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C O N T E N T S

P R O C E E D I N G S

Formulating Effective Policy in ART

Where Do We Go from Here?

DR. MCLAREN: Welcome to this morning's session. As you know, this session is on formulating effective policy in ART--where do we go from here? I thought it might be appropriate if I just showed a little bit of historical data on the UK because that is where I come from and what I know about, and not where we go from here but where we have come from and how we got here because that also is informative.

[Slide]

So, really the story starts back in 1978 with the birth of Louise Brown and the Warnock Committee that I was honored to be a member of. The report of the Warnock Committee received a rather hostile reception, I have to say, both from Parliament and from the general public. There was a lot of opposition to the report. There was a lot of misunderstanding, ignorance. There were some really genuine fundamental moral objections, but there was a lot of misunderstanding.

During the next few years, and the Enoch Powell Bill was one of the evidences of the opposition, the voluntary licensing authority was set up by the College of Obstetrics and Gynecology and the Medical Research Council to operate exactly along the lines that the Warnock Report recommended but, of course, since it was only voluntary there were no sanctions; it had no teeth. But it worked well, and I think it provided a very valuable reassurance to the public that there weren't nasty scientists doing wicked things behind closed doors.

[Slide]

Anyway, over the next few years there was a great deal of discussion, debate, information banded around and, by the time it came to 1990 and the important parliamentary debates, the opinion in the country had shifted a lot and the general feeling was quite well expressed I think by the Archbishop of York who is, after the Archbishop of Canterbury, head of the Church of England, and he said I believe that research must continue if IVF is to continue. One cannot separate them. I regard as totally unrealistic and, indeed, immoral any proposal to continue IVF without a proper backing in research, a simple and basic reason that

imperfect techniques without a backing in research are bad practice medically, and I believe wrong morally.

[Slide]

So, that set the scene for the acceptance of human embryo research for very specific worthwhile reasons, and well regulated. It set the scene for the passing of the Human Fertilization and Embryology Act, which was passed by both Houses of Parliament in the UK by substantial majorities. House of Lords is our upper house; House of Commons our lower house and, they not only agreed to human embryo research under license for very specific reasons, but they also agreed that there could be embryos produced specifically for research because there are valuable and worthwhile research projects, for example on egg freezing which, for obvious reasons, can't be done on spare embryos from IVF.

[Slide]

That was 1990. The authority that was set up, as I am sure you all know, was the Human Fertilization and Embryology Authority, the HFEA, which had a number of statutory functions. Essentially, it licensed and monitored clinics, IVF and donor insemination, and that

involved inspections every year or sometimes more often and for embryo research as well as for clinical treatment; storage of gametes and embryos; register of information, very important, very difficult to get the accurate information out of centers and I think we are still struggling with that; and a Code of Practice.

[Slide]

The purposes for which embryo research was allowed were very specific. There were five of them, and Henry Leese is going to be telling you more about that. But the point is that none of them allowed research for purposes of therapy, investigating new methods of therapy. Production of stem cells, embryonic stem cells from human embryos was permitted and there were licenses granted but not for purposes of therapy which, of course, today is the only reason we really think of stem cells for. In 1990, if Parliament had been asked to include that, I am quite sure they would have but the curious thing is only twelve years ago it didn't occur to anybody to talk about it.

[Slide]

So, in 1998, when ES cells and EG cells came along and the UK government realized the promise of stem cell research--

[Slide]

--they rapidly put in a new bill to Parliament and Parliament, again both houses, felt that if embryo research was allowed for the alleviation of infertility, the prevention of suffering and the prevention of genetic diseases, PGD, which had been practiced since 1990 or earlier, that there was no reason why research shouldn't also be licensed for research on serious diseases.

So, that is the present position in the UK. As to where we go from here in formulating effective policy, well, we are going to be hearing from Prof. Leese, of the University of York, who is our keynote speaker this morning. He is a member of the HFEA at the moment and has been for some years, and he is going to be talking about the regulation of assisted conception: the UK experience. So, I will hand over to Henry.

Regulation of Assisted Conception: UK Experience

DR. LEESE: Thank you to Christine Everett and Melanie Whelan and colleagues for your invitation to this

really quite stimulating, fascinating meeting. I really enjoyed yesterday's proceedings. And, thank you for paying me to come over here. For reasons quite unknown to me, I was upgraded from economy to business class at the airport two days ago, and I can't imagine some of you have influence in high places--

[Laughter]

The other thing I would like to say is that I wouldn't be here if it wasn't for two of the people who are here, that is, Anne McLaren and John Biggers, and to remind you that on any list of the major events in the history of IVF they would figure prominently.

[Slide]

In 1958 they were the first to show that you could grow an embryo. It was a mouse embryo and at the 8-16-cell stage of the blastocyst and they transfer it into a recipient and get live offspring. As they said at the time, this was potentially of immense value in investigating many biological problems in medicine and agriculture, a very prescient remark in 1958.

[Slide]

I thought you might just like to see a recent picture of John and Anne here hard at work--

[Laughter]

In fact, the title is test tube animals.

We now need the overhead off and we go over to the Power Point. The presentation is in the folder. It was sent in about three months ago because that is what I was asked to do. Most of the Power Points I am going to show are in the folder but I have added one or two more and updated a few as well but they are mainly as you have them there.

[Slide]

Anne has already covered most of this, the history at any rate. I will go over it very briefly. Then I will talk about the Warnock Committee and the HFEA. I will spend a little bit of time in the middle of the talk on really one of the themes of this meeting, how you move from the laboratory to the clinic. I will then return a little bit to the HFEA to say how it is managed there. I have one slide that contrasts the USA and the UK, and I am going to end with a little bit of science on an initiative we have going in the UK to look at early human embryos.

[Slide]

Echoing Anne's point, we had first of all a voluntary licensing authority, in other words self-regulation by the profession. It then became an interim licensing authority in 1989, before the passing of the Act of Parliament. Actually, preceding the Act there was widespread consultation. There was a Green Paper, which is a discussion paper, and then a White Paper, and then a Bill and then the Act. So, one of the themes I would say is that there has been very wide consultation and and equal lot of transparency about what was planned.

[Slide]

So, that was the remit of the Warnock Report that got this going. Although the first test-tube baby was in 1978, in fairness to Edwards and Steptoe, they had been calling for wider discussions at least ten years earlier and, indeed, I should have acknowledged in the overhead on the history Barry Bavister, who is here today. He was involved in many of those discussions at the time.

[Slide]

Following Louise Brown, the first test-tube baby in 1978, the government set up this inquiry in 1982 and it

took two years to report and that was its remit. That was the outcome, first of all, and it was obviously what it was planning to do.

I think it might be worth just spending a moment or two only on the question that sooner or later has to be confronted by anybody anywhere in this area, the status of the early human embryo. I found very useful a book by Ronald Green which is here and some of you may have seen. He is an American author and he catalogs the history of your experience this side of the Atlantic in trying to move forward in the direction of regulation. He draws a lot on the NIH and the various working parties you have, and I do recommend it to you.

The status of the early human embryo--in a later little book that includes the Warnock Report, which is this little book called "The Question of Life" and this shows you how really quite small the Warnock Report is, and it is very readable, she quotes the Scottish philosophy of David Hume, writing in 1738, that morality is "more properly felt than judg'd of." In other words, morality for some is obedience to established rules. The judgments have been made and there can be no argument about them. So, for such

people, usually on religious grounds, the embryo is treated as though it was already a person, which is what it will become.

Warnock approached things in a different way and asked why can't we look at the embryo at a particular time, really asking how do we view the early human embryo. An English philosopher thinker, Polymath Jonathan Miller, has expressed the same sentiment in a different way. He says that moral judgments are not absolute; they are negotiable. So, rather than looking to frankly religious views alone for an answer to these questions, the input is widened to encompass, for example, the biology of early development. That brings you into developmental biology which does have various key stages in it. It gets you into neurobiology, the origins of the nervous system; and then higher centers which characterize us as human beings. It would embrace the clinical aspects, as we heard yesterday, the high embryo loss and also egg loss and the social connotation of this that we don't tend to grieve over lost eggs or lost early embryos and, again echoing the overhead that Anne put up from the Archbishop of York, the moral imperative that

any area of clinical practice should have a firm backing in research.

So, this is not to belittle or in any way downgrade anyone's moral, religious view but it is to question the extent to which that, and that alone, should determine policy. Warnock managed to, as it were, get around that, in a way we will describe with the Act and it has served us well. For eleven years we have had human embryo research going on in I think a productive and highly responsible manner.

[Slide]

So, having dealt with that one--not quite dealt with that one, Alta Charo has said a similar sort of thing, that the value placed on the embryo should not be determined not by specific criteria that could be applied to determining the inherent value of the embryo because there will be so much disagreement but, rather, the value of all of us who have been born and thought about this have placed on the embryo.

And, Ronald Green speaks about minimizing the moral pain of those who would take the absolutist stance, the fixed stance, understanding the moral pain they would

have but, at the same time, not relinquishing vital social objectives and the need for a firm backing of research in this area.

[Slide]

So, back into the main thrust of my talk, the HFEA, the background really, as Anne has said, was widespread public concern about these new developments and where they might lead.

[Slide]

The Act basically governs about the creation of an embryo outside the human body. It does other things as well but that is the nub of the Act.

[Slide]

It is administered by an authority. There are 21 members of the authority. They are appointed by the Department of Health, which is a government department, and there is open recruitment. You will find advertisements in the papers and elsewhere inviting people to join the authority. I should emphasize the strong lay input throughout. This has never been run by scientists or clinicians; it is run by lay people. Indeed, the majority have been women, which I think is wholly admirable. I

think in any area you should have at least equal representation. In an area of reproduction where you need men and women, you should certainly have at least 50/50.

So, the chair, by law, has to be a lay person and the deputy chair is also lay and both, at the moment, are women. It has an executive of about 60 people. That may rise slightly as life gets a bit more complicated and there is more to administer. Its budget is about four million pounds or about six million dollars a year. Of that, the government contributes about a quarter and the rest is paid by patients in addition to the cost of IVF treatment so it goes on their bill, and it will often be itemized and say HFEA license fees. That hasn't really proved controversial, that the patients should pay the bulk of this. It would be very nice if the government paid the lot but they don't. If anything, the mood is the other way. The consumer is having to pay for these things. Anyway, that is just the way it is.

[Slide]

There have always been prohibitions in the Act from the word go, from 1990. So, you need a license to do any of this work, and equally to store gametes, which is a

part of the Act. You can't mix human and animal gametes. You wouldn't get very far if you did but to allay public concern that has always been disallowed. You can't work on anything beyond 14 days. We didn't really go into the reason for 14 days but will not propose that as the limit for human embryo research. It tends to have been adopted by other committees worldwide or the primitive streak, whichever is earlier. You can't do one form of cloning that they foresaw in 1990, replacing nucleus of a cell of an embryo with a nucleus taken from a cell of any person. So, that has always been disallowed. I should emphasize that this is a legal body. Disobeying this would be a criminal offense and you could go to jail, or whatever. So, it has the backing of the law.

[Slide]

As it were, the Act is a fairly formal thing. The bible in this area for all of us is this thing called the Code of Practice. I should really perhaps have brought a few more copies but they would have been too heavy. It makes for very interesting reading and everything you probably need to know is in here, and I think it is on the web and somewhere I have put the HFEA web page.

For example, all the consent forms at the back, consent is a major feature of the HFEA and all the paperwork. This guides the way the Act is administered or works in practice in the clinics.

So, the Code of Practice talks about the staff and they have to be responsible individuals. There is one person above all responsible in each clinic. The facilities are important. Assessment of people seeking treatment--I will come to that in a minute or two. Information and consent. Patient information has always been up in the forefront of this in consent. Counseling has to be available and, in some cases, has to be taken up. Research we will come to, and records are kept as well.

[Slide]

How does it work? Well, a week tomorrow I am chairing an inspection of a clinic in the UK, one of about 80, and I will go along and I will chair this inspection and I will have with me a clinician. There might be a scientist, though I am considered a scientist and they might decide that they don't want another one but sometimes they do. We will have a counselor on the team, possibly a nurse as well, and we will have someone from the executive.

So, it is a team of maybe three, four, sometimes five people. I think waiting for me when I get back will be quite a thick file of papers describing the clinic's activities and what they have been doing over the past year, including their success rates and everything like that. So, we go over that ahead of time and then we inspect them really quite rigorously to check for compliance with the Code of Practice, which is the way the Act works in practice.

The visit will take a day. I think increasingly they are going to spread to two days, and the executive will go in the day before and look at the records, the paperwork, the consents. Then, another day will be spent with someone like myself in the authority and other scientists, clinicians and counselors going over all this.

We then leave. We report back to a licensing committee that is separate from the inspection team so there could be no bias, and normally a three-year license will be granted to practice whatever they are proposing to practice. Despite the three-year license, they will be inspected every year probably by a smaller team. Depending

on the compliance, how compliant they were, that determines how rigorous and how severe is the inspection.

[Slide]

There are wo key features of the HFEA really relate to quite a lot of yesterday's discussion. Until recently you could transfer up to three embryos in any given treatment cycle. This was lowered to two. The strong pressure for this in the UK came not only from the HFEA but particularly from the professional bodies. The Royal College of Obstetricians and Gynecologists and the British Fertility Society really represent the persons responsible in the clinics, the practitioners, and also the Association of Clinical Embryology, the embryologists.

As we said, the culture is different. It is driven by the risk of multiple births in particular and I have a slide on that in a moment. So, we have gone down to two. I think ultimately everyone expects that sooner or later we will go down to one, except in exceptional circumstances.

There was really quite a seminal paper produced by Alan Templeton. One was published in The New England Journal of Medicine, and the other in the Lancet. He had

two papers building on data in the HFEA's database. One of the strengths of collecting data is that you can have a database of 30,000 patients and embryos. He showed, I think, for women under 35 that there was basically no difference whether you transferred three or two. This was quite instrumental in influencing the debate in the UK. So it is now two and clinics have to give a reason why it should be three.

The second is that success rates must be expressed as live birth rate per treatment cycle started. That includes cancelled cycles. So, if you start and you cancel a cycle, it still counts as a cycle and it must be take-home baby; it is not pregnancy rates. So, unlike the practice, I have to say, particularly over here where at scientific meetings you tend to get pregnancy rates which are pregnancy rates per embryo transfer which are only part of the story, in the UK you have to do this. For example, we scrutinize clinics' web sites before we go on an inspection to make sure that they are complying with this requirement.

[Slide]

Multiple births--one bit of data here, this is still births and neonatal deaths per thousand birth events. So, for singletons it is about one in a hundred. For twins it is four in a hundred, and this is per birth; a birth is an event. For triplets it is six. Triplets are highlighted, obviously, but there is a strong case, made probably even stronger, as I said, in the Scandinavian countries, that twins are not a desired outcome. The desired outcome is a single healthy baby.

[Slide]

Ronald Green put this in the book I quoted that you can read there, severe effects of multiple births is cerebral palsy. We will see how it goes. I suspect you are moving but not as quickly as we have moved to really try and tackle this problem.

[Slide]

Novel aspects of the HFEA Act--consent. The parents, the patients, both of them, man and woman, have to consent. There are separate forms for them. So, the couple both have to attend the clinic. Information is a major feature and we scrutinize it. When we go on inspections we will be sent the patient information that we

check to make sure it is as accurate as can be and not making false claims.

Counseling has to be available, and it has to be independent of the treatment, which can sometimes pose difficulties. If the counselor discovers something untoward about a couple, there can be difficulties in conveying this back to the people treating the couple but it can be done. Counseling has to be offered and for some things like donation of gametes it is mandatory; it has to be taken up.

Confidentiality--it is a criminal offense to disclose information about people seeking treatment. Welfare of the child--it is said that historians will find this one of the most interesting aspects of the HFEA Act.

[Slide]

Welfare of the child, a woman shall not be provided with treatment services unless account has been taken of the welfare of any child who may be born as a result of the treatment, including the need of that child for a father and the other child who may be affected by the birth. This was inserted by Parliament in 1990. Anne could describe this better than me, but I think it

reflected concern that this technique was not to be used in any way frivolously. I think it was concern about lesbian couples having children. Nowadays there would be less such concern, but the welfare of the child stayed in.

Now, I have to say I think it is a wholly admirable clause. If you think about it, virtually everything you do as practitioners should be concerned with the welfare of the child to be born, the unborn child and the child once it is born, and that embraces nearly everything. In fact, in the Code of Practice there is rather little about laboratory and clinical practice. I think that will change; I think there will be more requirements there. But you can, as it were, fall back on the welfare of the child and unless you are doing things in a rigorous manner you could be jeopardizing safety of the procedures and safety of the child. So, if you ever draft legislation, stick welfare of the child in. It is a very useful, very clever device.

[Slide]

It was originally, as I said, probably meant as social and psychological well-being--I am repeating myself on this overhead, but equally it should be physical well-

being and health. So, the twin words that we used quite a bit yesterday are we are all seeking to maintain are efficacy, does something work? How well does it work? Does it work well enough to be offered to patients? And safety. Those are the two watch words in ART.

[Slide]

HFEA, as Anne described, licenses and regulates research. The five purposes under which it was originally licensed are all to do with ART and fertility, general disease, miscarriage, contraception and PGD type things. It has to fulfill one of those purposes.

[Slide]

A case has to be made, paperwork has to be written. Ethics committees obviously have to be consulted. If it then happens, of course, the parents of the embryos or the gametes have to consent for the use of their material in research. So, if you are applying for a research license, and I have a research license in York to work on early human embryos, I have to make the case here. It has to be important; it hasn't been done before. I have to justify the use of human embryos as opposed to those of any other species. The methods have to be appropriate. It

mustn't be too unreal in terms of its length, its duration. You have to set milestones. And, the applicants have to be suitably qualified.

This, again, would be before a license committee and an inspection would be made of the premises, and the records and the confidentiality, and all the consents in place, etc.

[Slide]

I now digress a bit, still wearing an HFEA hat but looking at some of the things which this meeting as a whole is addressing, new developments.

[Slide]

All these points are made in the reprint that I have appended at the end of the Power Point, written by Hugh Whittal, who is the chief executive of the HFEA. What I have said here is the conventional route from the lab to the clinic will embrace not all but many of these things here. You will start with experiments on cells and tissues. You will then move to preclinical trials. You may have used human volunteers earlier then that. You then move to the gold standard randomized, controlled trials. You may do meta-analyses if you have lots of them. You

move to clinical practice. In the UK we have a new body that is called the National Institute of Clinical Excellence that is trying to look at, as it were, cost effectiveness for treatment on the National Health Service, which, in the light of this data, is which are the best drugs and treatments to adopt.

[Slide]

Various people, in different ways and different degrees of how they think about it, have said that really assisted conception is rather different. The Royal College of Obstetricians and Gynecologies had a study group on fetal programming, fetal origins of adult disorders, and they came up with this statement, that really much of what we are talking about was being introduced into the clinic before the basic scientific work had been done, and they supported, obviously, more research and, crucially, follow-up studies, which we talked about yesterday.

[Slide]

A very forceful critic of this was te-Velde in the Lancet. He is asking for an awful lot here. I think you would have to abandon much of what we do, but it is an ideal that is worth thinking about.

[Slide]

The Netherlands Council had a look at this, making the point that was made yesterday that if you don't do the required studies then in essence you are shifting the burden onto the woman and the child if you haven't done the basic research.

[Slide]

Under no circumstances whatsoever should women and children be turned into trial subjects for the sake of protecting embryos. Many have said this in different ways.

[Slide]

This is a very simplified diagram of how medical programs develop. You have the question of the basic science. You have the pull and the needs of patients who desperately want a baby. The new techniques are coming on, and this is very technique driven, and you have the economics that, again, was mentioned yesterday.

I am sometimes asked if it was 1977 would I approve going ahead with the creation of the first human test-tube baby? I would say, yes because the first overhead I put up cataloging the developments that have happened over this century, much greater than work in mouse

and in, obviously, human embryos to show they can be fertilized--work of Barry and Steptoe, and also work on primates as well by Maston, I would say a lot of basic science had preceded Louise Brown. Heaven forbid, if she turned out to be abnormal. I think it would have set us back ten or more years, but she didn't and there you go. I would be one of those who say the pendulum needs to shift to the left, but it is easier said than done but we do need more research, and we need people in this community here, in the US, because you are so good at doing research.

[Slide]

A few words on animal models, not a great deal because you talked about them yesterday. The main ones are those, the vertebrate research is promoted, particularly over here, sea urchins and the like. I don't know if NIH promotes that. I am not sure it should; I think it should concentrate on the models that are closer to being applied. I will come back to these later.

[Slide]

I have been a little bit involved in this. I worked with Tom Fleming in University of Southampton. He has a model where you feed a mouse or a rat a low protein

diet, but not that low; 9 percent as opposed to 18 percent. That is quite a respectful diet. Thomas found that if you feed this to the mother, prospective mother, just over the preimplantation period, the offspring of this feeding, when they become adults have elevated blood pressure. It is a small but quite a significant rise in blood pressure. We have confirmed this with longer periods of feeding.

[Slide]

Moreover, Tom Fleming has shown that this really quite modest perturbation to the mother just over the preimplantation period depresses the total number of cells in the blastocysts and significantly to the inner cell mass and trophectoderm, and the ICM cell number is thought to be critical for future offspring viability and health. I find it very difficult to know what to make of these. Indeed, from yesterday's proceedings I still feel, as it were, how much should we worry? Maybe we can come to this in discussion.

[Slide]

I also work on cattle embryos and pig embryos. We make them routinely every week from ovaries and follicles we get from an abattoir.

[Slide]

Cattle is quite an interesting model. It has been quite widely used and it is known that a great many things are involved in embryo-based technology, particularly in cattle and sheep, less so in pigs. All these things have been shown, one way or another, to give rise to some undesirable consequences, such as deviations in inner cell mass, metabolism during organogenesis which is, obviously, a key phase of development. Large offspring is probably the best known. There is no sign of this in the human. If anything, it is the other way, low birth weight. Probably the jury is out on that one. Deviations in relative size of adult organisms and, as I say, the elevated blood pressure.

[Slide]

It has to be said that in one major way and lots of others the domestic ruminants differ from mice and humans, primates. They have a prolonged phase in the uterus before they implant. So they form a blastocyst roughly the same time as the human, five, six, seven days. But then it sits around doing various things, elongating in the uterus before it implants. It actually coincides with

a lot of embryo loss. It peaks between day 8 and 16 and you can lose 40 percent of cattle embryo during that time. In that sense it may be similar to the human. But this free-living period I think makes them a less useful model for the human.

[Slide]

Against all that, what does the egg and the embryo got going for it? I and others have pointed to the astonishing regulative powers of eggs and embryos. I would agree with the use of the words relatively autonomous. For the first week or so they survive pretty well. You know, you can grow them in a dish, not a female tract, and you can do all manner of things to them--freeze them; thaw them; chip bits off them; chop them in half. They are incredibly resilient really.

Also, the egg is the largest cell in a woman's body. They have enormous reserves of energy. I am pushing the notion that, rather than worrying so much about what we add to media, we should just take out and let the egg and embryo sort itself out. They are very large cells.

So, those are things that give us reassurance. Against that is this statement at the bottom that we have

no in vivo controls in the human and are most unlikely ever to have them because of ethical problems. So, we have to study embryos in vitro. This, to me, is where the primate model is just par excellence. I think there should be studies on primate-derived in vivo embryos. I would go further. My hobby horse project--and it would have to be over here because in the UK it just couldn't work on primates--would be to say we have an in vivo primate early embryo. You study it and you put it in vitro, and what happens to it? What happens when you take an embryo and put it in vitro? I think that would yield a gold mine of information, and that is where I think you should put your money.

[Slide]

So, the conclusion of the last I suppose ten minutes or so is that most advances in our field have arisen from development of new techniques rather than from advances in basic science. We need to try to reverse that.

We do rely on the resilience of the egg and the early embryo. My present mood is more optimistic, that we are going to be okay. The worry is that when IVF offspring get to be early middle age they are going to get problems.

That is the worry. At the moment I am quite an optimist. I used to be more pessimistic and now I have swung back a bit. But we desperately need this research. The evidence base is weak and we need more research.

[Slide]

Just finishing then the animal models, pro and con mouse, cow, pig and primate--apologies to Barry, there is no hamster here; there is no sheep. The great thing about the mouse is its genetics and I think it could be used more. We have a world authority on mouse genetics right in front of us here, Anne McLaren. If the embryo transfers so readily in mouse and you can do second generation, there is some evidence from fetal origins of adults as well as in the human that effects of malnutrition in the mother are not seen until the second generation, the grandchildren. That would be best done in a mouse maybe, and you can get in vivo mouse embryos. The thing going against mice--I don't mean small size of mice; I mean small size of their embryos. Metabolically, they are a bit different. They are five times smaller than cow, pig and human, primate embryos and they are a bit different because of that.

And, they are so efficient. Mouse embryologists, some of you here, you get 100 percent zygotes going to blastocysts. They are wonderful things; fantastic. With none of those other species are you going to get anywhere near. So, the mouse embryo is wonderful in that sense, but it is just too good sometimes.

The cow--we get lots of in vitro produced cow embryos from abattoirs. It has a metabolism quite like the human. I am lucky, I am able to do what I like, I get the money so I work on cow, pig a bit of sheep and human as well. Cow is quite good from a human metabolism point of view. Its problem is this prolonged pre-attachment phase which is totally unlike human.

Pig in a way is better than cow because you get large litters and you can do nice genetic things. You can genotype them. You can also make them in vitro readily. The problem with pig embryos is they are full of lipid. They have 150 nanograms of lipid whereas a cow only has 30, the human 15, the sheep 15 and mouse zero. Pigs are just full of lipid and they do make problems and they have this capacity to elongate. They produce great thread-like

trophoblasts, meters long and it is not what happens in the human.

So, I think primate models. You have these primate centers; in the UK we don't. It is quite ironic, we work on human embryos in the UK and you cannot work on them over here. The opposite is the case with the primate. The animal rightists who are very strong and some are violent in the UK, would threaten primate research on the scale required. You have primate centers. I would put them to work as the animal model for the human. It is the closest. I think you need a lot of biology, is what I am saying, on the primate. You have the ICSI work as well, but you need to know about the biology of the primates.

There are ethical problems. You have to satisfy that, and there are some critics and high primates are probably out. I am uneasy about that sort of thing. But, nevertheless, if you asked me I would say you need to have a big push on the primate.

[Slide]

Back to the HFEA, how do we try to sort these things out? We have various subcommittees. One is called the working group on new developments in reproductive

technology. Anne chaired it for many years very successfully. I am the chair at the moment. We also have a license and fees committee. We have an information committee; an audit committee, everything has to be audited these days; and an organization and finance committee.

This is the one that dwells on the topics we are discussing. If some new development comes along, it would be nice if you could anticipate it but you can't always. Some clinic comes along, wanting to do something. We scrutinize the literature as best we can. We will seek expert opinion worldwide the best we can get. Some of you here may have been consulted by the HFEA. We then consult with professional bodies. The obvious ones are practitioners in the UK. If it has an ethical dimension, which it often does, we refer to the ethics committee.

With some things there is widespread public consultation. We are about to have a consultation on sex pre-selection. Should couples be allowed to select the sex of their offspring for social reasons? At the moment they can select sex by PGD or other means, the couples at risk for sex-linked disorders. In 1993 there was a consultation on this and it ruled out sex selecting for social reasons.

The Department of Health has commissioned HFEA to have another look at this. I predict it will still stay the same way. People will not want to move down that route but I think one day it will change. But that is very public consultation.

We are also having consultation at the moment on donor anonymity. Donor gametes, sperm and eggs are practices as they are here. Everything is done anonymously. That is not quite true, most is done anonymously and that anonymity is protected by the law. You can have known donation but most is anonymous. Should that remain the case or should anonymity be removed? That is a public consultation. If you get on the Department of Health web site in the UK you can look at the consultation; you can even participate if you want, although I think it is past the deadline.

We have also had consultations on fetal ovarian tissue, PGD and stem cell therapy, which I will come to in a minute. Again, I think one major difference with us is this strong lay input. It goes right back to the origins of this Act. It is not run by scientists and clinicians. It is basically run for the public and by the public.

If we think all this is okay, then the working group would say, okay, we need to go ahead with caution; maybe keep monitoring the new development as it comes along and get a report back to us. That can be difficult because we don't really have the resources. We are not a research organization but we try and monitor things. I would say that we do just the best we can with the resources.

[Slide]

What if we allowed egg freezing and thawing? After quite a lot of soul searching really because it doesn't work very well, I would say the real success is one to five percent, and couples must be apprised of that or women when they come in for it.

Screening for aneuploidy has just been allowed in the past couple of years in a limited number of centers. Each one has to apply separately. It is not a blanket ruling, and they have to report to us what they are doing and the outcome.

In vitro maturation was initially allowed for research purposes. It is now allowed for clinical purposes. Again, we want to know how it progresses

HLA tissue typing was a controversial one, allowed in the last year coupled to PGD. We may explore that in discussion if you want. HLA tissue typing on its own was disallowed quite recently because it wasn't attached to PGD. Again, maybe you want to explore that in discussion.

Human and embryonic stem cell generation has been allowed and the purposes of the Act have been widened to include that.

[Slide]

What has been disallowed? Has anything been disallowed? Yes, we disallowed ICSI with elongated or round spermatids. I chaired the little committee that looked into this. We were on the verge of allowing elongated LC but not allowing the round because they weren't mature enough. Then a paper came out in the Lancet pointing to some defects that had arisen supposedly--well, defects with this technique. So, we put it on hold.

Fragment removal, Anne chaired that item, and we decided evidence of efficacy wasn't there and safety, so we disallowed that. Cytoplasmic transfer we also disallowed. We allowed assisted hatching but we are awaiting a decent

study to show whether it works. Everybody uses assisted hatching, either by laser or by acid, but there have been no really good trials on it. We try to monitor it but does it work? I don't know. It would be a good case for a really good trial.

[Slide]

Stem cells--let me move to the next and then back.

[Slide]

I don't think we would have got anywhere--we would have got somewhere but the outcome would have been totally different, it would not have been what was desired, if the HFEA had not existed. So, this is one quote from the Guardian newspaper, a broad-sheet newspaper in the UK. It pointed to the effect of the HFEA in regulating for the past ten years and saying if you move down the stem cell route, you can feel reassured that, you know, things will be okay.

[Slide]

Again, we didn't just move to regulate the use of human embryos to generate stem cells. The history, you all know. Dolly is prominent in the history. So was the work

over here, Jamie Thomspon and Gerhardt in the isolation of human ES and EG cells. The HFEA then initiated a consultation with the Human Genetics Advisory Commission, a public consultation where anyone could contribute. There was a response in the Department of Health, the Department of Trade and Industry and the Office of Science and Technology and another report from the Department of Health. Bodies like the Royal Society came in as well and the Nuffield Council for Bioethics. It was all very transparent. It was all there, you could have your chance and state your view.

It eventually came to Parliament and, as Anne said, they voted strongly in favor. The House of Lords wanted a bit more time. They did vote in favor but there was an asterisk I think on Anne's overhead. They wanted to have another look at it and they did. The report they produced was brilliant, absolutely brilliant. There is a web site at the end on my last overhead. If you want a first-rate account of not only stem cell research but the whole history of regulation in this area, get on the House of Lords web site justifying the use of human embryos in research, a first-rate account, chaired by another bishop.

We have been lucky in our archbishops and bishops in the UK. Then the first HFEA license has been granted under these new purposes.

[Slide]

USA-UK--you have a very active pro-life movement. We have one too. It is fairly vocal but in practice it has little influence. I have met with them. The HFEA meets with all bodies. We invite them and we talk with them, and we agree to differ. It is all quite civilized. They don't get violent, or anything. I have been in these meetings and it is fine. We try to understand each other's view but then on some things, the basic things, we just have to differ. We try to give the reasons why as well. We try to give the reasons as I have tried to articulate them in the first part of the talk.

This is not quite the right way to put it, you are very pro-science over here but we have a lobby that has recognized that science can be protected by legislation, and the stem cells is a really good example of that. The record of the HFEA suggests we can trust them in this area. I gave evidence with Anne and the chair of the HFEA to the House of Lords and I remember saying HFEA is run by lay

people and women, as I have said before. Hopefully, you can trust such a constituency to protect you. So, practice has proceeded under that umbrella, the strict regulation that allows you to do certain things. You are not going to do frivolous things and silly things.

You have a problem over here framing US-wide legislation. You have the states and you have the federal. I noticed coming over, I read somewhere, I can't remember where it was--I think it was in Nature--that the Australians have a similar sort of problem and the states are quite powerful, there are less of them. In some area, and I think it was to do with stem cells, the states have gone different ways. Maybe Anne can clarify this. They have allowed certain things and they are legal. They said, sorry, federal, we are going to do it this way. They only have a small number of states. You would know better than me whether a state would break ranks and say we are going to allow this and that. This is a discussion point.

The lay control comes through so strongly. I keep pushing that. You have a stronger commercial drive in US clinics than in the UK. Most are still commercial but we try to just monitor, just calm them down a little bit

with the HFEA when they are getting too aggressive with their marketing techniques. We do publish success rates, really originally driven by patients wanting to know. There is a commercial drive but it is not as strong as here. You have professionally driven accreditation; we have government driven or devolved or passed down to the HFEA to drive.

[Slide]

Ronald Green was quite good on this. You can read what he said there. Your major problem is in the second paragraph there, that however much I might argue against the moral beliefs that tend to dictate or decide the way you are, you are just going to have a problem with that nationally.

Ronald Green, again, quite eloquently stated what the Archbishop of York said, the need is really to carry out research and the moral views of others. You can read what he says there.

[Slide]

Elsewhere--Germany is very restrictive. France allows exceptional research on spare embryos. Denmark is more liberal. Norway has gone the other way. The

government has changed; it has gone more conservative, more right wing and they have changed legislation and made it much more difficult. Sweden is more liberal. UK is the only country that allows creation of research embryos. So, as Anne said, if you want to study egg freezing, thawing and then fertilize the egg, which is the ultimate test, that would be allowed in the UK. That remains controversial. The House of Lords didn't suggest banning it in its recent report but using it only under exceptional circumstances. If, for example, you want to study fertilization, there is no other way.

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Finally, a little bit of science and how the legislation works in practice. I coordinate a cooperative funded by the Medical Research Council, with the people there. They are based in New York, Manchester, Southampton and Leeds.

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We are addressing the major problem of how you get from zygotes to blastocysts. If you like, the premise is that we know remarkably little about the early human

embryo. We know most about mouse embryos. It remains the standard animal model.

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We don't know much about human embryos. Those you get for research are, by definition, those that are not transferred for frozen so their quality is generally poor. We have rather few markers of normal development.

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So, our hypothesis, really borrowing from work on mouse, is to say that to form a viable human blastocyst you need to do certain things: generate normal blastomeres; express key genes; eliminate blastomeres by apoptosis; make intercellular junctions and you may need some metabolism to do that.

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The strategy was to maximize use of this precious resource. Human embryos are precious. Patients expect you to make good use of them. So, all the work was done on single embryos, virtually all of it. We have the facility, using non-invasive assays, first of all, to do dual assays and sometimes triple assays on the same embryo. So, non-invasive assays are done on live material.

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The way it works, the embryos are mainly derived from Leeds General Infirmary--two large IVF units. The larger one is Leeds General, the smaller provision of embryos is St. James's. The embryos are brought to York still alive. They are transported about 25 miles. There we perform non-invasive assays, particularly for amino acids. We are quite pleased about it at the moment.

The embryos are then fixed--if you like, killed. I always think killed is an emotive word. I realize you have to use it in a way. I prefer made non-viable. Killing is too emotive and it describes a humanity I think to the embryo that isn't there. I would say made non-viable. Anyway, they are fixed, whatever you want to say. They then go for a secondary analysis and, interestingly, once they are fixed, dead, killed, made non-viable, HFEA--it is without their remit. They are no longer alive. So, I think you should still do responsible research on them, but it is without the HFEA remit. They are then sent to these other centers to do their own bit of research.

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At Leeds they are doing the genetics with FISH karyotyping.

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Manchester is doing expression of about 50 different genes to do with these key events in blastocysts, all sorts of things.

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Tom Fleming, at Southampton, is looking at how you make junctions because in the early embryo you make junctions the first time in existence.

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In York we are doing metabolic profiles, putting embryos in little drops of media. It doesn't harm them in any way, and looking at that profile of consumption or appearance of physiological mixture of amino acids.

[Slide]

We are getting quite excited by this because--just a bit of science here--if you take a day two to three embryo, those that go on to form a blastocyst, the little bar, the kind of pale green bar, they have a much lower amino acid metabolism, depletion of amino acids than the pink bar, which go on to arrest. We can tell this on day

two to three. Similarly, those that go on to form a blastocyst have a quieter metabolism than those that arrest.

I have written a little review actually in Bioassays if anyone wants to read about this, and I have called it "Quiet, please. Do not disturb: A Hypothesis of Embryo Metabolism and Viability." So, you can read that and knock me down if you want.

[Slide]

Where are we moving to in this cooperative then is a picture of trying to unite and integrate various aspects of the biology of the early human embryo, the database because everything is logged; there is a process of an enormous amount of data to enter, maybe it is about 2000 embryos; I can't remember but there are a lot. So, we are trying to tie together the way that gene expression might impair membrane biogenesis, lead to ionic leaks, increase the need to pump sodium which provides oxygen, may lead to compromised mitochondria which is heavily involved in apoptosis; stress, something that John Biggers was talking about and Catherine yesterday; and leading to different protein syntheses, etc. So, we are trying to tie

all that together and, again, I would see enormous scope over here to do the same thing for the primate. Really, you could do this. When the United States scientists put their mind to something, you are in a class of your own to getting it done so I think you could do that sort of work.

[Slide]

Then there are some web sites. The HFEA one I think is already in the handout. The NIH have a first-class web site on stem cells, I use it a lot, a really good one. As I said, the House of Lords report is also very good on background. Thank you very much.

DR. MCLAREN: Henry, thank you for an impressive and very informative talk. We have half an hour before the break. After the break we will be joined by the panel and we can have then a discussion on formulating future policy. But I suggest what we do now is direct questions and comments to Henry about what he said about the science, about the UK regulatory situation, and about his views. So, who would like to start? Yes, back there?

MS. CHARO: Thank you for that incredibly informative summary. I wonder if I could trouble you to add some additional information though about the European

Union as opposed to the UK specifically? I wonder if you could describe to us the effect, theoretical and practical, of the debates going on at the level of the European Union on domestic policy in the UK or other EU countries and any other European body that might be having some influence on those debates?

DR. LEESE: I am delighted to address that because, if I have to face 30 minutes of questions, I was about to say a lot could be deflected to Anne. Anne is the one to answer that, quite frankly. Say what committee you are on.

DR. MCLAREN: I am on the European Group of Ethics, which advises the European Commission on ethical problems. It is only advisory. On the other hand, some of our opinions--and we produce one, sometimes two opinions in the sense of reports each year--can influence directives that the European Commission produces.

I would say that in the field of human embryo research there has been no influence on the UK domestic policy, and I doubt there would be because the European Union doesn't work that way. The directives are mostly concerned with economic, social issues, patenting. There

was a patenting directive, for instance, which, for one thing, prohibited any patenting on cloning which was one of the items in the opinion that the Ethics Group had offered.

There is also in Europe the Council of Europe. It was the Council of Europe that has put forward the Convention, which you probably know about, sometimes called the Bioethics Convention. It has a longer title. And, those who have signed and ratified the Convention then have to obey what it says. One of the article of the Convention is that producing embryos for research is prohibited. But there is also a reservation in the explanatory memorandum that explains that those member states who already have legislation in place allowing something will not be held by the articles of the Convention. So, if and when the UK signs that Convention, which they haven't so far--nothing to do with embryos but to do with social matters and labor laws--they would then enter a reservation on that issue, and some other countries in Europe are formulating laws which would, again, allow them to enter a reservation on that point so that in the future, where needed, they could produce embryos for research.

But going back to your original question, I would say, no, there is really no influence of the European Commission on domestic policy in any country, not just the UK, as far as embryo research or assisted reproduction goes.

DR. MAHOWALD: I agree with your emphasis on the welfare of the child as being politically and probably ethically a persuasive emphasis in the development of regulation, but when the whole discussion assumes two parents, male and female. I wondered about that being a requirement and the possibility of its being a discriminatory requirement. I am thinking of the studies that show, for example, that children raised by a lesbian couple and/or a single parent turn out just as well as those who may be raised by the traditional married couple. So, on what basis would your committee answer questions about possible discrimination based on sexuality and the requirement of a marriage? In our country those requirements are very idiosyncratically practiced by different clinics and by individuals.

DR. LEESE: I think things have moved on in the past ten years. So, the Act as originally formulated,

which was taking account of this--it will be a matter of finding a clinic to treat you. Lesbian couples are treated in the UK. It is a matter of finding a clinic to treat you. Then you would still be required to fulfill the welfare of the child conditions. But it is not as strict as when it was written. I think it was written in 1990 and attitudes have become more liberal. So, I understand your concern but I am not sure it is there in practice.

DR. MCLAREN: It is amazing actually how society does evolve because in 1990, in the House of Lords debate, there was an amendment to say that IVF should only be offered to legally married couples and that amendment was only lost by one single vote. But the Act does specify that any woman--it doesn't say any couple, it says any woman is entitled to be considered for treatment, and in practice some centers won't treat lesbian women but many do and they get simply passed on. I do think that attention is paid, under the welfare of the child, for single women whether they are lesbian or not, as to their family circumstances. For instance, a woman who has brothers and sisters, a network, friends, would be much more likely to get treatment than a woman who is totally isolated.

DR. LEESE: When it first came out it was portrayed as a license to breed, in a way, but there are no regulations preventing you from having children in any other circumstance. It is often asked are couples denied in our treatment? The answer is a handful. So, your average clinic, I suppose on somewhere between 500 to 600 cycles, might deny treatment to maybe three or four a year. This will be couples with a history of drug abuse, child battering, molestation of children, that sort of thing. So, there are a few who are denied treatment but very few.

DR. SCHATTEN: Henry, that was a wonderful talk. I have many, many questions for you later, but the one question I would like you to answer, you or Anne, and then hear from our physician colleagues is how much extra does the patient pay for this? And then, if I could hear a response from our colleagues in the clinical world, would that amount of money be acceptable to their patient?

DR. MCLAREN: Could I just clarify the question? How much extra does a patient in a private IVF clinic pay?

DR. SCHATTEN: No, what is the cost of the HFEA?

DR. LEESE: Yes.

DR. MCLAREN: Yes, because, of course, the patient who has treatment from the NHS doesn't pay anything. It is covered by NHS.

DR. LEESE: They pay nothing.

DR. MCLAREN: The cost is covered by the NHS, but in the private clinic there is a cost.

DR. LEESE: Yes, that is right. There are discussions on at the moment to increase it. I am trying to remember what the proposal is. Is it 100 pounds per cycle?

DR. MCLAREN: What proportion would it be of the fee?

DR. LEESE: The average cycle in the UK costs, I would say, 5000 dollars, cheaper than over here.

DR. SCHATTEN: You get what you pay for.

[Laughter]

DR. LEESE: And, I think the license fee for HFEA is about 100 pounds, so that is about 150 dollars. So, it is a modest sum, though there are proposals at the moment to increase it dramatically and I am not very happy about that. But I think it will be perceived over here as quite a modest sum only.

It is also the intention to move to try and provide all infertile couples I think two cycles as a right. The government has said they would like to move in this direction. At the moment treatment is very patchy on the National Health Service which is free. The further north you go, the better things are. The closer you get to London, where the big operators are making all the money, the poorer is the provision. If you go to Scotland you can get the treatment for free. The government has taken as its intention to try and make two cycles universally available, as is in the case in many other European countries where you pay insurance.

DR. BAVISTER: Henry, I want to add my thanks for that wonderful talk. I think, in particular, you beautifully illustrated the stark contrast between embryo research in the UK, which is focused on the human but not on the non-human primate, and embryo research in the US which is really not on primates at all, either human or monkey. I really appreciate that you, as an outsider who is not someone involved with US science at all, also perceives that we have an enormous strength in this country in non-human primate research capability and that we should

use it. It seems to me if we were able to join forces in some way with the capability for non-human primate research we have in this country in embryology and the human embryology research we do in the US, we could compare the two very nicely. One without the other is not really optimal.

I would like to make a suggestion for this meeting for the record that, based in part on what was said yesterday, the NIH should support a cooperative program, comparable to the one you are doing with humans, a cooperative program in this country focused exclusively on non-human primate research ART, and that that should be linked to the work that you are doing in the UK that we will never be able to do here.

DR. MCLAREN: There is an offer for you.

DR. LEESE: Yes, yes. I will convey it back.

DR. BAVISTER: There is also a personal element because I hold Henry in very high regard, and always have.

DR. MCLAREN: In the back? Yes?

AUDIENCE: Yes, you alluded briefly to the role of the HFEA in, as you put it, calming down the clinics, and I was wondering if you could elaborate on what role,

either explicitly under the authorizing legislation or more implicitly the HFEA plays in overseeing the claims and the information that clinics provide to patients.

DR. LEESE: We see all the information they give to patients and we check their web sites. Perhaps to put it in context a bit, when the HFEA started ten years ago many were quite hostile, particularly the clinicians. Put simply, they were not used to being told what to do by lay people and, dare I say women. Since then the vast majority have come to realize that HFEA offers them, in a sense, protection, an umbrella, a means to carry out their work and if they are doing it responsibly they have nothing to fear. It then facilitates practice and research in various areas.

Most are compliant but there are a few notorious clinics, mainly individuals who I think are forever in the media, the press, the television, and will take us to court now and again. We had a court case, the HFEA. Someone wanted to transfer four or five embryos in a 47-year old and we won. The court case was passed in the HFEA's favor. So, there are still a few clinicians who don't take kindly to being regulated, frankly, but a handful only. I could

name names but that is not the point. There are very few. The vast majority and, indeed, the profession, the British Fertility Society, which is the closest to the ASRM, the Royal College of Obstetricians and Gynecologists, which is wider than just reproductive medicine but is the whole of obstetrics and gynecology, they see strongly the need for the HFEA.

The specific answer is we look at their information, their paperwork and their web sites and we--I am trying to think of examples--we can insist that they have to have live birth per treatment cycle started pretty much up front, not hidden away somewhere. They have to also report national data. Part of this is that each year a patient's guide is produced and that is on the web with the data for all the clinics for people to see.

DR. MCLAREN: Advertising? Weren't we a bit down on aggressive advertising?

DR. LEESE: Yes, I think it then does stray a bit into what is our remit. It then can get a bit difficult.

DR. MCLAREN: Yes?

DR. JONES: Wanda Jones, DHHS. I actually have a thousand questions but I will limit it to one, maybe one

big one so others can ask theirs. I am intrigued by the consumer domination of your HFEA. I am not sure there is any precedent here in the US in terms of a regulatory or oversight body, what-have-you. We are fairly new to the concept of the "advisory council" and, yet, to think that those are openly recruited is only so much lip service or a pipe dream because, in fact, often advisory councils are stacked for one reason or another. So, I am intrigued by, number one, your open recruitment. Number two, do you do anything to provide, if you will, a floor of training to the lay members so they at least, you know, understand the science and the scientific processes and so forth? Because I know with the army's consumer involvement with the breast cancer research, they actually funded training for those lay people who contributed so massively and continue to contribute to the army's breast cancer research program.

Then, not unrelated to that, do they have a revolving cycle, like they serve for three years and then they come off so that you continually are refreshing your lay panel? Is it representative of the women or the families who access these services? Sorry, that is about six of my thousand questions.

DR. LEESE: Yes, but that is fairly easy to answer. Interestingly, the new chair of the HFEA is called Susie Leather and she is also deputy chair of the Food Standards Authority, which is not so far removed. It was set up in the UK in the wake of BSE and foot and mouth, and it is funded by levy on supermarkets and the like, but it is quite independent, and pretty independent of government actually though it gets a lot of work from the government and, again, I am sure that is lay, has a strong lay input.

Yes, training is offered. I actually feel a lot for the lay people. Some really try to become experts in the whole area. I can think of people who do and I really admire them. Others come on perhaps for their specialties in ethics. For example, we have a very good professor of ethics from my university who is on, and we have the Bishop of Rochester. He chose the ethics committee and that tends to be their focus. So, I think some try to get up to speed on the whole thing and training is offered. I think we could probably do the training better though.

DR. MCLAREN: Rotation?

DR. LEESE: It is three years normally, with extension for another three and then you come off.

DR. MCLAREN: Yes?

MS. FOUCRAY: Judy Foucray. Let me tag on to what I think they might also want to know, and that is, is there anything in your legislation that protects this committee from being changed by your government? Because we are actually going through that right now.

DR. LEESE: Oh, yes.

MS. FOUCRAY: So, do you have legislation that actually prohibits the government from changing it?

DR. MCLAREN: It wouldn't be the government; it would be Parliament, wouldn't it?

DR. LEESE: We are appointed by the Department of Health, which is a department of government.

DR. MCLAREN: But we report to Parliament.

DR. LEESE: Yes, the annual report goes to Parliament. Maybe you are onto something here. There is a sort of interesting relationship between the HFEA and the Department. We are autonomous but as it were semi-autonomous; we can't ignore totally the Department because it funds the NHS and everything. So, it is a sort of interesting relationship. They attend our meetings as observers and they keep an eye on us, as it were. I think

probably different chairs of the HFEA will have a different style. Some will perhaps be a little cozy with the department and some will not. Others will say "hold on that" with an independent "never mind, you lot; this is what we have decided." So, it is a bit of a balancing act but by and large it works fairly well.

DR. MCLAREN: But I do emphasize that the Department could not close down the HFEA.

DR. LEESE: No.

DR. MCLAREN: On the other hand, Parliament, they get our annual report every year --

DR. LEESE: Yes.

DR. MCLAREN: --and hold a debate on the HFEA, and if we did something that they really didn't like they could have a vote and they could close us down the next day.

DR. LEESE: I have always been very clear about this in my mind on who ultimately should make decisions on the status of the early human embryo, for example, which is the big one, and I have always been quite clear that it should be Parliament. The buck really stops there. They are our elected representatives and whatever way it goes, you live with it. But I have always been quite clear about

that in my mind. You have to influence as best you can. Anne, for example, said when the Warnock Report came out it was received--some were quite hostile to it. A vote held then would have gone against what has subsequently happened. It was Anne in particular and others who lobbied strongly Parliament and we had representatives up to my laboratory, showed them mouse embryos and this sort of thing, and we worked hard and the mood changed and the vote was won. But that is where the ultimate vote has to be, it seems to me.

DR. MCLAREN: Yes?

DR. BRACERO: Thank you for an excellent presentation. I am Bracero, from Johns Hopkins. During the last few years we have been trying to protect the privacy of our patients, especially in the insurance environment. How do you, in the UK, safeguard and what kind of fire walls do you have for this registry that you are keeping of these IVF and ART babies, and how will you keep that in the future?

DR. LEESE: I didn't catch the whole question.

DR. MCLAREN: The register, and how do you keep the register confidential?

DR. LEESE: It is part of the Act that it is a criminal offense if you breach confidentiality. So, anyone with access to the register--only known persons would be allowed access. I don't think there has ever been a breach.

DR. MCLAREN: No, but it is difficult because, for instance, when the computers break down --

DR. LEESE: Yes.

DR. MCLAREN: --we have to, as it were, sign on any specialist who comes in to look at the software for the register. We have to sign them on, to sign the confidentiality brief. Isn't that right?

DR. LEESE: Yes, that is true. A major problem with the confidentiality is the difficulty in allowing researchers access to all the data, and we have been criticized for that because there is a gold mine there. We have data on 30,000 cycles a year in the UK, going back over ten years and the information--you can have 60 bits of information on a treatment form and that could tell you a colossal amount.

The Department is aware of that. The IT system is a problem at the moment; it is dated. They are bringing

in at the moment new IT facilities, paid by the department, not the HFEA. They are putting in about three million dollars to do that so that you can have electronic transfer of data and bring in password protection, and everything so the scientific, social humanities community can get access to this data. It is a fair point. I think we have done okay so far but it is how to make the data open access.

DR. BRACERO: Could an adult in the future have access to his records?

DR. LEESE: I think that is the intention, yes. So, you wouldn't have patient names basically but you would have the details.

DR. MCLAREN: But there is another aspect to the register, which actually makes it a bit of a nightmare. If it was simply data collection for success rates, say, then if it was inaccurate, one or two percent in either direction, it wouldn't be a disaster. But it is also part of the Act that when children who have been the progeny of donated gametes, either donated sperm or donated eggs, get to be 16 if they want to marry, otherwise 18 --

DR. LEESE: Correct.

DR. MCLAREN: --they can go to the HFEA and ask--Henry, what are the questions?

DR. LEESE: Whether they have been born of licensed treatment and whether they are related to the person they wish to marry. This is to avoid incest and things like that. So, the law says that a given donor can provide sperm for ten births only, no more, and to prevent the possibility of someone marrying a sibling, a close relative, if you think you have been born of donor gametes you will be able to contact the HFEA. The first contact will be 1997 [sic] because it started in 1991 and the first person has to be 16 who might phone them up. But you can also phone them up to know if --

DR. MCLAREN: 2007.

DR. LEESE: I am sorry, 2007, yes. That was one of the reasons to produce a register. Another reason is that it enables you to build clinics on the basis of number of cycles. It also enables you to collect statistics on success rates and other things. So, the register is a key part of it but they have to get the IT sorted a bit better at the moment.

DR. MCLAREN: Yes?

DR. GOLDSMITH: Laura Goldsmith. Henry, congratulations. That was just a wonderful talk, extremely helpful on so many different levels for everyone. I particularly enjoyed your critical evaluation of animal models and the specifics of their different features. Actually, I would request that maybe additional talks in the future be given on exactly those kinds of subjects-- what is good about what specific models and what is bad.

I would like to add, however as an endocrinologist, that part of what is trying to be accomplished here is using those animal models as a model for a live baby, that some more of the endocrinology of the features of implantation and pregnancy maintenance be included in our consideration of use of animal models such that, for example, the cow is a particularly bad model for human implantation and pregnancy maintenance. You know, the hormones which exist are completely different. Primates have hormones that cows do not have, etc., etc.

DR. LEESE: Indeed, yes.

DR. GOLDSMITH: It would seem to me that as a group of investigators trying to make more progress in this field, those considerations should be included when one is

using a particular model for early embryo development, such that that work would be more useful for the total aspect of producing a live baby. It seems to me that part of where we are as a field now is that there is a disparity between the research that may be going on the early aspects of embryo development and pregnancy maintenance, and things like that--the discrepancy between making the embryo and keeping it between obstetricians and the endocrinologists, etc.

DR. LEESE: I agree with that. But there is, of course, embryo-based biotechnology, a whole embryo transfer industry. Barry, for example, is president of International Embryo Transfer Society. I agree with what you said. Maternal recognition of pregnancy is different.

The other thing that I think is unfortunate is, and I am quite unusual in that I do work on mouse, cow, pig, human--that and there are different communities. The mouse developmental biologists are one community. The cattle people tend to be more agricultural, so do the pig, and the sheep people. The community of human embryologists, they tend not to. There is not intermixing

of disciplines. I find it very sad. Barry has a comment on that I think.

DR. BAVISTER: May I, Anne?

DR. MCLAREN: Yes.

DR. BAVISTER: Dr. Goldsmith has made an excellent point, but it reminds me of one problem we have in this country with diversion of available research funds somewhat disproportionately. The reviewers don't seem to understand these gross differences at the endocrine level or the cellular level. As I tried to point out yesterday, reproductive strategies differ enormously. You know, cardiovascular systems are much the same in different species but reproduction is vastly different. I listed some of those. I think one of the problems we have in this country as reviewers--we have to have peer review of grant proposals, but a lot of reviewers seem to be ignorant of these vast differences. For example, using the mouse as a model for human implantation is just totally inappropriate and, yet, grants are funded, a large number of them, on implantation studies on mice and they are never going to be applied to the human. So, I think it is a very, very good point and maybe we need in this country more consciousness

raising about basic comparative physiology and endocrinology.

DR. MCLAREN: Okay, policy for this country can be discussed after the break. Are there more questions before the break? In the back?

DR. MALTER: Henry Malter, St. Barnabas. Henry, first I would like to congratulate you and Anne and your colleagues in Britain who have, obviously, taken this thorny problem and I think tried to do the right thing and to a great degree maybe succeeded in addressing this whole problem by creating and administering the HFEA.

At the same time, I feel compelled to kind of take a devil's advocate position on some of the issues of the kind of scientific gatekeeping that is part of what the HFEA is doing. It kind of goes to the issues of the way it is set up and the power that it has. From an anecdotal sense, one thing that bothered me is going to ooplasmic transfer. We have seen several kind of statements made by the people in the UK, including one by the head of the HFEA, that were, in fact, completely erroneous about some of the basic aspects of ooplasmic transfer. For instance,

we would never allow this because of X and Y, and these statements were simply incorrect.

I understand that is not the way the decision was made and there was, I am sure, a fair and balanced process that went into making that decision. But it seems that in this sense the HFEA is kind of acting as a global IRB for the entire country with legislative and legal power behind it, and the idea that 75 percent of the people on it are lay people--I don't know that this kind of IRB process would fly here in this kind of supreme gatekeeping capacity of what can and can't be done.

The other thing that I am a little uneasy about for instance was, as you showed, this absolute prohibition for nuclear transfer. Obviously, this is not saying you can't use nuclear transfer to try to make a baby; it is saying you can't do nuclear transfer at all. And, I think, you know, we should stand up and say that there are I think things in the future where nuclear transfer may be of some utility and this idea that there is this absolute legal prohibition against it--is that not true?

DR. LEESE: No.

DR. MCLAREN: HFEA would allow projects of nuclear transfer.

DR. MALTER: In fact, was there a mitochondrial disease protocol?

DR. LEESE: Yes.

DR. MALTER: Is that correct?

DR. MCLAREN: You have to distinguish between nuclear transfer and cytoplasmic transfer.

DR. LEESE: Yes. I mean, reproductive cloning is banned --

DR. MALTER: Right.

DR. LEESE: --to produce babies. The Dolly technology is allowed --

DR. MCLAREN: Yes.

DR. LEESE: --but for the moment for research purposes only.

DR. MCLAREN: And the cytoplasmic transfer is not legally prohibited; it is not licensed until it has been shown to be safe and efficacious. Do you want to comment further on that?

DR. LEESE: I think my response to that would be I would want to see animal models of cytoplasmic transfer.

You could do it in mouse presumably and get live offspring and second generations before moving to the human. I would prefer that route rather than having such a complicated genetic composition of the prospective child. That was the risk.

DR. MALTER: Right, and I wasn't perhaps speaking specifically to that issue entirely.

DR. LEESE: I think the HFEA would be flattered to think that it had global influence.

DR. MALTER: I am just saying obviously there is a compromise there and it seems that in compromising on the side of caution, which may very well be the right thing to do and obviously --

DR. LEESE: I think in the notes you have there I have "proceed with caution" as the slogan.

DR. MALTER: Right.

DR. MCLAREN: Last comment?

MS. CHARO: Another informational question, if I may, could you please describe the rules that govern either reimbursement or sale in conjunction with sperm and egg donation and contract or surrogacy motherhood? And, if you could speculate about the effect that whatever rules you

have in place on this, speculate about their impact on the scale of activity that involves sperm or egg donation or surrogacy in the UK?

DR. LEESE: The payment made is minimal. If you donate sperm you get 15 pounds, 25 dollars only. So, essentially you don't really get paid. You get expenses which, again, are very modest. So, there is no commercial market in the UK for donated sperm or eggs.

MS. CHARO: I am sorry, the payment for eggs?

DR. LEESE: It is $25 only.

MS. CHARO: For eggs as well as sperm?

DR. LEESE: There is absolutely no financial incentive at all. It is altruistic. The argument could be developed though because probably most young donors are students and even $25, if you give a number of donations, can mount to maybe $1000 if you give repeat donations and for a hard-up student it can help a little bit. The older donors tend to be--what am I trying to say? For an older donor the motive tends to be altruistic. If you are a young sperm donor it tends to be that you would quite like the money. But there are none of the large sums that you would get over here.

Some of us are quite concerned that if you remove anonymity, then the supplier sperm will dry up, as it were. A lot of sperm now in the UK is being imported from Denmark. That is, under HFEA conditions and the consents, and everything, have to be done but a lot is coming from Denmark. There is a big company over there that is doing this.

DR. MCLAREN: There was a center in Glasgow in particular that was very short of donors; had a long waiting list.

DR. LEESE: And you can imagine the tabloid headline--they just weren't coming through to donate sperm in Glasgow!

[Laughter]

MS. CHARO: So, you have had shortages of semen enough that you had to go to other countries --

DR. LEESE: Yes.

MS. CHARO: Would it be fair to presume that you are having similar shortages with egg donation?

DR. LEESE: If you needed eggs, say, over here you would travel to over here. You would do it that way.

I don't think eggs are being shipped around and you can't freeze eggs anyway.

MS. CHARO: No, but what I am asking is do you have a shortage of eggs for donation?

DR. LEESE: There is a shortage of egg donors, yes.

MS. CHARO: Okay, so the number of people who are using egg donors in the UK, would that be lower as a result of these shortages?

DR. LEESE: Yes, I think there will be a sort of supply and demand element in that, yes.

MS. CHARO: Thank you.

DR. MCLAREN: Right, I think we should break now for coffee. After the coffee, we will have panel discussion and, please, come back at 10:15.

[Brief recess]

Open Discussion

DR. MCLAREN: For the next part of the program, as you see, we have our panel here. We have Henry Leese, whom you all know by now. We have Phyllis, whom you also know from NICHD; Susan Wood, from the Office of Women's Health at FDA; Philip Noguchi, from CBER of FDA.

So, I thought we would start off by asking each member of the panel, maybe not Henry because he has had enough work already, but each other member of the panel just to say a few words about anything that occurs to them that arose from either his talk or the discussion before the coffee break. So, Phyllis, can I start off with you?

DR. LEPPERT: Yes, thank you very much, Anne. I thought it was a very good discussion this morning. I was very happy to hear Henry's comments about the fact that the United States has very good facilities for non-human primate research, and I agree with that.

I do want to say for the record that our branch has funded a number of projects using non-human primates. We have one very important center program which is the specialized cooperative centers program in reproduction research, which we call the SCCPR, which is funded--it happens to be 14 universities, and we do fund non-human primate work at the University of Maryland using baboons, and the University of Pittsburgh. Not only is Gerry Schatten part of that program, but we have another researcher there, Tony Plant, who is working with rhesus and other non-human primate animals. Then, we also fund

the Oregon National Primate Center. They have a whole SCCPR there. And, the University of Illinois is working with baboons. So, we have a whole group of researchers that are working not only just on ART, as Gerry is, but other things that are related to diseases and reproduction.

Then, the other thing that is very exciting is that we have just inaugurated an on-line tissue bank repository which will enable the center researchers to obtain tissue for studies. In addition to human tissue, we will have non-human primate tissue from Oregon. So, I am very excited. We have heard a lot about what we can do, and I do appreciate those remarks. I just wanted to clarify some situations.

DR. MCLAREN: Thank you, Phyllis. I guess it would be nice if any of your primate workers could form collaborative agreements, collaborations with colleagues in the UK who are working on human embryos and have no opportunity to work on primate embryos. That would be really good.

DR. LEPPERT: Right.

DR. MCLAREN: Susan?

DR. WOOD: I also thought the discussion over the past day and a half has been really very interesting. From the talk this morning I was sort of struck by the clear differences between both the regulatory approach of ART as we think of potentially regulating it here, at FDA, but also the greater acceptance and general practice of more regulation of the practice of medicine, and how that sort of stands between regulation and the FDA and the thought of how to address some of the many issues--ethical, policy, legal, financial, scientific issues in the US. And, it is something much broader than something just dealing with ART here; it has to do with our entire system and historical approach to medicine and service delivery. It also has to do with our insurance system and how that plays into this entire thing. Although it hasn't really been talked about today, that is certainly something that plays into how we, as a nation, approach our ability to say what happens in clinical care and what doesn't happen in clinical care.

I was also struck yesterday by the discussions in the afternoon where we saw the linkage between women as patients, women as donors, women as part of couples, and that certainly is our concern at the Office of Women's

Health as to how we address these issues very broadly and look at them from different perspectives and make sure that those questions are raised every time these discussions occur so that they are not forgotten, and we will continue to do that.

DR. MCLAREN: Thank you, Susan. Philip?

DR. NOGUCHI: Thank you very much and, again, I thank all the participants in this wonderful conference. My group in particular, the Division of Cell and Gene Therapy and soon to be an office, is particularly pleased because we have done this in many different fora. We have done it for various aspects of gene therapy, xenotransplantation with transplant surgeons, cardiologists. I used to think transplant surgeons were tough but cardiologists are far tougher. The common theme when we meet and get everyone in the room together is that almost--well, not almost but invariably right-thinking people think about the same way, and what I have heard over this day and a half is absolutely much more of a consensus than one might have imagined coming into this.

I think that the experience of our international colleagues obviously is of concern and importance to us.

Just as a detail, I would point out that FDA operates under Title XXI and Title XLII, which are civil codes in Title XVIII as the criminal justice code. So, the specter if you do something wrong you might land in jail, it is a far cry from being able to do that. It is a long process. Our job here is to do the right thing and to help you all do the right thing.

But, by and large, what I would just like to end with for this short introduction is that I see absolutely much to build on here; very little that really says no; and we should just get on with it.

DR. MCLAREN: Well, thank you, Philip. Now you have a panel with some very well-informed and influential people here to address comments to and ask questions of. We are discussing formulating effective policy in ART--where do we go from here? Which I think really means where do you go from here. So, who would like to start? Yes?

DR. MALTER: Henry Malter, at St. Barnabas. I feel like I should throw in my two cents here since I am part of the team that is getting ready to put together the IND for ooplasmic transfer which, as some have suggested, may be part of the reason we are here.

I just wanted to say getting into the process a little bit where we are at now, we are actually very positive about the process. I can say when we first got the letter, I think all the clinics involved were scared, angry, upset and confused but we have certainly moved well beyond that and, as I said, we are very positive about participating in the process and have, I think, good hopes that the process will lead to a positive result for everyone. We have had one meeting so far that was set up to try to kind of define some of the issues that will go into this. Since it is I think kind of a new IND in terms of dealing with the issues that it is dealing with and the outcome of that meeting and what was decided there, I think we feel very good about and feel that that is a framework that we can use to move forward. So, I just wanted to make that point.

DR. MCLAREN: Well, thank you. I think that is a very helpful and reassuring comment and it reminds me of a bit of history because, of course, in the UK we have had animal legislation governing the use of animals in labs since 1870, I think it was. When the suggestion that animal use in laboratories and medical research should be

regulated in the United States, I remember my colleagues over here getting very--what was your word?--hurt, angry, shocked but in the end they came to realize that the best protection against the animal rights people was, in fact, to run a tight ship; to have legislation; to have regulations; to be inspected; to run the animal houses properly and now everybody accepts that.

Again, with the human embryo and IVF work in the UK, when it was first suggested by the Warnock Report that there should be a regulatory system actually controlled by legislation, the clinicians in particular were up in arms. They were hurt, angry, shocked. But, again, they came to realize that it wasn't a big problem. HFEA always goes out of its way to respect clinical judgment--Henry nods--and I think that that is an essential part of any regulatory system. Would any member of the panel like to comment?

DR. NOGUCHI: Only to say we appreciate very much that it does seem like some experiences are rather universal rather than unique. We are just beginning our entry into a dialogue with the reproductive community. We have done it in other areas, but invariably it does seem

this way. I apologize that the government is so frightening to begin with; we are really not that bad!

[Laughter]

DR. MCLAREN: Right.

DR. LEESE: I think if it is not a partnership with the professions it won't work. I think Anne is quite right. In fact, the Code of Practice that I quoted says rather little about clinical practice and laboratory practice. We do look to the professionals here to, you know, act responsibly, and we just have to have dialogue with them. If the professions are hostile it won't work. We have to carry them with us.

DR. MCLAREN: Alta?

MS. CHARO: Listening to this, it seems to me that there is still, despite Dr. Noguchi's vision of harmony across the Atlantic, I think there are still some very big differences that may make taking lessons from the UK very difficult here.

Specifically, if you think about the two big pieces of the puzzle, what can you do and for whom may you do it, the first level of objection in the US, not in the medical community but generally, often has to do with the

idea of the government deciding for whom you may do it. You heard Marty Mahowald immediately focusing in on the implication of, for example, single or gay women couldn't be assisted to have children because it is somehow contrary to the welfare of children and your description of how that thinking has evolved, etc.

It is possible to imagine the federal government saying we are not going to touch that; we are only going to look at what you can do and we are not going to get into the business of saying for whom and try to get rid of that problem here. But, unfortunately, the way FDA regulation works, you do approve something for a particular indication in a particular context, but once it is approved it can then be used for other indications or in other settings. It simply can't be marketed for those purposes. You know, its labeling won't reflect those purposes, but it is back in the hands of the practitioner.

Your licensing approach in the UK is one that is premised on the notion that it is the appropriate role of the national government to regulate the practice of medicine. That is a completely novel idea in the United States where it is the role of the state governments

indirectly to regulate the practice of medicine through the competency testing, and licensing, and re-accreditation requirements, and indirectly through state tort law for medical malpractice. But never has it really been the role of the federal government to regulate medical practice.

So, the dilemma is that it is very hard for us in the United States to separate the questions of what may you do, or for whom may you do it, or in what context may you do it, what indications, because as soon as something is approved in any sense and for any purpose, it is now unleashed. That is why we live constantly on the slippery slope with people arguing about whether we have enough speed bumps because we can't seem to separate these questions and I don't sense in the US a willingness to move to the nationalist model of direct regulation of medical practice. So, given those limitations, I would be fascinated to hear people's suggestions for how to proceed.

DR. MCLAREN: The question of state versus federal is one that hasn't really come up before in the discussion. It is obviously a very difficult one, and not one that the UK can give advice on. Philip?

DR. NOGUCHI: First of all, I was not speaking of harmonization; I was speaking of universal experiences that are common.

MS. CHARO: I stand corrected.

DR. NOGUCHI: Actually, Alta, your comments throughout the course of this and other fora have really helped me, in my own mind, to understand that there are very real differences that need to be examined and taken into account as to how we move forward.

Your point about the dynamics of the differences is absolutely on point but, just remember, when we talk about--this is a pet peeve of mine, slippery slopes started when eukaryotes were discovered. You have immortality if you are an amoeba; they just keep on going; they don't change. Once eukaryotes or two-cell organisms started out, then you began to get the slippery slope. Or, you can argue that when man first said why do I have to die, that is where the slippery slope started.

From our perspective at FDA, and I can only speak for this part of the department, but from our perspective life happens, death happens and other body functions happen

and typically they come to our front door and we need to deal with it in the best way that we can.

I think whatever lessons we can learn from the UK experience that are relevant, we should take but, of course, you are absolutely correct, in terms of getting a consensus on anything in this country iit s a little bit of an oxymoron I think. Yet, we still move on. We make progress. Although it seems to have taken a number of years, I am astounded at how far we have gone without any particular "national" decision on whether or not reproductive cloning versus therapeutic cloning versus any cloning. There has been no real decision and, yet, we still struggle and move on, and I think the dynamic is that the struggle is continuous. But you are right. But harmonization is not what we are talking about.

DR. MCLAREN: Phyllis?

DR. LEPPERT: I wanted to make a comment, and I am going to make it partly as an individual, about your comment about medical practice. Before I was employed by the federal government I was a practitioner and an academician in New York State. I was a member of the New York State Office of Professional Medical Conduct which had

a lot to do with the regulation and licensing of physicians. I think the question of medical practice versus research is something that we need to talk about in this community because it is not a problem in some other areas.

I mean, I think physicians know what is physician practice and what areas need to be further researched. I think that partly what we need to do in our community of reproductive science is have some discussion of, you know, what we consider to be medical practice that is based on evidence and what areas of research are further needed. We do have a system in this country that accepts what has to be further researched, and physicians have systems, all the professional societies have systems of educating their membership about new research endeavors. ASRM sends out bulletins where they look at the research and make statements and opinions about how this will affect practice.

So, I would like to suggest that we do have a framework in which to deal with this issue of medical practice versus research and that kind of thing, and we need to dialogue on that a little more.

DR. MCLAREN: On the question of research, am I right in thinking there are differences between states in this country as to whether or not they allow human embryo research?

DR. LEPPERT: No.

MS. CHARO: Yes.

DR. MCLAREN: I hear no; I hear yes.

MS. CHARO: It depends on how you count them but there are like half a dozen to twelve states that have laws that have some regulatory or legislative authority over either embryo research or fetal research, where the definition of fetus could be interpreted to include embryos, or specifically on human cloning. Some are limiting in some ways; others are totally prohibitive. Then, there is at least one state that has a law that nobody has ever tested that makes embryos into what they call juridical persons. But it is a minority of states.

DR. WOOD: As a general rule in the United States, states can't be more liberal than the federal government if the federal government has acted properly within its jurisdiction. They can often be more restrictive, although not always even there. Sometimes

they are precluded from that but they can almost never be more liberal.

DR. LEPPERT: But then even in the states that have allowed this it becomes difficult because to do a lot of complicated research, researchers do want to apply to NIH and do NIH-funded research not only because of the peer review but many, many reasons. So, that is another issue that has to be discussed.

DR. MCLAREN: I was just going to draw an analogy, but I don't think actually it is a very helpful one. With the European Union harmonization on the question of human embryo research is totally impossible between different countries that have such different views, such different cultural and religious backgrounds. But the European Commission has money for research projects and is prepared to fund projects on human embryo research in those countries where it is legally permitted and regulated but, of course, not in those countries where it isn't.

MS. FOUCRAY: I am Jean Foucray, and actually I am a card-carrying member of ASRM and that may color what I am going to say. I think Phyllis has made an important statement that we need a framework. It is clear to me,

from the many hats I have worn, that it may not be the government that it is the framework for a variety of reasons. One, we don't trust our government to make some decisions, some of them for correct reasons. Our government regulatory ability is fragmented, I mean the ability of Dr. Noguchi to make decisions is limited within one very small segment of this reproductive dialogue, as is the rest of our government at this point.

It has always seemed to me that one of the frameworks for this dialogue should be the professional organizations, the Royal College of OB/GYN and the British Society for Fertility, and that framework would then rightly sort of sit in the fertility/sterility community or the ASRM. Unfortunately, that framework may be tarnished by commercial interests because many of the deciding decisions that are being made in ASRM tend to not always be based on evidence-based medicine but are actually pushed by commercialism to some extent, rightly or wrongly. That is the framework of US.

But let me throw out that maybe it is the professional organization with any other cohorts that fit into menage that actually should begin to build a framework

of an organization like your authority in England so that there is a lay constituency with the support of a scientific constituency that is perhaps funded by the industry itself, and is separate from the control and the whims of our interesting politics in this country.

DR. WOOD: But, Jean, I would come back and say one thing they mentioned was who ultimately holds the responsibility to hire and fire, and in their case it is independent as long as they maintain the support of Parliament. It may be to some degree separate from the immediate day-to-day political whims but is subject to the will of the electorate. I think such a framework as you described--it would be an interesting idea to say how would you maintain its independence if such a body were to do something that the parent funding organization chose not to support, not being an elective body.

MS. FOUCRAY: I don't have a clue. I am just putting this out as a beginning or start of a dialogue because I think we clearly need some kind of a framework from which to begin to control an industry that has been fairly uncontrolled in the last decade in this country.

DR. MCLAREN: Philip?

DR. NOGUCHI: I think it would be well worth discussing that, but I challenge you with one thing. When we talk about lay members in the United States, we typically say, well, he is just a bioethicist on the side. We are talking about taxi cab drivers. I remember going to Boston the other day when there was a meeting on bioengineered foods, and I had a quite interesting and quite learned and reasonable discussion with that cab driver. We need the people who are looking at Oprah Winfrey all the time. These are our constituents; it is not the professional community per se. We are merely the implementers of public health delivery.

So, if you were to pursue such a framework, then I would say put it in the hands of the people that have the most to gain or to lose if it doesn't work. But that is lay people, and by lay people I mean real lay people, non-professional. I participated in the breast cancer research panels where half of the people there had no professional degrees at all, and I can tell you their decisions were at least as good, if not better, than most peer reviewed panels that I have sat on as well at the NIH.

So, I think we do our population a great disservice by trying to separate us by any means where we say that somehow we are the gatekeepers; we are not. Nature is the gatekeeper. She has been everywhere; she has done everything and if it doesn't exist in nature, there is a good reason. We perturb that reason at our own risk. So, again, you know, nature is the gatekeeper; we are all in this together. If you want to do what you want to do though, let the real people, let the real public into the process.

DR. MCLAREN: Would you not feel, however, that any panel or any committee should be a mix of lay people and scientists?

DR. NOGUCHI: Absolutely.

DR. MCLAREN: Because I think each group has such a lot to learn from the other, and one doesn't want one panel which is all lay and then one which is all scientific.

DR. NOGUCHI: Yes, I agree.

DR. MCLAREN: Yes, Henry wanted to say something.

DR. LEESE: Very briefly, at the HFEA at the moment we have a bishop, a former editor of The Times

newspaper, and academic lawyer, a TV producer, a social worker, an accountant, a dentist and a midwife. So, it is quite a cross-section really.

DR. MCLAREN: We have always been short on cab drivers.

[Laughter]

DR. LEESE: I must say cab drivers and super shuttle drivers are much better informed over here than in the UK.

[Laughter]

DR. MCLAREN: Yes?

DR. MAHOWALD: Actually, you are speaking to the question that I was going to raise, but I would like you to amplify it because the question in my mind, other than lay, was are there any other criteria for selecting the lay participants, and by whom are they selected? What I am thinking of is yesterday afternoon we had what I think was an extremely important contribution from women's health perspective and from the patient perspective. In fact, I had suggested maybe that should have been first in the whole order of our proceedings as we used to, for example, open the breast cancer research panels through some

comments by a survivor and it was a very motivating contribution that was made.

A group that I don't think we heard from, although I know that Resolve, for example, represents infertile people who have had successful treatment as well as those who have not, I believe a really important input in all of these discussions and in the development of policy is input from women or couples who have gone through assisted reproduction and not had a successful outcome. I didn't hear that during this conference and it just seems to me that it is an indispensable kind of input.

DR. LEESE: We did have someone who had undergone infertility, in fact two people, one donor gamete treatments and the other had been infertile, patients in an infertility clinic. The HFEA would be very keen to recruit another such person.

The other thing that will happen--I was very impressed with the patient representative talk yesterday. The HFEA is very keen--the one constituency we don't tap is the infertile and those who have been through treatment, and ways are being sought to do that and, indeed, to canvass in a more formal way the patients who have been

through a clinic. There you have issues. They have to consent to being approached and this sort of thing. But that is firmly on the agenda. They have to be consulted, their feedback given.

DR. MCLAREN: Yes?

MR. YOUNGER: I am Ben Younger, the executive director for ASRM. I would like to just mention something that some of the people know about but probably most of you don't. One of the big problems when it comes to "regulation" or funding of research, ART-related research or control, as she said, is that there really isn't a central body that encompasses all of the different groups of people involved. But there is a little beginning. ASRM and its affiliated societies enjoy a very good relationship with our friends in the government agencies. Certainly, we work with CDC to publish the results of the registry, etc. We have had good dialogue with FDA, particularly on some of the regs coming up relative to gamete and embryo donation. We certainly meet regularly with our friends at NIH and recognize that all the people here can't solve all the problems in the country relative to funding of research. I mean, that has come to be really a political hot potato,

the whole issue. The abortion issue gets dragged in when you talk about embryos. I mean, the politicians are in the middle of it in this country and it is not the group that you see here.

But we do meet twice a year. We have a little organization called the National Coalition for the Oversight of ART. It is a powerless group. Its intention is really to be a liaison group. Our goal is influence. We meet with representatives from NIH and CDC and FDA, the AATB. The tissue bankers come. Our two patient support groups are represented there, the two larger in the US, and Resolve and AI. In fact, the group is chaired by a person from Resolve.

What we do when we meet really is identify issues, what they are. Then, each of the groups goes back and utilizes the mechanisms or authority that they have to best address an issue. One good example of that dealt with some of the immunotherapy that was being applied to people in ART programs that weren't successful. We, as a society, had heard about a case. Actually, the CDC ended up using its subpoena powers for mortality to look at the records of

the case and, actually, published it in the "Maternal Mortality" weekly report.

So, this is not a legal or formalized approach but I think the relationship between government, professional societies and at least the patients, not somebody from the general public that is not infertile, is a good one. It is great to hear what is happening in England, but the European Union can't reach a true consensus and I don't think all fifty states in this country will ever reach a consensus either.

I think it is a difficult issue to solve, but it would certainly help if we had adequate funding of embryo research or projects that involve an embryo. It would help to have adequate insurance coverage for our patients. I mean, we don't like to necessarily think of insurance companies as regulators of the practice of medicine but, to some degree, they are. For many insurance companies you have to met certain standards or they won't pay. So, there are pieces of the puzzle that are missing.

I think if we are going to have a system that would come close to satisfying everybody there have to be

more players at the table, and I don't know when we are going to get there.

DR. MCLAREN: Comments? Yes, would you like to comment on that particular point or those particular points because I think quite a number of different points were raised?

MS. WARNER: I guess what I am struck by, and I think it is very helpful to point out areas where we have differences, where we have difficulties in this country as opposed to the UK, or issues that make it difficult to reach consensus on these very broad and complicated issues, but what I would like to throw out is that perhaps we need to look at this more as a step-wise process where we can maybe take one thing at a time where there is some degree of agreement that we need to work together on.

I guess what comes to my mind is the question of research and trying to make sure that information about what funding is available is available to those who can really contribute in this area; to make sure that that research is supported and well designed, given the input, again, of all the people that are affected. You know, I

think that is a good place to start. So, I would just throw that out there.

DR. MCLAREN: I think there may be one difference between the UK and this country which hasn't been much emphasized, and that is that I think it is true, isn't it, Henry, that virtually all the organizations that are licensed for human embryo research in the UK are IVF centers, academic departments, medical school departments, not commercial companies. In the States there seem to be quite a few commercial companies who are doing human embryo research, and I don't know about you people but I was certainly surprised when the famous list of 64 human embryonic stem cells lines was published that there were several from companies in the USA that I had never heard of and I didn't know they were working on human embryos, let alone that they claimed to have made embryonic stem cells. So, that may be a difference which may affect the possibility of regulation or the need for regulation. I don't know, but it is a difference I think.

DR. NOGUCHI: It is complicated. Our FDA jurisdiction extends to public and private entities, however, the entry point for FDA in most cases, almost all

cases, is when the intent of the product, of the stem cells, is for clinical therapeutic use. Before that time our influence is more of the interactive type where we have in fact, with the NIH jointly, been interviewing and talking to the companies about how they are actually preparing them; whether or not they have grown them on animal cells or not as an example; and try to get more information through an informal process. The formal process starts when they come forward and say they would like to use these for clinical trials.

So, we solve a part of the puzzle between private and public funding in the sense that our oversight extends over both, but it is not directly back to the question of how are the embryos obtained, how are they made, and those sorts of issues which are integral but have been peripherally talked about at this conference.

DR. MCLAREN: Phyllis?

DR. LEPPERT: I would like to hear from more people in the audience but I will make one point, and that is that there are a lot of people in this country who don't really know what we can fund, or people who have said,

well, we can't fund anything at all. So, they have sort of given up.

One thing that I hope comes through with this conference is that despite the mandates that we are working under and the restrictions which we work under, which we are all very familiar with, we have funded lots of research. The question is how do we get this information out not only to the practitioner but to the lay public? I mean, you talked about the cab driver who is knowledgeable, and that is true but, yet, I think there is a lot that we can do in terms of educating the public about this issue and how important it is.

To me, it is such exciting science, it really is, so we should be really getting that message across to people. So, I want to hear from people in the audience. I wasn't being facetious yesterday when I said I want to know from you how we can really promote this endeavor, and how do we let people know about the importance of it.

DR. MCLAREN: Yes?

DR. SCHATTEN: I would like to underscore your comments, Phyllis, but also perhaps be a bit more animated and aggressive because I feel like we are all together for

just a very short time and, if we are all too polite, we are not going to make the progress that we need to make, and we do need to make progress because if we meet again in ten years I am going to be just a whole lot older and crankier.

[Laughter]

So, I feel like people are choosing their words carefully because there is a lot at stake, but if we can cut through some of that crap and I would like to. And, one of the differences is that, you know, you guys from the government--and I am not pointing to you guys, but here in our country you folks haven't been able to play for the last twenty years and now you are going to ride in on a white horse and tell us you are going to help us out. I understand all the constraints but it is just different than overseas.

Speaking as a federally-funded researcher but someone who has also done non-federally-funded work with all the fine print, Vatican approval, non-federal money and all that, there is a great deal of work that we need to do and, yet, the rules and the interpretation of the rules is not very clear. I know some of our colleagues have left

this country because of fears that a full audit might affect their livelihood or their institution, and if it were possible from an NIH perspective, or OMB or, I don't know, CIA, to get an analysis of what is permitted to do within an academic setting or within a private research clinic that doesn't jeopardize federal funding, I think that would help a number of us.

Also, I think that we could as a community say, gosh, there is some really important human embryo research that needs to be done and--let's just pick a number--that is going to cost roughly ten million a year to do nationally. As with RU486, as with some other things that the federal government has not been able to fund, I think as a community we could go to other benefactors and say, you know, we have all of these important questions, whether it is for stem cells or the health of ART, we have questions that need ten million a year now, can you help us meet the gap because of, you know, political or governmental restrictions? It strikes me that that would be a way to really move us off this dime. I am sorry for voicing frustrations but you know where I am coming from.

DR. MCLAREN: Certainly, that first question that was raised is a very important one, but is there any ambiguity in what is allowed in a federally-funded research center?

DR. LEPPERT: We know, and have published--I mean, we are talking about the Dickey-Wicker Amendment, we can fund animal research, as you know, and animal ART, as you know, non-human primate, all of that which we do fund. We can fund human ART work that has to do with outcomes. Everything we can fund, except we cannot fund the actual manipulation of the human embryo. We have funded several grants, I think maybe about six or seven, where we send out, at the time of the award, a comment in which the investigator then signs off and says I guaranty that I am not using any federal dollars to actually do the embryo work per se. We have arranged it so there can be that kind of fire wall and we have funded a number of grants under that.

DR. SCHATTEN: I agree with that. The awkwardness comes in when you have a laboratory next door to a federally-funded laboratory and you are using non-federally-funded personnel, non-federally-funded equipment,

non-federally-funded everything but then you hear stories that, you know, gosh, that chair was purchased in 1983 with a grant that was supposed to be in existence for twenty years. So, your butt is sitting in a federal chair and, so go to England. I think the interpretation of the rules is highly political, and for those of us that are not independently wealthy, we worry that our own livelihoods could be jeopardized by doing important work.

DR. LEPPERT: I have to also say, as long as we are being frank and you and I have always been frank, I was asked to make some phone calls around the time that we were funding or talking about funding the famous cells lines, and I did make phone calls to people and I was asked specifically to talk to various people in ART about how they had solved the problem of this fire wall. What I found out was that a number of people understood the rules but they were being constrained by their deans and others who were fearful. What has happened is that people don't do any research and I think that is what you are talking about. It isn't so much what we can do, but it is the fear factor and people even don't do what they can do --

DR. SCHATTEN: Self-censorship.

DR. LEPPERT: Exactly, it is self-censorship because of the fear that comes along.

DR. SCHATTEN: It is institutional fear.

DR. LEPPERT: And, that is something that we all have to deal with, not just NIH, but that is an issue.

DR. MCLAREN: Yes?

DR. GUIDICE: And there is a reason for that fear on the part of the deans and the heads of the universities, and it has to do with indirect cost because the issue of having human embryo research in a laboratory at a university, even though it may use non-federal funds, if the laboratory next door or the air ducts are connected from one lab to another, or the same janitor cleans both laboratories who is paid by indirect cost money, those are the issues that have frightened away universities from conducting research on human embryos. That is also another major reason why the numbers of companies, Anne, that you mentioned have come to fill the void because the academic medical centers have not been able to do so.

DR. MCLAREN: Would it help at all if there was some sort of inspection team, which only need be a couple

of people, who could go round and visit the centers and could say are we allowed to sit on this chair or not?

DR. LEPPERT: But I think what Linda is pointing out about the indirect, because that is the rule and you have to show that no indirect costs are involved in this too--I mean, I know when I was in academia, it gets very difficult to say where does the indirect cost go and who is paying for what, and who owns what pencil and what desk and what endpoint. That is where it becomes very difficult, and I do appreciate that.

DR. SCHATTEN: But a pre-audit would be a very good mechanism.

DR. MCLAREN: Question over there?

MR. CATO: Philip Cato. I am an Episcopal priest and I also work in the field of ethics having to do with medicine. You have painted a picture of the helpful role that Anglican bishops have played in the work that you do in the UK. It is also the case that in this country the kind of prohibitions that the government has put in place are driven as well by religious leaders with anyone who wants to recognize that or not. Unfortunately, they are

religious leaders who are very much on the conservative side of things, to put it politely.

There has been no attempt, to my knowledge, on the part of the scientific community, and particularly people involved in the field of ART and embryo research, to educate more moderate religious leaders in this country who also have considerable influence in order that their voices might be heard. The reactions that we see in Congress and in the federal agencies which derive from Congress are driven by people who share the point of view of these more conservative religious leaders. I don't know why in this country in our public arena we appear to be sort of careless about religious thought, but we aren't in fact because if you turn on any public medium you will find when any big issue happens that the people who they go to for their opinion about what the religious response should be always come from two largely identifiable groups and the rest of the people are not heard at all.

So, I would urge the people who are in this room and the people with whom you are associated to take the time to identify and educate moderate religious leaders who would be spokespeople for you in the public arena.

DR. MCLAREN: The UK experience would support that point of view very strongly.

DR. NOGUCHI: I would like to also support that view as well. I think that some of the things we have heard today are that the federal government should do things--power derives from the people regardless of how Polly-Anna-ish that may seem. There are remarkable self-motivated groups. We have seen in the gene therapy area and the genetics area and many disease areas remarkable amounts of funding. Gerry, when you are talking about ten million dollars, there are clearly organizations in the private sector that generate ten times, twenty times that amount on a regular basis. Cystic Fibrosis Foundation as an example, I am not sure--at one point they were about 15 million; it is well over 200 million dollars a year.

We in government have these blinders on as well, but really it is not an empowerment of the people that needs to be done, it is just that you forgot you could do it. It can be done. It is not at all easy but, actually, if you are talking about ten million dollars, that should be relatively easy for what I call the private sector, which is really patient groups, coalitions. I have seen

that generated in many different diseases, many different areas quite rapidly and I think that is another way to do it.

The point being made is, yes, everybody is involved; the point being made is that everybody needs to stand up if you don't like what is going on. If you like it, well, you will get what is there.

DR. MCLAREN: Henry?

DR. LEESE: Could I just ask a practical question? Presumably the bar on federal funding extends to fixed, as it were, human embryos. Right?

DR. MCLAREN: Before we leave that, is that true? Is it not possible to have federal funding for research on dead, fixed human embryos?

DR. LEESE: It is no longer, obviously, alive and you are allowed to use stem cells that are derived from formally living human embryos.

DR. SCHATTEN: Don't use logic.

[Laughter]

DR. LEESE: The other thing, just for information, Anne mentioned the types of institutions in the UK that do human embryo research. That is quite right.

In regard to stem cells, there has now been established the National Stem Cell Bank, administered by the Medical Research Council, and a contract has been awarded last week. So, whether you are a private or public company, if you are deriving certainly human embryonic stem cells you would require HFEA permission. A clause in that permission would say that you have to deposit a sample of your stem cell lines in the National Stem Cell Bank. Then, if you are an academic, with not much money, you could access that relatively cheaply. If you are a company and want to access it, you would pay much more. Eventually, it would be self-funding. But the intention is that these cell lines be open to the whole world really.

DR. MCLAREN: Yes?

DR. SCHATTEN: I appreciate your comments, Henry, and I think that the UK deserves a lot of credit for the National Stem Cell Bank which, as Anne pointed out, is not just embryonic but also adult stem cells.

One of the ironies in our country is that you tend to have federally-funded animal ART researchers in academic institutions and non-federally-funded typically ART embryologists, in ART practices. While it has not been

deliberate, there is this gulf between us, and it is only in rare cases that you cross that gulf and one of the ironies is that there are different levels of technological capabilities or sort of intellectual challenge and even just different missions. Inadvertently, these twenty years or so of ban have sort of led to the difference, sort of like an East Germany and a West Germany, and if there were ways of bringing it back I think it would be much better.

DR. MCLAREN: Yes?

DR. GUIDICE: I would like our colleagues from the UK to comment upon whether or not the following is true Polly-Anna-ish or potentially a good strategy on the part of both practitioners and also researchers in the United States, that is, in terms of public education about some of the issues at hand. We clearly have a very polarized society in the US with regard to the issue of abortion and this has very much colored the approach and the opinions on stem cell research.

There was an I think unprecedented demonstration of leadership on the part of President Clinton when he brought together Craig Venter from Celera and also Eric Lander and Francis Collins representing both the public and

private genomic projects, and made a very important point to both groups of investigators that the spirit of competition that was so well demonstrated between the groups would best be left outside the door so that the public could appreciate the value of the genome project.

That said to me that education of the public with regard to endpoints is a very important piece of acceptance, and I am wondering do you think that our professional societies, both on the clinical side as well as on the research side, should be making more of an effort in terms of public education?

DR. LEESE: Yes, the new chair of the HFEA would agree with you very much. He has a high profile. We get a weekly press cutting service as members of the HFEA. I have it in my bag; it is very thick. It tends to get a lot of coverage, some of it negative but on balance probably favorable.

I was going to say something else and I have forgotten. Do you have any answer to this, Anne?

DR. MCLAREN: Well, I was going to ask what the clinical ART organizations, like SART for instance, are doing in the way of public education. Also, as a follow-up

to individuals here who are working in IVF clinics, to what extent to do you go around talking to schools, talking to women's groups, talking to church groups? I don't know, but those are the sort of things that have been influential in England.

DR. LEESE: Yes, I would do about five or six of those a year, lawyers, sixth formers, religious groups, but I wait to be asked actually but sometimes the HFEA will be phoned up and nominate me to do some things. So, that does happen.

DR. MCLAREN: Yes?

MR. ORY: We do a fair amount of that on an ad hoc basis. We do sponsor a course at our annual meeting for school teachers. We prepare patient guidelines. We are available to the media. We do it on an ad hoc basis but a lot of us are quite involved with it but we could definitely do more.

DR. LEESE: I think the charities have a rare role to play. I have been very moved by the testimony of Christopher Reeve, poor man. The same, in different ways, happened in the UK with Parkinson's, cystic fibrosis, Alzheimer's. They were quite prominent in the debates on

stem cells. And, there is an organization called--what is it called?--Advocates for Research for the Seriously Impaired, or something like that. There is a body that promotes medical research outside of the Medical Research Council, the official one, for those seriously impaired and they can be quite vocal.

MR. ORY: We also recently had a national campaign addressing prevention of infertility--smoking, consequences of aging and so forth--which was a real educational experience for us. The national media seized on that and we ended up getting a great deal more publicity than we had bargained for, which was overall quite good but many groups were very troubled by this, in particular the National Organization of Women and some of the elementary schools declined to allow us to present, and some of the malls where we were going to advertise declined to allow posters to be put up because it was not family friendly. So, even a message that we thought was extremely well-intentioned and quite benign was interpreted in ways much different than we expected.

DR. MCLAREN: Well, I hope that you will let the success of that campaign be a pointer to possible future

campaigns even though you have come across opposition. Yes?

MS. MOORE: My name is Kirsten Moore and I work with the Reproductive Health Technologies Project, which has been an advocacy group in the US for about fifteen years and, actually, was the group that got the strategy together around RU486 and getting that into this country.

I am pleased to say that we are a bridging organization, a bridging community and we work across various aspects of the women's health and reproductive rights community and have had a couple of briefings for leading organizations--Planned Parenthood, NOW, etc.--on the issue of cloning, assisted reproductive technologies, and we will do one on PGD as well, and I am very pleased to say that we have had FDA representation at that meeting and ASRM representation at those meetings.

But as you are thinking through your outreach strategies and your education strategies, I think it is vitally important to include the reproductive choice and rights communities because we are a diverse group as well, even though it is the abortion politics that are extremely challenging. But this is a community that knows how to

mobilize people, and knows how to talk to people about reproductive rights, and has to be challenged itself to think harder about what we mean about reproductive rights.

That is a conversation that we have started to have. There are organizations that feel very strongly that the right to choose is the right to choose across the full reproductive spectrum. There are other organizations that have different concerns. They have some of the equity concerns that were heard yesterday. But it is a powerful group, and it is a group that is used to working in the face of adversity and used to working in the face of politics, this firewall challenge. I mean, these are groups that get funding from state and federal government and have to constantly keep their clinics clean and separate, you know, separate doors. So, there is a lot to be learned there.

In terms of thinking kind of about bridging conversations, there is a lot that needs to happen around educating people about ART and outcomes of that, and outcomes of embryo research, etc., and we are probably not the right community to do that for you. But in terms of infertility and one of the major causes of infertility

being sexually transmitted infections that is something that the reproductive community clearly has an interest and a stake in, and I think educating people about some of those outcomes is an area where we could work together. It is also an area where I think we can be a little aggressive in talking to the federal government or putting the burden back on the federal government, Centers for Disease Control, etc. about what are you doing to help us with this epidemic in this country.

DR. MCLAREN: I think that is very important. I can see that if the funding was available there could be a series of conferences across the country, in different parts of the country where these different organizations with somewhat different approaches because that is always interesting; I mean, you don't want everybody on the platform singing to the same song sheet and it is better if you have different points of view, you could have really interesting conferences and I you could attract audiences and it would be actually very educational. Yes?

MS. RICHES: Julia Riches, from Georgetown University. Just to back up to a certain extent to what Kirsten said but also to broaden the scope of this

educative function, when you talk about educating people, the populace, the real people about embryology and then say SCIs, you are also looking at a political climate which is pushing abstinence only education. So, the whole, you know, egg meeting sperm bit is being left out. So, it is a huge and much broader political issue. I am a political science professor so I would encourage practitioners to engage in politics, not just in the frustrations of negotiating the rules of the FDA but also in a more sort of direct lobbying kind of way, especially given the relatively high power of the professional organizations.

DR. MCLAREN: I would also just give a warning against putting too much emphasis on educating people rather than letting them educate you. I think it has to be a dialogue. Yes?

AUDIENCE: Yes, I think the discussion of advocacy is a very important one. In the '90s in this country we saw more not-for-profit advocacy groups develop than any time in the history of the United States. It was an exponential take off, probably aided in some part by the web and a few other things. But I was looking the other day at some of the filings of not-for-profit and we have

had advocacy groups now on many things and they are quite powerful, particularly when they get energized, and the last example is--what is it?--the chronic fatigue syndrome when they tried to eliminate the board on that and got into some people's face and were able to stop that.

What we have when we have a lot of advocacy groups is that there is a divide and we ignore the principle. That I think has been occurring, and it might be time to try to get some, as they say, common ground between some of the different groups so you can provide a united front. We did that early in the '90s with generic women's health issues and, in fact, reproduction was left out of it for the political expediency that there were so many groups at that time dealing with it, and they were stopped and it didn't seem that you should tread on other people's feet.

So, you know, there are ways we can do that and there are people in this room, I know, who have a tremendous amount of expertise in this. But my suggestion would be to find a very focused area. To assume that nothing has been done is a little strange since it was the stem cell people and the basic molecular biologists who

became our partners in this with the advent of stem cell research, and it was the cell biology public policy group, with Paul Burke and a lot of Nobel laureates, that ended up really having an overwhelming influence on this process, and it was by directly working with many of the Congress people from very right wing areas that, in fact, turned them around and allowed the 64 or whatever number to go to the point where we got a president who pronounced the word trophoblast correctly. I don't think I have ever heard a president pronounce a word like that.

So, we have partners that we never suspected. We should have had the basic scientists a long time ago; we now have them and that is part of the whole mix. But, you know, I notice that AAAS is here today because of some of the things, and I asked him why because when I was on the board I was shocked that they weren't interested and now they are, but it is because the basic scientists have joined us.

DR. LEPPERT: I would like to also say that I know for a fact that the Department of Genetics at the University of Utah has, for at least six years now, invited the Senator from Utah, Orrin Hatch, to their laboratories

on a yearly basis to look at what is being done and to talk to him about their science. That has been very powerful and I know that it has had an effect.

DR. MCLAREN: Thank you. Henry?

DR. LEESE: I think--dare I say tactically--I would really promote stem cells because I would be surprised if, when they move into therapy, you were making individual stem cells for a person, like you make Dolly, the sheep, by somatic cell nuclear transfer. My guess is you will need thousands of stem cell lines, like you have thousands in tissue banks, to find the best match. You will need more than 60 lines that you have at the moment. You will need thousands. And, you will need thousands of human embryos from which to make them.

I would also argue that to ensure safety when you start to use them, you have to understand these cells. You can't just go transplanting them into patients. You need to understand that biology to know that they are not going to go wrong when you transfer them and become something else because they are so plastic. That will require research. You must define what is a normal human embryo so you can define properties of stem cells.

The great advantage of promoting stem cell research is that it gets away from reproductive purposes and you bring in the treatment of diseases for which we have no cure, as well as those where you can treat them better such as diabetes. You are on very strong grounds because we are all going to get these diseases and die from them. You might be able to use adult stem cells and some diseases will require those; others will require embryonic stem cells simply because of their potential to give rise to every cell in the body, the 200 different cell tissue types. I would argue on the back of that and then inescapably I think to do it properly, you would have to use human embryos in a big way.

DR. MCLAREN: Susan?

DR. WOOD: I think that is a very important point and I want to link that back to Kirsten's question about tying this back to the women's health community. We did participate in the women's health community issues, and one of the questions is, is this relevant to women other than as patients of these diseases that we all will suffer. And, many questions have come up particularly related to the idea of women as donors of these eggs that will be

required to make embryos, and the rather invasive nature of egg retrieval in terms of exposure to various drugs, etc. Particularly when you talk about taking it beyond the need for an altruistic donation for particular individual reproduction but, rather, the generation of thousands or tens of thousands or individualized cell lines, we may be talking about a greater need.

So, we have begun looking at the question of when we are developing research on ART or looking towards stem cells, thinking futuristically in the area of stem cell development, that the women themselves are subjects of this research. Although the experimentation will occur outside the woman's body, the participation of the woman as a research subject in the donation of her eggs has to be considered as well in terms of issues around informed consent and so on. So, we are trying to think about how that plays into is, you know, as the FDA but also as the research community moves forward in developing these ideas, there is an additional research subject involved.

DR. MCLAREN: Given the tens of thousands of embryos frozen, my guess is that in the near future there won't be any need for large numbers of eggs being donated

but, of course, the women are very important because you have to have informed consent for donating those frozen embryos when they are no longer needed for the parental project, donating them for stem cell research. Yes?

DR. BRACERO: This may be an oversimplified question, and lack of grey hair may allow me to do it but how can we have the FDA help SART and the ASRM put into enforcement our guidelines? Sometimes when I have a question I go to my guidelines but I don't see the power for those guidelines to be enforced across the board.

DR. NOGUCHI: I believe our current strategy--correct me if I am wrong, Marty, but we have liaison with ASRM to, in fact, see how much is actually doable. We would say that FDA has some experience with tissue banks in general. We have less experience with reproductive gametes, storage and embryo creation, and the like. It is an interactive process--I hope I am saying the right thing here, Marty.

Marty says that we are interacting on that, and we are. In fact, that is our intent. It is not only our intent, that is what we have done with the general area of human banked tissue, taking the professional standards,

evaluating them, tweaking them when necessary. There are many things that FDA is aware of that you, as a singular community, may not be aware of. We may require in some places extra testing, but in general I think our experience has been almost invariably that which has already been established and has been proven to increase the amount of safety to human subjects and patients, that we will incorporate, absolutely. So, you may not see it right at this moment but it is occurring.

DR. MCLAREN: Yes?

AUDIENCE: A question for Prof. Leese, I can see the contributions that you have made through your regulation and your authority from a standpoint of limiting the number of embryos that can be transferred and reduction of multiple pregnancies. I can see the demonstration of the confidence that your government has had in allowing you to pursue some of these areas. I see you have the licensed, government-regulated evaluation of laboratories versus our more voluntary ones, but my question that is important for me and my colleagues would be, is where do you think you would have been if you had not had the authority? What are the benefits that you have accrued for

your patients and for yourselves had you not had this in place?

DR. LEESE: The first benefit is increase in success rates because of making this transparent and open, and that the data is expressed the same by all the clinics makes a level playing field. And, HFEA has the responsibility to ensure that failing clinics improve. So on inspections, if they are failing, ultimately they can be closed down. That has happened on a couple of occasions I think. So, one is to increase the chance of a baby and, secondly, a healthy baby because we try to regulate those procedures we think are, as it were, safe and efficacious.

The other major area is encouraging the climate for research, which I just don't think would have happened otherwise. Anne, do you have anything to add?

DR. MCLAREN: Well, as far as the second is concerned, I think that is crucial because I think if it hadn't been for a licensing authority, maybe voluntary, maybe HFEA, but without a licensing authority I think the British public would be exceedingly concerned about the thought that there was human embryo research going on. They wouldn't have known what was going on; they wouldn't

have known where it was happening; who was doing it; and what they were doing and why and there would have been big protests and centers would have been closed down I think. So, I think it has performed a very useful function in that way.

AUDIENCE: So, you are saying that had you not had an authority in areas that don't have authorities that their success rates would not have benefitted over time?

DR. MCLAREN: That is what Henry said.

DR. LEESE: Yes, I think it is a contributory factor but, of course, success rate is not everything. I think the requirement within the Act for the counseling procedures which are, in fact, very strong and on every inspection team a counselor will go and the need has been emphasized for the different forms of counseling implications and whatever. It helped the need to take this away from a pure technology and to see it more in the round and I think the whole counseling ethic has helped in that quite a lot.

DR. MCLAREN: I would make one other point, and that is a point that arises from us having a government-funded National Health Service, the NH, which, of course,

you don't have here. Most of the IVF clinics are private but the women who get pregnant have their babies on the NHS and, therefore, the multiple pregnancy rate is of even more importance to us than it is to you because it is not just the health of the mothers and the babies who are born in multiple pregnancies, but it is the health of the other twins and premature babies who don't have the cots available in the NHS intensive care because most of those cots have, in fact, been filled with the IVF and ART babies.

DR. LEESE: Anne is exactly right, a lot of pressure came from the perinatal pediatricians. The intensive care baby wards were full to bursting with multiple births, mostly derived from IVF.

DR. MCLAREN: So, if there hadn't been an HFEA with really rather strict regulations about numbers of embryos transferred, I think our multiple pregnancy rate, including higher multiples, would have increased and the pressure on those intensive care cots would have been even greater and that, of course, is a financial cost that rests on the state.

DR. LEESE: I have been at meetings where the pediatricians have found themselves in the same room with the clinicians in ART and they have taken them to task.

DR. MCLAREN: But that is not a problem I think that you have here.

I was very impressed yesterday when Steven Ory told us about the accreditation and regulation schemes that are carried out here by the professional organizations, which seemed very comprehensive, and I just wondered if there were views from people as to what was lacking in those schemes. Would anybody like to speak to that? Steven?

DR. ORY: I will make one comment. The obvious thing that is lacking is enforcement. It is completely voluntary at this point.

DR. MCLAREN: And if you feel the lack of enforcement, that suggests that there are infringements otherwise you wouldn't feel the lack of enforcement.

DR. ORY: Well, I think that the compliance with it is exceptional. Better than 95 percent of the ART programs in the country do comply and strive to improve their success rates. It is the small percentage of those

that don't that really create the most misery for us and the public.

DR. MCLAREN: Without an inspection system, how do you know that the 95 percent who report are reporting correctly?

DR. ORY: I will defer to Ben.

DR. YOUNGER: There is an inspection system. We do our job, or SART's job is to collect the data. It is paid for really by the programs and the patients. We get about $25,000 a year from CDC to let them have that data. That is probably about 0.25 cents a cycle that they contribute to that. Nonetheless, they analyze the data and publish it. For it to be valid data that the government is publishing, they insist on two things. One is that every program that submits their data goes back to them and the director of that program verifies that that information is correct. Then, about ten percent of the programs, in a random fashion except for outliers, are visited each year by a team from SART and from CDC. So, the data is verified and validated. On top of that, SART looks for other things that are not in the government mandate. They look at how well the clinic does, for example, with consent forms being

in the chart, and proper linkage between the clinical records and the laboratory records, etc.

Then SART also now has required that programs that are really outliers as far as their overall success rate have to have some mandatory mentoring to try to improve the program. The goal is not to shut down programs or to limit patient care. But if a program is not up to what we think is an appropriate success rate, then that program has to improve to maintain its SART membership.

One of the other things I would go back to, mentioned earlier, is about how do you regulate. It is really simple; it is what I said. If a program is not accredited then it is not going to get paid if it accepts third-party payment, and that is a powerful regulator.

DR. MCLAREN: That is all clinical treatment. What about embryo research?

DR. YOUNGER: Embryo research, because it is very minimal with human embryos in this country, one of the bigger problems --

DR. MCLAREN: How do you know?

DR. YOUNGER: It is regulated under a local IRB, and that is it. But the issue that they brought up about

institutional overhead, the program may be in a building, or the lab may be in a building and the electricity bill for that building is paid for by the institutional overhead that comes from the government. Whoever said it, I mean, it is the deans who live off the institutional overhead, somebody there that really restricts a lot of things that people would like to do.

DR. MCLAREN: But as I said earlier, there was a surprising number of human embryonic stem cell lines claimed to have been made in this country. So, maybe there is more human embryo research going on than you realized.

DR. YOUNGER: Most of the research I am referring to is aimed at improving infertility care.

DR. MCLAREN: Philip?

DR. NOGUCHI: Yes, I think that the numbers are perhaps more than you expect but they are not huge numbers. There are two different aspects too, the number of laboratories that we are aware of, both public and private are two handfuls. Their source of embryos, however, is truly a black box. We do not know that.

DR. MCLAREN: Right. So, that is an area perhaps where regulation might be useful?

DR. NOGUCHI: I can only speak to what we are even planning to do, but it is certainly an area where more information and really understanding the supply and demand aspect of it is an important factor in the overall evaluation of how we, as a government, approach it.

DR. MCLAREN: Right.

DR. NOGUCHI: Yes.

DR. LEESE: I think if you move to therapeutic use of stem cells the UK bank will build in the necessity to get back to the donors if they have a genetic condition, because if you don't use these in therapy you need to know that. So, you need to know the origin without question of the embryos from which you derive stem cells if you are to use them in therapy.

DR. MCLAREN: Lynette?

DR. SCOTT: As a clinical embryologist working in clinical ART, something that does trouble me, and this comes back to research that is being done, is that there is a lot of research being done on our clinical patients, and a little study is done in a mouse; it is picked up; it is taken into a clinical context; embryos are transferred; a paper is published; a lot of other people jump on board;

and a proper research project with an IRB to go with it is done and the treatment is shown to be non-efficacious. I think that if we had funding to do primate research, non-human primate research and funding to do proper research with IRBs that is approved like in the UK, then we would get proper research done on human embryos, along with non-human primates. We would get the right answers and what we would end up doing is treating our patients better as patients and not as guinea pigs, and as a community we would know more about what we are working with. You know, I see it happening and it does trouble me. We jump on these things; we take them to the clinic and then we step back and say, oops.

DR. MCLAREN: Thank you. Yes?

DR. MAYER: Well, Lynette echoed a lot of the things I wanted to say, but as an embryologist working in this area, clearly the discard patient material is the vast majority of what we get to use. Information from our clinical work is where we try to glean all of the information on human embryos.

But one other thing that I heard here was number of embryos that are available for research, and so on, and

I can tell you that SART has been working with the Rand Corporation and we have developed a survey to look at, in the US, exactly what the status of cryopreserved embryos is. Those numbers will be published shortly, and I don't know exactly what they say but my feeling about it is that they are going to show that truly the numbers that are available are much, much smaller than anyone anticipated and there is really not that much available for research from infertile couples in this country.

DR. MCLAREN: Does that include frozen embryos?

DR. MAYER: It is all frozen embryos.

DR. MCLAREN: Thank you.

DR. LEESE: Are you allowed to discard embryos over here?

DR. MAYER: Yes, almost in every case--I don't know of any clinic that would act otherwise. Patients are asked what to do with their embryos if they no longer want them for their own treatment. We have looked at our own clinic, in Norfolk, and I can tell you that close to 80 percent of the embryos that are frozen are actually used in patient treatment. There is only about two to three percent that are donated to research, another two to three

percent are donated to other couples, and about ten percent or so are actually asked to be discarded. So, I think that is pretty much what we are going to see nationally but I can't say that for sure. From our own clinic, with over 15 years worth of cryopreservation, that is what the numbers break down to.

DR. MCLAREN: Time is getting on. Are there any other members of the audience who have burning points that they would like to make now? Because if not, I am going to ask members of the panel if they have last words to say before I hand over to Philip to wind things up. Henry?

DR. LEESE: I guess just a plea to the community of you here, if you could find a way to move, I guess, in the way that we have, the world community of scientists would find it of immense value because you are so good at research. You are as good as anyone and if a way could be found you will produce benefits for people. So, good luck.

DR. MCLAREN: Thank you. Phyllis?

DR. LEPPERT: I think this has been a very helpful meeting. I think that we have been very open. We have learned a lot; we have talked a lot. And, I hope that

we have started a dialogue with each other that can continue and that is good.

DR. MCLAREN: Susan?

DR. WOOD: Just to follow-up on that, I think one of the goals that Phyllis and others, and the folks from FDA and the folks from the department sort of talked about why we wanted to convene this meeting was the interaction between the different types of communities, the basic research community, the clinical community, the patient community, the women's health community, the legal and ethical issues, and I think although there probably is more we could have taken in greater depth, I think this has really been a wonderful beginning. If we can look to future conversations where we take particular aspects, either some of the research questions or some of the legal and ethical issues, and try to drill down into what we really need to do and how we can get to it, we can take advantage of the opportunities that we have created with this meeting.

DR. MCLAREN: Philip?

DR. NOGUCHI: I echo everything that has been said. I will also reiterate my direct pleasure at seeing

that time and time again right-thinking people in a small room may have differences of opinion but I really think we all have consensus on what needs to be done in the broad scope. So, we will use this, as far as the FDA and, to our extent, through the department as a stepping stone to wherever we go next. For FDA, we are going to pursue more vigorously how we can embrace the community and really make it right in terms of our regulatory oversight.

DR. MCLAREN: Before handing over to Phyllis to wind up things, I would like once again to express how very grateful I am both to Phyllis personally and to NIH, FDA, DHHS, the organizers of this workshop. It has been a wonderful couple of days and I thoroughly enjoyed it. So, thank you very much. Phyllis?

DR. LEPPERT: Thank you very much, Anne, and everyone who has been here. This meeting had its genesis several years ago actually because there has been a trans-NIH working group of people who are interested in reproductive science and this is important for the federal government because we are large agencies and we haven't always dialogued ourselves. So, this is important.

Those of you who know me well know that I am really not a federal bureaucrat because I have only been here about three years, and I really come from the academic obstetrics and gynecology community and my loyalty is to really the people out there, the researchers, the extramural community and the clinicians because I understand all the issues.

Reproductive science is a very important part of what we do. It is also, by its very nature, very driven by emotions and controversy because everyone has so many thoughts and feelings, and deep-seated feelings about reproduction. In my experience, I have never been anywhere where reproductive science, or contraception, or whatever it is we are talking about in reproductive health doesn't cause controversy because we are human and it is so very deep with us. In fact, if we didn't have reproduction none of us would be here and we know that with all species the reproductive urge is so very vital. But I think it is important to get beyond the emotion, to get beyond the politics and that is what we have tried to do today.

I think we have also heard a lot about how it is important that we talk to people and educate people about

what we are doing. We can't be afraid of these emotional things that keep us from talking about our science. So, I think this has been very positive.

We will be having a follow-up meeting of the planning committee to discuss this. We would like to hear more from you so this is a beginning and I am very pleased with the conference and thank you very much.

[Whereupon, at 11:50 a.m., the proceedings were adjourned]

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