

Human Developmental Modification: Prospects and Perils

Submitted to the President's Council on Bioethics

by

The Council for Responsible Genetics

April 2003

Prepared by

Stuart A. Newman, Ph.D.

Department of Cell Biology and Anatomy

New York Medical College

Valhalla, NY 10595

newman@nyc.edu

New biotechnologies developed over the past three decades, together with changes in the public discourse around reproductive and reparative medicine, have led to an accelerated deconstruction of the notion of the human. Whereas biological, anthropological, philosophical and sociolegal definitions of human identity before this period were hardly consonant with each other, they were all constrained and unified by the inherent grounding of human identity and individuality in human biology. Members of the human species have a common, and coherent, evolutionary history, and therefore, a shared genome, which up to now has been subject to random shuffling, but not purposeful replication or manipulation.¹ The *uniqueness* of human individuals is also due, in part, to genetics, in particular, genetic variation. Correspondingly, the legacy of all persons having resulted from a genetic “roll of the dice,” and being therefore biologically unprecedented, has also contributed to the shared human condition. Finally, while there have been ambiguities and disagreements over whether certain naturally-occurring human organisms, such as embryos or the “brain-dead”, are part of the human community, it has previously not been possible to fabricate quasi-human entities for particular uses.

This is all changing. The capacity afforded by biotechnology to manipulate the human embryo at its early stages, including its genetic material (DNA), has placed the notion of a common humanity up for grabs. Modification of the early embryo, referred to in what follows as “developmental” modification or manipulation, is unlike manipulations of the fully formed individual, including provision of artificial limbs, heart valve and joint replacements, cosmetic surgery, and even “somatic” (differentiated body cell) gene therapy. Developmental modification changes the generative trajectory of the individual and turns it into something *intrinsically* different from what it would have become without the manipulation.² With these procedures there is no guarantee that even the original species-character will be maintained.³ Although one objective in applying such methods to our own species may be to fabricate improved humans, in some cases, by accident or by intent, the outcomes will be quasi-human, or less than human.

Developmental manipulation

At the present time, four distinct, but partially related, technologies have come to be applied, or seriously proposed to be applied, to human biology. These are *cloning*, *stem cell research*, *embryo gene modification* and *chimerism*.

We do not intend to lump these methodologies together and to assert, for example, that all techniques that employ human embryonic cells or tissues are morally problematic. The production of stem cells from stored “excess” embryos in IVF clinics can plainly be conducted without reconfiguring the material nature of the human organism. While such uses of human embryos are of deep concern to those for whom the embryo has the same moral status as full-term humans, The Council for Responsible Genetics, which supports the reproductive autonomy of women and their right to terminate their pregnancies, does not take this position. We are, on the other hand, very concerned about the transformative potential of methodologies that alter the developmental trajectory of human embryos and their capacity, when employed in particular combinations, to transgress any provisional definition of the biologically human, regardless of the belief system that stipulates it. We will therefore focus on these issues in what follows.

(i) *Cloning*—The cloning of a sheep by a Scottish agricultural research group, reported in February 1997,⁴ provoked a spectrum of responses from philosophers, ethicists and other observers of science. Opinions ranged from the assertion that cloning technologies should never be applied to humans, to enthusiasm for the prospects of doing just that.⁵ In interviews, and in testimony before the U.S. Senate, Ian Wilmut, the leader of the scientific group that accomplished the cloning feat, expressed his hope that no one would attempt to clone a human.⁶ Although the patents that he and his colleagues were awarded specifically covered human cloning, Wilmut stated that this provision was intended to foreclose others from attempting it.⁷ Two years later, after the report of the generation of ES cells from human embryos (see below), Roslin Bio-Med, the company Wilmut and his colleagues formed to exploit the cloning technique for animal breeding, merged with Geron, Inc., a U.S. company with patent rights on the ES cell technology. The stated business model of the new company was to generate ES cells of defined genetic constitution from clonal human embryos.⁸

Cloning to produce full-term human individuals currently has little support in the United States, or in other countries. One reason is the accumulation of data from scientific studies during the five years following the announcement of the first mammalian clone showing that the procedure is highly hazardous. Clonal mice, for example, exhibit perturbed patterns of expression in hundreds of genes,⁹ and cloned animals of all species in which it has been attempted have high rates of unexplained postnatal deaths, as well as anomalies such as enlarged hearts and grossly abnormal lungs and signs of premature aging.¹⁰ It stands to reason that a technique that brings together the remnants of two damaged cells, an egg from which the nucleus has been removed and the extirpated nucleus of a somatic cell, will have difficulty cooperating to produce a presentable

member of the originating species. Moreover, whereas many biological processes are protected by error-correcting mechanisms that have evolved over vast periods of time (for example, errors in the replication of DNA are repaired by numerous sophisticated enzyme systems), evolution has not confronted, nor arrived at correctives for, the errors introduced into the developmental process resulting from this atypical combination of cell parts.

On the other hand, the prospect of full-term human cloning was enthusiastically received by some opinion makers including a U.S. Senator¹¹ and the chief technology officer of Microsoft when Dolly the sheep was first announced.¹² More recently a specialist in bioethics and the law has opined that the Supreme Court has grounds to affirm the right to clone oneself.¹³ Claims by Clonaid, an affiliate of the Raelian religious cult, that they had produced several full-term human clones were met with skepticism and condemnation by the mainstream media,¹⁴ but the pioneering spirit of “early adopters” of such technologies has also been praised in some recent books.¹⁵ If a few confirmed human clones relatively free of obvious health problems were to be presented, it is reasonable to expect that opposition to cloning would diminish, despite the biological uncertainties. These uncertainties include the complete lack of knowledge of how the gene dysregulation that seems to inevitably accompany cloning would affect the “wiring” of the human brain that occurs during development.¹⁶

The motivations for producing full-term clones from a known prototype have been widely discussed.¹⁷ Common experience with natural human clones—identical twins, triplets, etc.—show that biologically-related traits such as personality, tastes and the occurrence of diseases, such as diabetes and cancer, are not fully determined by one’s genes. Most people now understand that producing genetically identical organisms, as effected by cloning, is not the same thing as producing organisms that are identical in every important respect. This has quelled some of the impulse toward full-term cloning, but not all of it. As we will see, the merging of cloning with stem cell research and germline manipulation are creating even greater incentives to produce full-term, or near full term clones.

(ii) *Embryo stem (ES) cells*—Embryo stem cells entered the world in 1981 and have since become a source of promised health benefits, secular-religious controversy, political realignments and new business models. Gail Martin, a researcher at the University of California, San Francisco, found that cells isolated from early mouse embryos (at a stage corresponding to about a week of human gestation) could, if exposed to appropriate growth factors and a “feeder layer,” (i.e., a population of nonembryonic cells) continue to divide in culture.¹⁸ Like certain cancer cells, ES cells would give rise to a variety of differentiated cell types if removed from the feeder layer. ES

cells have the potential to form neuron-like cells, cartilage, cells resembling the endodermal lining of the gut, and so forth. These cells continue to reproduce themselves as a tumorigenic stem cell population, as demonstrated by their propensity to form carcinomas when injected subcutaneously into adult mice. The potential of these cells to generate *any* cell of the juvenile or adult body was demonstrated by the ability of an ES cell to contribute to all tissues and organs of a developing embryo into which it had been incorporated at an early stage.¹⁹ It did so without inducing any tumors in the resulting individual—in effect, the microenvironment provided by the normal embryo could “tame” this abnormal cell type.

Between the time that Martin described mouse ES cells in 1981 and when James Thomson, a University of Wisconsin reproductive biologist, described human ES cells in 1998,²⁰ there had been little discussion of the reparative potential of ES cells. First, human cancer cells (“teratocarcinomas”) with properties similar to ES cells had been available for more than 30 years²¹ and no plausible therapeutic modalities had emerged from the numerous studies devoted to them. Second, even in the mouse system itself, where both authentic ES cells and virtually unlimited genetically compatible subjects had been available since 1981, there had been essentially no progress in curing or even palliating diseases or disabling conditions for which mouse “models” existed, such as diabetes, spinal cord injury, Parkinsonism and so forth.²²

But the intervening 17 years had been precisely the period in which the Bayh-Dole act of the U.S. Congress,²³ which enabled the privatization of federally-funded research, and the *Chakrabarty* decision of the U.S. Supreme Court,²⁴ which enabled the patenting of living organisms, had impressed their stamp on biomedical science.²⁵ A comparison of the last sentences of the summary paragraphs in the papers of Martin and Thomson and coworkers is revealing. Martin’s seems almost quaint now in its pure science orientation: “The availability of such cell lines should make possible new approaches to the study of early mammalian development.”²⁶ The corresponding sentence in the Thomson paper had a more 1990s flavor: “These cell lines should be useful in human developmental biology, drug discovery, and transplantation medicine.”²⁷ CNN’s web report of the announcement ran with the headline: “Researchers isolate human stem cells in the lab: Breakthrough could lead to treatments for paralysis, diabetes.”²⁸

As of early 2003, there remain few studies using the mouse as an experimental system that point to therapeutic efficacy for ES cells. Mouse ES cells or “pluripotent” (having several potential fates) subpopulations derived from them can sometimes repopulate damaged tissues in mice, but they usually also give rise to malignant tumors as well.²⁹ Human ES cells, when injected into immunocompromised mice incapable of rejecting them, usually form benign tumors in addition to

various differentiated cells.³⁰ But it is not clear whether human ES cells grafted into human patients would behave as they do in mice, or rather behave like mouse ES cell grafted into mice, forming malignant tumors.

A different kind of stem cell, the so-called embryo germ, or EG cell, is prepared by growing tissue isolated from 5-9 week fetuses rather than very early stage embryos.³¹ These cells have the advantage of not forming tumors when injected into immunocompromised mice.³² However, it is not clear how they would behave in human patients. EG cells appear to be capable of generating the full spectrum of cell and tissue types seen with ES cells and, therefore, would have equal therapeutic potential.

As noted, the reparative and tumor-forming potential of both mouse and human stem cells can be tested in immunocompromised mice. For human testing, or therapy, the transplanted cells would in most cases be rejected by the human host since they are of a different genotype and would provoke an immune reaction that could destroy the graft, or worse, prove fatal to the patient. The human ES cell lines that existed as of the summer of 2001, and were approved for further study using Federal funds by President George W. Bush in August, 2001, would, in general, not be tolerated by an arbitrary patient.

It is for this reason that proposals have been made, and have been strongly advocated by the spinal cord-injured actor and activist Christopher Reeve³³ among other patient and industry representatives³⁴ to permit Federal funding of the production of clonal embryos—embryos made by nuclear transfer that would have the same genotype as the patient—and to resist any legal restriction on these embryos being produced with private funds.³⁵ This prospect, termed “therapeutic” cloning, although “experimental” cloning is a more accurate term for it, has gained the support of pro-choice legislators across party lines, in both houses of Congress³⁶ and even some opponents of abortion such as Senator Orrin Hatch, who has reformulated his opposition to abortion as only pertaining to embryos that have been implanted in a woman’s uterus, and which the woman seeks to eliminate.³⁷ The drive to get Congress and the public to accommodate itself to experimental cloning has occurred with little acknowledgement that alternative strategies exist for altering existing ES cell lines so as to prevent their immune-mediated rejection.³⁸

Some research groups are working on culture methods to extend the viability of human embryos *in vitro*,³⁹ and this could afford the possibility of harvesting EG cells from 2-month fetuses (currently legal, though not approved for Federal funding). However, patient advocacy groups, biotech industry representatives and legislators have yet to specifically advocate the generation of clonal fetuses for the production of EG cells genetically matched to the patient.

Such reluctance could easily give way as better products from these technologies emerge. After Dolly the sheep was cloned, a British researcher speculated that inactivation of brain-inducing genes could be used to produce headless full-term human clones for organ harvesting.⁴⁰ A second British biologist, a prominent public spokesperson on scientific issues, opined that this proposal raised no ethical issues.⁴¹

(iii) *Embryo gene modification*—The hazards of genetic modifications to humans are usually discussed in terms of *somatic* (body cell) modification, in which only nonreproductive tissues are affected, and *germline* (egg or sperm cell) modification, in which changes to an individual's DNA can be passed down to future generations.⁴² However, genetic modification of early embryos, similarly to cloning, is hazardous to developing individuals even when there is no germline transmission to future generations.

The hazards of germline transmission of DNA modification are clear. For example, germline introduction in mice of an improperly regulated normal gene resulted in progeny with unaffected development, but high tumor incidence during adult life.⁴³ Such effects may not be recognizable for a generation or more.

It is important to recognize, however, that the hazards to the embryo of such alterations are not eliminated even if there is no germline transmission. The biology of the developing individual will still be profoundly altered by the manipulation of his, or her, genes at an early stage, hence the utility of the concept of “developmental manipulation” to cover both cloning and germline procedures. Laboratory experience shows that insertion of foreign DNA into inopportune sites in an embryo's chromosomes can lead to extensive perturbation of development. For example, the disruption of a normal gene by insertion of foreign DNA in a mouse caused abnormal circling behavior when present in one copy, lack of eye development, lack of development of the semicircular canals of the inner ear and anomalies of the olfactory epithelium (the tissue that mediates the sense of smell), when the mice were inbred so that the mutation appeared in the homozygous form (i.e., on both copies of the relevant chromosome).⁴⁴ Another such “insertional mutagenesis” event led to a strain of mice that exhibited limb, brain and craniofacial malformations, as well as displacement of the heart to the right side of the chest, in the homozygous state.⁴⁵ Each of these developmental anomaly syndromes were previously unknown. From current, or even anticipated,⁴⁶ models for the relationship between genes and organismal forms and functions, the prediction of complex phenotypes on the basis of knowledge of the gene sequence inserted or disrupted is likely to remain elusive.

Unexpected and even fatal outcomes of attempts at somatic cell gene modification have plagued this area of medicine.⁴⁷ But, attempts at developmental modification would be susceptible to a distinct category of hazard not shared by the somatic procedures. The tissues of a developed organism are in some sense modular—if blood, skin, a heart or a liver is diseased or damaged it can be replaced by a substitute without changing the “nature” of the individual. Similarly, with gene alteration in a developed individual, in reasonable candidate cases for somatic therapy, the gene is playing a defined role in a particular tissue or organ,⁴⁸ and the goal of the modification is to replace, or correct, the poorly functioning gene in one or a very limited set of tissues.⁴⁹

During development, the situation is much more complicated. Tissues and organs are taking form during this period, and the activity of genes is anything but modular. During development many, if not most, gene products can have multiple effects on the architecture of organs and the wiring of the nervous system, including the brain.⁵⁰ Individuals produced by developmental intervention (particularly as it comes to extend beyond the single gene, to chromosomes or groups of chromosomes⁵¹) could turn out to be “experimental artifacts,” in the sense that their bodies and mentalities could be quite different from those of anyone generated by natural processes using standard starting materials (including by IVF).

The prospect of linking the techniques of cloning and germline modification will create incentives that could cause some desperate parents to put aside these concerns. Some parents have already chosen to produce a new child in order to provide bone marrow or umbilical cord stem cells for an existing child with a treatable disease, such as Fanconi’s anemia.⁵² This is an uncertain procedure. In general, many attempts will be needed, and potentially scores of embryos will be produced and discarded, before an appropriate “match” in tissue type is achieved, the implanted embryo is brought to term, and the grafted tissue accepted by the patient. Nonetheless, success is not guaranteed.

In order to improve chances for success, it could be considered logical to *clone* the sick child. In this case, all the embryos generated would be a perfect match, and there would be no likelihood of rejection of tissue grafted from the second child into the first. If the original child’s condition was due to a gene variant, genetic manipulation of the clonal embryo could be performed to ensure that the grafted tissue (which would still remain immunologically compatible) could effect the cure. It must also be noted that even if the fetus dies prematurely *in utero*, as is often the case with clonal animals,⁵³ therapeutically useful tissues could still be harvested.⁵⁴ The uncertainties of the cloning process, therefore, might not be an important disincentive in such cases.

A recent study with genetically-impaired mice has demonstrated that cures, or at least palliation, of an immune deficiency can be achieved using bone marrow from their cloned, genetically-engineered siblings.⁵⁵ As would be the case with any human applications of this methodology, multiple clonal embryos were generated by first producing ES cells from an original clone. The gene modification was performed on the ES cells, which were then used to form viable embryos. Thus, all three techniques discussed so far were brought together in this experimental prototype for constructing a useful sibling for a sick child.

(iv) *Chimerism*—In November of 2002, a meeting took place at the New York Academy of Sciences to discuss the proposal, by a Rockefeller University scientist, to inject human embryo stem cells into mouse embryos in order to explore the developmental fate, and therapeutic potential, of the ES cells. The meeting was called because of brewing opposition among some scientists in the developmental biology research community. One leading stem cell researcher in attendance stated that, “I am completely opposed to putting human embryonic stem cells into any condition that will cause moral affront,” while others suggested alternatives to making such human-animal chimeras that could provide the same information.⁵⁶

As it happens, five years previously, a developmental biologist applied for a patent on chimeric embryos and animals containing both human and nonhuman, cells. Among the patent application’s claims was precisely what was being proposed at the New York Academy forum.⁵⁷ The applicant had no intention of producing such creatures, nor does U.S. patent law require that an actual prototype for an invention be supplied, only that feasibility, novelty and utility be demonstrated. Moreover, ever since the 1980 *Chakrabarty* decision by the Supreme Court, it has been legal in the United States to obtain a patent on living organisms and their descendants. Congress has drawn no clear line that would preclude a pre-term human embryo, if appropriately modified, from being patented. Further, Congress has not indicated how many human genes or cells an animal would have to contain before it could *not* be patented by virtue of the Constitutional protections pertaining to members of the human community.⁵⁸ Although a decision regarding patentability by human-animal chimeras by the PTO would not control whether or not it would be legal to produce such entities, it could influence the commercial drive to produce chimeras and other forms and products of human embryos.⁵⁹

At the time the original patent filing was announced in early 1998, both the PTO⁶⁰ and critics in the scientific community (including the researcher who patented the first mammal) accused the patent applicant of scaremongering—speculating about monstrous quasi-human concoctions that no responsible scientist would contemplate producing or patenting.⁶¹ Since then, however, Advanced

Cell Technology, a Massachusetts biotechnology company, announced its intention to obtain a patent on a technique for creating cloned embryos produced from human cell nuclei and cow eggs.⁶² And, as noted above, some mainstream scientists have subsequently announced their intention to produce human-mouse embryo chimeras.

As it attempted with the 1980 Chakrabarty microorganism patent application, the PTO rejected the chimera invention in its initial reviews, claiming, in the first instance, that the human-nonhuman chimera was inappropriate subject matter for a patent since it “embraces a human.”⁶³ One major difference between the *Chakrabarty* case and that of the chimera patent is that the PTO no longer opposes patents on organisms as it did in the late 1970s. Instead, it would like to draw a line between obviously disturbing inventions such as the chimera patent and other life forms for which they have already issued patents, such as human bone-marrow cells and pigs containing human genes.

From person to artifact

The prospect of human developmental manipulation holds out the promise of biologically customized, and eventually “better” people, as well as new modalities of reparative medicine. The first program, already underway, if claims of the self-described extraterrestrially-affiliated biotechnology company, Clonaid can be believed, is being promoted as benign⁶⁴ in that it is a eugenics of individual choice rather than state coercion.⁶⁵ Cheered on by futurologists devoid of scientific skepticism,⁶⁶ provided with the means by unscrupulous technologists and physicians⁶⁷ and motivated by a consumer ideology of the “new and improved,” technophilic early adopters will be tempted to subject their future offspring to methods that are inherently uncertain and fraught with potential error, for preemptive “cures” of disease and enhancement of appearance, intelligence and talent, motivated, in part, by the desire to gain competitive advantage.

Although one refrain of the advocates of this vision is that developmental manipulation of a child is just an extension of providing it with piano lessons,⁶⁸ a scientifically-informed appraisal would have to conclude (to stay with the musical motivation) that cloning, or genetic manipulation, to generate a talented performer is more akin to the commissioning of castrati by 18th Century kapellmeisters. And, unlike the products of those earlier experiments in biological improvement, whose culture and social environment may have made it difficult to resist being tracked into the profession their handlers chose for them, modern day children (and their lawyers) are likely to be less compliant.

An increasingly discussed scenario⁶⁹ is that if certain goals are actually achieved by the use of these techniques, genetically-modified offspring will become the new standard for those who can afford them. This will lead to society eventually separating into genetic “haves” and “have nots,” like the world portrayed in the 1997 film *Gattaca*.⁷⁰ The experience of the field of developmental biology suggests that this is much too optimistic concerning the likely success of these attempts. Contrary to popular misconceptions (often abetted by journalists and scientist-ideologues⁷¹) genes do not constitute an organism’s “blueprint,” or “program;” the genotype determines the phenotype in only an approximate sense.⁷² A study that compared outcomes of behavioral tests on inbred, genetically uniform strains of mice conducted in three different laboratories showed systematic differences across environments that were designed to be the same. The researchers concluded that assessment of effects of a given genetic alteration on behavior could differ markedly despite uniformity of genetic background and setting.⁷³

In another study where a mouse was actually genetically modified with the intention of inducing a changed behavioral profile, the mouse performed in a superior fashion on several tests of learning and memory,⁷⁴ and was featured in the popular media as the “Doogie” mouse, after a fictional child prodigy.⁷⁵ Not so widely reported was that these mice also exhibited enhanced sensation of pain when exposed to chronic stimuli.⁷⁶

Humans are much less genetically uniform than inbred strains of mice, and it is to be expected that many, if not most, attempts at genetically engineering children will have unexpected adverse outcomes. One way of controlling such uncertainty (to follow the logic of this questionable enterprise) is to start with ES cells derived from a clonal embryo produced from a known prototype, and attempt to correct or improve on the prototype. But then, ideology of enhancement would work against the acceptance of the inevitable experimental errors—children with brain damage and other profound disabilities resulting from genetic engineering gone awry—motivating parents in search of perfection to try again, with another of the inexhaustible clonal ES cells, for a better result. In effect, the quality control paradigm appropriate to any design-oriented technology would set in.

The products of mixing and matching fragments of cells and genes from different sources are not exactly organisms, or at least they straddle the categories of organism and artifact. At the furthest extreme, few would deny that a concoction of synthetic DNA and off-the-shelf chemical reagents that locomoted and replicated like a living cell, would have an ambiguous ontological status between life and machine.⁷⁷ One can question the Supreme Court’s description of

Chakrabarty's genetically variant bacteria as an "invention," but it is clear that we are moving toward an era of life-like artifacts.⁷⁸ What then would be the moral and legal status of humanoids?

Even with the more circumscribed aim of producing tissues for reparative medicine, human developmental manipulation can bring us to a similar pass. The boundary between the acceptable and unacceptable could easily drift under practical impetus. If ES cells (derived from one week clonal embryos) fail to live up to their promise in the repair of spinal cord injuries, infarcted hearts, or type 1 diabetes, there will surely be calls to permit harvesting EG cells from 5-9 week clonal embryos. Women could be encouraged to act as gestational surrogates for clonal embryos derived from the DNA of a patient. They may even be given the option of terminating the cloned fetus if anomalies are detected prenatally. (or even if they are not). In either case, useful tissues could be harvested. Much like the indigent woman in the documentary film *Roger and Me*,⁷⁹ who offered rabbits for sale as "pets or meat," it will become increasingly difficult to distinguish subjects from consumables.

While some advocates of producing clonal, genetically modified, or chimeric embryos for research and therapy are comfortable with growing the embryo for 14 days,⁸⁰ or only as long as it remains microscopic,⁸¹ or up to a defined developmental stage such as gastrulation (when the tissue layers of the body are established),⁸² or through the first trimester, or to any point so long as it is not implanted in a woman's uterus (apparently Senator Hatch's position, see note 37), there does not appear to be a scientifically- or philosophically-based stopping point that would attract universal assent. Once embryo modification technology is underway, the boundary of acceptability is in danger of being dictated by those with the loudest voices or greatest financial resources.

Drawing a line

These developments suggest that, in the absence of binding restrictions—which would represent a societal agreement not to cross certain troubling lines—the public could quickly accommodate itself to fabricated humans and near-humans, organisms that previously existed only in the realm of speculative fiction.

An international consensus to ban full-term human cloning is emerging,⁸³ and some national bodies have enacted, or are considering more comprehensive bans, including that on embryo cloning for research and potential therapeutic applications.⁸⁴ On the other hand, there are statements by bioethicists individually (see notes 13; 68), and organizationally,⁸⁵ affirming the "right" to genetically engineer one's offspring. The Council for Responsible Genetics, a public interest organization that has been scrutinizing the new biotechnologies since the early 1980s, has

proposed that all cellular and genetic manipulations of human embryos be prohibited, including cloning, gene insertion, and chimerism, arguing that drawing this sharp line is the only way to prevent the production of experimentally damaged humans and quasi-humans.⁸⁶

Under this legal framework, production of embryos would be permitted by IVF with the intention to implant or to be stored for future use or implantation. But they would not be allowed to be manipulated developmentally nor produced expressly for research purposes. Establishing this line would not prevent scientists from continuing research on ES cells from nonclonal embryos. It would, however, help individuals and societies who abided by it to resist entering into a series of dubious enterprises by which quasi-humans are produced for their capacity to provide spare parts and other functional utilities. It would, moreover, block a pathway along which “improved” humans would be intentionally created, with those brought about without the benefit of newest technologies, or those representing failed experiments, coming to be increasingly disdained.

No such legal framework can prevent the production of cloned and genetically-manipulated humans by rogue laboratories, but it can stigmatize such activities and guarantee that scientific “progress” in these areas does not find its way into the mainstream technical literature where it could enable further attempts. Notwithstanding recommendations that society accommodate itself to technological “inevitable”⁸⁷ in human developmental manipulation, the proposal outlined here, affirms the idea that humans should control technology rather than being controlled by and, in this case, defined by it.

This statement is adapted, in part, from S.A. Newman, “Averting the Clone Age: Prospects and Perils of Human Developmental Manipulation,” J. Cont. Health Law and Policy, in press.

Notes

1. See Lewontin, R. C. (1995). *Human diversity*. New York: Scientific American Library, and Cavalli-Sforza, L. L., Menozzi, P., & Piazza, A. (1994). *The history and geography of human genes*. Princeton, N.J.: Princeton University Press.
2. See Newman, S. A. (2000). The hazards of human developmental gene modification. *GeneWatch*, 13(3), 10-12.
3. For biological aspects of species identity and alteration See Newman, S. A. (1995). Carnal boundaries: The commingling of flesh in theory and practice. In L. Birke & R. Hubbard (Eds.), *Reinventing Biology* (pp. 191-227). Bloomington, IN: Indiana University Press; for legal aspects, see

- Annas, G. J., Andrews, L. B., & Isasi, R. M. (2002). Protecting the endangered human: toward an international treaty prohibiting cloning and inheritable alterations. *Am J Law Med*, 28(2-3), 151-178.
4. Wilmut, I., Schnieke, A. E., McWhir, J., Kind, A. J., & Campbell, K. H. (1997). Viable offspring derived from fetal and adult mammalian cells. *Nature*, 385(6619), 810-813.
 5. See citations in Newman, S. A. (1998). Human cloning and the law. *J. Biolaw and Business*, 1, 59-62 for some early reactions. For additional views, see Pence, G. E. (1998). *Flesh of my flesh: the ethics of cloning humans: a reader*. Lanham: Rowman & Littlefield, and Nussbaum, M. C., & Sunstein, C. R. (1998). *Clones and clones: facts and fantasies about human cloning*. New York: Norton.
 6. Statement before the Subcommittee on Public Health and Safety of the Senate Committee on Labor and Human Resources, March 12, 1997. See report at <http://www.cnn.com/HEALTH/9703/12/nfm/cloning/index.html>
 7. Comments before American Association for the Advancement of Science forum on cloning, Philadelphia, PA, June 25, 1997.
 8. Wadman, M. (1999). US stem-cell pioneers buy 'Dolly' cloning company. *Nature*, 399, 92.
 9. Humpherys, D., Eggan, K., Akutsu, H., Hochedlinger, K., Rideout III, W. M., Biniszkiwicz, D., Yanagimachi, R., & Jaenisch, R. (2001). Epigenetic instability in ES cells and cloned mice. *Science*, 293(5527), 95-97; Humpherys, D., Eggan, K., Akutsu, H., Friedman, A., Hochedlinger, K., Yanagimachi, R., Lander, E. S., Golub, T. R., & Jaenisch, R. (2002). Abnormal gene expression in cloned mice derived from embryonic stem cell and cumulus cell nuclei. *Proc Natl Acad Sci U S A*, 99(20), 12889-12894.
 10. Allen, J. F., & Allen, C. A. (1999). A mitochondrial model for premature ageing of somatically cloned mammals. *IUBMB Life*, 48(4), 369-372; Chavatte-Palmer, P., Heyman, Y., & Renard, J. P. (2000). Cloning and associated physiopathology of gestation. *Gynecol Obstet Fertil*, 28(9), 633-642; Jaenisch, R., & Wilmut, I. (2001). Developmental biology. Don't clone humans! *Science*, 291(5513), 2552.
 11. Comments at hearings of the Subcommittee on Public Health and Safety of the Senate Committee on Labor and Human Resources, March 12, 1997. See report at <http://www.cnn.com/HEALTH/9703/12/nfm/cloning/index.html>
 12. Myhrvold, N. Human clones: Why not? *Slate*, March 13, 1997.
 13. Weiss, R. (2001). Legal barriers to human cloning may not hold up. *Washington Post* (May 23), pp. A01.
 14. Grady, D., & Pear, R. (2002, December 29). Claim of human cloning provokes harsh criticism. *The New York Times*, pp. 18; Kolata, G., & Chang, K. (2003, January 1). For Clonaid, a

- trail of unproven claims. *New York Times*, pp. A13; Schatten, G., Prather, R., & Wilmut, I. (2003). Cloning claim is science fiction, not science. *Science*, 299(5605), 344.
15. See Silver, L. M. (1997). *Remaking Eden: how genetic engineering and cloning will transform the American family*. New York: Avon Books; Stock, G. (2002). *Redesigning humans: our inevitable genetic future*. Boston: Houghton Mifflin.
16. Known developmental disorders of the brain are associated with widespread gene dysregulation in brain tissue; see e.g., Freidl, M., Gulesserian, T., Lubec, G., Fountoulakis, M., & Lubec, B. (2001). Deterioration of the transcriptional, splicing and elongation machinery in brain of fetal Down syndrome. *J Neural Transm Suppl*(61), 47-57. It is reasonable to expect that the global gene dysregulation induced by cloning (see *supra*, note 9) would be associated with defects in the wiring of the neural circuits of the brain, although direct evidence is not available.
17. See discussions in references cited in note 5, *supra*.
18. Martin, G. R. (1981). Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci U S A*, 78(12), 7634-7638.
19. Saburi, S., Azuma, S., Sato, E., Toyoda, Y., & Tachi, C. (1997). Developmental fate of single embryonic stem cells microinjected into 8-cell-stage mouse embryos. *Differentiation*, 62(1), 1-11.
20. Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S., & Jones, J. M. (1998). Embryonic stem cell lines derived from human blastocysts. *Science*, 282(5391), 1145-1147.
21. Although any single cell line derived from a teratocarcinoma is not as versatile as an ES cell line (see Papaioannou, V. E. (1993). Ontogeny, pathology, oncology. *Int J Dev Biol*, 37(1), 33-37) no individual candidate for reparative therapy requires a fully totipotent cell population.
22. See, for example, Zoghbi, H. Y., & Botas, J. (2002). Mouse and fly models of neurodegeneration. *Trends Genet*, 18(9), 463-471, Wong, F. S., & Janeway, C. A., Jr. (1999). Insulin-dependent diabetes mellitus and its animal models. *Curr Opin Immunol*, 11(6), 643-647, and Beattie, M. S., Hermann, G. E., Rogers, R. C., & Bresnahan, J. C. (2002). Cell death in models of spinal cord injury. *Prog Brain Res*, 137, 37-47.
23. The Patent and Trademark Law Amendments Act, P.L. 96-517.
24. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
25. Press, E. and Washburn, J. (2000). The kept university. *The Atlantic Monthly* 285 (March), pp. 39-54. Available at <http://www.theatlantic.com/issues/2000/03/press.htm>;
- Newman, S. A. (2001). Embryo stem cells and biobusiness at 20. *GeneWatch*, 14, 5-6.
26. Martin, G. R. (1981), note 18, *supra*, p. 7634.

27. Thomson et al. (1998), note 20, *supra*, p. 1145.
28. See report at <http://www.cnn.com/HEALTH/9811/05/stem.cell.discovery/index.html>.
29. Martin (1981) *supra* note 18.
30. Reubinoff, B. E., Pera, M. F., Fong, C. Y., Trounson, A., & Bongso, A. (2000). Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. *Nat Biotechnol*, 18(4), 399-404.
31. Shambloott, M. J., Axelman, J., Wang, S., Bugg, E. M., Littlefield, J. W., Donovan, P. J., Blumenthal, P. D., Huggins, G. R., & Gearhart, J. D. (1998). Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proc Natl Acad Sci U S A*, 95(23), 13726-13731.
32. Shambloott, M. J., Axelman, J., Littlefield, J. W., Blumenthal, P. D., Huggins, G. R., Cui, Y., Cheng, L., & Gearhart, J. D. (2001). Human embryonic germ cell derivatives express a broad range of developmentally distinct markers and proliferate extensively in vitro. *Proc Natl Acad Sci U S A*, 98(1), 113-118.
33. A statement on stem cells and cloning by Christopher Reeve can be found at <http://www.genemedia.org/pdfs/cloningthedebate.pdf>.
34. See, for example, the June 2001 testimony of Thomas Okarma, President of Geron Corporation, on behalf of the Biotechnology Industry Organization, before the Committee on Energy and Commerce of the U. S. House of Representatives, available at: <http://energycommerce.house.gov/107/hearings/06202001Hearing291/Okarma450.htm>. Okarma spoke against H.R. 1644, the Human Cloning Prohibition Act of 2001.
35. Current administrative policy pertains to research done with Federal funds. The various pending Congressional bills call for legal bans on all forms of cloning or only full-term (“reproductive”) cloning. Any research not banned by Congress but subject to Administrative funding restriction could still be supported from private sources.
36. A Senate bill (S. 2439) introduced in the 107th Congress (2002) by Sens. Arlen Specter, R-PA, Edward Kennedy, D-MA, and Dianne Feinstein, D-CA, had the intention of permitting experimental cloning, as did a substitute amendment to a more restrictive bill (H.R. 2505) introduced in the House of Representatives the previous year.
37. House, D. (2002) Hatch stand stirs debate on cloning. *Salt Lake Tribune* (April 30), available at <http://www.sltrib.com/2002/apr/04302002/utah/732910.htm>; see also Russo, E. (2003) Clone hearings continue. *The Scientist*. (January 30), available at <http://www.biomedcentral.com/news/20030130/05/>.

38. Kaufman, D. S., & Thomson, J. A. (2002). Human ES cells—haematopoiesis and transplantation strategies. *J Anat*, 200(Pt 3), 243-248; Fandrich, F., Dresske, B., Bader, M., & Schulze, M. (2002). Embryonic stem cells share immune-privileged features relevant for tolerance induction. *J Mol Med*, 80(6), 343-350.
39. McKie, R. (2002). Men redundant? Now we don't need women either. Scientists have developed an artificial womb that allows embryos to grow outside the body (February 10, 2002), available at www.observer.co.uk/international/story/0,6903,648024,00.html.
40. J. Slack, quoted in Connor, S. and Cadbury, D. (1997) Headless frog opens way for human organ factory, *London Sunday Times* (October 19). Available at www.organicconsumers.org/Patent/headless.html.
41. L. Wolpert, quoted in Connor and Cadbury (1997).
42. See Billings, P. R., Hubbard, R., & Newman, S. A. (1999). Human germline gene modification: a dissent. *Lancet*, 353(9167), 1873-1875; see also Council for Responsible Genetics Position Paper on human germline gene modification at www.gene-watch.org/programs/cloning/germline-position.html
43. Leder, A., Pattengale, P. K., Kuo, A., Stewart, T. A., & Leder, P. (1986). Consequences of widespread deregulation of the c-myc gene in transgenic mice: multiple neoplasms and normal development. *Cell*, 45(4), 485-495.
44. Griffith, A. J., Ji, W., Prince, M. E., Altschuler, R. A., & Meisler, M. H. (1999). Optic, olfactory, and vestibular dysmorphogenesis in the homozygous mouse insertional mutant Tg9257. *J Craniofac Genet Dev Biol*, 19(3), 157-163.
45. Singh, G., Supp, D. M., Schreiner, C., McNeish, J., Merker, H. J., Copeland, N. G., Jenkins, N. A., Potter, S. S., & Scott, W. (1991). legless insertional mutation: morphological, molecular, and genetic characterization. *Genes Dev*, 5(12A), 2245-2255.
46. For deficiencies in the existing paradigm for genotype-phenotype relationships see Keller, E. F. (2002). *Making sense of life: explaining biological development with models, metaphors, and machines*. Cambridge, MA: Harvard University Press and Newman, S. A. (2002). Developmental mechanisms: putting genes in their place. *J Biosci.*, 27, 97-104; for alternative approaches see Newman, S. A., & Comper, W. D. (1990). 'Generic' physical mechanisms of morphogenesis and pattern formation. *Development*, 110(1), 1-18, Gilbert, S. F., & Sarkar, S. (2000). Embracing complexity: organicism for the 21st century. *Dev Dyn*, 219(1), 1-9 and Müller, G. B., & Newman,

- S. A. (Eds.). (2003). *Origination of organismal form: beyond the gene in developmental and evolutionary biology*. Cambridge, MA: MIT Press.
47. Somia, N., & Verma, I. M. (2000). Gene therapy: trials and tribulations. *Nat Rev Genet*, 1(2), 91-99.
48. Even in cases where the gene's protein product is confined to one or a few tissue types its function may depend in a complex and elusive fashion on other gene products or cell properties. This has proved to be the case for the β -globin protein compromised in sickle cell disease (Mozzarelli, A., Hofrichter, J., and Eaton, W. A. (1987). Delay time of hemoglobin S polymerization prevents most cells from sickling in vivo. *Science* 237, 500-6), the transmembrane conductance regulator protein compromised in cystic fibrosis (The Cystic Fibrosis Genotype-Phenotype Consortium. (1993). Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med* 329, 1308-13) among many others. This can affect the success of somatic gene replacement or repair, and therefore the health of the patient. The inherent identity of the individual, however, is not at issue in such manipulations the way it is with germline modification.
49. Anderson, W. F. (1984). Prospects for human gene therapy. *Science*, 226(4673), 401-409; Friedmann, T. (1989). Progress toward human gene therapy. *Science*, 244(4910), 1275-1281
50. Salazar-Ciudad, I., Jernvall, J. and Newman, S. A. (2003). Mechanisms of pattern formation in development and evolution. *Development*, 130, 2027-2037; Streidter, G. (2003). Epigenesis and evolution of brains. In G. B. Müller & S. A. Newman (Eds.), *Origination of Organismal Form: Beyond the Gene in Developmental and Evolutionary Biology*. Cambridge, MA.: MIT Press, pp. 287-303.
51. Shinohara, T., Tomizuka, K., Takehara, S., Yamauchi, K., Katoh, M., Ohguma, A., Ishida, I., & Oshimura, M. (2000). Stability of transferred human chromosome fragments in cultured cells and in mice. *Chromosome Res*, 8(8), 713-725.
52. Belkin, L. The made-to-order savior. Producing a perfect baby sibling. *The New York Times Magazine*, July 1, 2001, pp. 36 ff., available at <http://query.nytimes.com/gst/abstract.html?res=F60A10FF3B540C728CDDAE0894D9404482>.
53. Jaenisch, R., & Wilmut, I. (2001), note 10, *supra*.
54. Transplantation of human fetal tissues has proved effective in treating several conditions (see Crombleholme, T. M., Langer, J. C., Harrison, M. R., & Zanjani, E. D. (1991). Transplantation of fetal cells. *Am J Obstet Gynecol*, 164(1 Pt 1), 218-230; Bjorklund, A. (2000). Cell replacement strategies for neurodegenerative disorders. *Novartis Found Symp*, 231, 7-15; discussion 16-20;

- Freeman, T. B., Willing, A., Zigova, T., Sanberg, P. R., & Hauser, R. A. (2001). Neural transplantation in Parkinson's disease. *Adv Neurol*, 86, 435-445).
55. Rideout, W. M., 3rd, Hochedlinger, K., Kyba, M., Daley, G. Q., & Jaenisch, R. (2002). Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy. *Cell*, 109(1), 17-27.
56. DeWitt, N. (2001). Biologists divided over proposal to create human-mouse embryos. *Nature* 420, 255.
57. Chimeric embryos and animals containing human cells. Utility patent application submitted to the U.S. Patent and Trademark Office, December 12, 1997. See also Dickson, D. (1998). Legal fight looms over patent bid on human/animal chimaeras. *Nature* 392, 423.
58. See, for example, Thomas A. Magnani (1999). The patentability of human-animal chimeras. *Berkeley Tech Law Journal*;14,443-60; .James P. Daniel (1999) Note: Of Mice And 'Manimal': The Patent & Trademark Office's Latest Stance Against Patent Protection For Human-Based Inventions. 7 *J. Intell. Prop. L.* 99 and Mark Jagels (2000) Notes and Comments: Dr. Moreau has left the island: dealing with human-animal patents in the 21st century. 23 *T. Jefferson L. Rev.* 115.
59. Newman, S. A. (2002). The human chimera patent initiative. *Medical Ethics Newsletter (Lahey Clinic)*, 9, 4; 7.
60. Wadman, M. (1998) U.S. office claims right to rule on morality. *Nature* 393, 200.
61. Professor Philip Leder, Chair of the Genetics Department, Harvard Medical School and developer of the Oncomouse (see note 48, *supra*) stated on the National Public Radio program All Things Considered (April 5, 1998) "The creation of chimeras is an outlandish undertaking. No one is trying to do it at present, certainly not involving human beings." See <http://search.npr.org/cf/cmn/cmnpd01fm.cfm?PrgDate=04%2F05%2F1998&PrgID=2>
62. Hall, S. S. (2000). The recycled generation. *The New York Times Magazine*, January 30, 2000, pp. 30-35, 46, 74, 78-79.
63. Dickson, D. (1999). U.S. bid to patent human-animal hybrid fails. *Nature* 399, 626.
64. Buchanan, A., Brock, D. W., Daniels, N., & Wikler, D. (2000). *From chance to choice: genetics and justice*. Cambridge: Cambridge University Press, pp. 196-202; Stock (2002), *supra* note 15.
65. See Hubbard, R., & Newman, S. A. (2002). Yuppie eugenics. *Z Magazine*, March, 36-39.
66. Silver (1997), note 15 *supra*; Stock (2002), note 15 *supra*, at 104-111; see also the web site of the Extropy Institute at www.extropy.org/about/index.html.
67. BBC News report, Doctors defiant on cloning (Friday, 9 March, 2001) available at <http://news.bbc.co.uk/1/hi/sci/tech/1209716.stm>.

68. Caplan, A. L., McGee, G., & Magnus, D. (1999). What is immoral about eugenics? *BMJ*, 319(7220), 1284-1285.
69. Silver (1997) *supra* note 15, pp. 4-11; Thurow, L. (1999) *Creating Wealth: The New Rules for Individuals, Companies and Nations in a Knowledge-Based Economy* (New York: Harper Collins), p. 33.
70. *Gattaca* (1997). Sony Pictures.
71. Dawkins, R. (1989). *The selfish gene* (2nd ed.). New York: Oxford University Press.
72. See Newman, S. A. (1988). Idealist biology. *Perspect. Biol. Med.*, 31(3), 353-368. See also Müller, G. B., & Newman, S. A. (Eds.) (2003) *supra*, note 46 and Moss, L. (2003). *What genes can't do*. Cambridge, Mass.: MIT Press.
73. Crabbe, J. C., Wahlsten, D., & Dudek, B. C. (1999). Genetics of mouse behavior: interactions with laboratory environment. *Science*, 284(5420), 1670-1672.
74. Tang, Y. P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G. A., Zhuo, M., Liu, G., & Tsien, J. Z. (1999). Genetic enhancement of learning and memory in mice. *Nature*, 401(6748), 63-69.
75. Lemonick, M.D. (1999) Smart genes? A new study sheds light on how memory works and raises questions about whether we should use genetics to make people brainier. *Time* 154(10) (September 13), p. 54.
76. Wei, F., Wang, G. D., Kerchner, G. A., Kim, S. J., Xu, H. M., Chen, Z. F., & Zhuo, M. (2001). Genetic enhancement of inflammatory pain by forebrain NR2B overexpression. *Nat Neurosci*, 4(2), 164-169.
77. See Cello, J., Paul, A. V., & Wimmer, E. (2002). Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science*, 297(5583), 1016-1018; see also the recent report of plans by human genome mapper Craig Venter to build a partly artificial life form: <http://abc.net.au/news/newsitems/s732339.htm>.
78. See Lee, K. (1999). *The natural and the artefactual*. Lanham, MD: Lexington Books; See also McKibben, B. (2003). *Enough. Staying human in an engineered age*. New York: Times Books.
79. *Roger & Me* (1989). Warner Studios.
80. The 1984 Warnock Report in the U.K. (Report of the Committee of Inquiry into Human Fertilisation and Embryology, HMSO, Cmnd 9314) recommended a limit of 14 days for research with human embryos. This recommendation became law in 1990 as the Human Fertilisation and Embryology Act.
81. Kinsley, M. (200) Reason, faith, and stem cells. *Slate* (August 29); available at <http://slate.msn.com/id/88862/>.

82. See paragraph 137 of *Human cloning and human dignity: an ethical inquiry* (Report of the President's Council on Bioethics, July 2002), available at www.bioethics.gov/reports/cloningreport/fullreport.html#paragraph137.
83. The U.N. General Assembly, in resolution 56/93 of 12 December 2001, established an Ad Hoc Committee, open to all States Members of the United Nations or members of specialized agencies or of the International Atomic Energy Agency, for the purpose of considering the elaboration of an international convention against the reproductive cloning of human beings. See www.un.org/law/cloning/.
84. A House bill (H.R. 2505) banning all forms of cloning, sponsored by Rep. Dave Weldon, R-FL and Bart Stupak, D-MI, passed in the full House by a large bipartisan majority in 2001 and a modified version of this bill, retaining the full cloning ban (H.R. 534) passed in early 2003. Senators Sam Brownback, R-KS and Mary Landrieu, D-LA have recently introduced The Human Cloning Prohibition Act of 2003 (S. 245), essentially identical to H.R. 534.
85. See statement of participants in the Expert Panel on Inheritable Genetic Modification of Humans at the International Forum for Biophilosophy (6-8 December, 2002) at http://www.eurekaalert.org/pub_releases/2002-12/sari-ess121302.php.
86. Council for Responsible Genetics position paper on embryo manipulation available at <http://www.gene-watch.org/programs/cloning/embryo-statement.html>.
87. Stock (2002) at note 15, *supra*.