Genes and Genomes: Impact on Medicine and Society

Genes, Genomes, and Society
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Bioethics: Embryo Research, Genetic Diagnosis and Therapy, Stem Cells and Cloning

Introduction by Jonathan R. Cole

Jonathan R. Cole: Let me introduce Professor Anne McLaren. She's our first speaker. Professor McLaren was educated at Oxford University, where she did both her undergraduate and graduate degrees. She was director of the Medical Research Council of Mammalian Development Unit in London for 18 years until 1992. Prior to that she worked for the Agricultural Research Council in C. H. Waddington's Institute of Animal Genetics in Edinburgh. Her research has ranged widely over developmental biology, reproductive biology, and genetics, including molecular genetics, using the laboratory mouse as a model. Since 1992 she has been working at the Wellcome Trust/CRC Institute of Cancer and Developmental Biology at the University of Cambridge. She was a member of the UK government's Warnock Committee on Human Fertilisation and Embryology. She's a member of the European Group on Ethics, and advises the European Commission on social and ethical implications of new technologies. She's published widely in all of these areas, and most recently coedited a book entitled, *Adoption of Opinion on Ethical Aspects of Human Stem Cell Research and Use*. She was elected a fellow of the Royal Society in 1975, and from 1991 through 1996 she served as foreign secretary and vice president of the Royal Society. In 2002 she was awarded the Japan Prize for Developmental Biology. It is a great honor for me to introduce to you Professor Anne McLaren, who will speak to you this morning on the subject "Bioethics, Embryo Research, Genetic Diagnosis and Therapy, Stem Cells and Cloning."

Louise Brown, First IVF Baby

Anne McLaren: Can you hear me at the back of the room? Good. I feel hugely privileged and honored to have been invited to participate in this remarkable, remarkable symposium. So many thanks to the organizers for inviting me. I'm also delighted to find that Columbia University, which I've known for quite a while on and off, is, as it were, descended from Kings College of New York, because I'm a fellow of Kings College in Cambridge, so that makes me feel even more—even more friendly towards Columbia.

So, 250 years of Columbia, 50 years of DNA, 25 years of Pope John Paul, and 25 years of IVF, in vitro fertilization. It was 25 years ago, in 1978, Louise Brown, the first IVF baby, was born in the UK.

Now, the developments that led up to the birth of Louise Brown occurred in the UK rather than the USA, and the birth of Louise Brown in Britain was greeted by the British public and the media as a miracle baby and not a Frankenstein baby. And those two things, had they been otherwise, I think would've made subsequent events very different. Much of the ethical issues in this area relate to the status of the human embryo, and this was really first brought to public attention by the birth of Louise Brown and by the popularization, as it were, of IVF. Because by now something like a million babies all over the world have been born by IVF. But the British government realized that there would be social and ethical problems, so they set up a committee to report on infertility, surrogacy, for instance, and human embryo research. It was chaired by Mary Warnock, the moral philosopher, a moral philosopher, I think a very sensical moral philosopher, and an excellent, excellent chair.

Now there was wide consultation and the Warnock Committee got piles and piles and piles of documents, letters, from individuals, from groups, church groups, women's group, trade-union groups, neighborhood groups, many, many groups, and quite a few of these did comment on the moral status of the human embryo. Of course some thought that embryo meant something with arms and legs and a head and a nervous system, but not all that many; most people realized that one was dealing with maybe a dozen or so cells.

There were some who thought that this aggregation of cells was really just an aggregation, and had little or no moral value, but that few wasn't and isn't very common. But the other extreme, of course, the official Roman Catholic view and the view of some other people as well, is that from the one-cell stage onwards, from fertilization onwards, the moral value in embryo is equal to that of a newborn baby or an adult human being. But the majority of people seemed to think that the moral value of the embryo increases as it develops, first into a fetus and then into a baby. And that was in fact the view that the Warnock Committee eventually came to, and they concluded that of course the human embryo is entitled to respect because it is human and it has potential, but unless that

embryo is going to be put into a uterus, that respect can be weighed against the benefits to be derived from the proposed research. But the research should only be permitted, given certain requirements. Some were obvious: for instance, the informed consent of the donors of the embryo; a local ethics committee; the work would have to be scientifically valid; the need for human, not animal, embryos; enough animal research would have had to have been done first to make it essential now to check the results on human embryos. And they decided that it would have to meet acceptable objectives, purposes of clinical relevance, and also that no embryo which had been the subject of research should be transferred to the uterus, because of course that would imply research on the fetus and on the woman, because by definition with research you don't know what the outcome is going to be.

Also, if there was going to be legislation, then there had to be a time limit for in vitro development. One couldn't just airily say, "Yes, you can do embryo research." There had to be a time limit, and after some discussion the Warnock Committee decided on 14 days, which is the last stage before twinning is possible, before the formation of a primitive streak, so it's the beginning of individual development, in contrast to fertilization, for example, which is the beginning of genetic identity. And this 14 days, which I'll say a little more about later on, has been adopted by many countries who do allow some degree of human-embryo research.

The UK Human Fertilisation and Embryology Bill

Well, there were several years of consultation, and finally the British government brought the Human Fertilisation and Embryology Bill before parliament. There was by that time—after considerable debate—there was wide support for the view that the archbishop of York put forward in the debate in parliament, namely that if IVF was to continue, research must also continue, because it would be totally unrealistic and indeed immoral, he said, to continue IVF without a proper backing in research because imperfect techniques without a backing in research are bad practice medically, and I believe wrong morally.

Well, the vote in parliament supported that view. In 1990 the act came before both houses of parliament in favor of embryo research, you see both the House of Lords and the House of Commons large majorities, and also both houses of parliament voted in favor of allowing embryos to be made for research under certain very strict conditions, namely that it was only allowed if the project was essential and couldn't be done otherwise, couldn't be done on any other form of embryo.

The other thing that the act did was to set up the Human Fertilisation and Embryology Authority, which was a statutory body, and it has to license, monitor, and inspect every year all clinics that carry out IVF or donor insemination, also to license and monitor all centers carrying out human embryo research, so every

project has to be discussed. It may be accepted, it may be rejected, it may be modified, but it has to be licensed before it can be started. They regulate storage of gametes and embryos, keep a register of information about donors, treatment, and children born, and produce a code of practice.

There's quite a bit of debate going on at the moment in the UK about donor anonymity, because according to the act, both sperm and egg donors should be anonymous. But a lot of people feel now that that's wrong, that children have a right to actually know the identity of their genetic parents. I can see both sides of that argument, I haven't made up my mind, and parliament hasn't made up its mind either.

The other thing that the UK government has done quite recently is to set up a national stem-cell bank for both embryonic stem-cell lines and fetal and "adult" stem-cell lines; it's only just getting going, but I think it's an important development. The cell lines will be available to UK academics and overseas academics free of charge except for the cost of shipping and all of that. Industry will be charged. The ownership of the cell lines remains with whoever deposited them in the bank, and of course there'll be material trade agreements involved.

Stem Cells

So what are stem cells, what are stem cells? Well, stem cells are defined as cells that are capable of self-renewing; they could make more cells like themselves, or they can make cells which give rise to one or more differentiated cell types, so they're cells with a choice, they're cells with a choice. They can make one cell just like themselves, and another one which may develop into nervous tissue or muscle.

It became rapidly clear that stem cells had great promise for a number of reasons. First of all, of course, in experimentally basic research, they are enormously important because one can study in culture in the lab how cells develop into these different tissues. The pharmaceutical companies are very interested in stem-cell lines for drug development and toxicity tests. And in the future they hope to use a lot of stem-cell lines, human stem-cell lines, rather than animals, for instance, for toxicity testing. And again there's the possibility of cell and tissue therapy, because although sometimes whole organs need to be replaced, quite often it's enough just to replace some cells, some tissues, repair, as it were, and that can be so both of the—of the blood, bone marrow, nerve cells, the heart muscle, pancreatic eyelet cells, in diabetes—and indeed there are a whole number of diseases that I've listed here; some of them are neurological diseases, Parkinson's, Alzheimer's, stroke, Multiple Sclerosis, then we have the liver, the heart, diabetes, rheumatoid arthritis. And these tend to be, unfortunately, very common diseases. Diabetes, Parkinson's—I suspect we all know somebody who is suffering from one of these diseases. They're intractable, no real cures are known, and they cause a great deal of suffering. But they could

be alleviated or even cured if there was the appropriate cell type in a large enough quantity and appropriate condition to use for therapy.

Now, stem cells can come from different sources, they can come after birth, which is usually called adult. There are stem cells indeed in the brain. It used to be thought that we were born with all the neurons we were ever going to have, but now it's known that there are stem cells in the brain that can repair the brain, and animal experiments have shown that they can be removed and used for cell therapy. Bone marrow is already used, of course, for transplantation, and has been for a decade or two. Cord blood from the placenta is a possibility; satellite cells are muscle stem cells. Then it's possible to get stem cells from fetuses, on termination of pregnancy, and also embryonic stem cells, and it's these where the ethical issues are the most pressing.

Now, adult stem cells. The problem is that they're present in the body in only very small numbers, and they don't proliferate all that well in culture. So there's a numbers problems with adult stem cells if you want a large mass of stem-cell tissue for use in a hospital. Embryonic stem cells come from the blastocyst-stage embryo, and I'll show you in a minute what that means, it's a stage where 100 and 150 cells in an embryo not yet implanted in the uterus. They proliferate indefinitely in culture, are chromosomally stable, unlike transformed cancer cells, so one can get a very large number of cells from embryonic stem cells. They're pluripotent, they can give rise to any tissue if appropriate treated, but when a stem-cell line gets old, then it tends to be less capable of giving rise to all the desired tissues. And important from the ethical point of view, embryonic stem cells can't on their own make an embryo. An embryonic stem cell is very different from an embryo, and it can't make an embryo. But the derivation of these cells, which are called ES cells for short, the derivation of these cells involves the destruction of the embryo from which they come, and of course that is what raises the ethical problems.

Embryos

If we look at the first couple of weeks of human development, here we have fertilization, and of course fertilization is when the new genetic constitution is first established. Genetic uniqueness comes much earlier. Eggs and sperm—every sperm is genetically unique, different from every other sperm, different from the man who produces them. But the new genetic constitution starts at fertilization. Then you get cleavage into two cells, four cells, eight cells—this is the hundredth cell stage from which the ES cells can be derived from these inner cells here. That embryo will then after—about a week after fertilization it will implant in the wall of the uterus. That's about seven days after fertilization. And then during the second week the implantation process continues in the uterus, until you get this large mass of tissue derived from the fertilized egg, of which less than 1 percent, about 0.1 percent from the very middle here, this layer called the epiblast is going to develop into the fetus and the baby. And that's what's called at 14 days the

primitive streak stage, it's the last stage at which twinning can occur. One can get instead of one primitive streak two or, in the case of the Dionne quints, five monozygotic twins. Sometimes one doesn't get a primitive streak at all, and sadly one then just gets a tumor instead of a baby. But this is the stage at which individual—in the sense of undividable development—begins, at the end of the second week, once implantation is completed.

Now, embryos are of different sorts, and the source of the embryo determines the ethical problems associated with it. First of all, and most importantly, there are the embryos that are derived by fertilization in the course of IVF treatment. Because almost always there are more embryos produced, the woman is treated with hormones; otherwise, she would only produce one egg at a time, and IVF would be extremely inefficient, so she produces more eggs and more embryos, and the spare or supernumerary embryos are usually frozen for the couple's own use. But the time comes when they may no longer be required for the parental project; either the woman has got beyond the age of reproduction, or the couple have got the family, one or two children, that they wanted, or sometimes where IVF is private, rather than on a national-health system, they can't afford to have another cycle. So there are spare embryos, and the couple has the choice then of either donating them to another couple or donating them for research, for example, for research on stem-cell derivation, or just letting them die, and that is the fate of in fact most spare embryos at least in the UK.

Then, as I explained earlier, there are embryos that are made for purposes of research, donated oocytes, unfertilized eggs, which are fertilized for a research project, for instance. It may be a research project on fertilization itself, because fertilization is a process that quite often goes wrong and produces abnormalities; we don't know why, we need research.

And finally there could be embryos derived by somatic-cell nuclear transfer, cloning. So far that has not been successful in the human, but in principle one could have embryos of that sort.

International Laws on Stem-Cell Research

Now different countries all over the world have very different views as to which, if any, of these types of embryo should be used for research or for stem-cell derivation. Within Europe there are very big cultural differences between different countries, and therefore the European Commission has a problem in deciding what should be done. Should they give money for research on human embryos, or what? The European Group on Ethics gave an opinion to the European Union which said that for those countries where it was legal to do research on embryos, there was no reason not to develop treatments for serious diseases, which of course means stem-cell derivation, and no reason to deny European Union funding. But that would be on spare embryos, and then it went on to say that while spare embryos are donated, fertilization of eggs specifically for stem-cell

research is not ethically acceptable, and furthermore they said derivation of embryos by somatic-cell nuclear transfer, cloning, for stem-cell research would be premature at the present time.

So if we just look at what the situation is in Europe and elsewhere in the UK, Belgium, Sweden quite recently, and also China, all those types of embryo that I listed could in principle be used—it wouldn't be against the law. In a lot of countries, spare embryos can be used for research on stem-cell derivation, but not any other type of embryo. France and Spain are still—the law isn't quite through yet—but it looks as if that's what it's going to be. Australia has an additional condition, which is that it's only embryos that were frozen, fertilized and frozen before April 1 this year that can be used for stem-cell derivation. But that applies throughout Australia, both to government-funded and also to privately-funded research. Four countries in Europe, Austria, Germany, Ireland, and Norway, human-embryo research and stem-cell derivation are entirely prohibited. In Germany it's allowed to carry out research on imported stem-cell lines, and mainly those stem-cell lines are imported from Israel.

In the Czech Republic, Israel, Italy, and Portugal, there is no legislation yet. You might think that Italy would have strict legislation on these matters, but it has no legislation at all, anything goes. Czech Republic and Israel have both made stem-cell lines and, as I say, Israel is exported them, but there's no legislation, no regulations.

And then we come to the United States, but I think you know more about this than I do. Government funding is not available for human embryo research or for derivation of human embryonic stem cells, but scientists are allowed to do research with government funding on embryonic stem-cell lines that were made before August 9, 2001. On the other hand, if privately funded human embryo research and derivation of new stem-cell lines is not illegal. So I think this is the only country that actually has a distinction between government funding and private funding for the ethics of human embryo research.

Stem Cells for Gene Therapy

Now, another possible use of stem cells, which isn't often drawn attention to, is in fact for gene therapy, because gene therapy—namely the attempt to cure genetic diseases by replacing or substituting gene products—there are single genes which could be replaced like for cystic fibrosis, Duchenne muscular dystrophy, and SCID (severe combined immunological deficiency). This is what is sometimes called bubble babies, babies that have to be kept in bubbles because they have no immune system. And this is one of the more successful types of gene therapy, but gene therapy is proceeding very slowly at the moment. Then there is the possibility that genes for therapeutic proteins might be introduced into

the body, and this is where the stem cells could be useful, because stem cells that were producing these therapeutic proteins could be used for treating genetic diseases.

At present the vectors that are used for introducing these genes are less than satisfactory; a number of viruses are used, but they can be risky. Liposomes, which are little fat droplets, DNA conjugates, they are not very efficient. So engineered stem cells are looking more promising, for instance, mesenchymal stem cells; they're cells that can give rise to all sorts of cartilage, bone, muscle, fat cells, and they could be engineered to express some of these useful protein products.

Now, any new therapy, and this applies to gene therapy as well as any other sort of new therapy, any new therapy is risky. And there are two ethical issues that are really in conflict with one another. One is the precautionary principle, be careful. Now if one was totally careful, one would never introduce any new therapy. But then what about the serious diseases for which new treatments are urgently needed? You need a risk / benefit analysis. And then there are other risks; for instance, informed consent can be tricky. It's very important that false hopes should not be raised in patients' minds. I think that's happened in the past with gene therapy, at least the media have promised greater successes than have been apparent, and perhaps particularly in this country the role of litigation if things go wrong. Because indeed things can go wrong, for stem-cell therapy, good manufacturing practice, good clinical practice, are essential. One can't use mouse fetal layers, animal serum, that would be risky. There's a possibility that the stem cells might make the wrong sort of tissue—that could be very dangerous—or that if there were undifferentiated stem cells there they might cause tumors. For gene therapy, most of you probably know the tragedy of Jesse Gelsinger, a young man who died. I think it was an adenovirus vector. There were questions raised about whether the regulations were being followed, whether there had been adequate reporting of previous cases, and the suggestion that perhaps competition between different groups might lead to premature trials. But undoubtedly that case made something of a setback to gene therapy.

And then the SCID trial—I mentioned the SCID, the babies in the bubbles—that was going well, the 11 children were treated and appeared to be totally cured, clinical benefit; they came out of the bubbles, were leading normal lives, but 2 of the 11 then developed leukemia. And it was discovered that that was because the inserted gene had inserted in the wrong place, and that was what caused the leukemia. So that can be controlled, and since there is satisfactory clinical outcome in the other cases, and there is no other way of treating these very sad children, those trials are continuing, certainly in the UK.

Now, all of the gene therapy that I've been talking about is so-called somatic gene therapy, that is, treating the individual patient, the body, as with any drug.

But there is also the possibility that's been proposed of germ-line gene therapy, that one could treat a very early embryo, before the germ line that's going to give rise to sperm and eggs is developed. And in that case, the defective gene would be replaced not just for that generation but perhaps for future generations. But it would be risky, unpredictable, and it is not a good option because there is an alternative, which is not risky and which is frequently done, which is pre-implantation genetic diagnosis. Because there a couple who are at risk of producing a child with a genetic defect can have the embryos screened before they're implanted in the uterus to make sure that the embryo that is being put back doesn't carry the affected gene for which they're at risk.

This is what the implantation genetic diagnosis looks like. Usually at the eight-cell stage, one cell is removed from a number of embryos, and by either—usually by a polymerase chain reaction, which is a very rapid method of looking at the genes in the embryo, there may be two that carry the defect, three normals. The three normals will be replaced in the uterus or frozen for future use. It's also been suggested that germ-line gene therapy could be used for enhancement; in other words, to make genes better. Well that's not technically possible at present, and it's widely regarded as ethically unacceptable for reasons of equity, autonomy, and so forth.
Even pre-implantation genetic diagnosis has sometimes been termed ethically unacceptable, because it has a flavor of eugenics. But eugenics is a very confusing term. Historically it really implies coercion, and in the opinion of the geneticists who met in 1998, new genetic technology should be used to provide individuals with reliable information on which to base personal reproductive choices, that's the essence, not as a tool of public policy or coercion. Informed choice should be the basis for genetic counseling, and the term eugenics is so confusing, it really should no longer be used in the scientific literature.

Cloning

Well, finally what about cloning? Now, cloning has never been illegal in the UK, because the 1990 Act didn't prohibit making embryos for research, but equally it's never actually been done. Now, cloning involves first of all the removal from a donated unfertilized egg of the genetic material, and then replacement by a somatic cell, a body, say the nucleus of a skin cell. This has been done in animals, Dolly the cloned sheep was the first one, it's been done in cattle, goats, cats, not dogs, mice, not monkeys—it doesn't work in monkeys. And in animals the progeny born from this cloning technique produce many abnormalities, many deaths during pregnancy, deaths at the time of birth, and problems later in life. Some, just a few, are healthy, but so few that most people feel that cloning for babies in humans would be criminally irresponsible, much too high risk of fetal neonatal deaths, malformations.

Of course it might one day be made safe and effective; if it were, would we want it? There are many varied ethical objections. On the other hand, there are people

who say that it could be valuable for couples who are irremediably infertile, the replacement of a dead child—of course a dead child can never be replaced—or do-it-yourself female reproduction, where the woman produces the donor eggs that are going to have the genetic material removed and her own nucleus put in, and then they can be put back into her own uterus so as to produce a baby which is her identical twin, or I don't know what you'd really describe it as, but that's science fiction, that is not science fact at present. And certainly in the UK human reproductive cloning is now forbidden by law.

However, if such an embryo is not placed in the uterus, it could be used to make stem-cell lines to derive embryonic stem cells. And it's been suggested that that could be a useful way of getting around transplantation protection. Here you have the patient, the somatic cells, the body cells, are taken, the nuclei are put into a donated egg which has had its own genetic material removed, the embryos are cultured, stem cells are derived, and then differentiated to make muscle or nerve or pancreatic tissue, whatever the patient needs for their particular disease. And of course the stem cells will not be rejected because they will be the same tissue type as the patient.

Now, ideally of course, one would turn the somatic cells, the body cells, directly into stem cells without going through the embryo, but that's not possible at the moment. And I have to say that I think this whole process is never going to be clinically realistic. It's far too labor-intensive and costly to think of doing it for an individual patient. I really don't think it's practicable. There are other ways that one could envisage of getting around graft rejection, as well as this somatic nuclear transfer. You could take adult stem cells from the patient, though, as I said, there are rather few of those. You could genetically manipulate the stem cells to eliminate the antigens. You could have a large stem-cell bank so that you could select stem-cell lines that were reasonably compatible with the patient. You could induce specific immunological tolerance in the patient, with a lot of research going on along those lines. And of course there are immunosuppressive drugs which we use today for kidney and heart transplants. They are getting better all the time.

But I think it's important that the technology of somatic-cell nuclear transfer should not be prohibited, because it could be extraordinarily valuable for research. There are a whole number of very rare genetic diseases which at present are so rare that we really know very little about them, and it's difficult to get enough material to investigate them. If you could make stem-cell lines from such patients, you could have an indefinite amount of material to study. And the same is true of common but complex diseases. If we had stem-cell lines for some of these diseases with multiple causes, it would make it easier to study them and again. Research on the actual nuclear reprogramming might help to allow the sort of somatic to stem-cell conversion that I was talking about earlier. And in fact only last month sixty academies of science from all over the world signed a statement calling for a ban on human reproductive cloning, but requesting that

cloning for both research and therapeutic purposes should be excluded from such a ban. And that statement was sent to the United Nations General Assembly, because United Nations has a committee on cloning, which is at the moment considering a convention.

So finally—I'll skip the next slide—what are my conclusions? Well, I think that ethical objections are usually more appropriately addressed by regulation than by prohibition. I think stem-cell therapy may become important in clinical practice sooner than gene therapy, but gene therapy could use stem cells as vectors. And my own view is that cloning is unlikely to play any part in clinical practice, but it's going to be a valuable research tool.

And I'd just to end by showing you two passages from a Canadian report that I thought were really rather sensible, namely that the public tends to demand prohibition of conduct that's universally opposed but expects issues of moral ambiguity to be regulated, and criminal law should be an instrument of last resort to be used only in response to conduct which is culpable, seriously harmful, and generally conceived of as deserving punishment.

Thank you.