyping up CDX2 or whatever, that might actually be a more promising way forward for your case in the USA and you might find you are getting more congressmen supporting you.

Just going back to this question and the couple of points that were made earlier and taking your point about why are we so concerned about hybrids in this country compared with the human embryo itself. It's very much on people's minds at the moment so it's very topical and I think it is unfortunate that we have got to the point where The Sun, which is one of our popular newspapers, does describe it as Frankenbunnies already so that picture is already in people's minds. It's actually going to be quite difficult to advance from this position that we have in connection with the development of hybrids if it's actually going to be reliable in a scientific sense. Inevitably it does raise this question, particularly in this country which you would consider as being very liberal in these areas, of people thinking that we are moving increasingly on to the slippery slope. Bernard Williams, a distinguished philosopher from King's College Cambridge now deceased, once said the reason why people were worried about the slippery slope is because they don't know what's at the bottom! But I think there is a difference here and that is because of the 1990 act which actually laid down very clearly what the regulations should be, what the legislative position or the legal position is, and as a result of that there have been few, if any, cases that have actually come to a point of law because the legislation has been in place.

Martin mentioned earlier in connection with the hybrid debate the importance of having good regulations and I think that's one thing that has been achieved in this country, which unfortunately has never really been picked up in the USA. For example, Clinton, as you know, tried to get a ban on human cloning on to the statute book. That's never happened in the USA before. In 1990 we had encompassed in the bill a position that said it was a criminal offence, an order referred to previously, and that still stands. One of the interests in connection with the debate/discussion we've had this evening is to highlight again this huge contrast that exists on both sides of the Atlantic and clearly you are up against not only a scientific establishment that's

probably questioning what you are doing, but you're also up against a political establishment that is also fighting over it. So I find you are in a very vulnerable position and sympathise with the position you find yourself in, particularly since you and I come to this subject as people who, from the faith position, would actually arrive at totally different conclusions.

**Bill Hurlbut:** I'll take all the sympathy I can get!

**Brian Heap:** I am trying to help!

**Bill Hurlbut:** I would point out something about this: it is not just the United States versus the position in Britain, there is a spectrum of positions all over the world and it was an interesting point but maybe not quite fair when you put the population of the world up – I don't think the average Indian or Chinese knows what SCNT is at all, or even what embryonic stem cell research is about.

**Brian Heap:** I wondered if you might pick that up! But it is a position taken by those countries.

**Bill Hurlbut:** By the governments of those countries. If you're talking about governments, three-quarters of the governments of the world joined in supporting a voluntary ban, but still a ban, on all forms of SCNT with a United Nations mandate.

**Brian Heap:** Ah, but that's not a binding mandate and you must admit that that decision of the United Nations was a political decision, not a scientific decision. It was particularly spurred, as you know, by Costa Rica which was supported by a number of other countries and it was not only political but there was also a huge religious debate.

**Bill Hurlbut:** But my point is that if we're going to cite numbers of people we also need to look at numbers of countries and their governments. But more importantly, we need to recognize that in Canada, France, and several other civilized countries across the English Channel, there are some very strong feelings that are in some ways even more conservative than the United States. In the last five years I have been on all the continents in the world, except the penguins who didn't invite me, and everywhere you go it's a different debate and it's a strongly conflicted debate.

**Brian Heap:** Yes I agree, particularly in Germany where they have this extraordinary situation where Germany prohibits any sale for research but on the other hand they will permit the

importation of stem cells from other countries for German scientists to work on. So I think this is where, as I said earlier, that we do have a very confusing situation between different countries.

**Bill Hurlbut:** Just one final point on that – how much better if we could find a way where all the countries of the world could agree.

**Brian Heap:** Indeed.

**Denis Alexander:** I think that we are running over but I am aware that there are some people who haven't had an opportunity to speak. You may feel that you are not a stem cell biologist so are keeping quiet but if you have a question or a comment, we do like to give everyone an opportunity to speak.

**Bob White:** Yes, there's an interesting ethical argument that we might discuss. We are worrying about doing anything to an embryo, presumably because it hasn't given us its permission, but also because it is a potential, or an actual, human being. What I was thinking was that in the history of humankind people have continually given up some of their rights, sometimes their health, sometimes of their wealth, sometimes even of part of their physical bodies, for the sake of others – maybe for their offspring or their close family, often for people who are not related to them, for purely altruistic reasons, for the good of others. It seems to be a feature of humankind that humans do that sometimes. And I presume that's partly because humans are made in the image of God, and that it's in God's nature to sacrifice himself for the sake of others.

Now you could make the case, couldn't you, that perhaps some experimentation, even with potential human beings, may be permissible for the sake of others. Now the slippery and difficult part is that that person has not given their permission, or that potential person has not, but I would like to hear other people's reflections on this. Mandy, for instance, works with very new born babies that are at very high risk of dying – I guess if you didn't intervene many of them would die, wouldn't they?

**Amanda Ogilvy-Stuart:** Many of them would, yes.

**Bob White:** What's your perspective on this?

**Amanda Ogilvy-Stuart:** I think if you are unable to give permission yourself you require someone else to do it on your behalf, which I guess is what a lot of this debate is about that we have been discussing indirectly tonight. So if for neonatal intensive care research you are reliant on ethical committees and ultimately parents, obviously in embryo research it's much more difficult to get parents' permission but maybe that's another way of looking at how to take this debate forward.

**Roger Pedersen:** A point of correction – with respect to embryo research – every single embryo has parent permission. It has to have, because the parents are the only ones who are really qualified to make that decision.

**Derek Burke:** And do they raise issues that we have talked about tonight?

**Roger Pedersen:** It's usually that they just decline to participate.

**Denis Alexander:** I wondered if Bill or Brian or both wanted to give any closing comments – we're almost out of time so you are going to have to be really brief but I just wondered if there were any points you wanted to make before we stop.

**Bill Hurlbut:** Briefly I would like to say that I thought I had – and certainly intended, though maybe I mumbled – mentioned that Michael Roberts' paper was called into question and that some of the images are incorrect. There has been a letter of caution from Science magazine but it's not been withdrawn though I think it may very well be. But I did talk with Michael Roberts three days ago and he said that on substantive parts of that paper that apply to the Altered Nuclear Transfer project it does look like the relevant findings are going to hold – for whatever that's worth.

Two final comments I would like to make. First of all in your country and in mine there is some measure of equipoise between the moral and the scientific issues, and even if one takes a purely utilitarian approach, there are still balancing factors going on here. My own feeling is, for the good of the world we need to find a principled way to go forward because if you don't have a strong moral principle the balance of goods can tip in ways you don't want it to tip. I am hoping my country will hold on the federal prohibition against the destructive use of embryos simply

because, if for no other reason, it will push us to find better solutions and better – and I think broader – ways forward that will sustain social consensus for biomedical science.

Also there's something that I tried to mention but I didn't and I'll close with this. I think we need to find a way that isn't just one side *winning* – that's not the spirit of democracy even, not to mention love. I testified to a senate hearing at which Senator Arlen Specter presided. He has cancer and is a very, very strong advocate for embryonic stem cell research. I talked about Altered Nuclear Transfer in my testimony. That night I got a call – somehow they found a way to get through to my cell phone number and you know what that means – and this woman called me up. I had two calls from her, one very interesting. She was pregnant, she was paraplegic and she wanted to know if I would like to have her embryo to study. I said no, that there were plenty of aborted fetuses if we wanted to study them. Slowly but surely it came out that she was hoping she could have her fetus aborted, or actually her embryo as it was only at four weeks, and it slowly came out that she wanted it harvested to produce embryonic stem cells to cure her.

Second, I got an email that night from a young woman who wrote that her mother was recently diagnosed with Parkinson's disease at the age of forty-six. Let me read you part of it. She writes: "We have been devastated by the news and have since been educating ourselves on all varieties of treatment. My family is Christian, however, so previous stem cell therapies have seemed too unethical." And then she says "I have found that this experience has shaken my faith in a major way." I don't think that we want to end up 'winning' in a way that people with moral objections have to lose. Let's find a way forward for all – not just all Americans, which is what I usually say – so that all of us collectively can rejoice in this. Medical science should be part of our identity as a noble and progressive civilization.

**Denis Alexander:** Thank you very much. Brian – do you want to respond?

**Brian Heap:** Just if I may make a comment about Mike Roberts as well, because he's a good personal friend actually. Bob and I know him well and we have worked with him over the years. He was actually a visiting scientist in my lab some years ago. I would regard Mike as one of the

straightest people I know and consequently I was as shocked as anybody when seeing that there were questions about that particular paper and I am very pleased to hear – he told me in December – that his subsequent work seems to confirm that the suspicion which has been placed on that paper is probably ill-founded. I'm not sure that those results actually help our discussion of this evening because, at the end of the day, even if there is that asynchronist distribution at a very early stage, that still doesn't answer for me the issue of the twinning problem because even if there is asynchrony those embryos are still able to split and form into more than one.

A second point I would make is that I think we have both been as careful as possible to try to avoid over-stating the case of stem cell therapy. For instance, in the list of conditions that I quoted which was actually taken from a composite of several papers, I eliminated Alzheimer's disease which is often included. I think this is quite wrong because I think the prospects of using this therapy for Alzheimer's is very much in the future, even though there is a prospect of it happening. I think as scientists, and as people who are concerned by ethical presentation, we must be very careful that we don't overstate what the possibilities are. Unlike you, I would want to see the emphasis placed on reprogramming rather than altered nuclear transfer and I would put that as number one priority. That's why I was excited to hear this work which was written up in *Cell* late last year, and also presented in Cambridge, with further information about the experiments by the Kyoto group in December. I think this does open a very exciting door for us. Now there are obviously all sorts of questions that have yet to be answered, but it does at last give a glimpse of all the research that many people are doing all round the world, mainly to a mechanism by which it will be possible to reprogram adult cells. It's a great pity that Onora has left us because I think she raised an extremely interesting ethical question about the status of cells that are re-programmed in that particular way; but we can save that for another occasion.

Lastly I think we really should acknowledge Martin's presence this evening, because it's one of those few occasions when Martin is in college. I think you're a former Fellow of the college? (**Martin Evans:** Former fellow and an Honorary Fellow.) I was going on to say

Honorary Fellow but one has to be absolutely sure that memory is correct! We are delighted that you are an Honorary Fellow of St Edmund's and we are here tonight really, I think, because of Martin and it's a special feature that you are able to be with us this evening with your good wife, and also to chair the debate for us. Thank you very much.

**Martin Evans:** Well thank you very much, but I did very little here. I think we owe great thanks to Bill for having come all this way and given us an extremely open and generous presentation, and also to Brian for his usually measured and well-considered response that leaves a great deal for contemplation but nevertheless sums it all up.

**Bill Hurlbut:** From my side I want to say I have rarely had dinner with so many people whose work I have followed and whom I have always wanted to talk with, so thank you for that.

**Denis Alexander:** Thank you all very much for coming. If I may get in a little plug at the end, we have a number of Faraday courses at our college and in other colleges around Cambridge. We have got a biology workshop in September to discuss 'God and Biology' and I would like to extend an invitation, especially to the biologists around this table. We have got Francis Collins from the NIH, Simon Conway Morris and a number of other really good speakers so I hope that as many biologists as possible will be able to come along. Thank you again for coming this evening.

**Contribution added after discussion:**

**Jonathan Chaplin:** Perhaps the term "yuk" factor needs further exploration. In many cases, it's obviously a result of popular ignorance, as on some scientific issues, or popular prejudice, as in xenophobia, racism or homophobia. The latter is what unscrupulous politicians exploit through what is called "populism". There what is called for is clearly to try to educate people out of such responses. But in other case, what presents as a "yuk" factor response may in fact reveal the operation of a healthy (if not well articulated) moral intuition, as in the widespread revulsion against child sex abuse, or torture. The "yuk" factor is a mixed phenomenon, shaped as it is by many factors including complex culturally inherited perceptions. Is there a way for the

scientific and political communities to distinguish between plain ignorance and prejudice on the one hand, and healthy moral intuitions that should be taken as a salutary “alarm bell” for scientific researchers as they press towards ethically contentious boundaries? This, then, is an invitation to take the “yuk” factor seriously, not merely for pragmatic reasons (‘it might block our research’) but also as a possible source of moral insight.