Approved: February 22, 2006
Date

MINUTES OF THE SENATE PUBLIC HEALTH AND WELFARE COMMITTEE

The meeting was called to order by Chairman Jim Morrison at 1:37 P.M. on February 16, 2006, in Room 526-S of the Capitol.

All members were present.

Late Arrival:

Journey:	1:40
Wagle:	1:40
Palmer:	1:42
Haley:	1:45

Early Leave:

Haley:	2:00

Committee staff present:

Terri Weber, Kansas Legislative Research Department
Morgan Dreyer, Committee Secretary

Conferees appearing before the committee:

David A Prentice, Ph.D., Family Research Council and Gerogetown University Medical School

Others attending:

See attached list.

Presentation on Stem Cells

Upon calling the meeting to order Chairman Morrison welcomed the Senate Public Health and Welfare Committee for joining their Committee for a joint meeting. The Chair introduced Dr. David A Prentice, Ph.D., Family Research Council and Gerogetown University Medical School who gave a presentation on stem cells. Highlights of his presentation include:

1. Regenerative medicine with stem cells
2. Isolation and culture of embryonic stem cells
3. Human embryonic stem cell "contamination"
4. Human cloning
5. Cell cloning
6. Fertilization vs. Cloning (somatic cell nuclear transfer, SCNT)
7. Theoretical concept of "therapeutic cloning"
8. Adult stem cells
9. Diseases treated in human patients
10. Activation and mobilization of stem cells

A copy of his testimony is (Attachment 1) attached hereto and incorporated into the Minutes as referenced.

The Chair asked for questions or comments from the Committee. Questions came from Representatives Colloton, Mast, Miller, and SenatorWagle, regarding nutrient replacement, embrionic creationof tumors, unhealthy vs. healthy cord blood, cord blood donations, disabilities in female egg donors, old vs. and young stem cells.

Adjournment

As there was no further business, the meeting was adjourned at 2:30 p.m.

The next meeting is scheduled for Wednesday, February 22, 2006.

JOINT COMMITTEE MEETING: HOUSE HEALTH AND HUMAN SERVICES AND SENATE PUBLIC HEALTH AND WELFARE GUEST LIST

DATE: February 16, 2006

NAME	REPRESENTING
Blake Smith	Smith-3 Academy
Kevin Huppuch MD	Medical Society of Sg County
Patti Innes	Hatfield Govt Relations
BRAD KEMP	KCLC
Lisa Benton	American Cancer Society
Jace Smith	American Cancer Society
Kevin Siek	TILRC
Sharon Joseph	KS ADAPT
Alex Kotoyantz	P.I.A.
Chad Austin	KS Hosp Assoc
L. Therese Bangert	Ks. Cath Conf
Beatrice Swoopes	Ks. Cath. Conference
Janie Ann Powers	KAHP
John C. Peterson	Ks Assn for Safe Saving Energy
Lindsey Douglas	Heim Law Firm
Kevin J Bacon	KCDC
Mike Reedy	Civic Council of Greater KC
[illegible]	AARP
Alyce Brown	AARP

JOINT COMMITTEE MEETING: HOUSE HEALTH AND HUMAN SERVICES AND SENATE PUBLIC HEALTH AND WELFARE GUEST LIST

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DATE: February 16, 2006

NAME	REPRESENTING
Anne Gilchrist	public

Current Science of Regenerative Medicine with Stem Cells

David A. Prentice

ABSTRACT

Regenerative medicine with stem cells holds great hope for the treatment of degenerative disease. The medical potential of embryonic stem cells remains relatively untapped at this point, and significant scientific hurdles remain to be overcome before these cells might be considered safe and effective for uses in patients. Meanwhile, adult stem cells have begun to show significant capabilities of their own in repair of damaged tissues, in both animal models and early patient trials.

Key Words: regenerative medicine, stem cells, stem cell transplant

Regenerative medicine holds great hope for millions of patients with degenerative diseases and injuries. Repair of damaged organs and tissues using stem cells could potentially address the needs of these patients, encompassing most of the top 15 leading causes of death in the United States. However, the emotional appeal of stem cells and the political debate in which the science is embroiled have clouded much of the actual results in this area. It is imperative that a complete review of the scientific results and potential promises be a part of any fully informed debate.

A stem cell has two chief characteristics: (1) it continues to proliferate so that a pool of cells is always available and (2) it responds to appropriate signals by differentiating into one or more specialized cell types (Figure 1A). Numerous sources of human stem cells exist, including those from early (5–7 day postconception) embryos, fetal tissues, umbilical cord blood and matrix, placental tissues, and most or all body tissues; postnatal sources are often grouped together under the term "adult stem cells" (Figure 1B). The "plasticity" of a stem cell, that is, its ability to form differentiated cell types, ranges from unipotent (able to form only one differentiated type), to multipotent (able to form multiple cell types), to pluripotent (able to form most or all tissues of the adult body), to totipotent (able to form all postnatal and extraembryonic tissues, potentially able to regenerate a complete new embryo).

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EMBRYONIC STEM CELLS

Mouse embryonic stem (ES) cells were first grown in culture in 1981,[1,2] but human ES cells were not successfully cultured until 1998.[3] Isolation of ES cells requires the disaggregation of the early embryo—hence the ethical debate regarding these cells. At about the same time, another team successfully cultured stem cells, termed embryonic germ cells, with similar properties from fetal primordial germ cells.[4] ES cells are considered the archetypal pluripotent stem cell; they proliferate extensively in culture and, based on their normal function during development or results from reinsertion into another embryo, have the potential to form any tissue. Although this potential is attractive for treatment of degenerative disease, the results to this point have been modest, and there are still many scientific hurdles to overcome before ES cells might be used clinically, including generation of functional differentiated cells, tumor formation, and immune rejection.[5] The best examples of potential success to date are in animal models of spinal cord injury and Parkinson's disease. Keirstead and colleagues showed some success at ameliorating acute (although not chronic) spinal cord injury in rats, including improvement in locomotor activity,[6] and

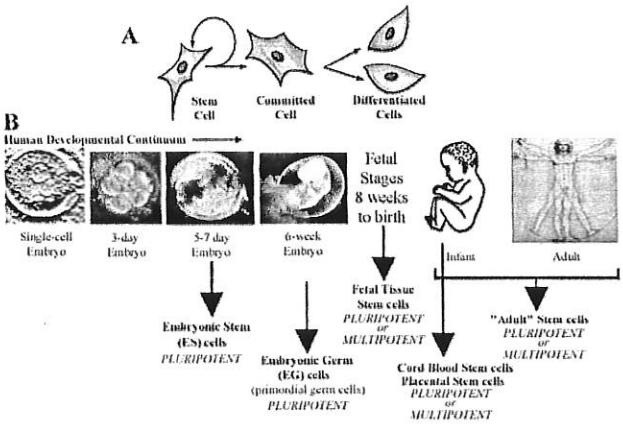

FIGURE 1 Characteristics and sources of stem cells. *A*), Stem cells maintain proliferation (*circular arrow*) and respond to differentiation signals (*arrow to right*). *B*), Sources include embryos, primordial germ cells, differentiated fetal tissue, and "adult" stem cells, including umbilical cord matrix and blood, placenta, and postnatal body tissues.

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Nistor and colleagues showed remyelinating activity of human ES cells in a rat model.[7] In animal models of Parkinson's disease, ES cells have been successfully transplanted and achieved dopamine secretion, alleviating some of the behavioral symptoms in monkeys[8] and rats,[9] although in the latter example, the ES cells stopped growth after 12 weeks. However, some experiments, although showing partial behavioral improvement, have also shown tumorigenesis of the injected ES cells.[10,11] Tumor formation continues to be a problem for the potential clinical use of ES cells; the uncontrolled growth of native or even ES-derived progenitor cells is one factor that has so far precluded their use in humans.[12,13] A few animal studies also show some ability of ES cells for cardiac repair,[14,15] although in vitro studies have indicated potential problems with arrhythmia induced by ES-derived cardiac cells.[16] Whereas some early work suggested possible use of ES cells for generation of insulin-secreting cells and diabetes treatment,[17,18] more recent studies indicate that the previously observed insulin secretion was an artifact of insulin imbibed from the culture medium[19,20] and that insulin-expressing cells derived from ES cells were not true beta cells, although they were still tumorigenic.[12] Thus far, it has been difficult to obtain a pure culture of ES-derived functional differentiated cells and to get physiologic integration into damaged tissues.

Another hurdle yet to be overcome in potential therapeutic use of ES cells is immune rejection. Animal studies have usually relied on immunosuppression or injection into immunoprivileged sites, such as the brain, and it is likely that such protocols would need to be followed for any human trials. Several possibilities have been proposed by Odorico and colleagues for overcoming potential rejection of ES cells, including genetic engineering of major histocompatibility complex (MHC) genes, induced hematopoietic chimerism, establishing "banks" of ES cell lines to match potential recipients, and somatic cell nuclear transfer (SCNT; so-called "therapeutic cloning").[21] Zwaka and Thomson demonstrated that it is possible to do homologous recombination in human ES cells, similar to that routinely done in mouse ES cells, opening the possibility of engineering ES cells to match the MHC antigens of different patients.[22] Transplant of ES-derived hematopoietic cells, producing an immune system chimerism, could potentially overcome immune rejection; the concept has already been demonstrated using adult stem cell bone marrow transplants followed by solid organ transplant.[23] Banks of human ES cells to match any patient might also be possible, although it is uncertain just how many ES cell lines would be required, with estimates ranging from 250 to 10,000 potential lines needed.

Therapeutic cloning has been hailed as a potential panacea for overcoming immune rejection. Theoretically, by creating an embryonic clone of the patient, from which matching ES cells could be harvested, patient-specific cell lines could be generated that would not be rejected. South Korean researchers recently claimed creation of scores of cloned human embryos from patients and production of 11 ES cell lines.[24] These claims have now been proven fraudulent and the published paper withdrawn. It is still uncertain whether the cells would actually be accepted by the patient's immune system, and prominent ES cell researchers have questioned the efficiency of using therapeutic cloning for clinical use.[25,26] In a previous experiment in mice, the cells from cloned embryos were rejected by the genetically matched host.[27,28] Reports of successful matching of cells derived by SCNT cloning are so far dubious; the best results to date in animal studies actually come from gestating cloned animals to the fetal stage and then harvesting tissue stem cells.[29–31]

ADULT STEM CELLS

Traditional dogma maintains that there are few adult (tissue or postnatal) stem cells present in the body and that they are difficult to isolate and grow in culture and extremely limited in their capacity to generate new cell types, being limited to forming more cells from their tissue of origin. However, an explosion in publications in the last few years is overturning this dogma and showing a remarkable flexibility for these cells.[32] In a 2001 publication, evidence was presented that a single adult bone marrow stem cell could contribute not only to marrow and blood but also to formation of liver, lung, digestive tract, skin, heart, and muscle.[33] Several examples now exist of some adult stem cells with pluripotent flexibility, including cells from bone marrow,[34–36] peripheral blood,[37] the inner ear,[38] umbilical cord blood,[39,40] nasal mucosa,[41] amniotic fluid,[42] and the placental amniotic membrane.[43] Many of these published studies also document that these particular pluripotent adult stem cells can multiply in culture for extensive periods of time while still retaining their ability to differentiate and providing sufficient numbers of cells for clinical treatments.

Relevant to their potential use in clinical therapies, there have been numerous reports of the effectiveness of adult stem cells in treating animal models of disease. In stroke models, adult stem cells have provided therapeutic benefit.[44–46] Interestingly, in some experiments, the cells showed a "homing" ability to the site of tissue damage. There is some evidence that c-kit ligand (stem cell factor) may be important for this homing behavior[46]; although this phenomenon is still not completely understood, it provides an intriguing possibility for targeting of regenerative stem cells. For spinal cord injury, adult stem cells have promoted neuronal growth and therapeutic benefit in rodent models.[48–50] A recent result that brings into focus some of the unexpected problems potentially faced with regenerative medicine was the discovery that, in successful transplants, the new nerve growth could result in increased pain; however, this could be managed by directed differentiation of the stem cells before trans-

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plant.[51] Initial clinical trials in Portugal are under way with approximately 36 patients.[52] In animal models of Parkinson's disease, adult stem cells have shown effectiveness at stimulating dopamine secretion and decreasing behavioral symptoms.[53,54] One patient received a transplant of his own neural stem cells, resulting in decreasing the symptoms of Parkinson's disease.[55] In a study designed not to transplant stem cells but rather to stimulate endogenous adult stem cells for repair, five patients were injected with glial cell–derived neurotrophic factor, resulting in an average 61% decrease in symptomatology.[56] Follow-up pathology with one patient showed that the growth factor stimulated sprouting of new neurons.[57]

Adult stem cells have also been effective at ameliorating retinal degeneration in animal models,[58–60] raising hopes for possible treatments for diabetic retinopathy and age-related macular degeneration. Regarding diabetes, several examples now exist showing generation of insulin-secreting cells from various adult stem cells, including the liver,[60] bone marrow,[62,63] and pancreas.[64] In some experiments, it appears that it is not the adult stem cells that form new beta cells but rather that the injected cells stimulated endogenous precursors within the pancreas to accomplish regeneration.[65] Using spleen cells, one group was able to achieve permanent disease reversal and now has approval from the US Food and Drug Administration to begin human trials for juvenile diabetes.[66]

Use of adult stem cells from bone marrow or mobilized into peripheral blood has become relatively common as an adjunct for cancer chemotherapy to replace the patient's hematopoietic system or for anemias. Similar techniques to replace the immune system are now being tested with some success in patients for various autoimmune conditions, such as scleromyxedema,[67] multiple sclerosis,[68] and Crohn's disease.[70] Such treatments have also shown promising results for metabolic disorders, such as Krabbe's disease.[71] Adult stem cells have also been used in bone repair protocols.[71] Repair of cardiac damage in patients has also moved to the clinical trials stage, with several reports of early success in repair of infarct damage.[72–74]

The mechanism for these regenerative results is still unclear. Adult stem cells in some cases appear to be capable of interconversion between different tissue types, known as transdifferentiation. In some tissues, adult stem cells appear to fuse with the host tissue and take on that tissue's characteristics, facilitating regeneration. In some studies, the adult stem cells do not directly contribute to the regenerating tissue but instead appear to stimulate the endogenous cells of the tissue to begin repair. Whatever the mechanism, adult stem cells are successful at regenerating damaged tissue.

In summary, a great deal of work remains to be done before widespread clinical application of stem cells for regenerative medicine. Given the scientific hurdles that yet remain to be overcome for ES cells, they may be less well suited for clinical applications than for basic scientific studies. Recent results from animal studies and early clinical trials indicate that adult stem cells, in contrast to previous theories, have significant capacities for repair of damaged cells and tissues, somewhat like a native repair kit. The flexibility and potential of these adult stem cells to impact disease appear to be enormous.

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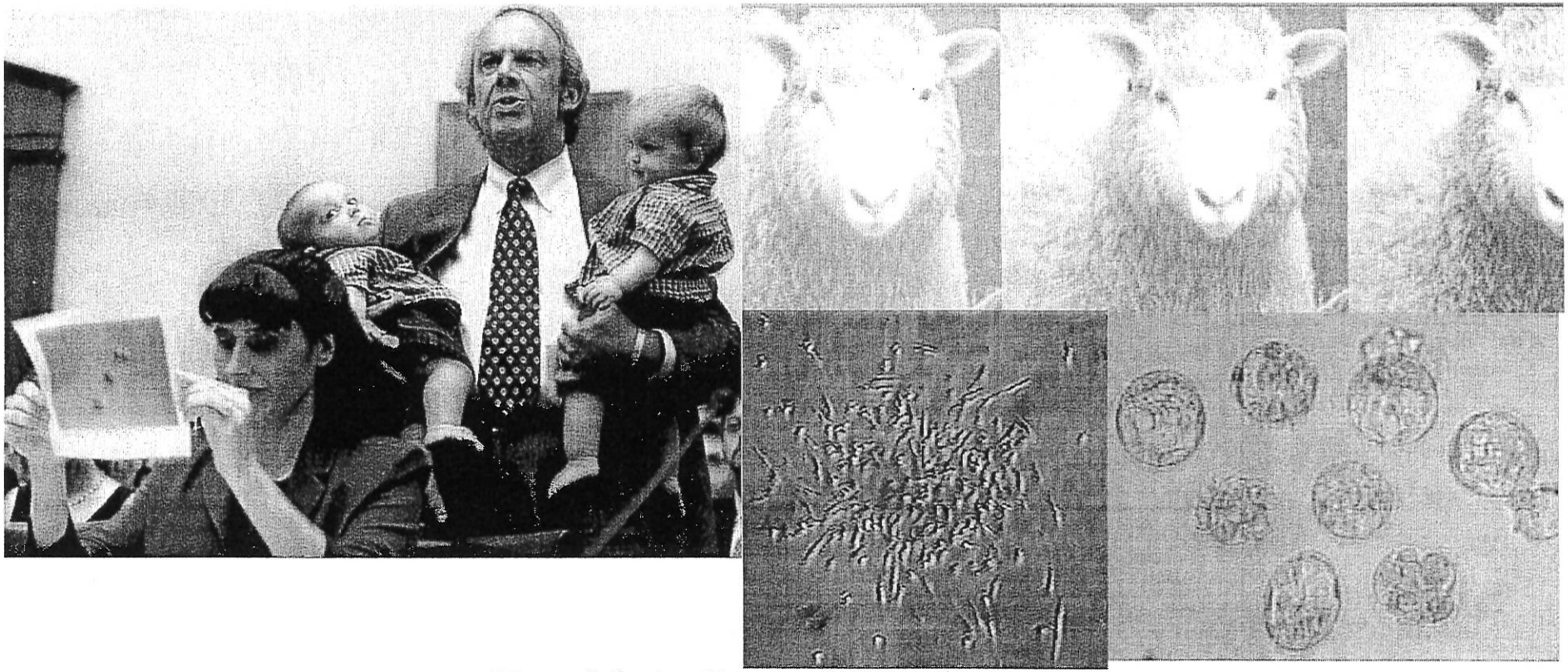
Stem Cells



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Family Research Council and Georgetown University Medical School
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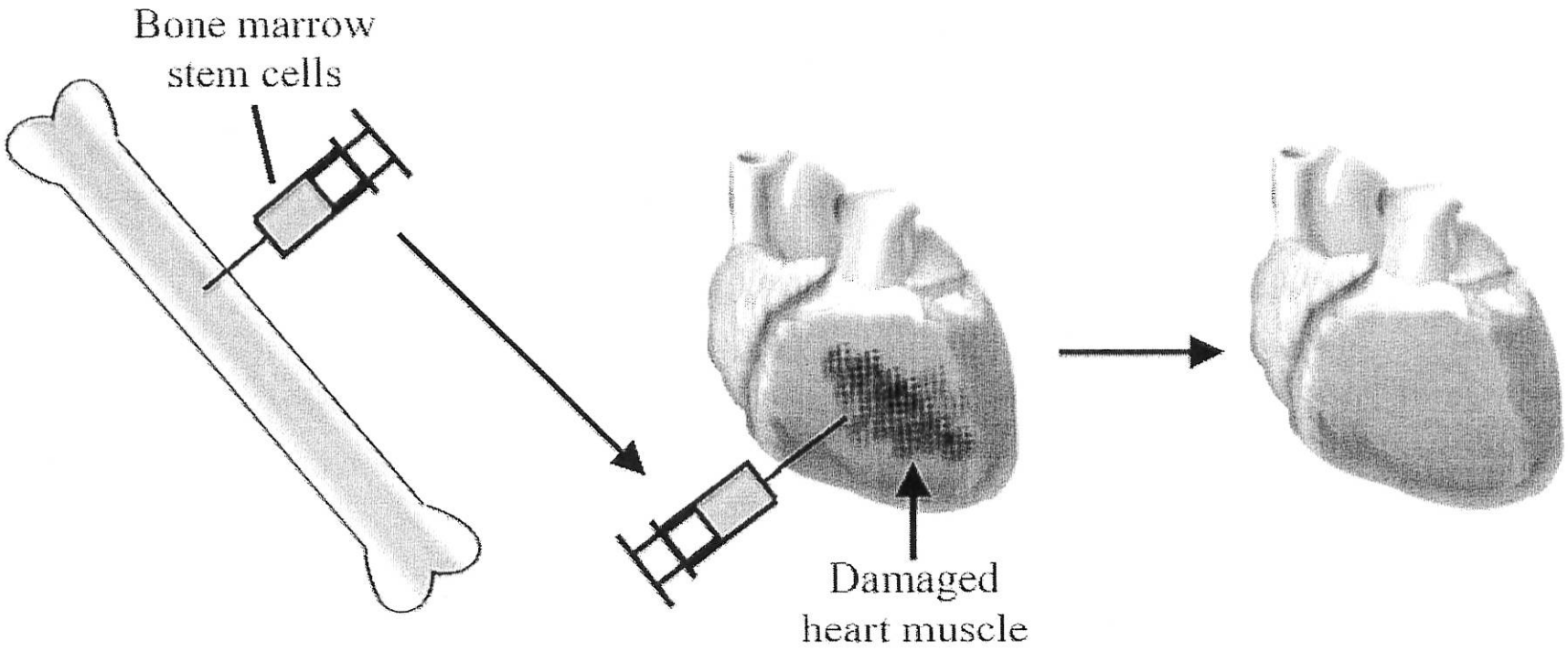
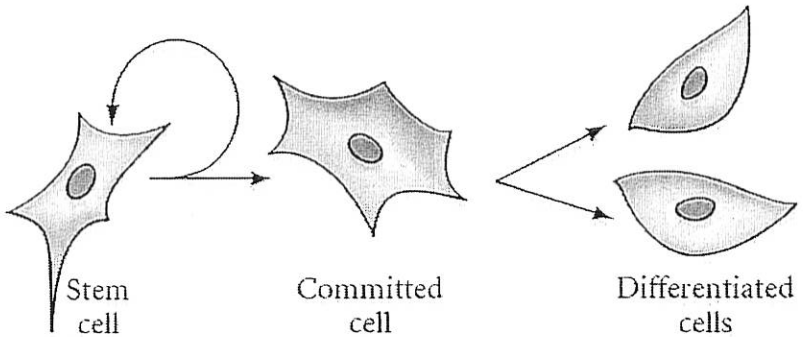
STEMCELL DEPOT

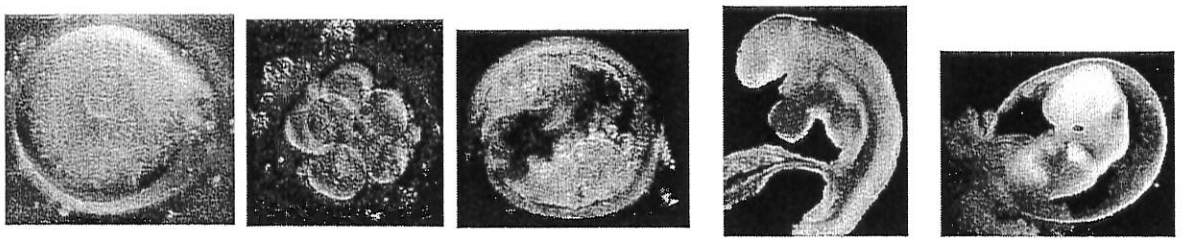
Regenerative Medicine with Stem Cells





Stem Cells

Human Developmental Continuum ⟶

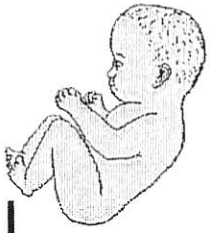


Single-cell Embryo | 3-day Embryo | 5-7 day Embryo | 4-week Embryo | 6-week Embryo

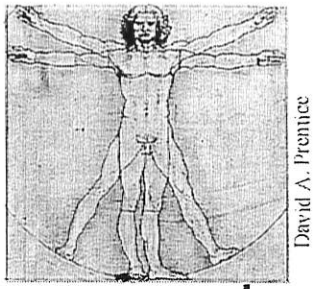
Embryonic Stem (ES) cells
Totipotent

Embryonic Germ (EG) cells
(primordial germ cells)
Pluripotent

Fetal Tissue Stem cells
Pluripotent or Multipotent



Infant



Adult

"Adult" Stem cells
Pluripotent or Multipotent

Teratocarcinoma (germ cell tumor)

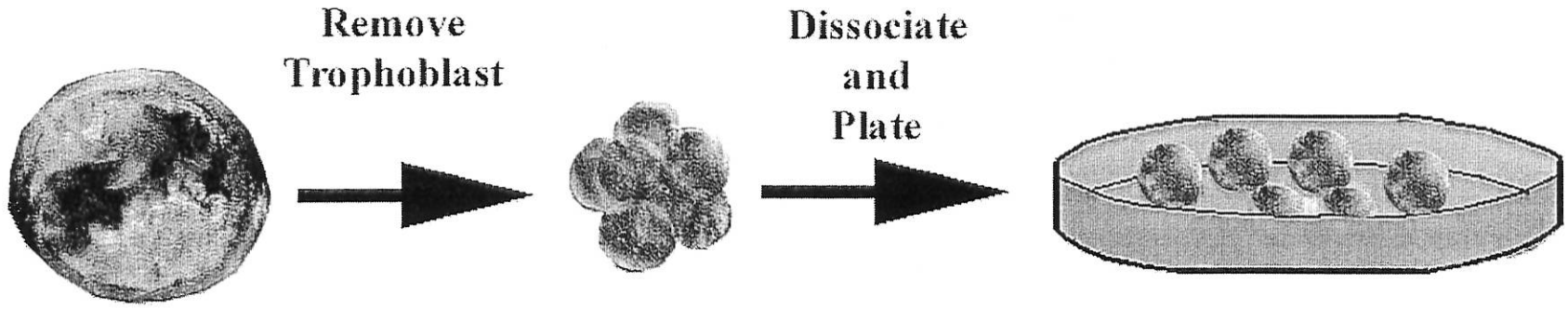
Embryonal Carcinoma (EC) cells
Pluripotent

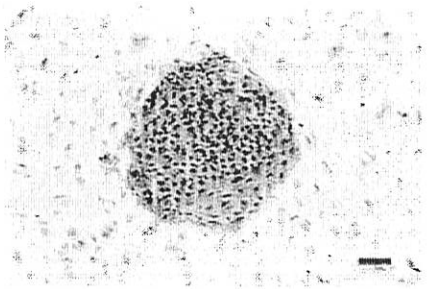
Cord Blood Stem cells
Placental Stem cells
Pluripotent or Multipotent

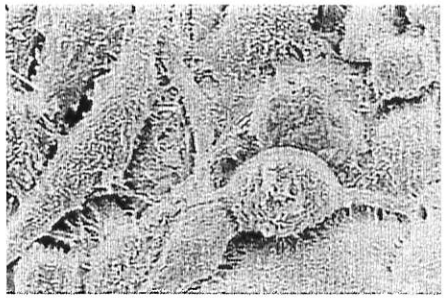
Isolation & Culture of Embryonic Stem Cells
(Human-1998; Mouse-1981)

Method patented
U.S. patent held by Univ. Wisconsin

Purported Advantages:
1) Proliferate indefinitely
2) Form any tissue







Promises, Premises, and Published Data…

Claims unsubstantiated for embryonic stem cells

Current or potential embryonic stem cell problems:

- Difficult to establish and maintain
- Difficulty in obtaining pure cultures in the dish
- Potential for tumor formation and tissue destruction
- Questions regarding functional differentiation

  *Hansson M *et al.*, "Artifactual insulin release from differentiated embryonic stem cells", *Diabetes* 53, 2603-2609, October 2004
  *Sipione S *et al.*, "Insulin expressing cells from differentiated embryonic stem cells are not beta cells", *Diabetologia* 47, 499-508, 2004 (published online 14 Feb 2004)
  *Rajagopal J *et al.*; "Insulin staining of ES cell progeny from insulin uptake"; *Science* 299, 363; 17 Jan 2003
  *Zhang YM *et al.*; "Stem cell-derived cardiomyocytes demonstrate arrhythmic potential"; *Circulation* 106, 1294-1299; 3 September 2002
- Problem of immune rejection

  *Swijnenburg R-J *et al.*, Embryonic stem cell immunogenicity increases upon differentiation after transplantation into ischemic myocardium, *Circulation* 112, I-166-I-172, 30 August 2005
- Genomic instability

  *Maitra A *et al.*, Genomic alterations in cultured human embryonic stem cells, *Nature Genetics* online 4 Sept 2005
  *Cowan CA *et al.*, "Derivation of embryonic stem-cell lines from human blastocysts", *New England Journal of Medicine* 350, 1353-1356, 25 March 2004
  *Draper JS *et al.*, "Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells", *Nature Biotechnology* 22, 53-54; January 2004
  *Humpherys D *et al.*; "Epigenetic instability in ES cells and cloned mice"; *Science* 293, 95-97; 6 July 2001
- Few and modest results in animals, no clinical treatments
- Ethically contentious

Human embryonic stem cell "contamination"

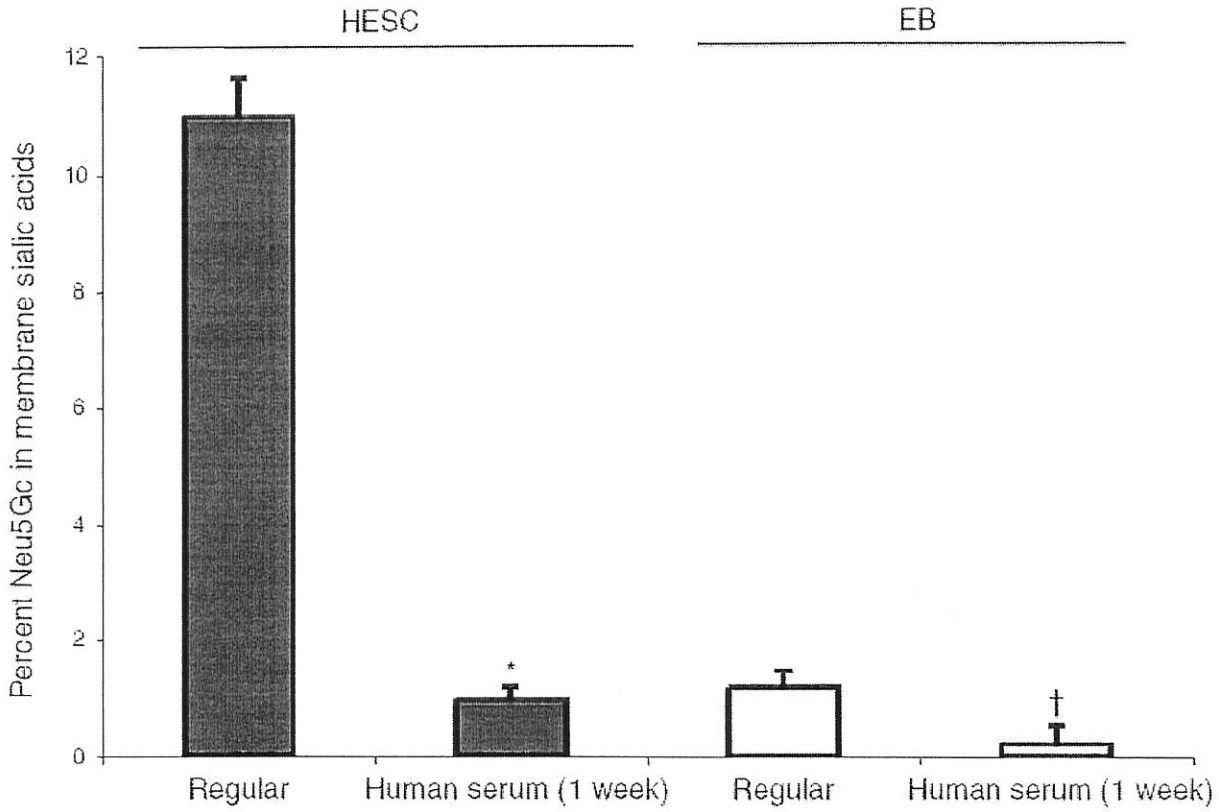
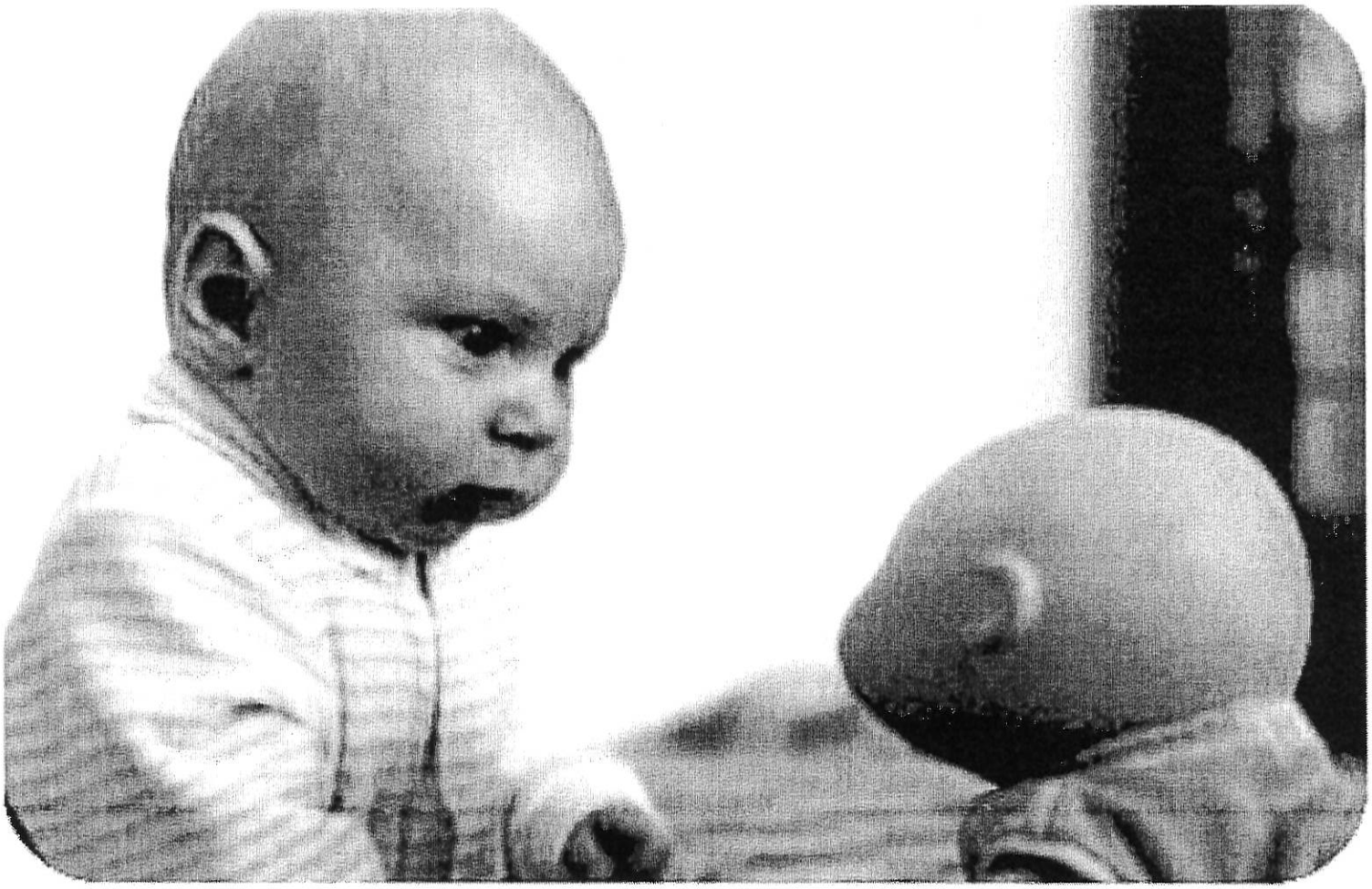


Figure 3 Effect of growth in NHS on Neu5Gc content of HESC and embryoid bodies. HESC or embryoid bodies were grown in NHS instead of the standard serum replacement. Membrane-bound sialic acids were studied for percentage of Neu5Gc as described in the **Fig. 1b** legend. Data represent the mean of two different experiments (mean ± s.d.). $^{*}P < 0.005$, $^{\dagger}P < 0.01$.

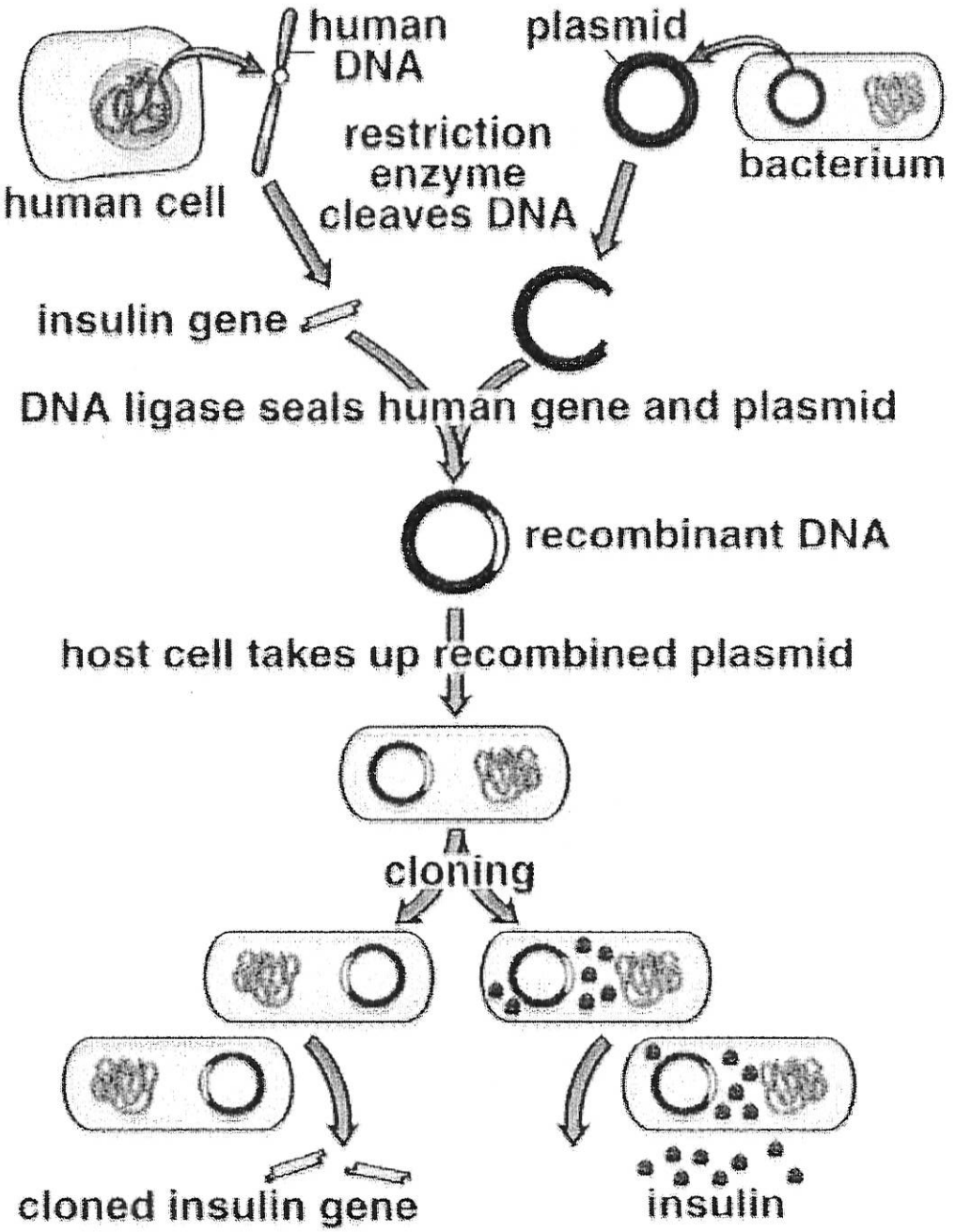
From: Martin MJ et al., Human embryonic stem cells express an immunogenic nonhuman sialic acid, Nature Medicine 11, 228-232, February 2005

Human Cloning



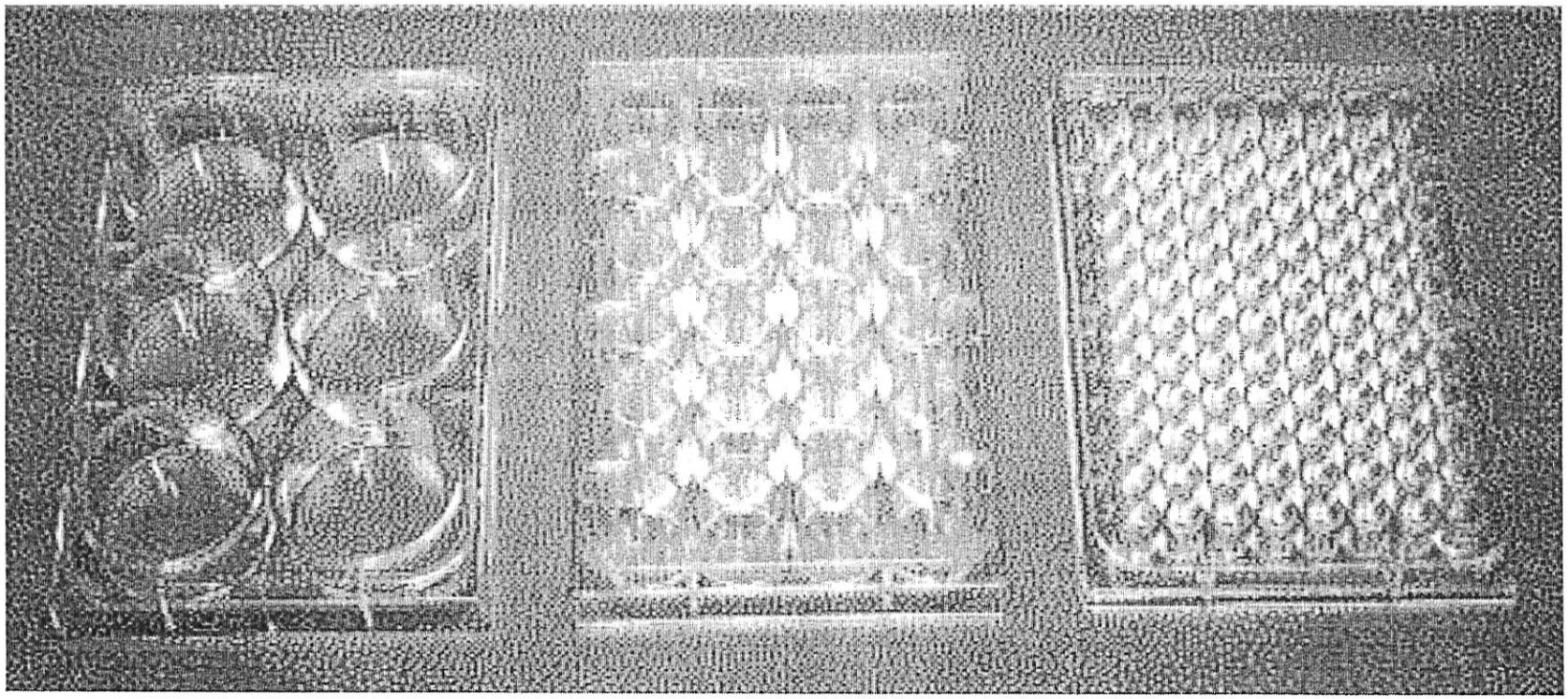
Good grief! I've been cloned!!

Human Gene Cloning

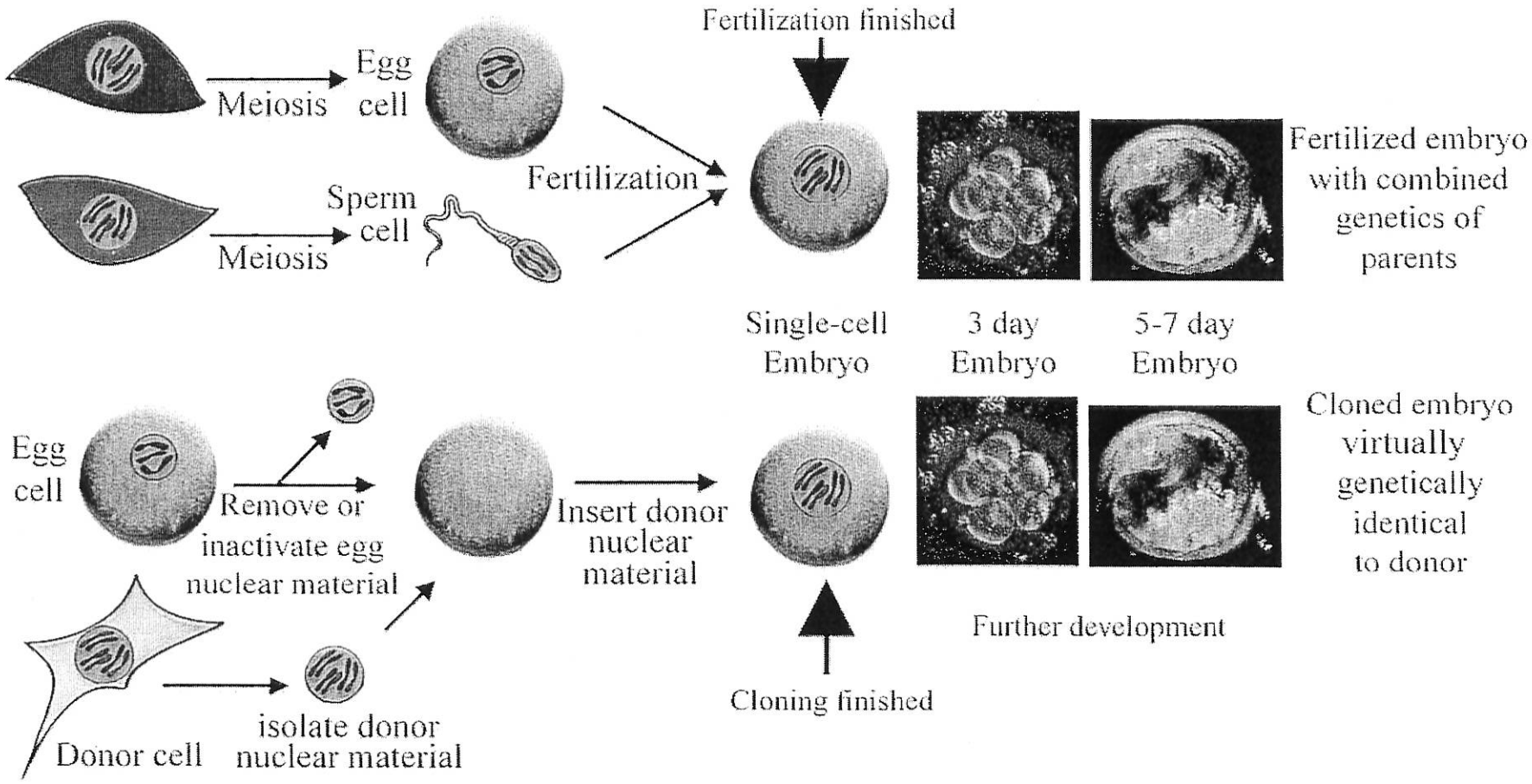


Cell Cloning

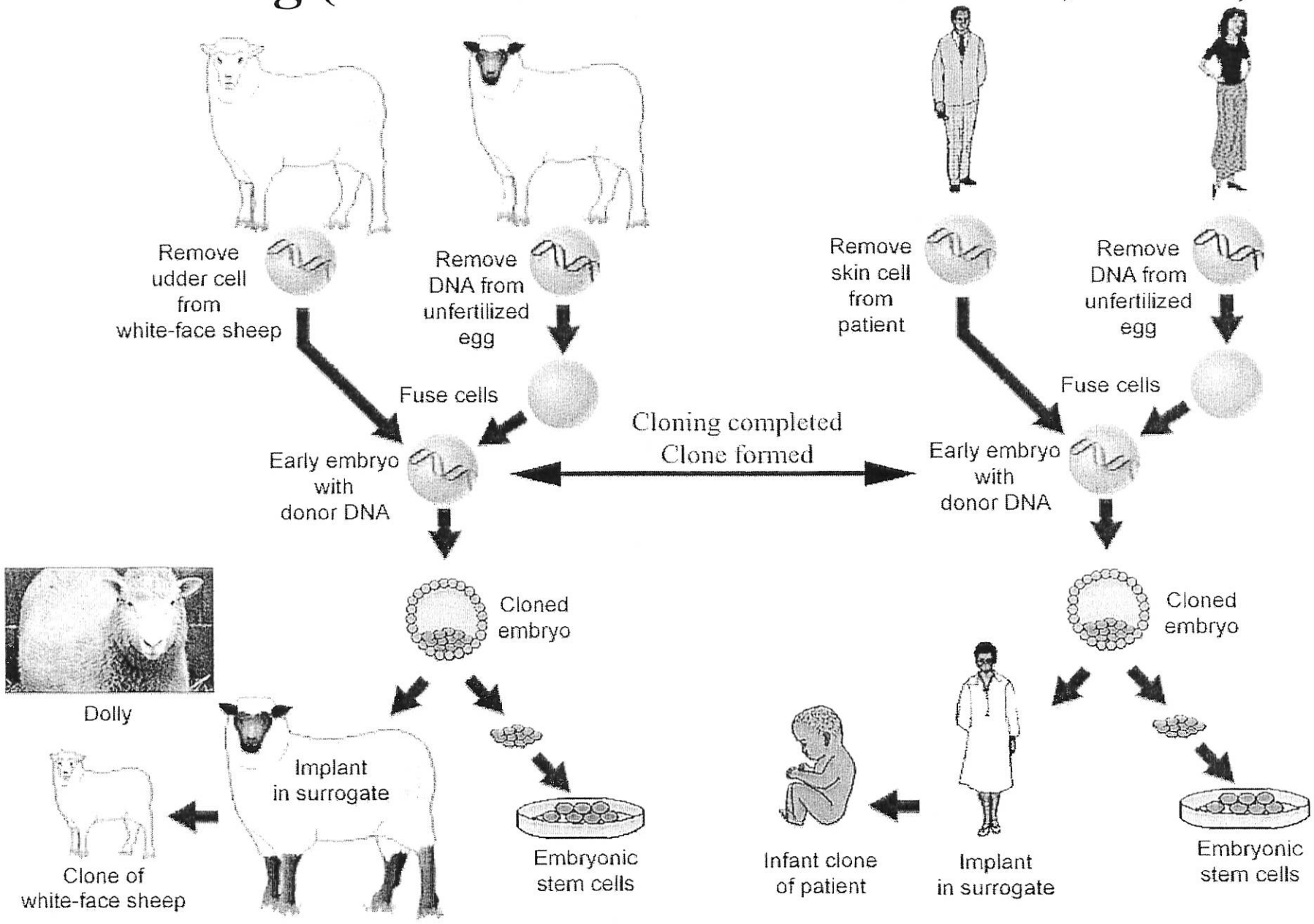
One cell is placed into the dish or well by itself. The cell divides and forms a population of identical cells (cell clones.)



Fertilization *vs.* Cloning (somatic cell nuclear transfer, SCNT)



Cloning (Somatic Cell Nuclear Transfer, SCNT)



Cloning (SCNT) produces a human embryo

"The Commission began its discussions fully recognizing that any effort in humans to transfer a somatic cell nucleus into an enucleated egg involves the creation of an embryo, with the apparent potential to be implanted in utero and developed to term."
Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission (Rockville, MD: June 1997), p. 3

"The first product of SCNT is, on good biological grounds, quite properly regarded as the equivalent of a zygote, and its subsequent stages as embryonic stages in development."
Human Cloning and Human Dignity: An Ethical Inquiry, Report of the President's Council on Bioethics, July 2002; p.50

Cloning (SCNT) produces a human embryo

"The method used to initiate the reproductive cloning procedure is called either nuclear transplantation or somatic cell nuclear transfer."

Scientific and Medical Aspects of Human Reproductive Cloning, Report of the National Academy of Sciences and the Institute of Medicine, National Academy Press, Washington, DC, Jan 2002

"anything that you construct at this point in time that has the properties of those structures to me is an embryo, and we should not be changing vocabulary at this point in time. It doesn't change some of the ethical issues involved."

Dr. John Gearhart, Johns Hopkins University, 25 April 2002; before the U.S. President's Council on Bioethics.

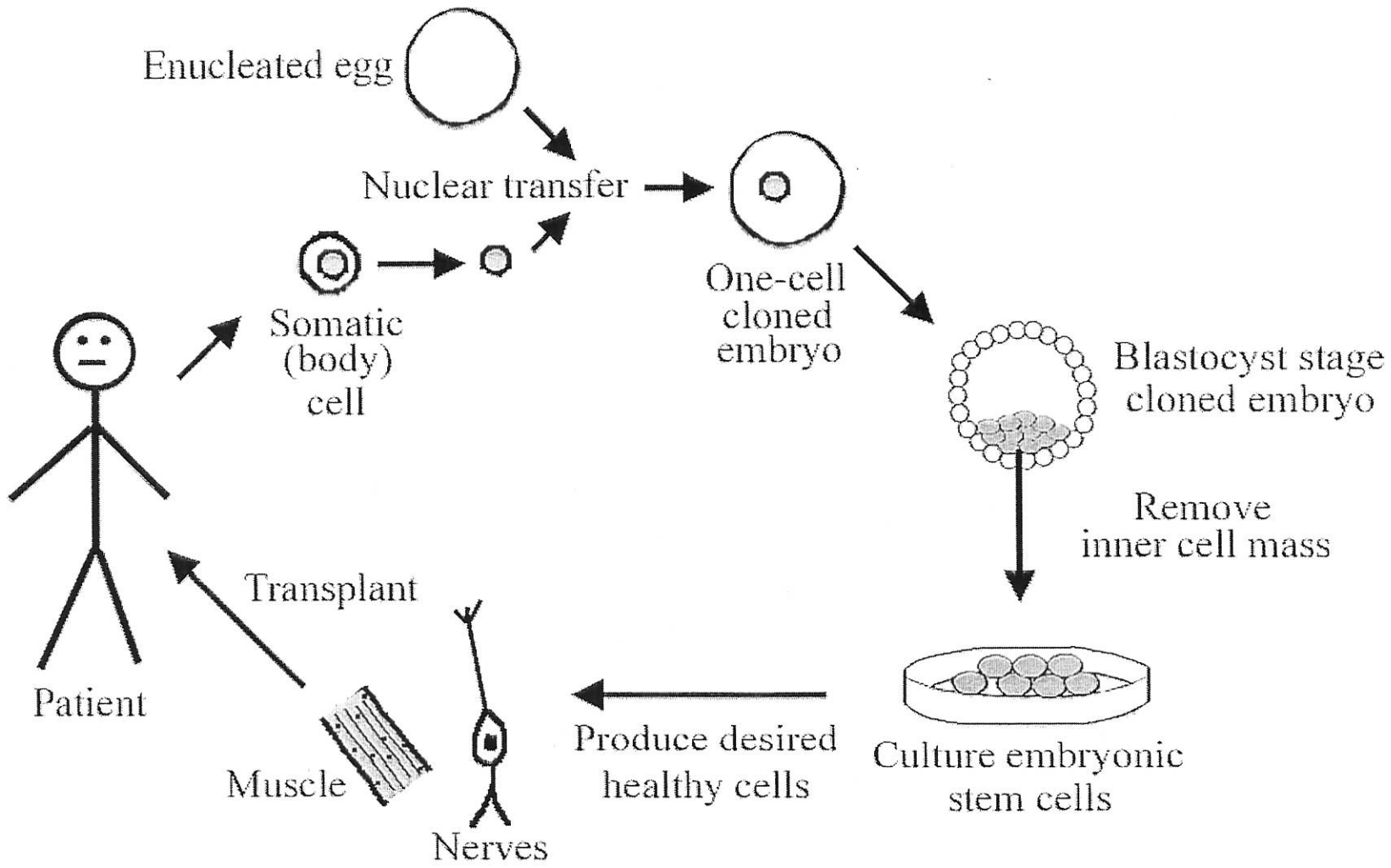
"Therapeutic" Cloning creates an embryo for destruction

"Moreover, because therapeutic cloning requires the creation and disaggregation ex utero of blastocyst stage embryos, this technique raises complex ethical questions."

"CRNT [Therapeutic cloning] requires the deliberate creation and disaggregation of a human embryo."

Robert P. Lanza, Arthur L. Caplan, Lee M. Silver, Jose B. Cibelli, Michael D. West, Ronald M. Green; 'The ethical validity of using nuclear transfer in human transplantation"; *The Journal of the American Medical Association* 284. 3175-3179: Dec 27. 2000.

Theoretical Concept of "Therapeutic Cloning"



Therapeutic Cloning is a Failure

- **Transplanted cells from cloned mouse embryo rejected**

  *WM Rideout *et al.*, "Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy," *Cell* 109, 17-27; 5 April 2002 (published online 8 March 2002)

  "Our results raise the provocative possibility that even genetically matched cells derived by therapeutic cloning may still face barriers to effective transplantation for some disorders."

- *RYL. Tsai, R Kittappa, and RDG McKay; "Plasticity, niches, and the use of stem cells"; *Developmental Cell* 2, 707-712; June 2002

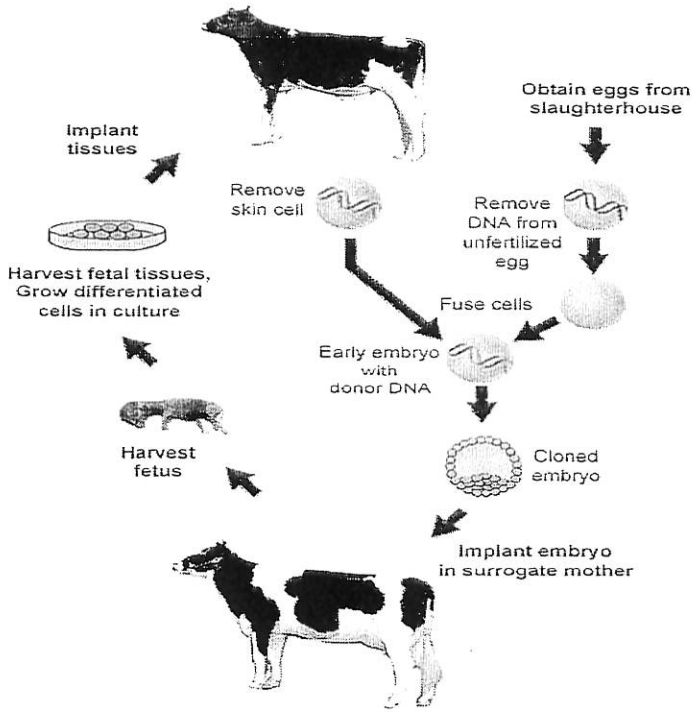
  "Jaenisch addressed the possibility that ES clones derived by nuclear transfer technique could be used to correct genetic defects… However, the donor cells, although derived from the animals with the same genetic background, are rejected by the hosts."

- **Clones may need to be gestated to "harvest"already-differentiated tissues**

  *R Lanza *et al.*; "Generation of histocompatible tissue using nuclear transplantation," *Nature Biotechnology* 20, 689-696; July 2002

  *R Lanza *et al.*, "Regeneration of the infarcted heart with stem cells derived by nuclear transplantation," *Circulation Research* 94, 820-827, April 2004

  *R Lanza *et al.*, "Long-term bovine hematopoietic engraftment with clone-derived stem cells", *Cloning and Stem Cells* 7, 95-106, July 2005



Cloning will not provide the claimed medical treatments

Unlikely chance of success in clinical use:

Dr. James Thomson, USA—Odorico JS *et al.*; "Multilineage differentiation from human embryonic stem cell lines," *Stem Cells* 19, 193-204; 2001

Dr. Alan Trounson, Australia—Trounson AO; "The derivation and potential use of human embryonic stem cells", *Reproduction, Fertility, and Development* 13, 523-532; 2001

Dr. Peter Mombaerts, USA, "Therapeutic cloning in the mouse", *Proceedings of the National Academy of Sciences USA* 100, 11924-11925; 30 Sept 2003 (published online 29 August 2003)

Transplant Rejection will still occur using cells from cloned embryos:

Dr. Irving Weissman—13 February 2002; before the President's Council on Bioethics

Dr. John Gearhart—25 April 2002; before the President's Council on Bioethics.

Cloning not commercially viable: **Thomas Okarma**, CEO, Geron Corporation

(Denise Gellene, "Clone Profit? Unlikely", Los Angeles Times, May 10, 2002)

Developing "therapeutic" cloning techniques can lead to "reproductive" cloning

Robert P. Lanza, Arthur L. Caplan, Lee M. Silver, Jose B. Cibelli, Michael D. West, Ronald M. Green; "The ethical validity of using nuclear transfer in human transplantation"; *The Journal of the American Medical Association* 284, 3175-3179; 27 Dec 27 2000

American Society for Reproductive Medicine Ethics Committee; "Human somatic cell nuclear transfer (cloning)"; *Fertility and Sterility* 74, 873-876; November 2000

"Therapeutic" cloning places women at risk

Because both cloning and embryonic stem cell production are extremely inefficient, a tremendous number of eggs will be required.

For example, to treat only the 17 million Diabetes patients in the U.S.:

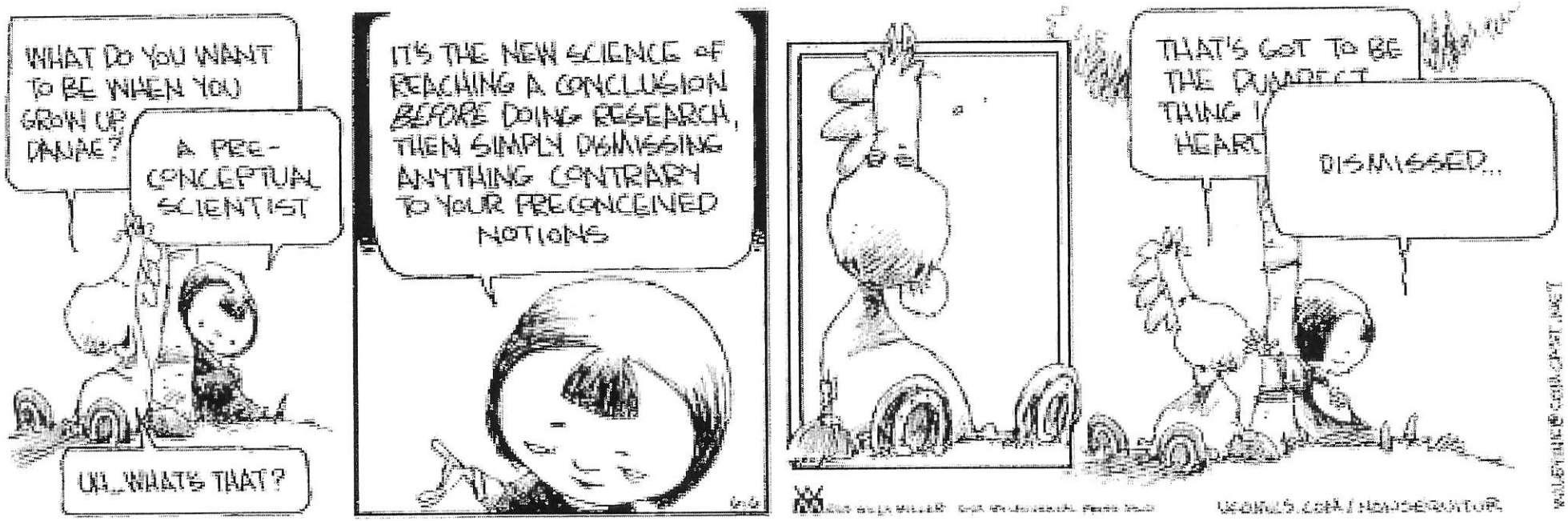
Will require at least 1.7 billion human eggs
(Optimistically 100 human eggs/patient, estimated cost US$100,000-200,000)
Mombaerts P, "Therapeutic cloning in the mouse", *Proceedings of the National Academy of Sciences USA* 100, 11924-11925; 30 Sept 2003; Prentice DA, Stem Cells and Cloning, 1st edition, San Francisco: Pearson Education/Benjamin-Cummings, July 2002

--Collecting 10 eggs/donor:
Will require at least 170 million women - childbearing age donors

Health risks—High-dose hormone therapy and surgery to obtain eggs risks the donor's health and future reproductive success

Commercial exploitation—of women globally

SOUTH KOREAN HUMAN CLONING FRAUD
Cloned human embryos?? no cells, faked data, paying women for eggs, coercion of women students


WHAT DO YOU WANT TO BE WHEN YOU GROW UP DANNE?
A PRE-CONCEPTUAL SCIENTIST
UH... WHAT'S THAT?
IT'S THE NEW SCIENCE OF REACHING A CONCLUSION BEFORE DOING RESEARCH, THEN SIMPLY DISMISSING ANYTHING CONTRARY TO YOUR PRECONCEIVED NOTIONS
THAT'S GOT TO BE THE DUMBEST THING I HEARD
DISMISSED...

Adult Stem Cells

Bone Marrow

Marrow
Bone
Cartilage
Tendon
Muscle
Fat
Liver
Brain/Nerve
Blood cells
Heart
All Tissues

Stem Cells from Fat

Bone
Cartilage
Muscle
Nerves

Peripheral Blood

Bone Marrow
Blood cells
Nerves

Hair Follicle

Skin Brain
Smooth Muscle Fat

Gastrointestinal

Esophagus Small Intestine
Stomach Large Intestine/Colon

Placenta

Bone Nerve
Cartilage Muscle Tendon
Bone Marrow Blood vessel

Skeletal Muscle

Skeletal muscle
Smooth muscle
Bone
Cartilage
Fat
Heart

Brain

Brain
Nerves
Blood cells
Muscle
All Tissues
Cornea
Retina
Pancreas
Liver
Heart
Lung
Spermatogonia
Amniotic Fluid
Umbilical Cord Matrix

CORD BLOOD

Various Tissues

David A. Prentice

Evidence that Some Adult Stem Cells show Pluripotent Capacity

Umbilical Cord Blood Stem Cells with embryonic-like stem cell properties

McGuckin CP *et al.*, Production of stem cells with embryonic characteristics from human umbilical cord blood, *Cell Proliferation* 38, 245-255, August 2005

Placental Amniotic Stem Cells express Oct-4, nanog; potentially form any tissue, no tumors

Miki T *et al.*, Stem cell characteristics of amniotic epithelial cells, *Stem Cells* published online 4 Aug 2005; doi:10.1634/stemcells.004-0357

Nasal Stem Cells form multiple tissues.

Murrell W *et al.*, "Multipotent stem cells from adult olfactory mucosa, *Developmental Dynamics* 233, 496-515, June 2005

Common Pluripotent Adult Stem Cell isolated from multiple mouse tissues

Case J *et al.*, Clonal multilineage differentiation of murine common pluripotent stem cells isolated from skeletal muscle and adipose stromal cells, Annals NY Acad Sci 1044, 183-200, June 2005

Bone Marrow Stem Cells can form all 3 germ layers, and regenerate damaged heart.

Yoon Y-s *et al.*, "Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction", *Journal of Clinical Investigation* 115, 326-338, February 2005

Human Cord Blood stem cells show pluripotent potential and extensive proliferation

Kögler G *et al.*, "A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential", *J. Experimental Medicine* 200, 123-135, 19 July 2004

Human Bone Marrow Adult Stem Cells with pluripotent potential, Oct-4 expression

D'Ippolito G *et al.*, "Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential", *J. Cell Science* 117, 2971-2981, 15 June 2004

Peripheral blood stem cells can form cells from all 3 germ layers

Zhao Y *et al.*; "A human peripheral blood monocyte-derived subset acts as pluripotent stem cells"; *Proceedings of the National Academy of Sciences USA* 100, 2426-2431; 4 March 2003

Adult stem cells from bone marrow can form new neurons in the human brain.

Mezey E *et al.*; "Transplanted bone marrow generates new neurons in human brains"; *Proceedings of the National Academy of Sciences USA* 100, 1364-1369; 4 Feb 2003

Adult stem cells from bone marrow can form all body tissues

Jiang Y *et al.*; "Pluripotency of mesenchymal stem cells derived from adult marrow"; *Nature* 418, 41-49; 4 July 2002

A single adult mouse bone marrow stem cell can form multiple functional tissues

Krause DS *et al.*; "Multi-Organ, Multi-Lineage Engraftment by a Single Bone Marrow-Derived Stem Cell"; *Cell* 105, 369-377; 4 May 2001

Adult stem cells effective in tissue repair

Stroke—Adult stem cells from brain, bone marrow, and umbilical cord blood provide therapeutic benefit after stroke. First clinical trials under way.

*Shyu W-C *et al.*, "Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells", *Circulation* 110, 1847-1854, 2004

*Willing AE *et al.*, "Mobilized peripheral blood stem cells administered intravenously produce functional recovery in stroke", *Cell Transplantation* 12, 449-454; 2003

*Arvidsson A *et al.*; "Neuronal replacement from endogenous precursors in the adult brain after stroke"; *Nature Medicine* 8, 963-970; Sept 2002

*Riess P *et al.*; "Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury"; *Neurosurgery* 51, 1043-1052; Oct 2002

*Li Y *et al.*; "Human marrow stromal cell therapy for stroke in rat"; *Neurology* 59, 514-523; August 2002

*Chen J *et al.*; "Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats"; *Stroke* 32, 2682-2688; November 2001

Adult stem cells effective in tissue repair

Spinal Cord Injury—Adult stem cells capable of re-growth and reconnection in spinal cord. Clinical trials started in Portugal, South Korea and Australia.

**Kang K-S *et al.*, A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood, with improved sensory perception and mobility, both functionally and morphologically: a case study, *Cytotherapy* 7, 368-373, September 2005

*Sigurjonsson OE *et al.*, Adult human hematopoietic stem cells produce neurons efficiently in the regenerating chicken embryo spinal cord, PNAS 102, 5227-5232, 5 April 2005

*Lu J *et al.*, Olfactory ensheathing cells promote locomotor recovery after delayed transplantation into transected spinal cord, *Brain* 125, 14-21, 2002

*Ohta M *et al.*, Bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery of the injured rat spinal cord with reduced cavity formation, Experimental Neurology 187, 266-278, 2004

*Hofstetter CP *et al.*, "Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery", *Proc Natl Acad Sci USA* 99, 2199-2204; Feb 19, 2002

*M. Sasaki *et al.*, "Transplantation of an acutely isolated bone marrow fraction repairs demyelinated adult rat spinal cord axons," *Glia* 35, 26-34; July 2001

*A. Ramon-Cueto *et al.*, "Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia," *Neuron* 25, 425-435; Feb 2000.

*M.S. Ramer *et al.*; "Functional regeneration of sensory axons into the adult spinal cord," *Nature* 403, 312-316; Jan 20, 2000.

*Shihabuddin *et al.*; "Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus," *J Neurosci* 20, 8727-8735; Dec 2000.

*Barnett *et al.*; "Identification of a human olfactory ensheathing cell that can effect transplant-mediated remyelination of demyelinated CNS axons," *Brain* 123, 1581-1588, Aug 2000

*A. Ramon-Cueto *et al.*, "Long-distance axonal regeneration in the transected adult rat spinal cord is romoted by olfactory ensheathing glial transplants," *J Neurosci* 18, 3803-3815; May 15, 1998

Adult stem cells effective in tissue repair

Diabetes—Pancreatic, liver, intestinal, spleen or bone marrow cells can form insulin-secreting islets. FDA approval of first clinical trial, Denise Faustman, Harvard.

*Sapir *et al.*, Cell-replacement therapy for diabetes: generating functional insulin-producing tissue from adult human liver cells, *Proceedings of the National Academy of Sciences USA* 102, 7964-7969, 17 May 2005
*Seaberg BM *et al.*, "Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic lineages", *Nature Biotechnology* 22, 1115-1124, Sept 2004
*Oh S-H *et al.*, "Adult bone marrow-derived cells transdifferentiating into insulin-producing cells for the treatment of type I diabetes," *Laboratory Investigation* 84, 607-617, 1 May 2004
*Kodama S *et al.*, "Islet regeneration during the reversal of autoimmune diabetes in NOD mice", *Science* 302, 1223-1227; 14 Nov 2003
*Hess D *et al.*, "Bone marrow-derived stem cells initiate pancreatic regeneration", *Nature Biotechnology* 21, 763-770; July 2003
*Steptoe RJ *et al.*; "Transfer of hematopoietic stem cells encoding autoantigen prevents autoimmune diabetes"; *Journal of Clinical Investigation* 111, 1357-1363; May 2003
*Suzuki A *et al.*; "Glucagon-like peptide 1 (1-37) converts intestinal epithelial cells into insulin-producing cells"; *Proc Natl Acad Sci USA* 100, 5034-5039; 29 April 2003
*Ianus A *et al.*; *In vivo* derivation of glucose competent pancreatic endocrine cells from bone marrow without evidence of cell fusion; *Journal of Clinical Investigation* 111, 843-850; March 2003
*Yang L *et al.*; "*In vitro* trans-differentiation of adult hepatic stem cells into pancreatic endocrine hormone-producing cells"; *Proceedings of the National Academy of Sciences USA,* 99, 8078-8083; 11 June 2002
*S. Ryu *et al.*; "Reversal of established autoimmune diabetes by restoration of endogenous ß cell function," *J. Clin. Invest.* 108, 63-72; July 2001
*Ramiya VK *et al.*; "Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells," *Nature Medicine* 6, 278-282, March 2000.

Adult stem cells effective in tissue repair

Heart Damage—Bone marrow, muscle, and heart stem cells repair heart.

**Ince H *et al.*, Prevention of left ventricular remodeling with granulocyte colony-stimulating after acute myocardial infarction, *Circulation* 112, I-73-I-80, 30 August 2005

*Dawn B *et al.*, "Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function", *Proceedings of the National Academy of Sciences USA* 102, 3766-3771, 8 March 2005

*Yoon Y-s *et al.*, "Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction", *Journal of Clinical Investigation* 115, 326-338, February 2005

**Wollert KC *et al.*, "Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial", *Lancet* 364, 141-148, 10 July 2004

**Britten MB *et al.*, "Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction"; *Circulation* 108, 2212-2218; Nov 2003

**Perin EC *et al.*; "Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure"; *Circulation* 107, r75-r83; published online May 2003

**Stamm C *et al.*; "Autologous bone-marrow stem-cell transplantation for myocardial regeneration"; *The Lancet* 361, 45-46; 4 January 2003

**Tse H-F *et al.*; "Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation"; *The Lancet* 361, 47-49; 4 January 2003

**Strauer BE *et al.*; "Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans"; *Circulation* 106, 1913-1918; 8 October 2002

*Orlic D *et al.*, "Mobilized bone marrow cells repair the infarcted heart, improving function and survival"; *Proceedings of the National Academy of Sciences USA* 98, 10344-10349, 28 August 2001.

Adult stem cells effective in tissue repair

Parkinson's Disease—Neural stem cells can form all neuronal types, migrate throughout brain to repair damage, and prevent loss of neurons associated with Parkinson's disease.

*Liker MA *et al.*; "Human neural stem cell transplantation in the MPTP-lesioned mouse"; *Brain Research* 971, 168-177; May 2003

*Åkerud P *et al.*; "Persephin-overexpressing neural stem cells regulate the function of nigral dopaminergic neurons and prevent their degeneration in a model of Parkinson's disease"; *Molecular and Cellular Neuroscience* 21, 205-222; Nov 2002

*Ourednik J *et al.*; "Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons"; *Nature Biotechnology* 20, 1103-1110; Nov 2002

Using the patient's own adult neural stem cells, a group at Los Angeles Cedars-Sinai Medical Center report a reversal of symptoms in the first Parkinson's patient treated.

Lévesque M and Neuman T, "Autologous transplantation of adult human neural stem cells and differentiated dopaminergic neurons for Parkinson disease: 1-year postoperative clinical and functional metabolic result", American Association of Neurological Surgeons annual meeting, Abstract #702; 8 April 2002

Injecting growth signals into the brain stimulates the patients' own adult neural stem cells, provided a 61% improvement.

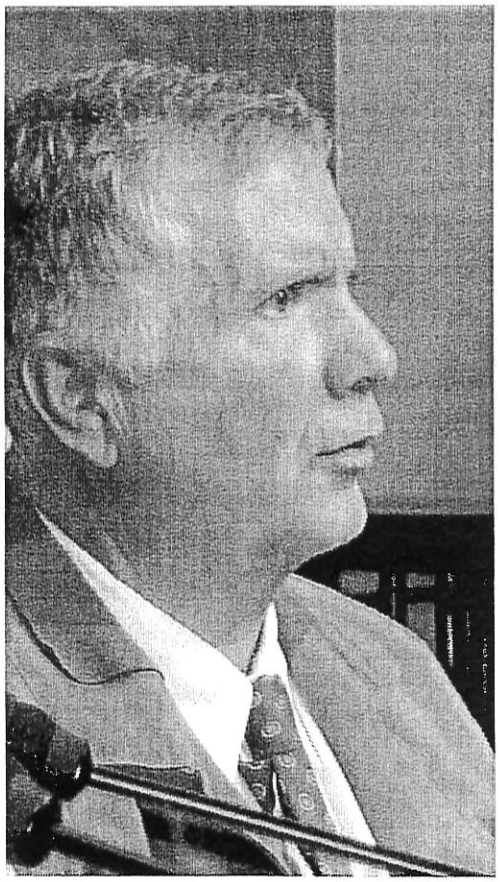
*Gill SS *et al.*; "Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease"; *Nature Medicine* 9, 589-595; May 2003 (published online 31 March 2003)

Current Clinical Uses of Adult Stem Cells

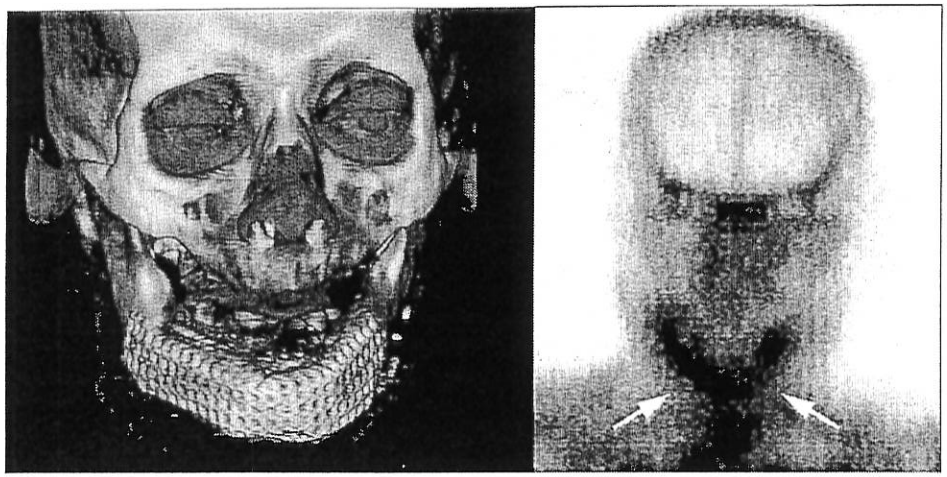
- **Cancers**—Lymphomas, multiple myeloma, leukemias, breast cancer, neuroblastoma, renal cell carcinoma, ovarian cancer
- **Autoimmune diseases**—multiple sclerosis, systemic lupus, rheumatoid arthritis, scleroderma, scleromyxedema, Crohn's disease
- **Anemias** (incl. sickle cell anemia)
- **Immunodeficiencies**—including human gene therapy
- **Bone/cartilage deformities**—children with osteogenesis imperfecta
- **Corneal scarring**-generation of new corneas to restore sight
- **Stroke**—neural cell implants in clinical trials
- **Repairing cardiac tissue after heart attack**—bone marrow or muscle stem cells from patient
- **Parkinson's**—retinal stem cells, patient's own neural stem cells, injected growth factors
- **Growth of new blood vessels**—*e.g.,* preventing gangrene
- **Gastrointestinal epithelia**—regenerate damaged ulcerous tissue
- **Skin**—grafts grown from hair follicle stem cells, after plucking a few hairs from patient
- **Wound healing**—bone marrow stem cells stimulated skin healing
- **Spinal cord injury**—clinical trials currently in Portugal, Italy, S. Korea
- **Liver failure**—clinical trials in U.K.

Diseases Treated in Human Patients

Laura Dominguez and her father.
Treated for spinal cord injury with
her own nasal adult stem cells.

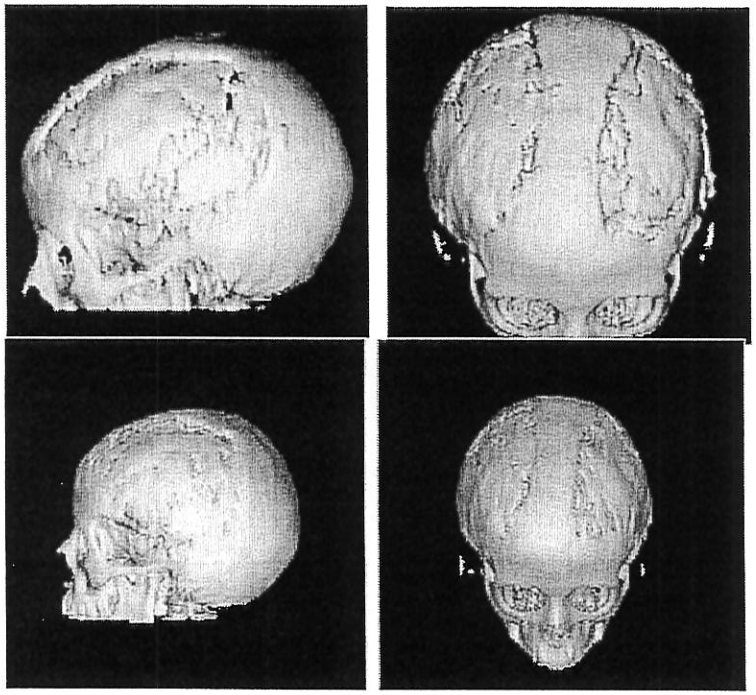


Dennis Turner.
Treated for Parkinson's with
his own brain adult stem cells.



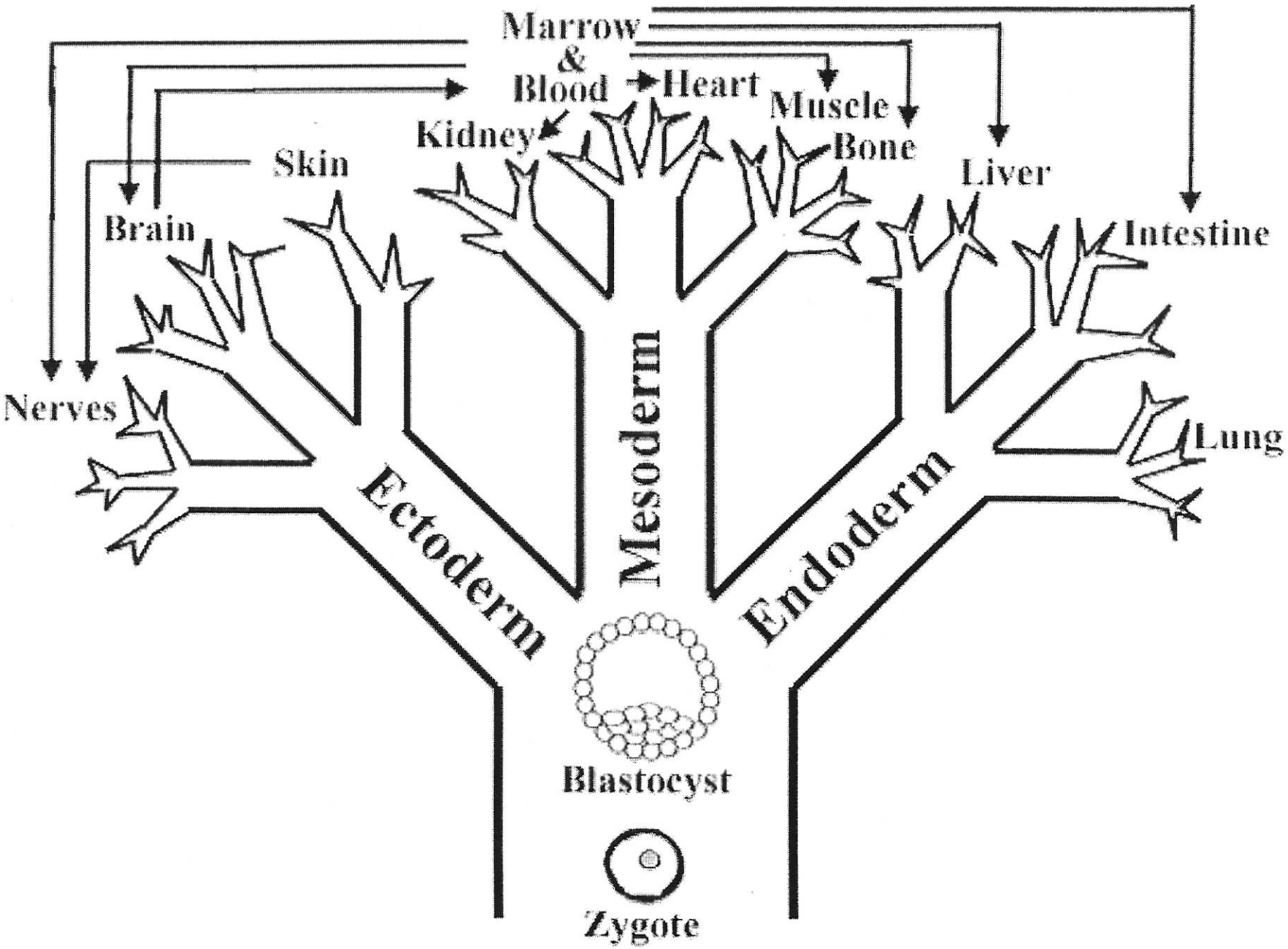
Jaw regrown with adult bone marrow stem cells.

Skull bone grown for 7-year-old girl
using adult stem cells from fat.

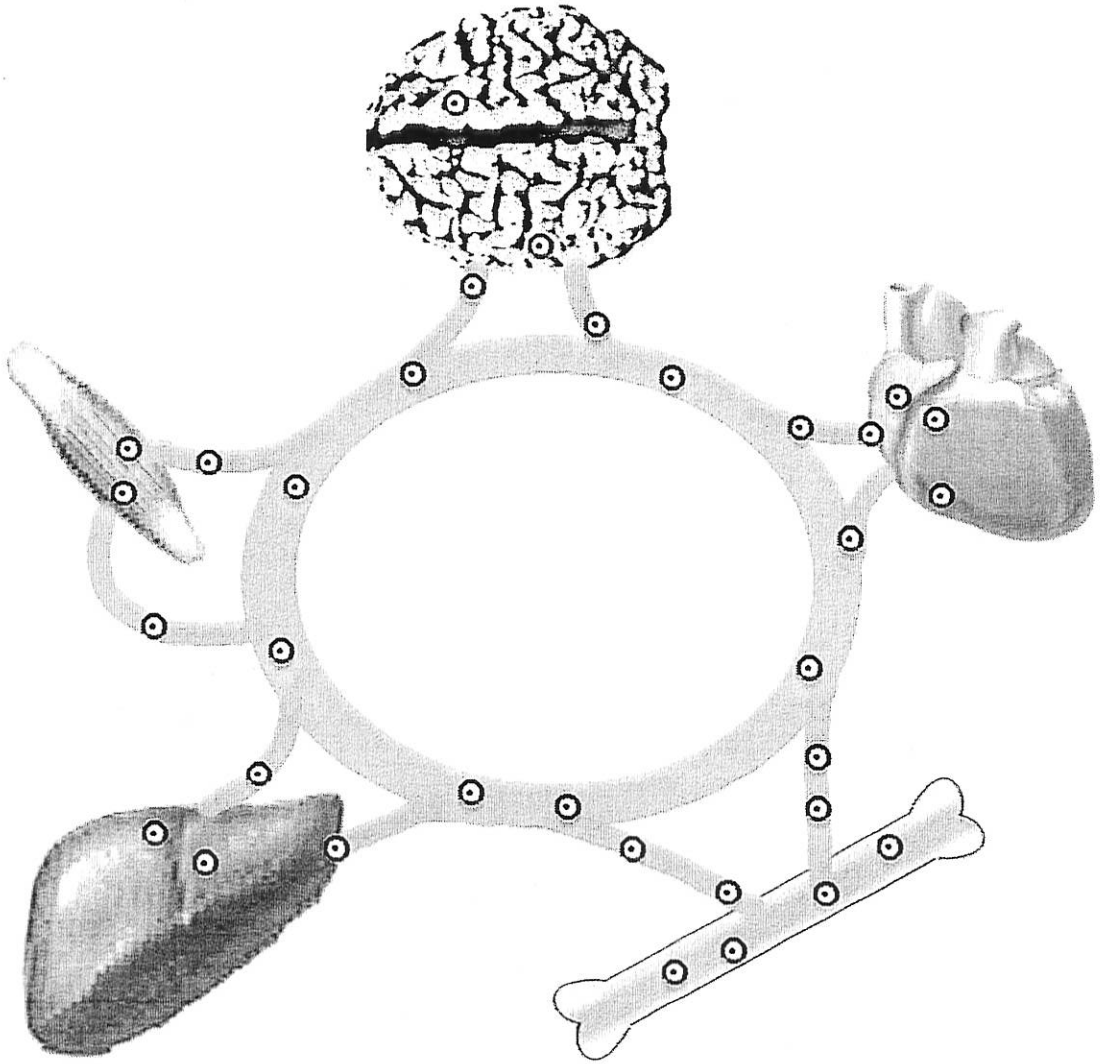


Anthony Dones with his father.
Anthony was successfully treated for
osteopetrosis with umbilical cord blood
stem cells.

The Developmental "Tree"

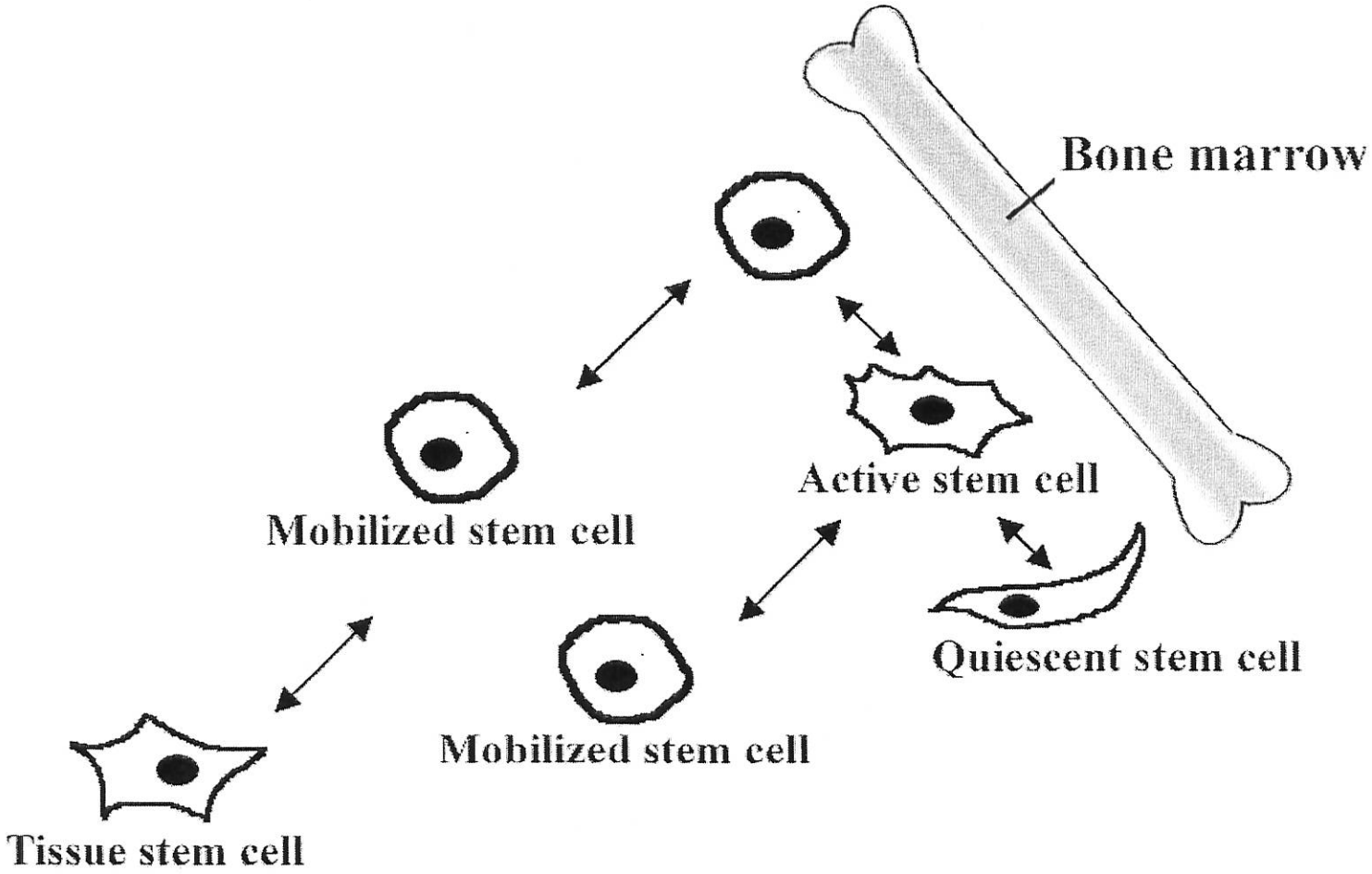


Concept of adult stem cells circulating between various organs for repair and maintenance of tissues



Activation and mobilization of stem cells

Inject cytokines such as GM-CSF to mobilize cells to damaged tissue (Successful trials with animal models of cardiac damage and stroke, and human patients after heart attack)



Regeneration Mechanism?

(evidence for all of these)

Dedifferentiation-Redifferentiation

Cell fusion with already-differentiated cell

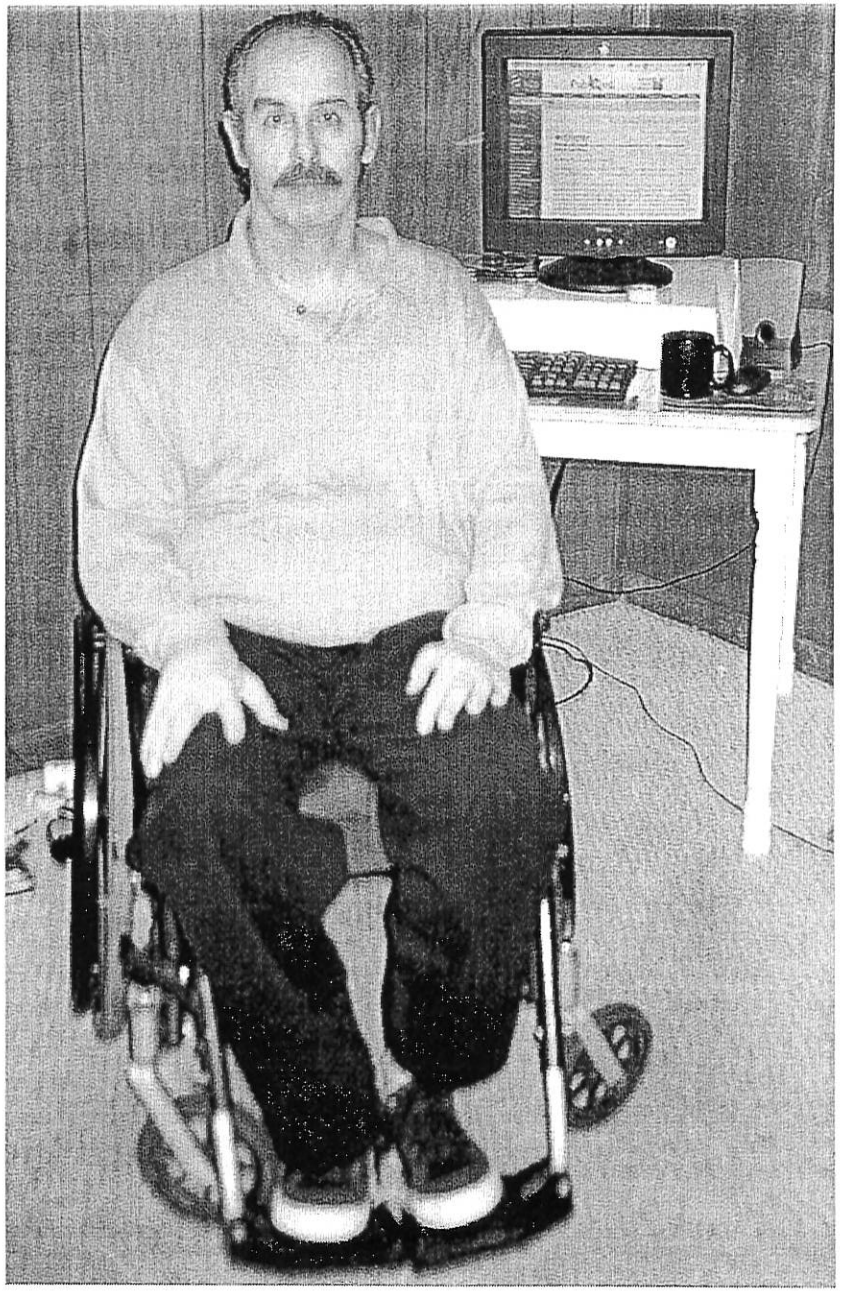
Transdifferentiation

Stimulate Differentiation of Tissue Cells

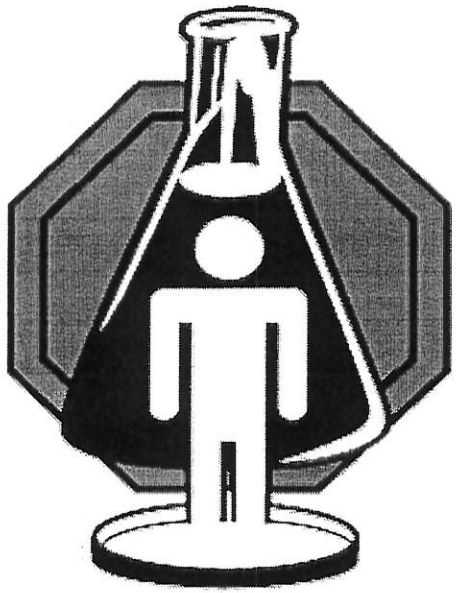
"[Robert] Lanza noted 'there is ample scientific evidence that adult stem cells can be used to repair damaged heart or brain tissue… if it works, it works, regardless of the mechanism,' he said."
Steve Mitchell, UPI; 12 October 2003

Jim Kelly

Spinal cord injury



Adult Stem Cells



The Coalition of Americans for Research Ethics

www.stemcellresearch.org

Most promising source for treatments

Able to generate virtually all adult tissues

Can multiply almost indefinitely, providing numbers sufficient for clinical treatments

Proven success in laboratory culture

Proven success in animal models of disease

Proven success in current clinical treatments

Ability to "home in" on damage

Avoid problems with tumor formation

Avoid problems with transplant rejection

Avoid ethical quandary