

OVERVIEW

STEM CELLS FROM A BIOLOGICAL PERSPECTIVE: WHAT THEY ARE, WHERE THEY ARE FOUND, AND WHAT CAN BE DONE WITH THEM

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Cells are the smallest living units of living systems. They can respire, respond, and reproduce. A single human cell, however, or even a conglomerate of human cells, does not a human being make. In fact, the human body is made up of trillions of cells that are organized into specialized tissues and organs, and many of these cells die each day and need to be replaced by new ones. Unspecialized and undifferentiated cells that are dormant are called upon to renew or repair the body; these are the so-called stem cells.

A given human being is never the same conglomerate of cells from day to day, but somehow remains the same person. It is the nervous system that provides the property (or, perhaps more correctly, the illusion) of *sameness*, i.e., the continuity of self. It is the organization and the activity of neuronal cells that allows for the emergence of the mind—for awareness, memory, and self-identity. It is the nervous tissue, therefore, that is most identified with “humanness.” For this reason, the taking of stem cells from embryos in which no nervous tissue has yet appeared has received more acceptance than the taking of stem cells from more developed embryos or fetuses.¹

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¹ See generally Myriam Marquez, *Life Saving Embryos: It’s Immoral to Destroy Them*, ORLANDO SENTINEL, July 6, 2001, at A17 (Editorial), 2001 WL 9195501; *The Right Call on Embryos*, Omaha World-Herald, Feb. 25, 2001, at 10B (Editorial), 2001 WL 9569367 (providing some discussion on the scientific differences between an embryo and a fetus, as well as some data on the public perception of this difference and how this has influenced

Recent evidence indicates that even in the nervous system some cell turnover can occur,² but this seems limited to a few specific areas and has not been observed in a non-pathological or non-treated human patient. In other words, evidence so far has only been gathered from autopsies of chemotherapeutically-treated patients. The assumption that brain cell turnover occurs normally rests mainly on animal studies and, even there, turnover is very limited.³

Stem cells are undifferentiated cells and have the potential to become many cell types and to form various tissues by mitosis (multiplication) and differentiation (specialization). The mother of all stem cells is the zygote, a fertilized egg cell that can give rise to every part of the human body and, therefore, is considered totipotent—capable of forming both embryonic and extraembryonic tissue (placenta and yolk sac). Totipotency is also characteristic of cells from the next six cell divisions of the zygote. During the first week (around day three) the zygote has divided to form a solid ball of cells called the morula (thirty-two cells, each of which is a totipotent stem cell).⁴ One could theoretically harvest the cells of the morula prior to blastocyst formation; each of these thirty-two cells is capable of producing both placental and embryonic tissue and therefore has totipotentiality while the inner cell mass of a later embryo has pluripotentiality. By the end of the first week of embryonic development, a blastocyst (a ball of cells with a cavity containing an oval disc of cells—the embryonic disc) is present containing an inner mass of 128 cells.⁵ In natural development this point in time would also coincide with implantation in the uterine wall, although not all blastocysts implant—some pass out the uterus. It should be noted that if a splitting of the inner cell mass were to occur at this time, identical twins (or even triplets) could develop in the implanted embryo.⁶

Human embryonic stem cells (HESCs) are usually isolated manually from the inner cell mass of an embryo grown in vitro by a skilled technician using a micromanipulator-controlled micropipette and microscope. These inner mass cells, if separated and cultured

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² See Jack Price & Brenda P. Williams, *Neural Stem Cells*, 11 CURRENT OPINION IN NEUROBIOLOGY 564, 564–66 (2001); Bettina Seri et al., *Astrocytes Give Rise to New Neurons in the Adult Mammalian Hippocampus*, 21 J. NEUROSCI. 7153, 7153–60 (2001).

³ See Ron McKay, *Stem Cells—Hype and Hope*, 406 NATURE 361, 361–64 (2000).

⁴ See KEITH L. MOORE, *THE DEVELOPING HUMAN* 2 (2d ed. 1977).

⁵ See *id.* at 2.

⁶ See *id.*

in vitro, can give rise to all tissue types (pluripotency), but not a placenta. Therefore, they have no potential to develop into a human being. In the second week, the inner cell mass divides into three layers and these cells are considered to be multipotent, capable of becoming a number of different tissue types, but not as many types as a pluripotent cell can. As development proceeds (i.e., additional cell divisions), these cells become more differentiated and their multipotentiality and their self-renewal ability decreases, making them less desirable for treatment or transplant. In the third week of development, we see a primitive streak and then a neural groove indicating that progenitor cells of the nervous system have taken up their positions. It is both scientifically and ethically preferable to harvest stem cells before this time.

During development various stem cells take a “fork in the road” of development, and proceed on a path of differentiation toward specialization, thereby becoming committed to being a specific cell type. They do not “backtrack” under normal conditions, although backtracking to a limited extent has been recently achieved in vitro.⁷ Some stem cells halt their differentiation midstream and reside in the adult body as pools of “committed” stem cells tucked away here and there—difficult to detect and isolate (sometimes referred to as progenitor cells because they will give rise to cells of a particular lineage). There is some question about the extent of commitment these adult stem cells possess. Are some of them as “naïve” as embryonic stem cells? Unique markers expressed at the stem cell surface are being discovered as this paper is written, and these will make stem cell isolation and characterization easier.⁸

Normal stem cells seem to obey the “Hayflick limit,”⁹ i.e., they will divide approximately fifty times and then undergo senescence. Maintaining stem cell inventories required starting new cultures from new embryos. A breakthrough in culturing embryonic stem cells occurred in 1998 when James Thomson of the University of Wisconsin discovered a line of so-called immortal embryonic stem cells that do not seem to obey the Hayflick limit.¹⁰ At least sixty-

⁷ See Irving L. Weissman, *Stem Cells: Units of Development, Units of Regeneration, and Units in Evolution*, 100 CELL 157, 157–68 (2000), available at http://www.med.umich.edu/biochem/courses/coursepages/biochem491/BC491_DOCS/morrison_handout.pdf.

⁸ See Vi T. Chu & Fred H. Gage, *Chipping Away at Stem Cells*, 98 PROC. NAT'L ACAD. SCI. USA 7652, 7652–53 (2001), at <http://www.pnas.org>.

⁹ See L. Hayflick, *The Illusion of Cell Immortality*, 83 BRIT. J. CANCER 841, 841–46 (2000). See generally L. Hayflick, *Hormesis, Aging and Longevity Determination*, 20 HUM. & EXPERIMENTAL TOXICOLOGY 289, 289–91 (2001).

¹⁰ See James A. Thomson & Vivienne S. Marshall, *Primate Embryonic Stem Cells*, 38 CURRENT TOPICS DEVELOPMENTAL BIOLOGY 133, 133–65 (1998).

four lines are now known, but their immortality has not been established.¹¹ Each line is also a little different from its cohorts. It may be said that a stem cell is a stem cell as a rose is a rose, each type beautiful in its own right, having a lot in common with its peers, but slightly different in certain, potentially important characteristics.

Another category of stem cells is the adult stem cell. A few years ago it was thought that only certain tissues—such as bone marrow, skin, liver, and most organs except for nerve and skeletal muscle—had adult stem cells. In some bird species, seasonal hormonal and neural activity of the brain have been shown to cause new brain cell production in mature birds.¹² More recent evidence indicates that brain and muscle seem to have stem cells as well, but they normally do not get activated to repair injuries as the stem cells in other tissues do.¹³ In culture with the appropriate factors added, adult human stem cells from bone marrow have been coerced to divide and/or differentiate and, when transplanted successfully, to take up residence and become functional in a host.¹⁴

Some “reprogramming” can occur in development, provided that the proper micro-environmental factors are present. Recent research has shown that some adult stem cells when transferred to another tissue take on the characteristics of that tissue,¹⁵ e.g., bone marrow cells to muscle cells, bone marrow cells to nerve cells,¹⁶ and the reverse;¹⁷ glial cells to nerve cells;¹⁸ neural stem cells to blood cells;¹⁹ HESCs to heart tissue;²⁰ mesenchymal stem cells stimulate

¹¹ Nat'l Insts. of Health (NIH), *NIH Update on Existing Human Embryonic Stem Cells*, (Aug. 27, 2001), at <http://www.nih.gov/news/stemcell/082701list.htm>.

¹² See Arturo Alvarez-Buylla, Marga Theelen & Fernando Nottebohm, *Mapping of Radial Glia and of a New Cell Type in Adult Canary Brain*, 8 *J. NEUROSCI.* 2707, 2707–12 (1988).

¹³ See Fred H. Gage, *Mammalian Neural Stem Cells*, 287 *SCIENCE* 1433, 1433–38 (2000).

¹⁴ See Fred H. Gage et al., *Survival and Differentiation of Adult Neuronal Progenitor Cells Transplanted to the Adult Brain*, 92 *PROC. NAT'L ACAD. SCI. USA*, 11879, 11880–81, 11882 (1995), at <http://www.pnas.org>.

¹⁵ See Robert Cassidy & Jonas Frisén, *Stem Cells on the Brain*, 412 *NATURE* 690, 691 (2001). See also Jean G. Toma et al., *Isolation of Multipotent Adult Stem Cells from the Dermis of Mammalian Skin*, 3 *NATURE CELL BIOLOGY* 778, 778–84 (2001).

¹⁶ See Juan R. Sanchez-Ramos et al., *Expression of Neural Markers in Human Umbilical Cord Blood*, 171 *EXPERIMENTAL NEUROLOGY* 109, 109–15 (2001), available at <http://www.idealibrary.com/links/doi/10.1006/exnr.2001.7748/pdf>.

¹⁷ See A.L. Vescovi, R. Galli & A. Gritti, *The Neural Stem Cells and Their Transdifferentiation Capacity*, 55 *BIOMEDICINE & PHARMACOTHERAPY* 201, 203 (2001); see also Rosella Galli et al., *Skeletal Myogenic Potential of Human and Mouse Neural Stem Cells*, 3 *NATURE NEUROSCI.* 986, 986–91 (2000).

¹⁸ See Václav Ourednik et al., *Segregation of Human Neural Stem Cells in the Developing Primate Forebrain*, 293 *SCIENCE* 1820, 1820–24 (2001).

¹⁹ See Christopher R.R. Bjornson et al., *Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in Vivo*, 283 *SCIENCE* 534, 534–37 (1999).

chondrocytes to make bone;²¹ embryonic stem cells to beta cells of the pancreas;²² and dermal stem cells to nerve and muscle cells.²³

Scientists can also induce “reprogramming” in adult somatic cells using somatic cell nuclear transfer technology²⁴—whereby a nucleus from a mature adult cell is placed in an enucleated egg, that nucleus is “reprogrammed,” and then proceeds to make a complete new individual—“a la Dolly.” Dolly, the cloned sheep from Great Britain, was derived from a nucleus that was taken from a mature udder cell and placed into the enucleated egg from the same individual—in this case, Dolly’s mother.²⁵

Theoretically, it is possible to use the chemical environment provided by any fertilized mammalian egg to convert an adult somatic nucleus into a stem cell. In this instance, one places a nucleus from the donor species into the cytoplasm of a recently fertilized enucleated egg; this can grow in vitro for some weeks before the lack of a placenta causes it to fail, or it can be placed into the uterus of a hormonally-treated female. It is also possible to mix genetic material across species lines and have both sets of genes expressed. For example, the human growth gene when placed into the embryos of dwarf mice causes them to grow to twice their normal size.²⁶ Furthermore, bacteria can express human genes, for example, *E. coli* bacteria containing human insulin genes or clotting factor genes have provided valuable products for medicine that are indistinguishable from the native human products. So far, animal genes have not been placed into human eggs. However, rats have had HESCs placed into areas of their brains that were lesioned to

²⁰ Izhak Kehat et al., *Human Embryonic Stem Cells Can Differentiate into Myocytes with Structural and Functional Properties of Cardiomyocytes*, 108 *J. CLINICAL INVESTIGATIONS* 407, 407–14 (2001).

²¹ José J. Minguell, Alejandro Erices, and Paulette Conget, *Mesenchymal Stem Cells*, 226 *EXPERIMENTAL BIOLOGY & MED.* 507, 512–13 (2001).

²² See Suheir Assady et al., *Insulin Production by Human Embryonic Stem Cells*, 50 *DIABETES* 1691, 1691–97 (2001), available at <http://diabetes.diabetesjournals.org/>; see also B. Soria, A. Skoudy & F. Martín, *From Stem Cells to Beta Cells: New Strategies in Cell Therapy of Diabetes Mellitus*, 44 *DIABETOLOGIA* 407, 407–15 (2001).

²³ See Toma et al., *supra* note 15, at 778–84. See also Sanchez-Ramos et al., *supra* note 16 (discussing how stem cells obtained from the blood of umbilical cords have been converted into neurons); Emily Sohn, *Therapy by the Pound: Human Fat is a Source of Coveted Stem Cells*, *U.S. NEWS & WORLD REP.*, Apr. 23, 2001, at 54, available at 2001 WL 6320159 (reporting how human fat tissue has been found to harbor adult stem cells).

²⁴ See S. Geuna et al., *Adult Stem Cells and Neurogenesis: Historical Roots and State of the Art*, 265 *ANATOMICAL REC.* 132, 138–39 (2001).

²⁵ See, e.g., Ian Wilmut, Lorraine Young & Keith H.S. Campbell, *Embryonic and Somatic Cell Cloning*, 10 *REPROD. FERTILITY & DEV.* 639, 639–43 (1998).

²⁶ See Robert E. Hammer, Richard D. Palmiter & Ralph L. Brinster, *Partial Correction of Murine Hereditary Growth Disorder by Germ-Line Incorporation of a New Gene*, 311 *NATURE* 65, 65 (1984).

produce simulated stroke conditions and these HESCs have repaired the damaged brains to some extent as evidenced by the formation of new synapses and improved maze learning.²⁷

Scientists also have the ability to take an unfertilized egg or an enucleated egg, fuse it with a nucleus from any cell of that individual or another individual, and, with an electric shock, induce this fused cell to divide.²⁸ This is called parthenogenesis when an unfertilized egg is used, and somatic cell nuclear transfer when an enucleated egg is used. The former leads to offspring derived from an unfertilized egg, i.e., offspring that was not “fathered.” This process would allow the production of artificial embryos which would be of tremendous benefit to humanity—since the nucleus can come from the person in need of the tissue, with no fear of tissue rejection. The potentiality of these artificial embryos to become fetuses is at the moment unknown and is likely to remain untested. In animal experiments most of these embryos fail to develop. Stem cells from these embryos, however, when placed in a given transplant site take on the characteristics of the host tissue.

Human embryonic stem cells are being considered for their potential utility in the following treatments: to replace insulin producing cells in children with Type 1 diabetes;²⁹ to replace dopamine producing cells in individuals with Parkinson’s disease;³⁰ to restore immunity in cases of primary immunodeficiency diseases;³¹ to correct disorders such as osteogenesis imperfecta and chondrodysplasias, diseases of bone and cartilage;³² and as a means

²⁷ See Peter J. Donovan & John Gearhart, *The End of the Beginning for Pluripotent Stem Cells*, 414 NATURE 92, 95 (2001) (discussing how germ-line stem cells can also be used in much the same way as HESCs). Gearhart took cells from the region destined to become testes or ovaries in fetuses and found these cells’ properties to be similar to those of HESCs. Getting them to reproduce indefinitely, though, has not yet been achieved. See *id.* Amniocentesis also can provide HESCs that multiply well in culture. See Amir Kaviani et al., *The Amniotic Fluid as a Source of Cells for Fetal Tissue Engineering*, 36 J. PEDIATRIC SURGERY 1662, 1664 (2001).

²⁸ See Nicholas D. Allen et al., *A Functional Analysis of Imprinting in Parthenogenetic Embryonic Stem Cells*, 120 DEV. 1473, 1473–82 (1994); see also Michael J. Shamblott et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, 95 PROC. NAT’L ACAD. SCI. USA 13726, 13726–31 (1998), at <http://www.pnas.org>.

²⁹ See Assady, *supra* note 22. See also James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145, 1145–47 (1998).

³⁰ See Evelyn Strauss, *Stem Cells Make Brain Cells*, collected in *American Association for the Advancement of Science: Globe-Girdling Science in the Golden Gate City*, (Meeting Report), 291 SCIENCE 1689, 1689–90 (2001).

³¹ See Rafael G. Amado, Ronald T. Mitsuyasu & Jerome A. Zack, *Gene Therapy for the Treatment of AIDS: Animal Models and Human Clinical Experience*, 4 FRONTIERS BIOSCIENCE d468, d468–75 (1999), available at <http://www.bioscience.org/1999/v4/d/amado/fulltext.htm>.

³² See Barbara A. Huibregtse et al., *Effect of Age and Sampling Site on the Chondro-Osteogenic Potential of Rabbit Marrow-derived Mesenchymal Progenitor Cells*, 18 J.

of replacing tissue damaged by radiation and/or chemotherapy cancer treatments.³³ In clinical trials, scientists are attempting to use adult stem cells to correct aberrant immune reactions in patients with autoimmune disease.³⁴ HESCs also are being used to build new body parts—using collagen scaffolding to create a nose or an ear.³⁵ It is conceivable that this technology would extend to the building of bladders, knee ligaments, and heart valves. It might also be possible to build a contracting muscle chamber for pumping blood.

We are presently at a stage that the Wright brothers were at as they attempted to fly. If we learn how to control stem cell development, artificial organs may be commonplace by the end of this century. In combination with gene translocation technology, stem cells could be used to correct—or even cure—inherited diseases. Stem cells also play an important role in basic research in that they could reveal how a single cell becomes a human being, and perhaps even the relationship between senescence and telomeres (which HESCs have more of, and mature cells less of).

Either through government-sponsored or privately-funded research, human embryonic stem cells will become an important part of a broad spectrum of new technologies. HESCs are the most versatile of the stem cells and the easiest to produce in quantity. In addition, one-week-old embryos have no tissues, and, more importantly, no nervous system. Because these embryos have the greatest developmental plasticity and are very far removed from “personhood,” their use in emerging medical technologies should be at least as ethically acceptable as (if not more so than) the use of either spontaneous abortions or frozen embryos that are not utilized in the in vitro fertilization process.

ORTHOPAEDIC RES. 18, 18–24 (2000).

³³ See Rita C.R. Perlingeiro, Michael Kyba & George Q. Daley, *Clonal Analysis of Differentiating Embryonic Stem Cells Reveals a Hematopoietic Progenitor with Primitive Erythroid and Adult Lymphoid-Myeloid Potential*, 128 DEVELOPMENT 4597, 4597–604 (2001).

³⁴ See Alan Tyndall, *Autologous Hematopoietic Stem Cell Transplantation for Severe Autoimmune Disease with Special Reference to Rheumatoid Arthritis*, 28 (Supp. 64) J. RHEUMATOLOGY 5, 5–7 (2001).

³⁵ See Paolo Bianco & Pamela Gehron Robey, *Stem Cells in Tissue Engineering*, 414 NATURE 118, 118–21 (2001).

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