Conquering Aging with Cloning

Life Extension Interviews **Michael West** on new breakthroughs in anti-aging cloning research


Dr. Michael West, President and CEO of Advanced Cell Technology - Photo by Matthew Pace

Cloning: The word sounds like science fiction. But cloning is now science fact for many species, and it could hold the answer for the majority of problems of aging humans. Recent advances in cloning have come with remarkable speed, but doubts about their applicability to aging have remained. Now, in a major new paper published in the April 28, 2000 issue of the journal *Science* (1), a group led by Dr. Michael West has reported what may be the most revolutionary advance in cloning research so far. They have found that cloning can totally reverse cellular aging. To give you the inside story of this breakthrough, and on how it fits in with prospects for using cloning to intervene in aging, Gregory Fahy, Ph.D. and Saul Kent, President and founder of the Life Extension Foundation, interviewed Dr. West by telephone on March 18th, 2000. Dr. West is the founder of Geron. He is currently President and CEO of Advanced Cell Technology in Worcester, Massachusetts, where the research reported in *Science* was conducted.

Life Extension (LEF): Let's start at the beginning. Given that you left Geron to pursue cloning opportunities with Advanced Cell Technology (ACT), cloning obviously must be pretty important. But what is cloning?

Mike West: Cloning, as it is used in popular language, means the process we call nuclear transfer, which is an asexual way of reproducing an animal. Rather than using a sperm and an egg cell and getting a genetic mix between two animals, making a unique offspring, cloning uses an egg cell which is stripped of its DNA and a cell from the body of an existing animal. That body (somatic) cell is then placed into the egg cell.

LEF: The whole cell is placed in the egg cell?

West: Yes. This is the step we call nuclear transfer.

LEF: Even though it's more than the nucleus.

West: Yes. What we typically do is take the whole somatic cell and transfer it into an egg cell whose DNA has been removed. The result is a cell that has all of the DNA from an existing animal, so the resulting embryo and then, eventually, the animal is genetically identical to the original animal from which the cell was taken, unlike normal sexual reproduction, which leads to a unique new animal. In a sense it is being born again. It's a rebirth of a genetically identical copy of the original animal (2,3).

LEF: Are there different ways of doing cloning? Does it matter what the source of the cells is for example?

West: The technology has really only been used in a somewhat widespread manner over the last five years or so. So there hasn't been, to my knowledge, a complete survey of all of the different kinds of cells in the body from which we could clone an animal. But we do know that it is possible to clone an animal from cells that are usually easily accessible, such as skin cells or mucosal epithelial cells from the inside of the cheek.

LEF: How could cloning impact the field of anti-aging medicine?

West: Well, in the course of human aging, we have damage to the tissues and the cells in our body, not completely unlike the damage you see to your automobile over time. So, just like your carburetor needs to be replaced at some point, or your spark plugs need to be replaced, just through wear and tear you have organs that need to be replaced. I guess a striking example would be something like the loss of a tooth because of falling off a bicycle in a cross country race. Or a skin burn or other trauma. Also, of course, you can have an infectious disease, like a kidney infection which can damage the kidneys. Since the kidneys will not regenerate, they need to be replaced. So over the course of aging, we may need to have cells and/or tissues and organs replaced.

LEF: What is therapeutic human cloning?

West: Therapeutic human cloning is cloning for the possibility of recreating young cells and tissues (potentially of any kind) genetically identical to the person who needs them in order to replace worn out cells and tissues (4-7).

LEF: I think we need to clarify that when you are talking about therapeutic human cloning, we are now changing the definition of cloning that you gave us earlier. We are not talking about growing say a 12-year-old child and then taking the organs out of that child in order to replace old tissues in an adult, right?

West: Right. What we are proposing as an ethical and moral use of cloning technology in the arena of human medicine is the creation of microscopic balls of cells, called blastocysts. These are aggregates of about 100 cells that exist up to about 14 days of development. At 14 days, small aggregations of cells begin to individualize. By that, we mean the cells begin to become the various cells and tissues of the body, or that they've committed themselves to become an individual human being. Prior to day 14, the small ball of cells can still become two individual human beings. They can become identical twins, and indeed that is how identical twins form: the small ball of cells divides into two. So prior to day 14, this small ball of cells has not individualized, it has not decided to become one individual or two individuals.

LEF: Or even any particular part of any individual.

West: Yes. There is no skin, there is no blood, there is no bone, there is no tissue of any kind. So, because they have not individualized, they have not committed to becoming a person. And because there is no person there, and there are no differentiated cells of any kind, the blastocyst is often called a pre-embryo to distinguish it from an embryo which is committed to becoming a given individual. And because of that primitive state of the cells, the majority of ethicists have agreed that the creation of such an aggregate of cells to benefit people who are sick and in need of therapy would be a good and moral use of technology.

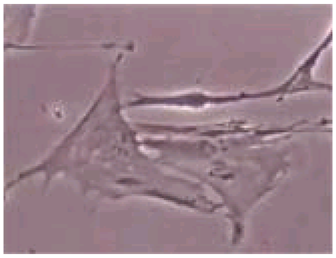
So what we envision is that the cloning step, the nuclear transfer step, is a bit like a time machine. We believe we can take a cell from a patient, even from a very old patient, and put it back into an egg cell, and that egg cell would be like a time machine, taking what was once a skin cell back in time, making it young again and erasing its memory of what it was, taking it back to the state of complete power, or as we say, "totipotency," such that the cell can then become any cell in the body. So once we've taken the cell back in time, and we have this small little ball of cells that can form anything, we can go in two directions. First, we could implant this small ball of cells into a uterus, and it could become a human being, or two human beings, forming identical twins. That would be reproductive cloning of a human being. The second path, which is the path that we are advocating, would be to use the cells to create specific cell types that a particular patient needs. So if the patient has Parkinson's Disease, rather than creating a human being, we would create just the dopaminergic neurons that they have lost, the loss of which is causing their Parkinsonian symptoms (8).

LEF: But the pre-embryo, in and of itself, doesn't spontaneously form wanted tissues. You would have to coax the pre-embryo cells to turn into the types of cells you want to form. Could you do that in tissue culture?

West: Yes. We believe that all of this could be done in tissue culture, growing individual cells, without creating a cloned human being.

LEF: What are embryonic stem cells?

West: Technically, an embryonic stem cell is a cultured inner cell mass. So the blastocyst is a little ball of cells, and inside it is a cluster of cells called the inner cell mass, and surrounding them is a shell of cells called the trophectoderm. The trophectoderm will become the placenta, and the inner cell mass will become the entire animal or, in the case of humans, the entire human being. The inner cell mass cells are totipotent. They have complete power. And because they have not yet committed to either becoming the germ line or the body (soma), they have not yet committed to the mortality of the soma, so they still have the immortality of the germ line. As you know, germ line cells have the ability of proliferating indefinitely, and that is why the species is immortal. We keep making babies generation after generation, so these cells are in this immortal germ line in a state of total power. When they are grown in the dish, they are called embryonic stem cells.



Young and old cells show dramatic differences. Cloning can convert old cells into young cells.

LEF: Has anyone taken these embryonic stem cells and turned them into specialized cells in tissue culture?

West: Yes.

LEF: Has this been published?

West: The first demonstration that human embryonic stem cells could be grown was published in the collaboration that I set up while I was at Geron with James Thomson at the University of Wisconsin at Madison (9), and then also in a collaboration with John Gearhart at Johns Hopkins University Medical School (10). That was in the Fall of 1998.

LEF: And what was done in this study, exactly?

West: It was the first time human embryonic stem cells were ever grown in vitro ("in the dish"). Also in this publication was evidence that they could be shown to differentiate into skin, neurons, heart muscle cells, blood cells, and all of the many different kinds of cells in the body.

LEF: But in that case, was the differentiation random, or was it directed in some way?

West: The initial work, of course, was random. The cells were either just allowed to haphazardly differentiate in the dish, or they were injected into mice which had an impaired immune system. Since the mice could not reject the human tissue inside them, the human cells grew into what is called a teratoma, which is a conglomeration of different kinds of cells and tissues.

LEF: We recently met a scientist who said he was able to transform skin cells into neurons. Our impression was that they weren't embryonic skin cells.

West: They were probably adult stem cells such as mesenchymal stem cells.

LEF: So to summarize what you've said, basically you can take a totipotent cell and instead of letting it commit itself to form of an individual, you can take that cell and, at least in principle, direct it to become any type of cell. As you said, you can make brain cells to treat Parkinson's disease or perhaps skin cells to treat facial aging, that sort of thing.

West: I think that is an accurate statement. A good example was reported just in the last couple of weeks or so. There was a paper where mouse embryonic stem cells were differentiated into beta islet cells. That is one of the more difficult examples. In normal embryological development, you are pretty far along before you get the gut, and then the gut evaginates into a pancreas, and then out of that pancreatic tissue a beta cell finally forms.

LEF: Yes, that is impressive.

West: It would be much easier to get, you know, a cardiac myocyte, which differentiates very early in embryogenesis, or neurons, or skin cells, but nevertheless they were able to develop embryonic stem cells into beta cells, isolate the beta cells in relatively pure form, and put them into a mouse and cure diabetes (11,12).

LEF: That's fabulous!

West: Yes, and I think the demonstration that you could go and do such a difficult project is good evidence that there are going to be many, many applications of this technology.

LEF: Are you doing any work in the area of directing the differentiation of cells in your company?

West: Yes, though the majority of the work at Advanced Cell Technology has been focused on taking the cells back in time. It is relatively easy to take a cell at the beginning of life, one of these totipotent stem cells, and steer its development through the differentiated lineages, like the branches of the tree, because that's the normal path of development. What's almost miraculous is that you can take a differentiated cell and take it back to a totipotent state, because that's taking differentiation in reverse. It's a bit like if I were to tell you that I had taken a baseball bat and hit a ceramic vase and broken it into a million pieces on the floor, and then that I could, through a magic wand, have that go in reverse and have all of the pieces of the vase fly together and fuse back into a vase and then go back up on the table top, like reversing a video tape. That would be near miraculous. And to have development go in reverse, which it never does in nature, through cloning is pretty amazing, and that's why the scientific community was so amazed that you could actually clone an animal from a body cell. But what I think is the second level of amazement is the fact that not only does the development go in reverse, but the animal is actually made young again in the process, and I think that's what impressed us even more.

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> **LEF:** This takes us right to the paper that has just come out in *Science* (1). Please explain what was different about what you observed and how it relates to the practicality of using therapeutic human cloning.

West: Well, the story really begins with efforts to find cells that could be turned into cells that are used to treat age-related disease, so, for example, a patient who has lost heart tissue because of a heart attack and needs new heart tissue could receive tissue to restore normal heart function. My thought was that if we went back to embryonic stem cells, the mother of all cells in the body, we could potentially make anything for the patient, because these cells have the power to become any cell in the body. And because they are still in the immortal germ line, the reproductive lineage of cells, any cells you made from them would be young. The problem was, however, that the embryonic stem cells we now have growing in laboratories around the world are not you, so any cells that we made from them would be rejected by your body as foreign cells. So I set out to try to find a way of making an embryonic stem cell identical to the patient's cells by cloning, creating them just like you would if we were going to clone a human being, but instead of cloning a human being, we would make embryonic stem cells.

After I left Geron, they evidently agreed that therapeutic cloning was the way to go, and they set up the collaboration with Ian Wilmut, the man who cloned Dolly at the Roslin Institute. Dolly came from a sheep that I think was about six years' of age, from a cell grown in the laboratory from breast tissue. So obviously they named Dolly after Dolly Parton.

In 1999, they announced that cloning did not reset the clock of aging in cells (13). In other words, they claimed that Dolly is "a sheep in lamb's clothing." That she is older than she appears to be. Ian measured the clock of aging, the telomeres, in the blood cells of Dolly. The telomeres are like a burning fuse. They measure how many cell doublings have passed and the life span of these cells. And he said the telomeres of Dolly, or the cellular age of Dolly, was quite old. Her telomeres were shorter than would be expected for normal sheep of the same age. His data were very preliminary, and it has been difficult to pin down, but I guess the best estimate is that Dolly appeared to be older than six years of age, even though she was in reality only one year at the time her cells were analyzed.

LEF: I think everybody agrees that this is a burning issue.

West: Not only for animal cloning. As you know, there is a theory that human progeria is a condition of premature telomere shortening. This is not completely documented, but it is a theory that is out there. And no one would want to have all of these cloned animals that were made for agriculture, or as seeing eye dogs or whatever, age prematurely.

LEF: Well, if you really wanted to have something like a cloned cow, presumably you would want to clone the clone and then clone the clone of the clone and so on, which wouldn't work if the clones get older and older with each generation.

West: Correct. But for human therapeutic cloning, the condition is even more profound, because many of the people who need transplantable cells and tissues are elderly. So if we had an 80- or 90-year-old individual who had aplastic anemia and we needed to replace blood cells, or who had cirrhosis of the liver and you needed to make new liver tissue or heart tissue for example, obviously it would not be optimum to replace them by therapeutic cloning with old, worn out cells and tissues.

LEF: So, essentially, you would end up giving old tissues back to the old person.

Healthy young calves at five months of age, with telomeres longer than normal, all produced by cloning from highly senescent skin cells. Their nicknames are Lily, Daffodil, Crocus, Forsythia and Rose

West: Right. So we decided to do a very careful study of what happens to this clock of cell aging, the telomere, in the course of cloning. In our case, we used some novel approaches to cloning. Our technique differs considerably from the technique the Roslin Institute used to clone Dolly, for instance.

An additional difference is that we cloned from cells at the ends of their life spans, cells which we grew completely to old age in the dish. The cells grown old in the dish had shortened telomeres, and indeed we believe the reason cells grow old and stop dividing in the dish is because the telomeres become critically shortened, the fuse burns down. We took these senescent cells and we put them back in this time machine called nuclear transfer. What we observed and reported in the paper in *Science* is that a gene for the enzyme telomerase that normally keeps our reproductive cells immortal, was activated shortly after the transfer. The level of telomerase was increased far beyond the levels you see in some other immortal cells, such as cancer cells. The telomeres were extended in the same way that a key can be used to wind an old antique clock. Telomerase rewound that clock and interestingly, in our experiments, wound the clock beyond the normal starting point the cells had at the beginning of life, so the telomeres were extended beyond what a normal animal would be born with.

LEF: Wow!

West: So we then studied what happened to the cells that resulted from that cloned embryo, and we saw that their life span was longer than a normal cow cells' life span. Also, the animals that resulted from this work appeared to be healthy, even though they were cloned from senescent cells, cells that could no longer proliferate. The animals were born, the animals appear to be healthy, and the animals have telomeres longer than a normal animal of the same age, just the opposite of what Ian Wilmut reported. Will this lead to these animals having a longer life span than normal animals? That remains to be seen. We do not know.

LEF: How can you be sure that the cells that gave rise to viable clones were really senescent cells, and not rare, contaminating young cells?

West: We specifically addressed that issue. First, the entire population of cells was able to grow for less than three doublings, so the cells were within three doublings from senescence. Second, we grew individual cells from that population. In the paper we show data on about 300 cells that were individually studied, and out of these 300 cells, not one of them would go more than 3 more doublings. Nevertheless, we had the same efficiency of cloning animals from the senescent cells as we did with an entire population of cells that were young.

LEF: That's fantastic.

West: So it's a simple matter of statistical analysis to demonstrate that it is very improbable that we had a very young cell in the dish from which we were cloning these animals.

LEF: It sounds extremely improbable. But did you also attempt to clone from an old animal, or just from cells that were old by cell culture standards?

West: We did not. However, Mark Westhusin's lab, at Texas A&M University, has done it. Mark, incidentally, is participating in a project to clone a dog, the Missyplicity Project (the dog's name is Missy). Mark has also been involved in cattle cloning. He managed to clone a steer that was 21 years old, which is an old animal. There was evidently a piece of skin that was removed from the animal and frozen away. Years later, and long after the steer was gone, it was remembered how great an animal it was. The original animal was called "Chance." They thawed some of the cells from this 21-year-old steer, years after it had died, and managed to clone it. They named the new animal "Second Chance," and again, it appears to be normal.

LEF: Did they look at telomere length in the cells of Second Chance?

West: I believe they have, and I believe that in Second Chance the telomeres were shortened, consistent with the Dolly results.

LEF: So we need to get a clear idea of why your method allowed for a reversal of the cellular aging clock, and why the method used by Westhusin and by Ian Wilmut did not.

West: I don't think we want to elaborate on that at this time.

LEF: Could you at least confirm that the cloning technique that Wilmut used was based upon cloning from quiescent (non-dividing) cells, and that the cloning technique that ACT owns (14) is based upon cloning from non-quiescent (dividing) cells?

West: Sure. The patent has issued (15). Second Chance, as far as I know, was cloned from a quiescent cell.

LEF: Okay, so both of the quiescent-cell nuclear transfer experiments led to a negative result (no rejuvenation), whereas one infers that perhaps your cells were not quiescent.

West: Oh, ours were definitely not quiescent because, as you recall, senescent cells block late in the G1 phase of the cell cycle near the G1-S boundary, whereas quiescent cells are arrested at early or mid G1.

LEF: In other words, cellular senescence arrests cells in a state that is not defined as "quiescence" even though senescent cells are not actually dividing or able to divide.

West: Yes, senescence is very distinct from quiescence.

LEF: Are you doing or planning to do an experiment using your method to clone from an old animal?

West: Yes, we are. We're expanding out and doing a lot of different kinds of studies with this. But of course the most exciting thing is applying this technology to human medicine and being able to give the patient any kind of tissue that they need as a result of disease, such as heart tissue, kidney failure or whatever. Being able to give them back their own cells which have the full proliferate capacity they were born with, would be a real boon to medicine.

LEF: It would be terrific. How much of aging do you think could be addressed with that approach?

West: I think theoretically a very large part of aging. One can think of an extreme example, I guess maybe a thought experiment. One could imagine creating in vitro, in a laboratory, virtually all of the components of the human body by cloning, making you a new heart, a new kidney, new lungs, new skin and replacing virtually your entire body in parts or in conglomerate. Cloned animals, even when they are made from very old animals, appear to be young and are able to reproduce. There is no evidence of premature aging. There is no reason we couldn't find ways of applying this technology to transplant cloned young cells and tissues into an aged person.

New stem cell technologies actually offer the promise of distributing new young cells throughout the body. One could imagine, for instance, the transplantation of mesenchymal stem cells into the bone marrow. Those cells have been shown to travel throughout the body to seed muscle tissues with new muscle cells, bone with new bone cells and so on.

Persephone, an older clone made from a senescent cell, still going strong at the age of 10 months.

LEF: So in other words, you would inject a particular kind of cell that is not muscle and not bone, and it would then find places where there is a deficiency in muscle cells and bone cells, somehow sensing this deficiency, then turning into muscle or bone cells to overcome the deficiency?

West: Correct. That is all published data (16,17). These technologies could potentially allow you to restore back into aging patients stem cells that are the patients' own cells and would not be rejected, which have their whole life span ahead of them, and have the potential of distributing themselves throughout the body, seeding cells and tissues with new, young cells to replace those that are worn out. There are potentially many applications for diseases that are not normally thought of as a part of aging. One could think of muscular dystrophy as an example, or even diseases such as AIDS. We think both are examples of cells reaching the end of their life span in a premature manner because of an accelerated turnover of cells.

LEF: Are you also talking about eventually growing organs in culture, not just cells, but organs that consist of several different types of cells?

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West: The most difficult part, the nearly unthinkable has already been done. We know how to take a patient's cell, an old patient's skin cell, for example, back to the beginning of life, both in terms of its differentiated state and its replicative life span. That nearly miraculous event is now practical and achievable for human medicine. The concept of taking these resulting stem cells and turning them into heart muscle, bone, cartilage, skin or blood cells, is straightforward engineering. It's like saying that once we have electronics and we have the ability of making metal alloys and we understand basic Newtonian physics, we can go to the moon. It's simply a matter of engineering. In the same way, now that we have these technologies in our hands, like the ability to reprogram an old cell back to the beginning of life, applying them to medicine is simple engineering. It's a straightforward use of technology. This certainly doesn't mean that there aren't going to be many bumps in the road, a lot of hurdles in terms of regulatory approvals and finding the financial resources to move all of these projects forward, but it should be relatively straightforward engineering. We know how to get there.

LEF: Do you think there would be major problems getting, let's say, a cloned therapeutic cell line or cell type through the FDA approval process?

West: Well, we don't really know. What we do have is a fair amount of input from the National Bioethics Advisory Commission; the position of Harold Varmus, Director of the NIH; and of course from the scientific community. There is broad support for the use of cloning technology to make stem cells and to apply these cells to the problems of the human condition. What is not clear is what would be the regulatory mechanisms from the Food and Drug Administration to allow these technologies to move forward. To my knowledge, that has not yet been directly addressed or answered by the FDA.

Ping Jiang, Department of Molecular Development, Advanced Cell Technology - Photo by Matthew Pace

LEF: What would be the full impact of this sort of technology if it could be brought into full use?

West: Well about half of all health care expenditures in the United States, now upwards of 500 billion dollars a year, can be attributed to transplantation-related costs. And given an aging population, the numbers are expected to increase. It is important, of course, to point out that a lot of current health care expenditures are for conditions not treated by transplantation. A salient example would be diabetes. We don't have the ability to cure diabetes by replacing the beta cells that are lost and cause type 1 juvenile onset diabetes, so we give insulin instead, which is not a cure for the disease. As another example, Parkinson's disease is typically not treated by replacing the neurons that are lost and whose loss causes the disease, it is treated instead with L-DOPA. So what would be potentially useful would be to find a way of meeting this already significantly large need, representing upwards of half of all health care expenditures, with transplantable cells and tissues that are identical to the patient, and would not require immunosuppressive therapy. Therapeutic human cloning could enable us to meet this need.

LEF: Would replacement cells have to be human cells, or could they be cells from other species?

West: The whole field of xenotransplantation, obtaining tissue from other species, is increasingly promising with the recent cloning of the pig for instance. Cloning allows us to create sophisticated genetic modifications in animals, making those tissues potentially acceptable into patients. What therapeutic cloning, making tissues and organs directly from the patient's own cells, offers is perhaps the ultimate solution to the problem of transplant rejection. If we could make it easily available to a broad array of people, it has the potential to make xenotransplantation unnecessary. Why would you want a pig kidney if you could have your own kidney back?

LEF: Until the experiment is actually done, is it still possible to question whether genetically identical tissue would truly be immune from rejection? Might there be something during development that could trigger a later immune response?

West: Well, we do know, of course, the work performed nearly 40 years ago by Joseph Murray, who performed the first transplantation of tissue between identical twins. Those tissues were accepted long-term with no evidence of rejection. And, of course, a clone is essentially an identical twin, just separated in time.

LEF: One of the things that happens with aging is not just a wearing out of cells and tissues, but a change in the hormonal environment that affects tissue and cell function. One often-cited example is the diminution of the secretion of growth hormone with aging. This may be due to damaged cells in the base of the brain which could be replaced, but it may be due to some sort of aging clock. If it is the latter, do you see the possibility of cloning your own body cells with genetic modifications that could then be transplanted into the body to change that type of aging program?

West: Well, there certainly are such possibilities. The beauty of cloning technologies is that everything starts with a single cell. Whether it be a skin cell or a blood cell from the patient, from that single cell, stem cells would be created that would then be turned into whatever cell or even complex tissue the patient needed. Single cells can be genetically engineered in the laboratory. DNA can be added or even taken away from cells grown in a dish. The most sophisticated of these technologies are called gene targeting technologies, where we could actually go in and edit DNA in a living cell similar to the way words are altered on a word processing program in a computer. We could go in and change a given letter or indeed a whole paragraph of text. Technologies exist to do gene targeting in cultured cells, removing DNA, even changing DNA down to a single nucleotide. These technologies are relatively inefficient. Nevertheless, because we're cloning from a single cell, we could identify a cell in the dish that has undergone a specific type of genetic engineering and then create all resulting cells and tissues from it. What that means is, it could be possible in the future for us to genetically engineer a patient's cell to any desired degree of sophistication, including inserting genes from other species, eliminating genes, indeed engineering the very blueprint of life itself to any degree that we wish, and then creating any cell or tissue in the body, indeed even complex tissues, from that original cell. We can envision cells that self-assemble into intestines, for instance, complete in all of its architecture, all of the cells of that intestine being genetically engineered in a very sophisticated manner. This, or course, is a whole quantum leap forward from anything that is currently available. With the unlocking of the human genome, understanding the function of all of the human genes, the amount of creativity that can be brought to bear, the amount of engineering is mind boggling. We could conceivably make thousands of new inventions and new ways of treating diseases.

LEF: What about the cells that comprise our identity and our memories? Most cells are interchangeable, but in this case, a brand new cell or a group of cells would not contain the information originally there. How do you deal with that?

West: I think one of the strongest arguments for cloning, beyond the obvious issue of preventing tissue rejection, is the issue of identity. One can imagine in a world without human therapeutic cloning, engineering cow heart valves, pig kidneys and pig hearts. As you know, there are people walking around today with pig neurons in their brains for Parkinson's Disease. One can imagine ones' self as a patchwork of tissues from animals and nieces and nephews, and one wonders at some point, are we in a sense becoming someone else? The beauty of therapeutic cloning is that we are talking about replacing the body with its own genotype, with cells and tissues that have the same genetic blueprint that we were born with. Admittedly, inasmuch as we do genetic modifications or alterations of that blueprint, and as we seed the body with genetically engineered stem cells, which diffusely spread new cells throughout the tissues of our bodies, in a profound sense, we would be changing who we are. But I think therapeutic cloning offers the best approach to maintaining ones' identity in the face of a very clear need for cell and tissue transplantation.

LEF: That doesn't answer the question about those few cells that encode memory and identity.

West: As you know, cells within the brain are turning over to an unexpected degree as well. Stem cells planted in the brain can also distribute themselves throughout the brain. It is possible to imagine technologies that would seed new embryonic stem cells into the brain that would graft into existing tissue. What this would mean in terms of memory and the preservation of psychic identity remains to be determined. We simply don't know at this time.

LEF: Might the infusion of new cells rejuvenate cells that are dying, or aging or however you want to describe it?

West: We simply don't know. I think what we can be optimistic about is that these new technologies should play some role in helping us repair our aged bodies, heart disease, kidney disease or blood cell disorders. How profound a role it would be, and what role it could play in the brain, are currently unanswered questions.

LEF: Also, in the absence of brain diseases, people can maintain their identities and their memory pretty well, even when they may be about to die. There is also a recent paper in the *Proceedings of the National Academy of Sciences* (18) showing reversal of age-associated neuronal atrophy by growth factor gene therapy in aged monkeys, so the ability to generate patient-identical brain cells to carry transgenes into the brain for permanent growth factor therapy of cells that can't be replaced, for example, remains very important in light of this experiment. Perhaps there is no intrinsic need to replace identity-critical cells.

West: Interesting.

LEF: But what about problems? Are there any smoking guns out there? Are there any red flags that have been raised?

West: The one problem which concerns me to some extent is that there are opponents to this technology. The opponents say that they don't like two major things about the technology. The first is that we use the word "embryo" a lot. The second is that we use the word "cloning" way too much. I think this is more of a battle over words than substance.

ACT researchers can inject new life into old cells.
Photo by Matthew Pace

LEF: It may be that the problem is that the technology has rushed ahead of the lexicon. You may need to invent new, more precise terms to avoid these problems.

West: We have been labeled as part of a "culture of death" that wants to destroy primitive human beings for the benefit of existing human beings. I believe these opponents are people who have not carefully thought through the issues. When I have debated them and discussed the actual data, the science, they don't dispute them. What they do instead is revert to demagoguery. In one example, in a recent debate, one of my opponents referred to one of the movies in the "Raiders of the Lost Ark" trilogy, in which a voodoo priest thrusts his fist into the chest of a living man who is tied to a rack, wrenches from his chest his own beating heart, and holds it in front of his failing eyes as he dies. My opponent then said "Dr. West would say, this is the retrieval of stem cells for a humane and moral medical benefit."

But there is a very large difference between this and extracting cells from a microscopic ball of cells that has not individualized. To anyone who understands the facts, there is no individual and therefore no person or even any differentiated cells of any kind. Second, we are talking about saving lives, alleviating human suffering, allowing fathers to go back to their children and children to go back to their families. I think these technologies will be allowed to move forward, but it doesn't help to have people be demagogues and try to raise specters over "Brave New World" scenarios.

LEF: As soon as one person's life is saved, it will probably become a moot point.

West: It is parallel, in many respects, to the adversarial position many people had in regard to in vitro fertilization. The critics stated that it was a "Brave New World" scenario too. They accused the inventors of in vitro fertilization of "playing God," and said that science had gone too far, and that embryos created in the test tube would not have a soul and would be just hulks of human beings without personality. But when people saw Louise Brown, the dimpled babe in the arms of the smiling mother, I think many people thought, well, look, you know, maybe this technology isn't so bad after all and that, in fact, it's pro family.

LEF: Yes. But there are people who believe that life starts at conception, and that intervening even one cell beyond that is immoral and wrong.

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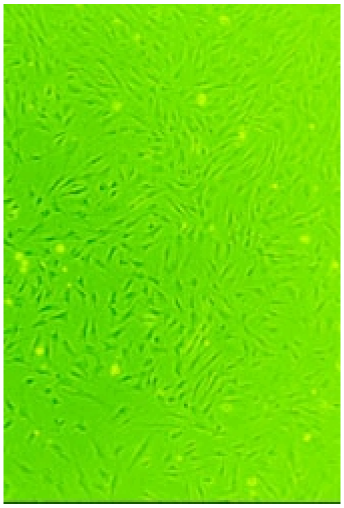

Bovine fibroblast cells extracted from cow cartilage - Photo by Matthew Pace

West: There is nothing in the Bible that you could bring as evidence that life begins with a fertilized egg. It is more an aesthetic preference, the sense that life should begin with a compassionate and loving act of making love, not with some stranger inserting a sperm head through the zona pelucida into an oocyte (egg cell) under a microscope and culturing in a CO2 incubator.

What I think we need to do as a society is to grow up. We are living in an age where it is in our power to do good, to alleviate human suffering, and we need to be mature and use our discoveries to make the world a better place.

LEF: A lot of people have been conceived from rapes, so even when it is done in the "natural" way, it isn't always a product of love.

West: Fair enough. You know, I think the ultimate act of love here is recognizing and responding to the needs of the thousands of people who need kidneys, livers or hearts, yet all too often are left to die while waiting for such tissues.

The Bible says, "to him that knows to do good and does it not, to him it is sin." I don't mean to be necessarily referring to the Bible as my authority, but I think it is important that if we know how to do something good, that we do it and that we do it quickly. One of the criticisms that was made is that the NIH has been proactive, and Health and Human Services and the President have been supportive, but that NIH hasn't actually spent the money to move embryonic stem cell research forward because of pro-life opposition. Every day that goes by, there are more people dying. We published a letter in *Science* advocating that funding move forward on this technology, and we had some 60 Nobel Prize winners signing that letter (19).

LEF: Well, even if the government doesn't support it, it is moving forward anyway. You are moving forward with it, and other companies are moving forward with it.

West: Yes, the private sector is moving, but you know, Advanced Cell Technology has only a couple of dozen people, and there are hundreds of cell types in the body, so we literally need thousands of researchers working on these new technologies, not dozens.

LEF: You said the President has been supportive, but the President was also somewhat alarmed by your announcement in 1998 that you or your colleagues had transferred a human cell nucleus into the enucleated egg cell of a cow. People were very worried about crossing the line between species and so forth. In fact, with therapeutic human cloning to treat aging, getting the donor cell is not a problem, but the recipient cell, the egg cell, has to be obtained somewhere, and getting it from human beings may be difficult. What is your plan to deal with that? Are you contemplating using bovine egg cells for therapeutic human cloning and, if so, are there mitochondrial or other problems or other problems that you would be concerned about?

West: We share, I think, the present concern about mixing DNA across species. There have been reports over the last few years of the transfer of whole human chromosomes into animals such as mice, and there are, I think, ethical concerns about what kind of life forms we might create. What we are talking about doing in cloning across species, with human cells and cow egg cells, is not mixing species. The President simply misinterpreted the discussion. The *New York Times* article he read talked about "minotaurs and mermaids," but what we are proposing is different. Rather than getting human egg cells, which as you point out they are to obtain, we propose using cow egg cells, which are widely available from slaughter houses at a dollar or two per egg, and removing the genetic information from the cow's egg cell, so that we put a human cell into it, we would provide the genetic information from the human nuclear DNA and mitochondrial DNA, which would then completely transform the resulting cells into human cells. We do not believe that any animal DNA would remain, either mitochondrial or nuclear.

LEF: You think that the original mitochondria from the cow would die off?

West: Yes, we do.

LEF: Because they wouldn't have sufficient genetic support from the human nuclear and mitochondrial genes to keep going?

West: Exactly.

LEF: So part of the beauty of injecting an entire cell into the egg of the cow is that all of the human mitochondria go along.

West: Yes. As far as the cow egg cell proteins are concerned. As you know, protein does not make one a cow. Drinking cow's milk does not make you a cow. DNA, the blueprint of life, confers those characteristics, and we're not talking about mixing DNA across species. That was the debate of the 1970s, the recombinant DNA debate, where scientists actually put a moratorium on their own research, because they were mixing, in a very profound way, DNA across species. Those concerns have been addressed, and recombinant DNA is now routine. I think you would be hard pressed to find examples where that technology has done harm, but you can find thousands of examples where recombinant DNA technology has saved lives.

LEF: Can you project a credible timetable for advances in this field? Please also address the issue of what is the best way of accelerating this timetable.

West: The easiest products of cloning are simply cloned animals. Improving the genetics of agricultural animals, cloning search and rescue dogs with improved genetic traits, and so forth.

LEF: What about human therapeutic cloning?

West: On the human therapeutic front, it is likely that the early products are going again to be human therapeutic protein drugs made in cloned transgenic animals. We are now making human medicines in the milk of cloned and genetically engineered cows for instance, such as human serum albumin.

LEF: Is that the main current business of ACT?

West: It's part of our near-term business. Human therapeutic cloning is clearly a long-term project. I think the earliest clinical trials of human cells made by human therapeutic cloning are likely 5-10 years from now at the earliest.

LEF: What are the main bottlenecks? Manpower?

West: Certainly. The major determinant of where we'll be five years from now or ten years from now, really will be a matter of how many people can be put to work on the project.

LEF: You mentioned that Advanced Cell Technology is a very small company. What plans do you have to get investment capital to speed the rate at which your company can proceed in this direction?

West: The first step toward that took place in December of last year, 1999, when we acquired Advanced Cell Technology from its parent, Avian Farms, in Waterville, Maine. We acquired Advanced Cell Technology in a new holding company, called ACT Group, so that we could pursue private financing for the company according to the more traditional model with private rounds of funding, leading to an IPO. For now, ACT remains a privately held company.

LEF: In order for these technologies to be applied in humans, you are going to have to get them through Human Subjects Committees, and you are going to have to have physicians who are willing to infuse the cells into their patients. Can you anticipate what the concerns might be on the part of the physicians?

West: Well, one of the concerns about using an animal egg cell is that we are introducing a potential source of contamination into the equation.

LEF: You mean xenoviruses (viruses transmitted from non-humans to humans) or something like that?

West: Yes. That's one of our reasons for exploring the use of the bovine oocyte, because cows can be cloned so easily by us. It will be possible, we believe, to make oocytes from a herd of genetically identical cloned cows to be used in therapy. Then, at least, we would know, in a very precise manner, the background from which these cells came. I think that would be one of the major concerns. I guess the second concern would likely be dealing with undifferentiated, totipotent cells. Because these cells can become anything, a few of them contaminating the graft could have a rather disastrous effect. You know these cells will self-assemble even into things like teeth, whole teeth. A friend of mine once said that it certainly wouldn't be good if you were transplanting cardiocytes into a heart and a tooth developed in the heart wall, because then the patient would "eat his heart out."

LEF: That's too much!

West: As I said earlier, these are issues of engineering, and we believe there are straightforward means of addressing the issues of potential animal viruses and/or contaminating cells entering the equation. We know how to address those issues.

LEF: Will therapeutic cloning be expensive?

West: We have a real concern about two issues: cost and having time to treat the patient. Cost is one of the reasons we are looking for an alternate source for the egg cells. The nuclear transfer procedure is actually not that labor-intensive, and the cost of materials is small, but the egg cell expense potentially could be large if you had to use human egg cells.

LEF: Right.

West: The second issue is the time to treat the patient. This procedure requires time. The nuclear transfer to create the stem cells will take a couple of weeks. The creation of specialized cells and tissues will take about seven additional weeks. So what we envision for chronic long-term disease, such as Parkinson's Disease, heart failure, kidney failure, and so on, is plenty time to create cells and tissues to help the patient.


ACT's laboratory, where pioneering work to develop cloning techniques to combat aging and disease continues. Photo by Matthew Pace

LEF: Right, they are not going to die suddenly in the middle of the preparation process.

West: But when it comes to acute conditions, it's a different story. For example, with skin burns the patients come in and need immediate treatment. In the future we will likely have cells taken from people and reprogrammed, back to a totipotent state as well as young differentiated cells and tissues kept frozen in waiting for sudden trauma needs.

LEF: So, for example, if somebody is planning ahead, they might have the therapeutic human cloning process begun, let's say, when they are 50, so that when they are 75 have a sudden heart attack, or their doctor tells them they are in danger of a sudden heart attack, they'll have a young healthy copy of their own heart sitting in a bank some place waiting for them (20).

West: I think that's likely where we will be headed in the future. We do that now with things that matter far less to us, like our car. We have parts in waiting. We have a spare tire in the trunk.

LEF: We sure do. Meanwhile, we'll be waiting for news of more progress in this field. Congratulations on your major accomplishment, and thank you for a very informative interview.

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