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Altered Nuclear Transfer: Scientific, Legal, and Ethical Foundations

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ALTERED NUCLEAR TRANSFER: SCIENTIFIC, LEGAL, AND ETHICAL FOUNDATIONS*

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Throughout the 20th century, the great advances in molecular and cell biology were accomplished largely through the study of limited biochemical processes apart from their natural place within the whole organism. By breaking down organic systems into their component parts and looking at living beings in terms of inanimate matter, we opened an era of scientific discovery that has culminated in the sequencing of the human genome. Now, however, as we move from genomics to proteomics and on to the investigation of developmental biology, we are returning to the study of whole living beings. When applied to human biology, this inquiry reopens the most fundamental questions concerning the very definition of life and the adequacy of our current scientific approach to inform discussion of the ethical and legal dilemmas raised by our new perspectives and powers.

These questions have been forced to the foreground of public awareness by our deepening controversy over embryonic stem cell (ESC) research, and more specifically by proposals for the production of cloned human embryos as a source of these cells. This conflict is sometimes framed as a battle between the subjectivity of personal religious belief and the objectivity of science, but it is far more fundamental than that. Distilled in this difficult debate are the most profound considerations concerning the relationship between the material, physio-chemical mechanisms and the moral meaning of human life.

A careful consideration of the foundations of this controversy can place it within a broader social and scientific context and bring into focus the crucial concerns that underlie our present political impasse. Drawing on this debate, particularly as it developed within the President's Council on Bioethics (on which I serve), we can discuss the immediate ethical issues in ESC research.

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At the same time, we can seek a wider understanding that may set the frame for scientific and medical advance in the era of developmental biology. It is clear that ESC research is just the first of many dilemmas that will challenge our traditional understanding of human life. Parthenogenesis, human-animal chimeras, human body parts grown in laboratories—these and a wide range of other emerging technologies make it imperative that we define the boundaries of humanity with clarity and precision in order to preserve the essential unity of the human person.

Through such a reflection on the meaning of human embodiment, we may draw a distinction between the material parts and the living whole that defines the locus of our moral concern. This distinction may suggest a way forward that will allow positive progress in biomedical science while preserving our most fundamental principles for the protection of human subjects and the defense of human dignity.

SOCIAL AND POLITICAL FOUNDATIONS

On August 9, 2001, President Bush, in his first major policy address to the nation, discussed what he described as "a complex and difficult issue, an issue that is one of the most profound of our time," the scientific and moral considerations in stem cell research.[1] He described the wide consultation and deep reflection that had gone into his consideration of the important yet competing goods at stake. And he announced that after several months of difficult deliberation he had decided that federal funds would be made available to support research with certain already extant ESC lines, but would not support research that would encourage any further destruction of human embryos. Some regarded this decision as a cynical political compromise while others saw it as a courageous acknowledgement of the important values on both sides on this difficult debate. Few, however, seemed to have understood either the historical foundations or the legal constraints within which this policy decision was made.

The issue of research on embryos and fetuses has been the subject of controversy and conflict for more than thirty years. With the advent of *in vitro* fertilization (IVF) in the late 1970s, the laboratory production of large numbers of human embryos became possible, and, with them, opportunities to study fertilization and early embryonic development. At the same time, strong objections were raised that taxpayers' dollars not be put toward

1. President George W. Bush, Address to the Nation on Stem Cell Research from Bush Ranch, Crawford, Texas (Aug. 9, 2001), *available at* http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html (last visited Sept. 1, 2006).

specific sorts of research that violates the moral convictions and sensibilities of a large portion of the American public.

Over the next decade and a half, a series of national commissions and advisory boards made various recommendations, but funding was effectively blocked; first by a congressional moratorium, and then by a de facto ban by the Department of Health and Human Services (HHS). In 1994, the National Institutes of Health (NIH) convened the Human Embryo Research Panel that made two recommendations. First, they recommended federal funding for some forms of research using embryos left over from IVF procedures. And second, they concluded that, in some circumstances, federal funds should support the direct creation of human embryos with the explicit intention of using them for research purposes.

President Clinton overruled the panel on the latter point, but he did accept the panel's first recommendation and permit the NIH to consider applications for funding of research using embryos left over from IVF procedures. Congress, however, did not endorse this course of action. Toward the end of 1995, before any funding proposals had been approved by the NIH, Congress attached language to the 1996 Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act (the annual budget bill that funds HHS and the NIH) prohibiting the use of federal funds for any research that destroys, discards, or seriously endangers human embryos, or that creates them for research purposes. This provision, known as the "Dickey Amendment,"[2] has been attached to the HHS appropriations bill each year since 1996. Everything about the subsequent debate must be understood in the context of these legal restrictions.

The Dickey Amendment effectively prohibits the use of federal funds to support any research that endangers or destroys human embryos; it does not prohibit the conduct of such research using private funding. The amendment expresses the ethical conviction, as represented in the United States Congress, that nascent human life should be protected, not instrumentally used in scientific research, however promising that research may be. And, while not proscribing such research, it affirms that, at the very least, the destruction of human embryos should not be supported or encouraged by taxpayer dollars.

The first year after the Dickey Amendment took effect the cloning of Dolly was announced, and just two years later the isolation of human ESCs from IVF embryos was accomplished. These developments, with their promise of new avenues of progress in science and medicine, caused great excitement within and beyond the scientific community. There were new calls for federal funding of embryo research and specifically for the creation

2. *See, e.g.*, Pub. L. No. 104-99, § 128, 110 Stat. 26.

of tissue compatible sources of ESCs by "therapeutic cloning." Most Members of Congress, however, did not change their position, and the Dickey Amendment has been reenacted by a large majority every year since—most recently with a provision prohibiting federal funding for the creation of cloned embryos.

This seemed to close the question of the use of federal funds for human ESC research, but in 1999 the General Counsel of the HHS argued that the wording of the law might permit the use of federal funds for the study of ESCs lines if the actual destruction of the embryos from which they were obtained was done off site and with private funds. Critics objected that such an interpretation was a technical loophole, consistent only with the letter but not the spirit of the law. President Clinton, however, accepted this approach and ordered that guidelines be drawn up for its implementation. But these guidelines were completed just before the end of the Clinton administration and were never put into practice.

When President Bush took office, in January 2001, these new regulations were put on hold pending review and the search for a way forward that would uphold the spirit (and not just the letter) of the Dickey amendment. The hope was expressed that, while continuing to withhold taxpayer support for the destruction of human embryos, some moral good might be drawn from the existing stem cell lines, given that the destructive acts that produced these lines could not now be undone. It was with this combination of concerns and intentions (and within the constraints of existing law) that, on August 9, 2001, the President announced the approval of federal funding of research using ESC lines created before the date of his announcement, estimated to be in the range of 60-70 lines. At the same time, acknowledging the serious ethical dilemmas across a range of issues raised by rapid advances in biotechnology, the President announced the establishment of the President's Council on Bioethics.

THE PRESIDENT'S COUNCIL DELIBERATIONS ON CLONING

President Bush set the following mandate for this Council: first, to monitor stem cell research and to recommend appropriate guidelines; then to consider more broadly the medical and ethical ramification of biomedical innovation. Further, he asked that the Council help serve as the conscience of the country, to engage and educate the public and to advise him and the nation by articulating the strongest arguments on all sides of these difficult issues. Our initial assignment was to address the controversy over human cloning, including its implications for stem cell research.[3]

3. In the account that follows I speak from the perspective of my own experience and not for the Council as a whole.

In reflecting on these dilemmas, it was immediately clear that we were at a defining moment in the progress of science. The choices our society makes now regarding ESCs (and other ethically controversial uses of biomedical technology) will put into place both the conceptual principles and practical foundations for future techniques of research and patterns of clinical practice. Once established, these moral precedents and scientific techniques will serve as the platform on which further practice will be built layer upon layer; like the foundations of a building, these will be difficult to retract or revise. There was an earnest intensity and sense of seriousness to the Council's discussion of these matters; we recognized that the issues were of broad significance for our civilization and, indeed, the future of our species. Therefore, the foundations we set had to transcend pre-established cultural preferences and partisan political agendas; they had to establish the basis for social consensus and global cooperation. We understood that without clear and distinct ethical principles, grounded in scientific evidence and reasoned moral argument, no policy could be effectively formulated or enforced.

The Council's discussion of the ethical issues centered around two poles, with the scientific and medical promise on the one hand, and the prudential and moral concerns on the other. Through a wide range of expert testimony and public comment, a compelling case was made for the importance of stem cell biology and its potential significance in medical application. The convergence of technologies following from advances in genomics, cytology, and developmental biology were delivering unprecedented powers for scientific research and intervention at the most basic levels of human biology. The fundamental questions of human embryology were opening up: studies of cell signaling, imprinting and differentiation, the positional cues that establish the body axes, body plan, and patterns of organogenesis. An understanding of these basic biological processes, together with a resource of ESCs from a full range of genotypes reflecting both normal and pathological potentials, would provide extraordinary tools for the modeling of disease, studies of toxicology and testing of pharmaceuticals. An estimated 150,000 babies are born every year in the US with congenital defects, and evidence suggests that a range of later pathologies have their foundations in early development. Furthermore, basic developmental processes, and their disordered dynamics, seem to be at work in a number of adult pathologies including some forms of cancer. Notwithstanding the obvious hyperbole in the political promotion of ESC research—"128 million Americans with incurable diseases might benefit"—it seemed clear that we truly were entering a new era of uncharted opportunity for scientific and medical advance. The age of regenerative medicine, cell therapies, tissue rejuvenation, and custom organ replacement seemed conceptually real even if not within immediate reach. Far more than just ESC science was at stake;

hanging in the balance were the wider scientific and medical prospects of this whole emerging era of discovery.

We recognized, however, that the same technological powers that offer such positive possibilities might also radically revise the traditional conduct of scientific research and its application in clinical medicine. Of central concern was the "embryo issue." All of the other considerations, including the troubling issues related to the use of human eggs for projects of nuclear transfer, seemed to be more matters of prudent regulation than disagreements over fundamental principle. But with regard to the moral standing of the embryo, it was apparent that deep differences in basic assumptions were precluding social consensus. Yet it was not simply personal beliefs or different cultural traditions, nor was it lack of scientific understanding that was causing the divide. It seemed clear that, within the current frame of discussion, we lacked conceptual tools and terms of understanding adequate to bring resolution. It was as though the conceptual revolution that had opened such extraordinary avenues of advance in basic biology had now delivered dilemmas which its analytic and reductive assumptions and methodologies were inadequate to address.

To resolve the conflict concerning the human embryo, we needed to find a framework to explore the most fundamental questions concerning the very source of our moral standing and the ways human life is morally different from the other life forms that we use respectfully but instrumentally for human good. We had to ponder what potential capabilities and manifestations of form or function, endow a developing life with human value and inviolability. Similarly, we had to ask what lack of these qualities or capacities rightly reduces biological material to mere matter and information, available for instrumental use in projects of medical science.

Ultimately, we recognized that more time was needed for a thorough and thoughtful consideration of the moral status of the human embryo. The Council as a group acknowledged that this was not simply an issue of balancing competing goods, but that fundamental principles were at stake that would not be amenable to compromise or negotiated resolution. After extended deliberation, a majority of the Council felt that the wisest course of action for our nation was a four-year moratorium on cloning for biomedical research ("CBR"). Several members of the Council added personal statements to an appendix of this report. In my own comments, I expressed the hope that the period of the moratorium might be used to seek a scientific solution to our national impasse and described one possible technological approach to which I gave the name "Altered Nuclear Transfer" ("ANT").

The Council's recommendations concerning cloning were never implemented as specific legislation, but the constraints of the Dickey Amendment and the guidelines of the President's executive order against

embryo destruction effectively precluded federal funding both of research cloning and the production of new ESC lines from IVF embryos. Eighteen months after our report on cloning, the Council issued a broader analysis of the social, legal and scientific dimensions of stem cell research entitled "Monitoring Stem Cell Research." This report included a short discussion of scientific proposals to obtain embryonic stem cells by means that do not require the destruction of human embryos. A year later, in May 2005, we returned to this topic and issued a White Paper entitled, "Alternative Sources of Human Pluripotent Stem Cells." Our report outlined a range of proposals that might allow the procurement of pluripotent stem cells (cells with the same functional properties as embryonic stem cells), without the destruction of human embryos. Among the proposals discussed and recommended for preliminary exploration in animal models were two approaches that would allow the production of patient-specific pluripotent stem cell lines of any genetic type: direct reprogramming and ANT. In what follows I will draw on the moral and scientific foundations of the ANT proposal to discuss how our nation may open a way forward for stem cell research and, at the same time, set guiding principles that will allow ongoing advance as we enter the era of developmental biology.

THE MORAL MEANING OF EMERGING LIFE

Assessing the moral status of the embryo begins with affirming the moral status of human life in general.[4] The principle that human life constitutes the fundamental good serves as the cornerstone of law for our civilization. In no circumstance is the intentional destruction of the life of an innocent individual deemed morally acceptable. This valuing of human life is indeed the moral starting point for both advocates and opponents of CBR, and it flows from the reciprocal respect that we naturally grant as we recognize in the other a being of moral equivalence to ourselves. It leads to the principle of inviolability of human life and the prohibition against using human life instrumentally.

From the perspective of those who object to research that involves the destruction of embryos, an evaluation of the moral significance of human life must take into account the full procession of continuity and change that is essential for its development. From this perspective, we must consider how, from conception, our unique genetic endowment organizes and guides

4. This section draws heavily from the following source: William B. Hurlbut, *Personal Statement* to PRESIDENT'S COUNCIL ON BIOETHICS, HUMAN CLONING AND HUMAN DIGNITY: AN ETHICAL INQUIRY 267 (President's Council on Bioethics 2002), http://www.bioethics.gov/reports/cloningreport/appendix.html#hurlbut.

the expression of our particular nature in its species and individual character. With regard to fundamental organismal existence (and inviolable moral standing), the act of fertilization is a leap from zero to everything. The gametes, which are properly understood as instrumentalities, parts of the bodies of the parents, are not, in themselves, potential life; they are potential causes of conception. The gametes themselves cease to be; they do not unite in the sense of merely forming a larger composite, but bring into existence a whole new entity, a new human life.

In both character and conduct, the zygote (the one cell embryo) and subsequent embryonic stages differ from all other cells or tissues of the body; they contain within themselves the organizing principle of the full development of a human being. This is not an abstract or hypothetical potential in the sense of mere possibility. Rather, it is a self-contained "potency," an engaged and effective potential-in-process, an activated dynamic of development in the direction of human fullness of being.

Unlike an assembly of parts in which a manufactured product is in no sense "present" until there is a completed construction, a living being has a continuous unfolding existence that is inseparable from its emerging form. The form is, itself, a dynamic process rather than a static structure. In biology, the whole (as the unified organismal principle of growth) precedes and produces the parts. It is this implicit whole, with its inherent potency, that endows the embryo with its human character and therefore, from this perspective, its inviolable moral status. To interfere in its development is to transgress upon a life in process. The principle of this analysis will apply to any entity that has the same potency of a human embryo produced by natural fertilization, regardless of whether it is the product of IVF, cloning, or other processes.

ACCRUED MORAL STATUS

The major alternative to the view that an embryo has an inherent moral status is the assertion that moral status is an accrued or accumulated quality related to some physical dimension of form or function. Several arguments have been put forward for this position.

Gastrulation

One such accrual argument is based on the assumption that before gastrulation (which begins with the formation of the primitive streak around the fourteenth day), the embryo is an inchoate clump of cells with no actuated drive in the direction of distinct development. It is argued that the undifferentiated quality of the blastocyst (the 4-5 day embryo) justifies its disaggregation for the procurement of stem cells, while the evident

organization at gastrulation reveals an organismal integrity that endows inviolable moral status to all subsequent stages of embryological development.

Scientific evidence, however, supports the opposing argument, i.e., that from conception there is an unbroken continuity in the differentiation and organization of the emerging individual life. The anterior-posterior axis appears to be already established within the zygote; the first cell divisions are asymmetric and early differences in gene expression suggest distinct cell fates; and an overall pattern of integrated unity seems to indicate a coherence of coordinated growth from the beginning.

All this implies that the changes at gastrulation do not represent a discontinuity of ontological significance (a change in the nature of being) but merely the visibly evident culmination of more subtle developmental processes at the cellular level that are driving in the direction of organismal maturity.[5]

Twinning

Another argument for accrued moral status is that, as long as an embryo is capable of giving rise to a twin, it cannot be considered to have the moral standing of an individual. Yet monozygotic twinning, which occurs in just one in 240 births, does not appear to be either an intrinsic drive or a random process within embryogenesis. Rather, it results from a disruption of normal development by a mechanical or biochemical disturbance of fragile cell relationships. This provokes a compensatory repair, but with the restitution of integrity within two distinct trajectories of embryological development.[6]

In considering the implications of twinning for individuation, one might better ask the question from the opposite perspective. What keeps each of the cells of the early embryo from becoming a full embryo? Clearly, crucial relational dynamics of position and intercellular communication are already at work establishing the unified pattern of the emerging individual.[7] From

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5. R. L. Gardner, *Specification of Embryonic Axes Begins Before Cleavage in Normal Mouse Development*, DEVELOPMENT, 2001, at 839–47.; L. Grabel et al., *Using EC and ES Cell Culture to Study Early Development: Recent Observations on Indian Hedgehog and BMPs*, 42 INT'L J. DEVELOPMENTAL BIOLOGY 917, 917–25 (1998); K. Piotrowska & M. Zernicka-Goetz, *Role of Sperm in Spatial Patterning of the Early Mouse Embryo*, NATURE, 2001, at 517–21.

6. A.L.E.da Costa et al., *Monozygotic Twins and Transfer at the Blastocyst Stage After ICSI*, 16 HUMAN REPRODUCTION 333, 333-36 (2001).

7. Q.T. Wang et al., *A Genome-Wide Study of Gene Activity Reveals Developmental Signaling Pathways in the Preimplantation Mouse Embryo*, 6 DEVELOPMENTAL CELL 133, 133-44 (2001).

this perspective, twinning is not evidence of the absence of an individual, but of an extraordinary power of compensatory repair that reflects more fully the potency of the individual drive to fullness of form, even in the earliest stages of embryonic human life.

Implantation

Some have argued that the implantation of the embryo within the uterine lining of the mother constitutes a moment of altered moral status. Implantation, however, is actually a process that extends from around the sixth or seventh day to about the eleventh or twelfth day, when the utero-placental circulation is established. The more complex circulatory exchange of the placenta simply extends the earlier relationship between mother and embryo, in which diffusion of essential nutrients and growth factors sustain the life and nourish the growth of the developing embryo. Implantation, then, must be viewed as just another step in a continuum of ongoing intimate dependence, all occurring along the trajectory of natural development that begins with conception and continues into infancy. This continuity implies no meaningful moral marker at implantation.

Some argue in the case of IVF, however, that before implantation the embryo has no future prospects of development and therefore no natural potential on which to base moral valuation. They speak of the "unenabled" character of these entities, and claim this deficiency of context justifies their use in scientific research. However, depriving an embryo of its environment does not change its intrinsic nature. To deny the moral standing of the pre-implantation embryo shifts the moral basis away from its intrinsic nature and places it entirely within the realm of external intention, subject to the whim of the research scientist.

Function

Most other arguments relate in some way to the onset of a specific function or capacity. The first and most obvious problem is that the essential functions (and even their minimal criteria and age of onset) are diverse and arbitrarily assigned. Generally, they relate to the onset of sentience, awareness of pain, or some apparently unique human cognitive capability such as reflective self-consciousness.

This approach raises a number of disturbing ethical questions. If human moral worth is based on actual manifest functions, then does more of that function give an individual life a higher moral value? And what are we to make of the parallel functional capacities in animals that we routinely sacrifice for food and medical research? Furthermore, what becomes of human moral status with the degeneration or disappearance of such

functions? While we might argue that our relational obligations change along with changes in function, such as occur with senile dementia, our society would not sanction a utilitarian calculus and the purely instrumental use of such persons, no matter how promising the medical benefits might be.

More fundamentally, from a scientific perspective, there is no meaningful moment when one can definitively designate the biological origins of a human characteristic such as consciousness. The human being is an inseparable psycho-physical unity. Our thinking is in and through our bodily being, and thus the roots of our consciousness reach deep into our development. The earliest stages of human development serve as the indispensable and enduring foundations for the powers of freedom and self-awareness that reach their fullest expression in the adult form.

From the perspective of this analysis we can conclude that the embryo has a moral status that is inherent and not an accrued or accumulated quality, and that moral status must begin with the zygote (or clonote, as some call the one cell product of nuclear transfer). Because it is intrinsic, such moral status, as distinguished from developing relational obligations, is therefore independent of: (a) the means by which the entity came into being (sexual intercourse, IVF, cloning or other); (b) the present location of the entity (in or outside of a natural or artificial womb); and (c) the intention according to which such entity was produced (human reproduction, scientific and medical research, medical therapeutic use, or other).

Failures of Fertilization

While inviolable moral standing is attributed to the human embryo, not every combination of sperm and egg initiates a life; recent scientific evidence suggests that many, perhaps most, early natural initiations in reproduction result in 'failures of fertilization.' If the zygote lacks essential elements, such as the necessary complement of chromosomes, epigenetic configuration and cytoplasmic factors for gene expression, it will also lack an inherent potency, a self-organizing drive in the direction of the mature form. It will not have the characteristics necessary for it to be an organism, and therefore will not be rightly considered a human embryo. Naturally occurring failures of fertilization may still proceed along partial trajectories of organic growth, however. For example, some gross abnormalities in the combination or configuration of chromosomes will form a blastocyst but will not exhibit the ordered growth and capacity for implantation that characterize a natural embryo.[8] Even an egg without a nucleus, when artificially activated, has the developmental power to proceed through

8. A. Boue et al., *Cytogenetics of Pregnancy Wastage*, 4 ADVANCED HUM. GENETICS 1, 1-57 (1985).

several cell divisions, yet clearly it is not an embryo—or an organism at all. Like a spinning top, the cells contain the molecular elements for a certain biological momentum that propels a partial trajectory of development, but unlike a normal embryo, they are unable to bootstrap themselves into becoming an integrated and self-regulating organism.

Some of these aberrant products of fertilization that lack the qualities and characteristics of an organism, appear to be capable of generating embryonic stem cells or their functional equivalent.[9] Mature teratomas are tumors (generally benign) that generate all three primary embryonic cell types as well as more advanced cells and tissues, including partial limb and organ primordia—and sometimes hair, fingernails and even fully formed teeth. Yet these chaotic, disorganized, and nonfunctional masses are like a bag of jumbled puzzle parts, lacking entirely the structural and dynamic character of organisms. Neither medical science nor the major religious traditions have ever considered these growths to be 'moral beings' worthy of protection, even though they appear to produce embryonic stem cells.

SYSTEMS BIOLOGY

This example of disorganized growth provides a window into an important new conceptual realm in the study of life. Through systems biology, we are beginning to recognize how even a small change of one or a few genes can affect the entire downstream working of an enormous network of biochemical processes. Systems biology offers us the view of an organism as a living whole, a dynamic network that is more than the sum of its parts.

The very word organism implies organization, an overarching principle of unity, a cooperative interaction of interdependent parts subordinated to the good of the whole. As a living being, an organism is an integrated, self-developing and self-maintaining unit under the governance of an immanent plan. The philosopher Robert Joyce explains: "Living beings come into existence all at once and then gradually unfold to themselves and to the world what they already but only incipiently are." Joyce continues: "No living being can become anything other than what it already essentially is."[10] For an embryonic organism, this implies an inherent potency, an activated drive toward the mature human form. By its very nature, an embryo is a developing being, its wholeness is defined by both its manifest expression

9. J.A. Byrne et al., *From Intestine to Muscle: Nuclear Reprogramming through Defective Cloned Embryos*, 99 PROCEEDINGS OF THE NAT'L ACAD. SCI. 6059, 6059–6063 (2002).

10. Robert E. Joyce, *Personhood and the Conception Event*, 52 NEW SCHOLASTICISM 97, 97-109 (1978).

and its latent potential; it is the phase of human life in which the organismal whole produces its organic parts.

Such a conception of the biological organism transcends the "nothing but its parts" perspective of reductionism. It adds the understanding that a living being is not merely a mechanism, but rather, a dynamic system, an interactive web of interdependent processes that expresses emergent properties not apparent in the biochemical parts.[11] Within this dynamic self-sustaining system is the very principle of life, the organizing information and coordinating coherence of a living being. It is this over-arching harmony of the whole, its internal balance, that distinguishes an organism from the mere physio-chemical material of its parts. This inherent principle of organic unity, in turn, provides the physical identity and continuity (and therefore the moral continuity) of a human being from conception to natural death.

The new perspective of systems biology forms the intellectual grounding for appreciating the physical and moral difference between an embryo and an entity such as a teratoma. A teratoma is an inadequately constituted biochemical system, a partial trajectory of development with an inherent potential for only incomplete and unorganized growth. With the full complement of coordinated parts, an organismal system subsumes and sustains the parts; it exerts a downward causation that binds and balances the parts into a patterned program of integrated growth and development. Incompletely constituted or separated from the whole, the parts, as subsystems of growth (cells, tissues and organs), may temporarily proceed forward in partial development, but, without the self-regulating powers of the organismal system, they will ultimately become merely disorganized cellular growth. This distinction could provide the principle for the resolution of our current controversy over ESC research. Altered Nuclear Transfer (ANT) proposes that small but precisely selected alterations will allow the harnessing of partial developmental trajectories, subsystems of growth, apart from their full natural context in order to produce ES cells.

ALTERED NUCLEAR TRANSFER

As discussed above, natural conception signals the activation of the organizing principle for the self-development and self-maintenance of the full human organism. In the language of stem cell biology, this capability is termed "totipotency," the capacity to form the complete organism. A naturally fertilized egg, the one cell embryo, is totipotent. In contrast, the term "pluripotency," designates the capacity to produce all the cell types of

11. The Greek root of our word organ means tool: an organism is an organic unity whose parts subserve the whole.

the human body but not the coherent and integrated unity of a living being. ESCs are merely pluripotent. This is a difference between the material parts and the living whole.

In standard nuclear transfer, the cell nucleus is removed from a somatic cell and transferred into an oocyte that first has had its own nucleus removed. Following the transfer, the oocyte has a full complement of DNA and, after it is electrically stimulated, starts to divide like a naturally fertilized egg. This is how Dolly the sheep was produced. ANT uses the technology of nuclear transfer, but with a preemptive alteration that assures that no embryo is created. The somatic cell nucleus or the enucleated egg's contents (or both) are altered before the somatic cell nucleus is transferred into the egg. The alterations cause the somatic cell DNA to function in such a way that no embryo is generated, but pluripotent stem cells are produced.[12] The laboratory construct that is produced by ANT has only partial developmental potential. It lacks the integrated unity that characterizes a human embryo, so the above ethical analysis would permit harvesting its ESCs.

ANT is a broad concept with a range of possible approaches; there may be many ways this technique can be used to accomplish the same end. As described in a January 2006 paper in *Nature* magazine, stem cell biologist Rudolf Jaenisch has established the scientific feasibility of one method of ANT. In a series of dramatic mouse model studies, he procured fully functional ESCs from a construct that is radically different in developmental potential than a natural embryo.[13] Using the technique of RNA interference, he was able to reversibly silence the gene *Cdx2* in the donor nucleus before nuclear transfer to the enucleated egg. And a study just one month later in the journal *Science* suggests that it may be possible to achieve the goals of ANT through the preemptive silencing of *Cdx2* in the egg even before the act of nuclear transfer, thereby producing the biological (and moral) equivalent of a single lineage tissue culture.[14] This article showed that in mice, messenger RNA for *Cdx2* is present in the egg and asymmetrically distributed in the first cell division after fertilization. This asymmetric distribution of *Cdx2* messenger RNA directs the cells at the two-cell stage to form two distinct cell lineages. One of the cells at the two-cell stage goes on

12. Hearing on An Alternative Method for Obtaining Embryonic Stem Cells, Subcomm. of Labor, Health and Human Services, Education of the S. Comm. on Appropriations, 108th Cong. (Oct. 19, 2005) (testimony of Rudolf Jaenisch, M.D.).

13. A. Meissner & R. Jaenisch, *Generation of Nuclear Transfer-Derived Pluripotent ES Cells from Cloned Cdx2-Deficient Blastocysts*, NATURE, Jan. 12, 2006, *available at* http://www.nature.com/nature/journal/v439/n7073/abs/nature04257.html.

14. K. Deb et al., *Cdx2 Gene Expression and Trophectoderm Lineage Specification in Mouse Embryos* 311 SCI. 992, 992-96 (2006).

to become the trophectoderm and forms the outer layer of the embryo (and later the extra-embryonic membranes, including the placenta). The other cell forms the 'inner cell mass,' which is the source of embryonic stem cells. By selective silencing of *Cdx2*, the authors were able to produce an unorganized mass composed exclusively of cells with the character of inner cell mass.

Unfortunately, the news reports describing the laboratory construct produced by ANT have emphasized the inability to form the placenta. The preemptive alteration of ANT, however, results in a failure of formation that is earlier and far more fundamental than a mere inability to implant in the womb. Due to the alteration, the first division into different cell lineages does not occur, the body axes (top/bottom, front/back) cannot form, and the basic human body plan is never established. There is no evidence of unifying organization and no capacity to from a functional blastocyst, the first structure with a clear distinction of parts. At this stage, such a critical 'deficiency' is more rightly considered an 'insufficiency,' not a defect *in* a being, but an inadequacy at such a fundamental level that it precludes the coordinated coherence and developmental potential that are the defining characteristics of an embryonic organism.

ANT-OAR

Another variation of ANT called Oocyte Assisted Reprogramming (ANT-OAR) has been put forward by Markus Grompe, Director of the Stem Cell Center at Oregon Health Science University. In this variation of ANT, alterations of the nucleus of the adult body cell and the enucleated egg's contents before nuclear transfer would force early expression of genes characteristic of a later and more specialized cell type that is capable of producing pluripotent stem cells. Scientific evidence suggests that this technique could be combined with the direct alteration of *Cdx2* described above to provide a complementary approach with increased scientific and moral certitude. Such a creation, from its very beginning, would never have the actual configuration or potential for development that characterizes a human embryo. As documented on the Ethics and Public Policy Center website this proposal has drawn wide endorsement from leading scientists, moral philosophers and religious authorities.[15]

15. Joint Statement, Ethics and Public Policy Center, Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming (June 20, 2005), *available at* http://www.eppc.org/publications/pubID.2374/pub_detail.asp.

The Preemptive Nature of ANT

The crucial principle of any technical variation of ANT, however, must be the preemptive nature of the intervention. This process does not involve the creation of an embryo that is then altered to transform it into a non-embryonic entity. Rather, the proposed genetic alteration is accomplished *ab initio*: the laboratory construct is brought into its very existence with a genetic structure insufficient to generate a human embryo. From the beginning, and at every point along its development, it cannot be designated a living being. If such a limited biological construct were accorded a certain cautionary respect—as with all human tissues—this project would not compromise any fundamental moral principles. Moreover, such techniques could be developed using animal models and confidently extended to work with human cells without engaging in research that involves the destruction of human embryos.

The Advantages of ANT

ANT would provide a uniquely flexible tool for embryonic stem cell research. Embryos left over from IVF procedures represent a limited pool of genotypes, all (presumably) from infertile couples. Furthermore, the genomes of these embryos have never proven their capacity to form an organism and, due to mutations, recombinations and reassortment of alleles in gametogenesis, may carry unrecognized genetic defects. Embryonic stem cells produced by ANT, however, would have genotypes of proven potential from an adult donor. Furthermore, ANT could provide a full range of genotypes, including patient-specific genetic types for tissue-compatible transplantation. In addition, this technique would offer a far wider range of scientific and medical possibilities than embryonic stem cell lines derived from "left over" IVF embryos, including generation of diverse and pre-designed stem cell lineages for disease modeling and pharmaceutical development. Indeed, in allowing controlled and reproducible experiments, ANT might serve as a temporary bridge to technologies such as direct nuclear reprogramming. Furthermore, in establishing a morally acceptable means for the procurement of ESCs, this important realm of scientific investigation would be opened to federal funding and the advantages of both broad public support and cooperative research collaboration on a national level.

ANT would also unburden ESC research from the additional ethical concerns of the "left over" IVF embryos, including the attendant clinical and legal complexities in a realm of great personal and social sensitivity. The one remaining link with IVF, the procurement of oocytes, is a subject of intense scientific research and there appear to be several prospects for

obtaining eggs without the morally dubious and expensive super-ovulation of female patients.

CONCLUSION

As we enter the era of developmental biology, there will be many moral dilemmas; the current conflict over ESCs is just the first in a series of difficult controversies over the experimental use of emerging life that will require that we define with clarity and precision the boundaries we seek to defend. Similar concerns were raised over the past century as we came to understand that human parts such as cells, tissues, and organs are not themselves alive in a moral sense. Now, as we deepen our scientific inquiry into human development, we may once again find a way forward by studying parts apart from their place within the living whole. This will be a more difficult challenge, however, both technically and conceptually; our natural intuitions identify the dynamics of developing systems with the moral meaning of living beings.

With the exploration of Altered Nuclear Transfer we open a realm of intellectual dialogue and creative scientific investigation in the search for a solution to our current impasse over the procurement of embryonic stem cells. Such a solution must be grounded in deep ethical reflection and careful preliminary studies with animal cells. The incommensurate good of human life, and the corresponding danger of its instrumental use, means that the highest levels of caution must prevail as we proceed forward with this project. We must initiate the cooperative dialogue that is essential to frame the moral principles that can at once defend human dignity and promote the fullest prospects for scientific progress and its medical applications. The constructive engagement of science and moral philosophy is a crucial component of this dialogue—the very preservation of our humanity may depend on it.

CODA

In May 2005, less than two weeks after publication of the White Paper on "alternative sources" by the President's Council on Bioethics, the House approved legislation (H.R.810) that would override President Bush's executive order and allow federal funding of new stem cell lines created from IVF embryos. In the succeeding months there was increasing media attention to the quest for a technological resolution to our nation's impasse over embryonic stem cell research. The expected mid-summer vote in the Senate on H.R 810 was postponed due to an inability to establish a 'unanimous consent' agreement. Without such an agreement the House bill would have been subject to amendment and forced into committee to

reconcile the House and Senate version, or possibly even into filibuster. Just before the summer recess, however, Senate Majority Leader William Frist announced a change in his political position to one of support for the pending legislation, and promised to bring the bill to the floor in a timely manner.

Over the succeeding twelve months the politics of embryonic stem cell research grew increasingly bitter. Finally, in July 2006, a unanimous consent agreement was reached by packaging the House bill (H.R.810) with two other bills, including one (S.2754) to mandate federal support for projects such as ANT seeking 'alternative sources' of pluripotent stem cells. This legislation was co-sponsored by Pennsylvania Senators Rick Santorum and Arlen Specter, two politicians with opposing views on moral matters related to stem cell research, and represented a rare but hopeful movement toward common ground that could allow forward progress within social consensus. Meanwhile the President reaffirmed the principle of his August 9, 2001 executive order, and promised to veto any legislation that would seek to overturn his prior ruling.

On July 18, 2006, the Senate voted 63-37 for passage of H.R. 810, but this left the bill short of the 2/3 needed to override a presidential veto. On the same day, the "alternative sources" bill passed in the Senate by a vote of 100-0. This legislation was then sent immediately to the House with the hope of delivering both bills to the President at the same time. This scenario, however, was not to be. The proponent of H.R.810, in an apparent effort to deprive the President of any pro-stem cell legislation to counterbalance his veto, managed to muster enough votes to prevent the 2/3 needed under the procedural rules necessary for passage of the legislation without amendment.

The following day, in a formal statement in the East Room of the White House, the President cited the long-standing legislative tradition on which his policy is built and strongly reaffirmed his administration's position on research that involves the destruction of human embryos. Surrounded by young couples holding "snowflake" babies, born though embryo adoption, he said, "These boys and girls are not spare parts. They remind us of what is lost when embryos are destroyed in the name of research." And, reproaching Congress for failing to pass the 'alternative sources' legislation, he announced his intention to issue a Presidential Directive to promote this "vital and ethical" approach toward a resolution of our nation's difficult impasse over embryonic stem cell research.