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Cloning: Who Defends the Offspring?

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Abstract: The history of nuclear transplantation, or cloning, is both intriguing and chilling in its implications. The question of human cloning is such a burning one philosophically, medically, and psychologically for humanity, the unfolding story from 1885 onwards is vital to the understanding that eventually human cloning will become a reality. Someone will submit to its lure legally or illegally because many ethicists are convinced that greed, pride, and vanity are too powerful factors, particularly as ethics and philosophy are increasingly ignored or not taken into consideration in the face of pragmatic, so-called humanitarian goals.

Today no comprehensive literature exists, except Gina Kolata's book *Clone: The Road to Dolly and the Path Ahead*, whom I have followed in summary. Professor Lee Silver, a molecular biologist at Princeton University, has written *Remaking Eden: Cloning and Beyond in a Brave New World*. But, he sees nothing wrong philosophically and rationally with human cloning, including the production of headless humans for organ harvesting. To stay current with the advances underway in molecular biology, embryology, and genetic engineering, one has to scour the printed media on a daily basis which I have done to give an impression of the legal, pre- and perinatal, reproduction, organ donor, and humanitarian issues. Regrettably, hardly any flags have been raised as to what it all will mean for our offspring. They seem to be forgotten in the race to 'improve' humanity.

Zusammenfassung: *Cloning: Wer verteidigt die Nachfahren?* Die Geschichte der Transplantation eines Zellkerns bzw. des Cloning ist in bezug auf ihre Implikationen sowohl verwirrend wie auch erschreckend. Das Problem des Klonens von Menschen ist für die Menschheit philosophisch, medizinisch und psychologisch auf das Tiefste berührend. Es ist eine Geschichte, die sich ab 1885 zu entwickeln beginnt, und für unser Selbstverständnis ist es von zentraler Bedeutung, daß das Klonen von Menschen schließlich Wirklichkeit werden wird. Irgend jemand wird es schließlich legal oder illegal realisieren, da auch viele Ethiker davon überzeugt sind, daß Gier, Stolz und Gedankenlosigkeit zu wirksam sind und zudem noch Ethik und Philosophie in wachsendem Ausmaß unbeachtet bleiben und nicht angesichts praktischer, sogenannter menschlicher Ziele in Betracht gezogen werden.

Heutzutage gibt es keine Übersichtsliteratur außer dem Buch von Gina Kolata „Cloning: Der Weg zu Dolly und darüberhinaus", dem ich im wesentlichen folge. Professor Lee Silver, ein Molekularbiologe von der Universität Princeton, hat das Buch „Die Wiedererschaffung des Paradieses: Klonen und mehr in der schönen neuen Welt" geschrieben. Und er sieht unter philosophischen und rationalen Gesichtspunkten nichts falsches im Klonen von

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Menschen, einschließlich der Produktion von kopflosen Menschen für den Organersatz. Um mit den Fortschritten in der Molekularbiolgie, der Embryologie und der Genetik auf dem laufenden zu bleiben, muß man die täglichen Meldungen in den Zeitungen verfolgen, was ich getan habe, um einen Eindruck von der legalen prä- und perinatalen Reproduktion, den Organspenden und den menschlichen Implikationen, die damit verbunden sind, zu haben. Unglücklicherweise warnt niemand davor, was all dies für unsere Nachkommen bedeuten wird. Sie scheinen in dem Rennen um die „Verbesserung" des Menschen vergessen zu werden.

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Introduction

Nuclear transplantation, or cloning, has been in ascendance since 1885 when August Weismann, a German professor of zoology and anatomy, posited the theory that the genetic information in cells changes, diminishes as a cell differentiates. Upon the formation of the zygote, consisting of two blastomeres, this diminution begins (Kolata 1998a, p. 51).

Today, more than a hundred and twelve years later, Dr. Richard Seed, an itinerant physicist, announced publicly he will raise money to open a commercial human cloning clinic in the Chicago area, or offshore from the United States if prohibited by law. "He said: 'He foresaw as many as 200,000 human clones a year once his process was perfected ... for a price ...'" (Kolata 1998b; Reuters 1998).

As Gina Kolata sets forth in her book *Clone: The Road to Dolly and the Path Ahead* the approaches to science had vastly different interests. Well, over a hundred years ago, scientists were prone to philosophize and look for broad implications of their work set forth in voluminous published papers. Today, scientists are utterly pragmatic in their often necessarily commercialized research sponsored by pharmaceutic and therapeutic companies. Among the media, journalists are relentlessly pursued for front page publication of new discoveries without a thought about the philosophical implications. The middle road is traveled by scientists – notably embryologists, endocrinologists, geneticists, infertility specialists, and others – whose motives are seemingly humanitarian in that they perceive cloning as a necessary good for mankind in combating mortal diseases, for harvesting organs for transplants, and in helping the plight of infertile woman and men who desperately want offspring by any means.

Between 1885 and 1998, two major trends have developed: on the one hand, science and technology have made unprecedented advances which, on the other hand, are less and less scrutinized for their ethical appropriateness and more and more for their pragmatic and monetary value. To quote Bertrand Russell: "Pragmatism is like that warm bath that heats up so imperceptibly that you don't know when to scream" (Kolata 1998a, p. 20). The question is: Who will scream in time for the offspring who are bound to be heard screaming at their progenitors: "Are we but carbon copies? Whose children are we? Were we conceived as experiments?" At this time, the genetic parents of a clone are the man and woman whose sperm and egg formed the person who, in turn was cloned. But the legal parent is the woman who carries the cloned fetus to full term and onto delivery

(Kolata, p. 32). But do these determinations hold when the DNA has been altered during the cloning process? And, what if the cloned child was born in a country were nuclear transplantation is outlawed? To date human cloning is against the law in nineteen European countries (Stolberg 1998). But in the United States, the Senate defeated the bill that sought to ban human cloning on February 11, 1998. A majority of senators were unwilling to enact sweeping restrictions on cloning experimentation because of its potential value to medicine and to bring hope to millions of citizens. However according to *The New York Times*, biotechnology and pharmaceutical companies, as well as twenty-seven Nobel Prize winners lobbied heavily against "legislative language that impedes critical ongoing and potential new research" (Alvarez 1998). It defies the imagination. What could society possibly say to such high-tech children if the nuclear manipulations and procedures were not executed flawlessly? As the history of cloning will illuminate, practice does not guarantee perfection. Ad hoc experimentation leads necessarily to failures before success, if at all, is possible. As we shall see later, deliberate manipulation to create headless 'organ-farms' is in progress.

Materials

"The Road to Dolly" is a fascinating history of trial and error, of dedication and determination, from awesome successes to gruesome failures and mishaps, though the latter are contextually minimized in Gina Kolata's book as she never mentions the cloned headless creatures produced by experiments done since the early 1990s. For the following historical overview of embryology that eventually led to Dolly, I am quoting or summarizing from Kolata's book indicating the relevant page numbers, unless otherwise indicated.

In the late nineteenth century – the days of natural philosophy – developmental biologists were driven by a deep curiosity to understand the mysteries of embryology in both scientific and philosophical terms. As Herman Spemann wrote in 1938: "It is almost as though the cells of the embryo have psyches" (p. 49). From the Greeks and Romans they had accepted the theory of preformationism – the idea that each sperm contained the blue print of a tiny human being (p. 42). These pre-molecular researchers depended largely on the naked eye. They used frogs, toads, and salamanders whose eggs were large in comparison to human ones and developed in the open. Frogs, in particular, spawned large quantities of eggs in their breeding season. They could easily observe the cell division and growth of the embryos.

Weismann, the forefather of cloning, wondered why development was so unidirectional. Why did certain cells become brain or liver cells? He theorized that each right and left cell of the zygote contained all the information necessary for each side. When these two cells divided further, each of the four cells would hold the information needed to make one fourth of an embryo. Upon further division, each cell would keep less and less genetic data. In the end, each cell contained enough material to be a liver, a brain, or a kidney cell (p. 50–51).

To prove or refute this theory, Wilhelm Roux, a German embryologist, reasoned that if he broke up the embryos, new intact frogs could not materialize from each cell since these cells had smaller chromosomes with less genetic infor-

mation. Roux collected fertilized frog eggs from a nearby pond and waited until they had formed into two-celled embryos. In each embryo he punctured one of the blastomeres with a hot needle. Thus the remaining blastomere should develop into half an embryo. It did (p. 53–54). As was proven later, the use of a hot needle to destroy one cell affected the other preventing it from growing into the space occupied by the dead cell (p. 57). Without considering the intricacy and easily affected delicacy of an embryo cell, the cellular manipulation not only determined development of half embryos, but sparked the scientific community with excitement and vigor in support of Weismann's hypothesis (p. 54).

Hans A.E. Driesch, a scientist from Leipzig, used sea urchins. As their eggs were so much smaller than frog eggs, he separated the cells by shaking the embryos vigorously until they split apart. Except, the separated cells developed into completely normal sea urchins (p. 53–55). Others carried out successfully the same experiments as Driesch did and so apparently disproved Weismann's theory. However, since very young eggs were used, specialization might not have begun yet. Weismann could be partially right in that the diminution of genetic information commences at a later stage in development.

In 1902, Hans Spemann used salamander embryos and spliced them in two with a hair taken from his baby son's head. He tied the hair in a noose and slipped it over a two-cell embryo. Each cell developed into a salamander. However, if he did not tighten the noose completely, the salamanders grew into two-headed creatures with one body (p. 57–58) – monsters as a result of human intervention.

In that same era, Jacques Loeb, a German-born embryologist from Chicago, tried to create embryos that had only mothers and no fathers. He tricked unfertilized eggs from sea urchins to divide as if they had been penetrated by sperm. A solution of seawater and magnesium chloride would shock the egg into dividing and further development. Except, sometimes this harsh chemical would herniate the egg as it tore its membrane. Cytoplasm would bulge out. If the cell itself had not cleaved in two, one of the newly formed nuclei would ooze into a herniated bulge after which it might break off from the egg. The result would be an identical-twin embryo – a natural cloning (p. 59). Spemann used his own noose technique with salamanders to force a nucleus to one side of the embryo which divided into sixteen cells. Then he loosened the hair noose so that one of the nuclei crossed over into the area of empty cytoplasm. When this cell began to divide, he tightened the lariat again separating the larger embryo from the newly dividing cell. The result developed into an identical twin. Still in his 1938 work *Embryonic Development and Induction*, he wondered whether his primitive cloning experiment would work with older embryos or even with specialized cells from adults. Not until 1952, eleven years after his death, would his queries find an answer (p. 60–61).

Robert Briggs, an embryologist at the Institute for Cancer Research and Lankenau Hospital Research Institute in Philadelphia with a grant from the National Cancer Institute, wanted to understand how genes were activated and turned off during development. How does a cell 'decide' to use or not to use certain genes in the growing organism? Briggs worked with leopard frogs, *Rana pipens*. He had a frog blastula cell nucleus transplanted to an enucleated egg cell by microsurgery (Bromhall 1975). Blastula cells are from ova containing 8000 to 16,000 cells and

consisting of a hollow sphere of cells enclosing a cavity or a blastocele (Thomas 1973, p. B-34). These cells are not irreversibly differentiated. The procedure consisted of siphoning the nucleus from an unfertilized frog egg with a glass pipette, then add a nucleus from a blastula cell to that emptied egg. The cell broke apart as he sucked it into the pipette, but its nucleus remained intact. Care had to be taken that neither the egg nor the nucleus were damaged. The first blastula was cloned. Of the 197 frog eggs, 35 became embryos and 27 developed into tadpoles. Scientists and others thought it was phenomenal (p. 61–65). However, the more advanced the embryo cells were the less the procedure succeeded. Only 0–2% developed into tadpoles versus 44% of the clones that emerged from young embryos. After all, Weismann was, in part, correct: DNA does pass a point of no return in the process of an organism's development. Cloning may be impossible for genetic reasons (p. 66).

Around 1965, professor F.E. Steward, a cell biologist at Cornell University, discovered that he could literally shake apart a cell of a differentiated carrot root. To his amazement, he was able to carry one root cell to the ultimate stage of a full grown plant – roots, stalks, leaves, flowers, seeds, and all. He demonstrated that any cell could be forced asexually to come to full fruition (86).

In the late 1960's, John Gurdon, a developmental biologist at Oxford University, tried the transplantation experiment using cells from the intestinal lining of tadpoles old enough to begin feeding, i.e., their intestines were presumed to have differentiated. His success became famous and was cited for decades by developmental biologists. Though the trials worked 2% of the time, Gurdon felt he had proven that fully specialized cells retained all the genetic information to direct the development of an adult organism. The problem, he said, was not with the cell genes but with human manipulation (p. 69). He had a point. However, these intestinal cells apparently were undifferentiated as they turned out to be primordial sperm or egg cells that were formed in the lining of the stomach and moved to the gonads. These cells had not begun their final process of meiosis (cell division) upon which they do lose half of their chromosomes. So far, no one could clone an adult frog from an adult frog cell yet (p. 67–69). No one had shown that fully differentiated cells could be made to revert back to their embryonic state.

In the spirit of the times, many people were ecstatic with the possibilities offered by science and technology. The moon was possible. Why not the sun? In 1963, J.B.S. Haldan, a biologist from Britain used the term 'clone' for the first time in a published speech, called: *Biological Possibilities for the Human Species over the Next Ten Thousand Years*. We would clone humans, he said, from the best and the brightest who had demonstrated their superiority. We would gradually increase the number of great thinkers, artists, athletes, even beauty queens in the population. As these clones were created, he went on, the average achievement of the population would increase (p. 71–72).

Joshua Lederberg, Nobel Laureate, speculated in 1966, that human cloning was around the corner once the technical difficulties were overcome. He welcomed it to improve mankind (p. 73).

Bentley Glass, the outgoing president of the American Association for the Advancement of Science, the nation's largest professional organization of scientists proclaimed in his speech in 1970: "No parents will in that future time have a right

to burden society with a malformed or a mentally incompetent child. Just as every child must have the right to full educational opportunity and a sound nutrition, so every child has the inalienable right to a sound heritage or genotype" (1971, p. 28).

Linus Pauling, the Nobel Laureate from the California Institute of Technology proposed in all seriousness in the UCLA Law Review (1968) that we tattoo the foreheads of people who carried a copy of recessive, disease-causing genes so that they would not accidentally have children with someone else who carried the same gene (p. 76).

Fortunately, other intelligentsia cautioned against the fervor for scientific projects and enterprises. An ethics movement began upon the public discoveries of unbridled scientific malpractice such as the "Tuskagee Study of Untreated Syphilis in the Negro Male" in 1972 that aimed to discover the course of the disease when left untreated. The study lasted for 40 years. Similarly, in the Willowbrook study, doctors infected mentally retarded children at the Willowbrook State Hospital in Staten Island with the liver virus, hepatitis B, in order to develop a vaccine against it (p. 77–78). The Institute of Society, Ethics, and the Life Sciences was founded by Willard Gaylin, a psychiatrist, and Daniel Callahan, a philosopher, which later became the Hastings Center. Chilled by the fact that no philosophical, theological, and ethical questions were raised as to where medicine and science were headed in their unbridled freedom to experiment at hoc, they felt society needed a wake-up call. They chose cloning as their core issue for such research might have such terrible consequences, it ought not be done (p. 79–80). As another Nobel Laureate and author of *The Double Helix*, James D. Watson, testified in 1971 before Congress on the future of biology: "If we do not think about the matter [of cloning] now, the possibility of our having a free choice will be gone one day" because there will always be someone who will want to try legally or illegally. His warning fell virtually on deaf ears (p. 82–83).

But the march was on. In 1969, James Shapiro and Jonathan Beckwith announced they had isolated the first gene – a bacterial gene that microorganisms use to digest milk sugar (p. 108). Subsequently, scientists learned not only how to isolate but to move genes which meant they could create artificial genetic combinations. Genetic engineering, such as Paul Berg and Janet Mertz' plan in 1971 to join DNA from a cancerous tumor virus (SV40) with a bacterium that inhabits human intestines (Escherichia coli or "E" coli), meant that recombinant DNA, or DNA from different sources, could be combined. Genes could be moved from cell to cell and organism to organism which did become a reality in 1973 (p. 109–113). Berg's plan was aborted due to the possible dangers of passing to human hosts the E.coli bacteria containing cancerous SV40 genes that could possibly spread and turn epidemic like the AIDS virus. By 1981, recombinant DNA became a business opportunity. Genetech, a company founded by Stanford scientists who had helped discover the powers of genetic engineering, went public, valued by Wall Street at more than $200 million. The founders became millionaires (p. 115).

In 1978, the first IVF (in vitro fertilization) baby, Louise Brown, was born. Two British scientists, Patrick Steptoe and Robert Edwards, had successfully fertilized eggs in vitro and grown a few eggs to embryos that could be implanted in a woman's womb. Thus, from now on human egg manipulation in the laboratory was on its way to become a common practice (p. 82) in the free market of private

practice. By 1996, the freezing of human embryos became possible, but no flags were raised concerning the possible effects on resulting fetuses and born children. It should have because it is an established fact that embryos are harmed, if not irreparably, by drugs and substance abuse.

The story of the German researcher, Karl Illmensee, considered a superstar among scientists and a world renown lecturer, sheds light on a darker side of science. In 1979, he announced he had cloned mammals – three mice. He worked with Peter Hoppe at the Jackson Laboratory in Bar Harbor, Maine – a nonprofit research institution devoted solely to the study of genetics in mammals. Illmensee and Hoppe mated mice. Four days later they flushed microscopic embryos from the uterus of the females. The embryos were advanced enough to have arranged themselves into a ball that will become a fetus surrounded by a shell of cells that develops into the placenta. They dissected the inner cell mass away from the rest of the embryo and used an enzyme to dissolve the biological glue that holds the cells together. Next, they shattered the embryo cell and extracted the cell's nucleus from the cytoplasmic mass. As with Briggs' experiments on the blastula cells, the cell was so delicate it would break during the extraction. Yet, the tiny nucleus enclosed in its own gelatinous membrane remained intact inside the pipette. Illmensee injected the isolated nucleus into a newly fertilized mouse egg and then with the same pipette withdrew the egg's own genetic material so as not to harm the delicate egg unduly. He let the cloned embryos grow in the laboratory for several days before they were implanted in the uterus of female mice where they developed into normal mice. These mammals were cloned from early embryos and not yet from adult mice (p. 121–128). The entire scientific community felt inspired by this breakthrough, especially people like Keith Campbell, the collaborator of Ian Wilmut who created Dolly and Steen Willadsen who would clone a sheep from a sheep embryo cell (p. 129).

In the meantime, Illmensee had accepted a position at the University of Geneva where he kept his research techniques to himself. He would not teach his methods to his junior assistants and colleagues at a time when all other scientists were failing to repeat his procedures; that is, the technique led to embryos but none survived. Gradually, colleagues of Illmensee had misgivings about his secretive behavior concerning ongoing experiments. In 1983, professor Illmensee was publicly accused of having falsified his results. He signed a statement, saying: "Protocols of Dr. Karl Illmensee have been manipulated in a way which is contrary to the scientific ethics in some period of 1982" (p. 130–139). A five-member international commission, appointed by the University of Geneva, ameliorated this verdict due to lack of hard evidence and suggested that a new series of experiments should be repeated with full scientific rigor. They were never done by Illmensee as his professorship was not renewed in 1985 (p. 142–144). Many of his colleagues came to his defense publicly, refusing to believe he had committed any fraud (p. 147–148).

Two other researchers, Davor Solter and Jim McGrath, picked up the thread of cloning mice. After the application of Illmensee's methods failed, they used an inactivated Sendai virus to fuse the egg cell, whose nucleus had been removed, with a cell from a mouse embryo. Then they would allow the nucleus of the mouse embryo cell to float into the egg and take over. Their main aim was to transfer nuclei from one mouse to another. It worked. Yet, when they fused more advanced

embryo cells to a mouse egg whose nucleus had been removed, the experiment failed. Especially forty-cell embryos that Illmensee and Hoppe had used failed to develop at all. They died immediately (p. 144–146). They were mystified and claimed that nuclear transplantation in mammals was biologically impossible. Illmensee's experiments could not be duplicated. The problem of cloning had to be approached from a different avenue. In fact, interest in cloning by molecular biologists waned considerably.

Yet, the research was not abandoned. It was quietly pursued by specialists in the animal sciences who were supported by corporations for economic advances. Instead of mice, frogs, and salamanders, they studied large farm animals like sheep, cows, and pigs. Two scientists, Steen Willadsen in Great Britain and Neal First in Wisconsin, USA, would prove that Solter was wrong. Willadsen and First were funded by the British Milk Marketing Board and W.R. Grace and Company respectively.

At the University of Wisconsin, Neal First's team planned to create an unlimited source of identical priced cows by cloning each cell of an eight- or sixteen-cell embryo, repeating the process with each cloned embryo ad infinitum. Peter Hoppe had been invited to demonstrate his methods of cloning mice. Their enthusiasm was severely dampened, first, when the cells kept dying and, second, when Davor Solter's paper was published in *Science* stating categorically the biological impossibility of mammal nuclear transplantation. How to justify the funding from W.R. Grace and Company if the project were to be continued? When Prather, a doctoral student, inherited the project, he could be risking failure thus losing out on getting his Ph.D. degree. The prospects were daunting as the cloning of cows was a totally different proposition from cloning mice. After all, cows embryos were ill suited for laboratory conditions so unlike mice cells (p. 159–164).

Steen Willadsen had reported in a paper that he had successfully grown an eight-cell cow embryo in sheep oviducts. First's team reasoned that it would be easier to let an one-cell embryo incubate in a sheep oviduct until it reached the blastocyst stage. The surgery involved, however, was too cumbersome. Why not legate the oviduct from the sheep and keep that alive in the lab? Indeed, the oviducts stayed alive for a month, long enough to nourish the cow's embryo into an advanced stage (p. 159–165).

Next came the cloning of the blastocyst. The experiment was aided by the use of a machine that fused an embryo cell with an enucleated cow's egg by means of a brief burst of electricity. In 1986, they also succeeded in transferring the nucleus from an early cow embryo to a cow egg, grew the cloned embryo in a sheep oviduct and implanted the blastocyst into a surrogate mother cow. The calf cloned from an embryo was born ten months later.

Since Steen Willadsen had reported his cloning of sheep from early embryos in the British journal *Nature* in March, 1986, the First team could not delay announcing their work which was printed in *Biology and Reproduction*, November, 1987 (p. 166–168).

Across the Atlantic in Cambridge, England, Steen Willadsen was convinced that cloning from adult animals was possible. He said that "the role of the scientist is to break the law of nature rather than establish, let alone accept them" (p. 168). His expertise was in reproductive physiology. During his Ph.D. project of

maturing cow eggs in the laboratory, he developed special skills in handling the delicate and tiny cow eggs under a microscope – an ability most researchers do not bother to acquire (p. 171–172).

When he came to the Cambridge Research Center, his first assignment was to perfect the freezing of livestock embryos. It was thought that the process required three mandatory steps: the cell's water had to be replaced by dimethylsulfoxide (DMSO); the cells had to be frozen ever so slowly; and, the thawing had to be done just as gradually. Willadsen disproved all three requirements. At that time, the idea of freezing living embryos was awesome. How could they survive such treatment? Willadsen successfully froze both sheep and cow embryos. He also developed a normal calf from one of the frozen cow cells (p. 174–175).

Willadsen invented new methods in the cloning of sheep embryos. First, he removed fertilized eggs from the sheep oviducts. In order to sever the fertilized egg, he decided to use Spemann's mode of applying a hair tied in a noose. Only sheep embryos are so much smaller compared to those of a salamander. The zona pellucida, or gelatinous coating surrounding the egg, cracked easily. To grow embryos in rabbit oviducts, the zona had to remain intact otherwise the rabbit's immune system would attack the embryos and destroy them. His solution was to encase the embryos in agar – a jellylike substance made from seaweed – before he put them into the oviducts. The agar could not be penetrated by the immune system, yet the nutritive fluids from the oviduct could diffuse through it. His agar protocol allowed him to split fertilized sheep or cow eggs and grow the twin embryos in a rabbit until they were ready for implantation in a surrogate mother. He could freeze the new embryos and produce identical twins born at different times (p. 176–178)

Next, he asked himself how many times can an embryo be subdivided and still produce a normal animal? The answer to the question was important to breeders of livestock whose inbreeding practices for valuable traits in animals amounted to a sort of genetic lottery. The trouble was that the more an embryo was divided the less the return of young produced. Two-cell divided embryos yielded 60–80% of those transferred to surrogate mothers; only half were successful when four-cell embryos were divided; and, 5–10% of the embryos matured when they were separated from eight-cell embryos. But, an embryo consisting of eight cells showed that some of its independent cells had retained the potential to become a complete independent embryo. They could really manipulate the embryos at will.

Willadsen began to create chimeras – animals made from mixing together cells from different embryos. He would slice the jellylike shell that surrounds the egg, pull the sheath gently open and expose the embryo inside. Using such a fine pipette that only one cell could enter it at a time, he could replace individual cells with those from another embryo. They even mixed cells from different species. For example, his team created fourteen sheep-goats and some sheep-cows. His justification was to see whether he could break the species barriers in pregnancy in order to breed animals of endangered species. He wondered whether or not one species could carry the fetus of another one since the endangered variety couldn't provide enough surrogate mothers. He found he could. From there, the step toward cloning had become easier. Soon thereafter, he heard a lecture on cloning of mice by Karl Illmensee in Cambridge, U.K. (P. 178–180).

Steen Willadsen wasn't successful. The sheep and cow eggs were so small they were traumatized by the blunt injection of a new nucleus. He tried again using the Sendai virus to fuse a cell from an eight-cell embryo with an enucleated sheep egg. The virus melds the membranes of the two cells. An eight-cell embryo has already begun to specialize. If it worked, the embryo cell's DNA would be reprogrammed by the egg. It worked in so far that the fused cell did not die immediately. Yet, the procedure was dangerous. First, the Sendai virus had to be grown in fertilized chicken eggs and later inactivated by exposing them to ultra violet light. But the contamination by bacteria and other viruses was real. "In addition," he said, "it was not really acceptable to use viruses in experiments with livestock, or someday with human embryos" (p. 183). He tried something new: fusing unfertilized sheep eggs with an enucleated egg. Pregnancies followed. Two cloned lambs were born in 1984. He soon abandoned the Sendai virus replacing it with the electrofusion apparatus Neal First had used (p. 182–184; Willadsen 1986).

In 1991, Willadsen had created a line of sheep that made the drug alpha-1 antitrypsin every time the sheep made milk. This valuable drug is used to treat an inherited lung disease and cystic fibrosis (p. 25, 215).

And so, the cattle-cloning business began. Soon researchers were able to clone horses, pigs, rabbits, and goats from early embryo cells. In fact, in 1997, scientists in Oregon cloned rhesus monkeys. Still, how to bring back the DNA from specialized adult cells to its primordial state, especially as the cells of older embryos stick so tightly together, they are very difficult to separate. Yet, Willadsen's cloning experiments worked taking week-old cow embryos that consisted of 60 to 120 cells. At a new job with Alta Genetics, Alberta, Canada, Willadsen was asked to clone a hundred embryos in a year for $1 million contributed by the venture capitalists to Alta Genetics. He and his team did it. However, the cloning business collapsed within a few years (May, 1993) as the cost was too high for the American farmer. The cloning issue retreated to the background. But, as there will always be somebody who can't resist its lure, the cloning problem was quietly picked up in Scotland by Ian Wilmut and Keith Campbell at the Roslin Institute, supported by a company that wanted to make pharmaceuticals (p. 186–191).

Ian Wilmut, too, got his degree for work in the freezing of boar sperm – sperm of price pigs to be used later for artificial insemination (p. 192). Later he was assigned the project of gene transfer – the idea was to make genetically engineered animals by adding genes to new fertilized eggs. For example, adding a gene for a protein like insulin to a sheep cell and arrange it so that the gene was only turned on in udder cells when the sheep made milk. Except, only about one embryo in five even survived the injection and became a lamb. The rest died of trauma or natural causes. Only one cell in one hundred takes up the added gene and even those that do usually use it in all their cells. He came upon the idea to add genes to laboratory-grown embryo cells en masse, using vast sheets of cells and flooding them with genes. Genes added to calcium phosphate tricked the cells into swallowing them as though they were salt granules. Or, an electrical current might force the cells to open the pores of their outer membranes and let the genes in. But, growing early embryo cells in the lab was difficult: they died or grew into something entirely else. Once the cells changed, they were useless. What if he grew older cells from fetuses or even adults in the lab and add genes to them?

Then he could clone them. They are easy to grow and simple to get in quantities. After all, Willadsen had used 60- to 120-day old cattle embryos. A few years passed before his ideas were granted to be tested (p. 194–200).

A doctoral student at the Roslin Institute, Lawrence Smith, had tried a few cloning experiments. He noticed that the success of cloning seemed to depend on the cell cycle or pattern. Immediately after a cell divides it enters a stage called G1, or "gap 1," during which period the cells check their own DNA and enlarge in size. Then the cell enters the S or synthesis phase when they copy their DNA in preparation for dividing. The S phase is followed by the G2 ("gap 2") during which the cell checks its DNA for mistakes and gains even more bulk. The final stage is mitosis or M stage when the cell actually divides in two to start the same process all over again. To clone a cell, the cell cycles of the two eggs have to be in synchrony otherwise the egg with the new DNA may not accept it and the clock is not set back to the beginning of embryo development (p. 200–201).

In 1990, Keith Campbell was hired by Wilmut for his knowledge of cell growth and cell cycles. One of his experiments involved adding human DNA to extracts of frog egg cells to see whether or not the frog cell could copy the human genetic material. The reverse happened: the human DNA looked like the DNA of a frog embryo. Campbell thought it was possible to trick an egg cell into using a foreign nucleus (p. 200–203).

Campbell set to work. He synchronized all of the sheep embryo cells so they were going through their cycles in lockstep. To synchronize the cells of intact embryos he used drugs. They died due to the high doses needed. Breaking the embryos apart, growing them individually in the lab, and then synchronizing them failed too. What if he used more mature cells, starve them to put them in a state of quiescence or suspended animation which is called the G0 or "gap zero" state? Wouldn't all the cells be in a perfect state for cloning? The hypothesis was that when cells specialize they must rearrange their proteins that mask most of their DNA, using only ten percent of their function as a liver or brain cell. The vast majority of a cell's genes remain hidden and unused under a cloak of proteins. The suspended animation or G0 phase is used by the cell to reprogram its gene expression. Would a newly fertilized egg reprogram the DNA of the sperm to mesh with its own during a G0 phase (p. 204–205; Campbell et al. 1996)?

Campbell and Wilmut quiesced fetal skin cells by serum starvation, forcing them to enter the G0 state, and tried cloning. They grew into blastocysts. With further trials and errors, they discovered that as long as the cells were in the G0 stage, sheep eggs accepted the cells's DNA and used it. The eggs turned into embryos. They had fourteen embryos ready for transfer to surrogate mothers. Six were cloned from early sheep embryo cells not grown in the lab; one came from an embryo cell grown in the lab before it changed its embryonic shape; and, seven were from embryo cells that had flattened and differentiated in the lab and that looked like skin cells. In July 1995, five lambs were born. Two died a few minutes after birth. One died ten days later as it had a hole in its heart – a fairly common birth defect in the type of sheep used. The two that survived were cloned from differentiated cells. The identical twins were named Megan and Morag. Upon the publication of their work in *Nature*, March 7, 1996, Davor Solter ended his editorial with: "Cloning mammals from adult cells will be considerably harder but

can no longer be considered impossible; it might be a good idea to start thinking how we are going to make sense of such an option" (p. 205–208; Campbell et al. 1996).

The birth of Megan and Morag was not appreciated by most scientists or many members of the press. *The New York Times* never reported this momentous event in the history of cloning. In fact, the world had never heard of Ian Wilmut until February 24, 1997 when the birth of Dolly was announced – a cloned sheep after 277 trials from frozen udder cells of a six-year old ewe that had lived on another farm and was no more (p. 211–216).

Discussion

The history of cloning is both fascinating and terribly chilling in its implications. One, the march has been going on inexorably at an ever accelerating pace. Of interest is that most of the research was quietly pursued in different parts of the world in a manner that the right hand of the scientific community didn't know what its left hand was doing. As Willadsen said, he is pretty sure that humans will be intentionally cloned one day. "But, it probably will not be called cloning" (p. 48).

Two, I, too, think that human cloning will happen and it chills me to the marrow for if we reflect carefully it stands to reason that the trials and errors – true experimentation – on human embryos will necessarily be numerous. No matter how much the methods of animal and rodent cloning are perfected, fetuses must be created to test hypotheses and to get results. Women need to be recruited to function as surrogate mothers ... unless science would steep so low using other mammals as surrogates.

Three, some of the ramification have already materialized and the reader can draw his/her own conclusions in determining whether or not a thorough philosophical and ethical discussion is needed before science proceeds with actual human cloning. Among scientists the term 'somatic cell nuclear transfer' is applied (Kolata 1998c).

1) Baby Jaycee was carried to term by a surrogate mother for Luanne and John Buzzanca who had tried artificial insemination and in vitro fertilization four times at a cost of $10.000 each. A month before the birth of Jaycee (April 26, 1995), John filed for divorce. When the child was born, Luanne sought child-support payments but John claimed he was not the baby's father even though he had signed a contract. A California Judge declared that Jaycee had legally no parents. A Superior Court Judge, Robert Monarch, confirmed that not only was John not the father but Luanne Buzzanca was not 'entitled' to be declared the legal mother either since the baby, Jaycee, was conceived in a petri dish from an anonymous donated egg and sperm. Thus the child had no genetic ties to either John or Luanne Buzzanca. Neither filled the definition of fatherhood and motherhood by California law (Foote 1998). What will be the legal entanglements once human cloning with its initial high ratio for error becomes a reality?

2) A recent Canadian study showed that early amniocentesis performed at eleven or twelve weeks in pregnancy resulted in an increase in miscarriages and stillbirths. Amniocentesis can safely be performed after the fifteenth week of preg-

nancy. Dr. R. Douglas Wilson of British Columbia's Women Hospital and Health Center in Vancouver studied the procedure because doctors at many medical centers in Canada, the United States, and Europe were performing it without proof of its safety. In 1995, 124.000 women out of four 4 million who gave birth had amniocentesis according to the National Center for Health Statistics in the U.S. The rate of miscarriage upon early amniocentesis was 7.6% compared to 5.9% in woman who had the procedure after the fifteenth week. But, the increase in foot deformities was 1.3% in the early group versus 0.1% in the standard group. Of half the affected babies, both feet were misshapen. These babies had to be treated with casts and sometimes surgery (Grady 1998). Is it unreasonable to assume that the cloning of human embryonic cells may cause much greater defects as they are vastly more delicate and subject to trauma? If human intervention for whatever reason at the twelfth week of pregnancy is risky wouldn't the dangers increase exponentially with the decrease in the embryo's age?

3) Jonathan Slack, a developmental biologist at the University of Bath, U.K., experimented by controlling signaling proteins known as fibroblast growth factors. Slack altered embryonic processes that are instrumental for the growth of the head, or of the trunk and tail, of the frog *Xenopus laevis*. He was able to grow not only embryos with no head but also ones that were nothing but a head. The embryos were not kept alive beyond about three days. Slack observed in an interview with the local press that no biological principle would keep a technique similar to his from working on a human embryo. Thus, he said, it was time to ponder the possibility of headless humans cloned and grown for the express purpose of providing any needed vital organ for its anatomically complete genetic donor. "You can't stop things once they start, and it is sensible to talk about it now," he told the Daily Telegraph. Biologists were baffled by the outpouring of the indignation. Genetically created headless embryos is not at all new. Headless frog embryos have been made by various pseudogenetic techniques since the early 1990s. In 1994, headless mouse embryos resulted from studies of a gene known as *Lim1* by William Shawlot and Richard R. Behringer of the M.D. Anderson Cancer Center in Houston. "We should not permit the nightmare visions (of the public) to impede research now," says ethicist Ronald M. Green of Dartmouth College. "Research on cell differentiation and the genetics of embryological development [has] great potential benefits" (Zorpette 1998). For whom? The offspring? According to Charles Krauthammer (1998), "other prominent scientists are perfectly prepared to acquiesce in the deliberate creation of deformed and dying quasi human beings. Professor Lee Silver, a molecular biologist at Princeton University, for instance, not only sees 'nothing wrong philosophically or rationally,' with producing headless humans for organ harvesting; he wants to convince the skeptical public that it is perfectly OK." Besides, as Silver discussed in his book *Remaking Eden: Cloning and Beyond in a Brave New World*, it has been done. A baby was purposely conceived to become a bone-marrow donor for her sister, Anissa Ayala, in California in 1992. Diagnosed with myelogenous leukemia, other means to find a compatible donor were fruitless. Though with a 25% chance that the baby would be compatible, the transplant was performed with success fourteen months after the infant's birth.

However, an alternative is xenotransplantation. Several companies are raising genetically altered pigs whose organs are made closer to those of humans. At the moment, there is a deep concern that such animal organs may harbor possible deadly viruses, called xenozoonoses, that could spread among an unsuspecting public. "Xenotransplantation is a unique medical enterprise," said Dr. Fritz Bach, a genetic immunologist at Harvard University's School of Medicine. "It puts the public at risk for the benefit of the individual." Animal tissues and cells, like pig heart valves and insulin, are routinely used to treat humans, but these products are heat-treated or otherwise processed so as not to pose the same health risk as transplanting living organs. The real problem with xenotransplantation is that doctors do not know when viruses that pigs inherit will become active after transfer to humans. Only two viruses (porcine endogenous retrovirus) have been identified so far. Nobody knows the true risk to humans involved. Still, many scientists, including the Food and Drug Administration (F.D.A.), consider exploring this avenue worthwhile – though with caution (Stolberg 1998).

There is a third approach to meet the crisis in the supply of human organs for donation. As of January 1, 1998, the Government of Brazil considers "all Brazilian citizens over twenty-one [years of age] potential organ donors unless they have registered their objection on their official identity cards. Doctors do not have to notify relatives of the dead, let alone ask permission, to remove organs for transplant." This new law is similar to legislation already in place in several European countries, particularly Spain, where accident victims are presumed to be donors. Many Brazilians fear that, somehow, hearts, livers, and kidneys would be extracted from the living to kindle the black market for organs as has happened. A worker got drunk one Saturday night and woke up in the field without his eyes which appeared to have been surgically removed. The doctors who fail to remove the organs of the deceased can be prosecuted for failing to assist a person in need – people waiting for transplants. This law went into effect without a system to collect, preserve, and transplant the organs around the country (Schemo 1998).

4) On the upside, in the case of macular degeneration – a disease that destroys vision – healthy tissue can be cloned from a patient's own cells and cultivated in a dish. Or, healthy cells can be obtained from a patient with leukemia or a burn victim. These cells would not have to grow in fetuses. The addition of powerful growth factors could ensure that the clones developed into specialized cells and tissue. These cloned cells pose no danger of rejection; patients would not need to take powerful drugs to suppress the immune system. Still, "to apply genetic engineering to humans, parents may first want to banish inherited diseases such as Tay-Sachs. Then they will try to eliminate predispositions to alcoholism and obesity. In the end," says Professor Silver, "they will attempt to augment normal traits like intelligence and athletic prowess" (Nash 1998).

The pros and cons in this debate will make it exceedingly difficult to draw a line voluntarily, especially as the research in cloning has invisibly marched on for many years while peers in science weren't looking and the public at large knew nothing. After all, commercial greed, overweening pride, and narcissistic vanity in parents wishing for the 'perfect' child are powerful vices with no regard for the offspring itself in spite of so-called best intentions. Richard Seed may well succeed in getting his clinic for human cloning off the ground as long as there

are people who hold "the view that the United States' Constitution necessarily guarantees every individual the right to reproduce through whatever means become technically available" (Associated Press 1998; Robertson 1998; Tribe 1998). Surely, those from Aristotle to August Weismann must wonder in their graves: What happened to the natural philosopher who ponders the rights and wrongs of human affairs and enterprises? Who will speak in defense of our offspring?

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