HUMAN CLONING AND STEM CELL RESEARCH

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Opening

I am grateful for the opportunity to speak on the subject of medical biotechnology and cloning from a Christian perspective. At Dordt College we stress the relationship between our Christian faith and *all* areas of our studies, but this is particularly evident in the area of medical technology. Thanks to the development of biotechnology, we are experiencing a rapid increase in our understanding and treatment of human diseases. However, we are also witnessing the development of technology that can manipulate the very beginning of our lives, and which challenges our conception (pun not intended!) of what it means to be human.

Although there are many things I can talk about, I will focus primarily on some of the most controversial areas of medical technology today, namely the biology of reproduction, human cloning and genetic engineering as well as the stem cell research that underlies these. We will also discuss the political situation as it has developed in Canada and the U.S.A.

Before I begin, I need to clarify my task for this evening. I have been asked to speak about the scientific aspects of this subject, with Dr. Kloosterman speaking on the theological aspects.

However, as a Reformed Christian, I believe that *everything* belongs to God and we can make no distinction between sacred and secular, or between scientific and theological. Thus I will address the theological aspects of this subject as well. However, I will try to demonstrate that, even from a "scientific" perspective, human life begins at conception, and therefore must be protected.

The Beginning of Life

In normal human development, life begins at conception. The egg has been released from the ovary, and sperm have made their way up to the top of the oviduct (or Fallopian tube) where fertilization occurs. The first sperm cell to make it through the protective layers surrounding the egg and contact the egg cell membrane will penetrate that membrane and introduce the genetic material of the sperm cell (father) into the egg cell. At this point the fertilized egg is called a zygote and has the full complement of the genetic material, from both mother and father. From this point on the exquisitely choreographed process of embryonic development takes over which ends up eventually as you or me.

The only discontinuity is at the very beginning, at fertilization, and everything else is a continuous process, even birth. By "discontinuity" I mean a *genetic* discontinuity, which gives the embryo a unique genetic composition that is derived, yet distinct, from the mother and father. Thus, scientifically speaking, we are actual and individual human beings from the moment of conception onwards.

It is true that we are more than a collection of genes and cells, but fertilization is a necessary condition for the beginning of life, and the rest of our being human follows from that. Although embryonic development is a routine process, it is anything but

simple. It is a fascinating and enormously complex process, one that truly demonstrates the power and wisdom of the Creator. In fact, it is extreme arrogance to claim that the early human embryo is "just a clump of cells." Such a comment reveals an ignorance of the developmental events that occur at the molecular level in the early embryo.

What are Stem Cells?

Let's look further into the process of embryonic development and see how it applies to the use of stem cells. Although the zygote is but a single cell, it has the potential to develop into all the different cell types of the body. Such a cell is called totipotent. After this one cell divides into two cells, then four, eight, sixteen, etc., we start to see a change in this potential, as the cells begin to develop, or differentiate. The first stage in this differentiation process is the blastocyst stage. What was previously a solid clump of cells in the morula has now filled with fluid, leaving two cell types. Cells on the outer surface of this ball form the trophoblast, while a collection of cells attached to the inner surface of the trophoblast is called the inner cell mass. It is the inner cell mass that develops into the embryo, while the outer cells will form the placenta and other tissues.

As the process of embryonic development continues, each cell will keep dividing to make more cells, but also begin to differentiate into the type of tissue it will eventually become, whether nervous tissue, muscle tissue or something else. The more a cell is differentiated, the less is its ability to develop into different cell types. Thus the early embryonic stem cells in the inner cell mass are totipotent, and these are the cells whose potential is so attractive to many scientists.

What Other Sources of Stem Cells are There?

Even as adults, however, we have cells that have not completely differentiated and retain the potential to develop into different cell types. These are also called stem cells. For example, in the bone marrow we have stem cells, which develop into all the different white blood cell types, red cells and platelets. Such cells are not totipotent, for they are restricted to become blood cells only, so they are called pluripotent. Stem cells are present in muscle, skin, bone marrow, and even neural stem cells have been identified, which can develop into different types of brain cells.

Stem cells are useful in medicine because they can replace cells lost through disease or other causes. For example, one treatment of leukemia involves killing off all the cancerous blood cells in the patient's body, then re-seeding the patient with stem cells from a donor (usually a close relative), which will repopulate that person's body and make all the blood cells that are needed.

Treatments are also being developed for people with degenerative diseases of the brain like Parkinson's disease. If neural stem cells can be introduced into the brain, they may be able to replace the ones that have died off through disease. It's not that simple of course, and there are many technical challenges, but the potential is there.

All this sounds relatively non-controversial, but there is a more sinister side to this. The "best" stem cells for such treatments are those that have traveled the *least* down this differentiation pathway, namely the totipotent cells of the early embryo. Thus if we were to harvest the cells of the inner cell mass and grow them in culture, these would have the broadest therapeutic potential.

Where can we get these cells? It is normal procedure

during in vitro fertilization to fertilize extra embryos, choose some to implant in the uterus, and freeze the rest. If the parents do not want these embryos, they will eventually be destroyed. At present it is thought that there are about 100,000 such "surplus" embryos in the U.S.A. These "extra" embryos are currently the source of cells used to generate stem cell lines. The argument is that they would have been destroyed anyways. Furthermore, it is a simple matter to produce these early embryos by in vitro fertilization and then to harvest the cells only for use as stem cells. In July, 2001, it was reported that a fertility clinic in Virginia was performing in vitro fertilization purely for the purpose of producing stem cells. Such a practice is presently illegal in Canada.

Since we regard such techniques as unacceptable, is there any bright side to this stem cell technology? Yes there is. Researchers are discovering that the pluripotent stem cells isolated from adults have a greater differentiation potential than first thought. By manipulating the culture conditions and the environment to which these cells are exposed, one can change and broaden the differentiation pathway of these cells. For example, in one study, researchers isolated neural stem cells from the adult brain, and found they could differentiate into a variety of different cell types. Recently, researchers in Montreal have isolated stem cells from the skin and converted them to other cell types, including neural cells. It appears then, that there are adult stem cells that may become totipotent by appropriate manipulation of their culture conditions. What does this mean? It means that these adult stem cells might be used instead of embryonic stem cells, while still providing the benefits of stem cells.

Adult stem cells have another benefit as well. If they are derived from the person who will use them, there is little concern about rejection by the immune system. This technology has a long

way to go, because at present the embryonic cells are more versatile, but there is hope. At present these cells are not as robust and fast growing as the embryonic cells, and the therapeutic potential is not yet known.

I should point out as well that research is also ongoing on stem cells derived from umbilical cord blood cells. This would be another non-controversial source of stem cells.

The Process of Cloning

How does cloning fit into this scenario? You've probably heard of Dolly, the cloned sheep, and subsequent cloning of other mammals. There are even people working on cloning humans, although not too much progress has been made thus far. The principle of the technique is straightforward, but inefficient, and was first developed about 50 years ago in frogs. It basically bypasses the process of fertilization (Figure 5).

One starts with an unfertilized egg, the *oocyte*, which contains only half the genetic complement which is provided by the mother. One then removes the nucleus, which contains the genetic material. What we have then is a cell having basically no genes, but which does provide the environment or *context* to develop these genes into an animal. The genes can be provided by the nucleus of almost any cell in the body; in Dolly's case it came from an udder cell. The nucleus from a donor cell is injected into the oocyte, to produce a zygote. This zygote then divides and develops as usual into a blastocyst, which is then implanted into the uterus of a surrogate mother, and develops, in this case, into a sheep.

It must be noted that cloning by this technique is a very inefficient procedure. The egg cell does not respond well to being punctured with a needle to remove the original nucleus and replace

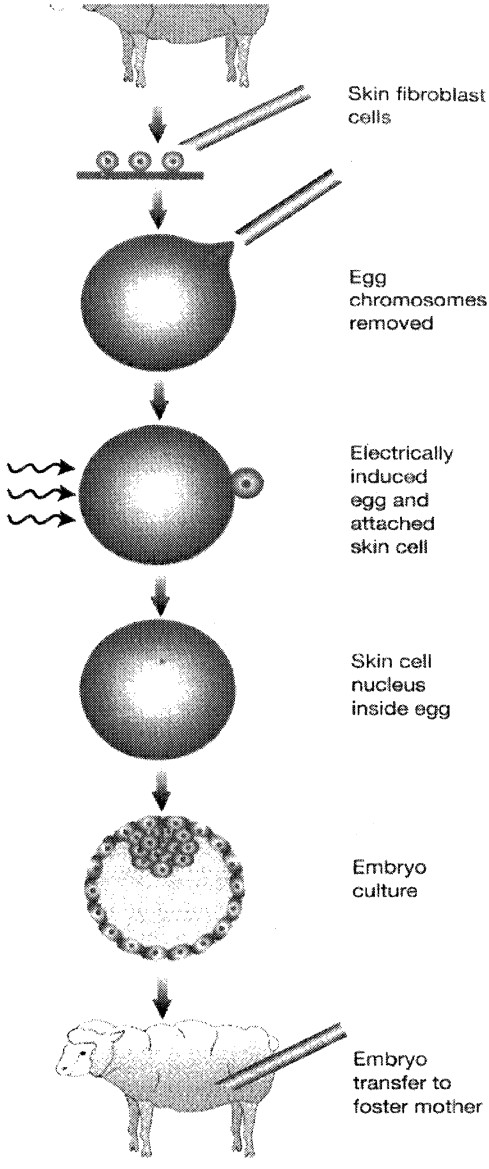

Fig. 5. Cloning by nuclear transfer (from Gurdon and Colman 1999)

it with another. Dolly was the only one of 270 attempts to succeed and even she needs to be kept on a special diet or she would be grossly overweight. Furthermore, she appears to be suffering from premature aging, which is probably related to cloning. Although the success rate has improved, it is still only a few percent. Human cloning would likewise be very inefficient, and could produce a large number of grossly abnormal babies, which would presumably be aborted spontaneously or by choice.

Therapeutic Cloning

Reproductive human cloning has been almost universally condemned, but can this technology be put to other uses for humans? Another possibility is known as therapeutic cloning. This technique uses the technology of cloning, but only to grow cells and tissues that may be used to replace defective tissues in patients, not to produce babies.

In this procedure, tissue is taken from the patient. The nucleus (containing the genetic material) is removed out of one of the cells from this tissue. This nucleus is then injected into an unfertilized egg, the oocyte, which has had its nucleus removed. The new embryo is allowed to develop, but just to the blastocyst stage. The embryo is then broken apart, and stem cells are taken from this embryo. The stem cells are cultured to grow sufficient numbers, and then injected into the patient.

Proponents of this technique claim that therapeutic cloning is not unethical because a new person is not produced, although a "potential" person is. Let's think about this for a minute. If we regard the beginning of human life as fertilization, it is true that this step does not occur in cloning. However, once implanted into the uterus, this "clump of cells" will develop into a baby, so a human

being must already have been created. Here we must redefine the beginning of that life, but we can draw parallels to the normal situation. In this case I would say that the beginning of life occurs when the full complement of genes exists in the environment in which it can develop, that is, in the environment of an egg cell.

What would happen if therapeutic cloning were to become commonplace? We can conjure up horrific images of organ farms, but the more likely scenario would be to generate and store away totipotent cells to be used as "spare parts" if the need arose. If needed, the cells could be grown up again and used for treatment. However, I feel personally that this technology will not develop much further, partly due to the poor success rate and ethical problems of cloning procedures, and partly due to the promise of the better development of adult or umbilical stem cells. For example, although Advanced Cell Technology, a biotechnology company in Worcester, Massachusetts, has for the past couple of years been trying to clone human embryos, they have not succeeded in developing these to the blastocyst stage. Thus these embryos cannot be used as a source of stem cells (Advanced Cell Technology 2001).

The Legal Context

What are the present laws in Canada and the U.S.A. governing this new technology? As you have probably seen in the news, there are not many definitive laws yet that apply specifically to cloning and stem cells, but legislation is being drafted both in Canada and the U.S.A. to address the situation.

In Canada, human cloning is illegal. According to a discussion paper put out by the Canadian Institutes of Health Research (Rossant et al. 2001) which proposes legislation on this

area, it is legal at present to carry out research on human embryos up to 14 days after conception. The age of 14 days was chosen because by that time the embryo has developed to a point where a "body" is present, which can be distinguished from the other tissues that will not form the embryo. These embryos are available from in vitro fertilization clinics that have "spare" embryos stored away. It is illegal to create such embryos specifically for research. Any research involving human embryos must be approved by the ethics board of the institution in which that research is being carried out, and such an ethics board is not yet likely to approve the use of the embryos for cloning.

There is a moratorium on the production of human stem cells in Canada until legislation is in place. Such legislation is being drafted but will not likely be in place until late 2002.

In the U.S.A., the situation is different. There is a distinction between what is legal for government funded and privately funded research to do. For example, federally funded research does not allow the formation of human embryos specifically for research, but it is still legal if funded by other means. This is an important distinction because there are many well-funded biotechnology companies such as Advanced Cell Technology that carry out private research. Indeed, the formation of human embryos specifically with the intent of generating stem cells has been going on for the past several years.

As for federally funded research, in August, President Bush made a compromise decision, which stated that there would be no federal funding for the destruction of human embryos to make stem cell lines (Bush 2001). However, federal funding could support research on pre-existing stem cell lines. This means that new embryonic stem cell lines can still be made through private funding. I am concerned that if private companies make better and

more "successful" embryonic stem cells, the pressure will be on Bush or his successor to change the law and allow these too to be used. In a sense Bush has condoned the actions of those people who destroyed embryos to make stem cell lines by allowing federal funding of research on those cell lines, but on the other hand he is also blocking government funding of the destruction of more embryos.

Legislation has been proposed in the U.S.A. that would prohibit human cloning, including therapeutic cloning, but it has not yet passed. It is likely that intense lobbying on the part of certain special interest groups will delay the implementation of this legislation as long as possible.

Human Genetic Engineering

This lecture series also included a talk on genetic engineering of the food we eat. Such engineering is common in plant agriculture and is on the horizon for the animals we eat as well. It is already routinely done in the research laboratory on animals such as fruit flies and mice. When we think of genetic engineering in humans, we need to distinguish two types of genetic engineering or gene therapy, namely Somatic Cell gene therapy and Germ Line gene therapy.

Somatic Cell gene therapy involves genetic manipulation of some of the body cells ("soma "means "body"). This could be to treat a genetic defect in humans like cystic fibrosis or to fight some diseases like leukemia. I would like to make two comments on Somatic Cell gene therapy. Firstly, I don't see this as fundamentally any different from someone who is taking medication for the rest of his or her life to treat a chronic condition, and thus I don't see it as ethically unacceptable. Secondly, the

techniques that have been tried have not met with much success. Genetic manipulation of blood stem cells can be done outside the body and subsequently reinjected into the bone marrow. However, there are only a few conditions that can be treated in this way. Gene delivery to other tissues in the body, for example the lungs, have not been efficient enough to have any beneficial effect, and have usually met with complications.

Various techniques of Germ Line genetic engineering are used in the lab to generate transgenic mice. One technique is to inject genes directly into the zygote, or fertilized egg. These genes may be incorporated into the genetic material of the zygote and therefore into the developing embryo. This is called Germ Line genetic engineering because the genes will also be incorporated into the animal's ovaries or testes, and therefore will be passed along in the germ line from parent to offspring. Thus not only is the "patient" (the mouse zygote) "treated," but all the descendants of that mouse are as well.

While it may be possible to do this technique in humans, there are significant ethical reasons why we should not do so, even if the intent is to repair a defective gene. Such manipulation of the zygote puts it at great risk, and embryos need to be screened to see if the gene was incorporated correctly and will work. Since this technique is at present quite inefficient, many human embryos would be discarded. Secondly, while it may be morally defensible to "correct" a genetic defect, at what point are we saving a life, versus expressing our genetic preferences? In many cases the gene mutation that caused the condition can be determined, but in other cases it's not so clear. For these reasons, I do not anticipate this kind of genetic engineering taking place in the foreseeable future.

What is more likely to take place than Germ Line genetic engineering is the genetic screening of embryos. It is possible to

create an embryo by in vitro fertilization, remove a single cell at the eight-cell stage, and test it for the presence of any gene sequence, like a mutated gene, or even the sex. If the embryo passes the test, it can be implanted into the mother, otherwise it will be discarded. As scientists identify more and more such gene mutations, particularly with the ongoing deciphering of the human genetic code (or genome), more couples may opt for this type of genetic screening. Indeed, such procedures are at present legal in both Canada and the U.S.A.

Much hype has been made of the sequencing of the human genome, but this must be placed in the proper perspective. It is an impressive technological feat to identify virtually all the genes present in our DNA, but it is another matter entirely to determine the function of all these genes. This is progressing at a much slower pace, particularly when we begin to appreciate the complexity of the regulation of these genes and the interactions of the proteins encoded by them. Nevertheless, it is becoming more frequent that a specific medical condition can be correlated with a specific gene mutation.

Thus the knowledge obtained by the sequencing of the human genome can be beneficial in the identification of the cause and possible treatment of many diseases, but there is also the potential for great harm in the context of the genetic screening of embryos. In particular, since many gene mutations do not guarantee but only increase the probability of developing a particular disease, using the presence of such a mutation as a reason not to implant the embryo would result in the death of many embryos which would have developed normally. Another undesirable use of one's genetic information would be by insurance companies or prospective employers, which would use this information as a basis to decide whether or not to grant life insurance or employment to an

individual. Finally, the overemphasis of the importance of one's genetic makeup leads to a "genes are everything" mentality, or a genetic determinism. We are much more than the genes we inherit from our parents.

When Does Life Begin?

There are three positions on when human life begins. One position is that it begins at conception. This is when the genetic material of the embryo becomes distinct from the mother because it contains genes from the father. A second position is that human life begins at 14 days, when a single body can be distinguished. It can no longer divide in two to make twins. A third position is that when brain waves begin, human life begins, which is analogous to the end of life being when brain waves end.

My position is the first one: human life begins at conception. It is true that the early embryo is a "clump of cells" and does not look like a baby, but it is distinct from other clumps of cells, and its development to a newborn baby is a gradual and normal process. As I said earlier, the only clear discontinuity is the genetic one, which occurs at conception.

What kind of guidance can we get from God's Word? Does the Bible tell us when human life actually begins? We know from various texts that the Biblical writers understood that we are human from the time of conception onwards. Think of only two passages. In Psalm 51:5, David says that "my mother conceived *me*." At the very beginning of his life, at the point of conception, that was David and not just a clump of cells (see also, e.g., Psalm 139). When the Saviour's birth was announced, the angel said to Mary that "the holy one that is *conceived* shall be called the Son of God" (literal translation of Luke 1:35b). As Dr. Nigel Cameron has

pointed out, if we look at the incarnation of Jesus Christ, we see that the miracle that occurred was at his conception, not his birth (Cameron 1992, 174). The above clearly demonstrates that the biblical understanding is that life begins at conception.

Underlying Motives

What about the ethics of in vitro fertilization and other reproductive technologies? It is possible to fertilize only a few eggs and implant all of them to avoid the formation and destruction of "surplus" embryos. This practice occurs in Germany and Austria which have strict laws on reproductive technologies.

However, a major danger of this technology is that the fragile and vulnerable beginnings of our lives, which normally occur in the safe confines of the mother's body and follow the divinely ordained process of embryonic development, now occur in a plastic dish. This fragile beginning of life will require human intervention to *save* that life by implanting the embryo into the mother's uterus. This makes it far too easy simply to discard the product of conception by in vitro fertilization and disregard its status as a human being created in the image of God.

Further, the creation of a new human life, which was intended by God to occur with only two "participants," the husband and wife, now requires the involvement of several other people, namely those working in the fertility clinic.

But there is also a broader question that needs to be asked in the use of any of this technology, a question that is not always so easy to answer. All our actions must be guided by what the Westminster Shorter Catechism calls the chief end of man, namely, "... to glorify God and enjoy Him forever." When we are developing and using such technologies, is it our motive to glorify

and enjoy God? If not, we need to reconsider the appropriateness of our actions. Every action we take must be judged whether it honors God or ourselves. When it comes to human cloning I think the answer is obvious, but we also need to think hard about in vitro fertilization.

Let us consider the motivations behind the medical technology, including in vitro fertilization. One motive is healing. This is certainly sanctioned by God and indeed was an important part of Jesus' ministry on earth. Sin brings physical as well as spiritual suffering, and part of our mandate on earth is to alleviate such suffering where possible. Of course, healing cannot take place at the expense of the lives of human embryos.

Another, less straightforward motivation to consider is reproduction. Certainly part of our creation mandate is to be fruitful and increase in number. And so efforts to treat infertility are not wrong in themselves. However, in the New Testament era, this mandate can also be obeyed by bringing children into the covenant community through adoption. Here we must consider the motive. Is it our intention to have our (genetically) *own* children, or to maintain and increase Christ's church?

In Conclusion

To sum up, we are living in a time when advances in medical technology allow us to manipulate the very beginning of our lives. As with any powerful technology, the potential for great good is balanced by the potential for great evil. Stem cells provide promise to treat and cure diseases, but at what cost? Even more frightening is our ability to create and manipulate human embryos in a culture dish. This technique undermines our appreciation of these embryos as created in the image of God.

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