DO NO HARM
The Coalition of Americans for Research Ethics

www.stemcellresearch.org

1) To advance the development of medical treatments and therapies that do not require the destruction of human life, including the human embryo.

2) To educate and inform public policy makers and the general public regarding these ethically acceptable and medically promising areas of research and treatment.

3) To support continuation of federal laws prohibiting the federal funding of research that requires the destruction of human life, including the human embryo.

1101 Pennsylvania Avenue
Suite 600
Washington, DC 20004
Office: (202) 756-4947
Fax: (202) 756-7523

Selected References Documenting the Scientific Advances in "Adult" Stem Cell Research – Potential Treatments Update

(Post-Natal or Tissue Stem Cells, which are not derived from embryos)

The majority of the sources cited in this reference list are articles published in peer-reviewed scientific and medical journals. Some are reviews of scientific research. This document is organized by subject area, so some references may appear more than once.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

POTENTIAL CLINICAL APPLICATIONS OF ADULT STEM CELLS:
ANIMAL AND HUMAN POST-NATAL STEM CELL RESEARCH RELATING TO VARIOUS CELL AND TISSUE TYPES
BRAIN AND CENTRAL NERVOUS SYSTEM STEM CELLS
Scientist purify pluripotent adult neural stem cells from brain
Scientists at Australia's Walter and Eliza Hall Institute of Medical Research announced they had isolated an "extremely pure batch" of adult neural stem cells from the brains of mice. As reported in the journal Nature, the scientists were able to isolate the elusive neural stem cells with 80 percent purity, compared to a previous rate of 5 percent. "It proves that embryonic stem cells are not the only stem cells able to develop into new cells," ("Scientists find key to growing nerve cells, AAP Newsfeed, August 16,2001). The finding highlights the potential to use adult stem cells to treat Alzheimer's, Parkinson's, and other neurodegenerative diseases. Perry Bartlett, a member of the Australian team, says the research shows unequivocally that adult stem cells can become other types of cells: "It's important in the sense that there's been a debate about whether stem cells from adult tissues, whether that be brain or blood or elsewhere, do have the potential to give rise to various

tissues. I guess this is one of the very first unequivocal demonstrations that these cells are able to give rise to a larger number of cell types than was previously thought." The neural stem cells were also transformed into muscle cells.

References

R.L. Rietze *et al.*; "Purification of a pluripotent neural stem cell from the adult mouse brain"; Nature 412 736-739; Aug. 16, 2001

"Australian researchers claim stem cell breakthrough," Agence France Presse, August 16, 2001

"Scientists find key to growing nerve cells," AAP Newsfeed, August 16, 2001.

Japanese Scientists use Neural Stem Cells to Decrease Parkinson's Symptoms

An Okayama University research team has succeeded in decreasing symptoms of Parkinson's disease in mice. The team used neural stem cells to demonstrate the ability to increase the number of dopamine-producing cells. By combining substances that increase numbers of cells and adding them to the stem cells, they increased the number of dopaminergic neurons significantly. After injecting the substances directly into the brains of mice suffering from Parkinson's disease, symptoms of the disease were reduced. The research results were released at an academic meeting of the Japan Neurological Society on Oct. 24 in Okayama.

References:

"Team finds Parkinson's treatment for mice", The Daily Yomiuri (Tokyo); October 26, 2001 Friday, Pg. 3

Spinal Cord Regeneration Using Adult Cells

Scientists at McMaster University in Canada have achieved successful regeneration of spinal nerves by transplanting intestinal cells into severed spinal cords of animals. "This means there is a method here for regenerating fibres through the central nervous system with a relatively innocuous technique," said lead researcher Dr. Michel Rathbone. So far, they have had a 100% success rate in animal experiments. The researchers note that there is no fear of rejection because the transplanted
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
cells can come from the same person, and that using these mature cells gets around the thorny moral issue surrounding stem cells which are harvested from embryos.

Reference:

The Edmonton Sun August 15, 2001 Wednesday, Final Edition; Pg. 20

Human adult neural stem cells can be isolated from cadaver brains up to 24 hours after death.

Reference:

Palmer, TD *et al.*; "Progenitor cells from human brain after death"; Nature 411, 42-43; May 3, 2001.

NT2 (hNT, human cultured cells derived from teratocarcinoma) neurons differentiated into dopaminergic neurons in vitro. May serve as source of human DA neurons for use in transplantation therapies.

Reference:

Iacovitti L *et al.*; "Differentiation of human dopamine neurons from an embryonic carcinomal stem cell line"; Brain Research 912, 99-104; 2001

Geschwind, DH *et al.*; "A genetic analysis of neural progenitor differentiation"; Neuron 29(2), 325-339; Feb. 2001.

Fallon, J *et al.*; "*In vivo* induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain"; Proc. Natl. Acad. Sci. USA 97, 14686-14691;
Dec. 19, 2000 (growth factor successfully used to stimulate brain stem cells to reverse brain damage that is similar to Parkinson's disease).

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

Uchida, N *et al.*; "Direct isolation of human central nervous system stem cells"; Proc. Natl. Acad. Sci. USA 97, 14720-14725; Dec. 19, 2000.

Aboody, KS *et al.*; "From the cover: neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas"; Proc. Natl. Acad. Sci. USA 97, 12846-12851; Nov. 7, 2000 (study reporting that implanted neural stem cells show the ability to

migrate extensively throughout the brain to reach sites of damage).
Taupin, P *et al.*; "FSF-2-responsivie neural stem cell proliferation required CCg, a Nov.el autocrine/paracrine cofactor"; Neuron 28, 385-397; Feb. 2001.
Hodge, CJ Jr. and Boakye, M; "Biological Plasticity: The future of science in neurosurgery"; Neurosurgery 48, 2-16; Jan. 2001 (reviewing stem cell plasticity).
Galli, R. *et al.*, "Skeletal myogenic potential of human and mouse neural stem cells", Nature Neuroscience 3, 986-991; Oct. 2000 (reporting on the ability of human and mouse adult neural cells to transform into skeletal muscle cells).
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Toda, H *et al*.; "Neurons generated from adult rat hippocampal stem cells form functional glutamatergic and GABAergic synapses *in vitro*"; Experimental Neurology 165, 66-76; Sept. 2000.
Villa, A *et al*.; "Establishment and properties of a growth factor-dependent, perpetual neural stem cell line from the human CNS"; Exp. Neurol. 161, 67-84; Jan. 2000
Clarke *et al*.; "Generalized potential of adult neural stem cells"; Science 288, 1660-1663; June 2, 2000 (research with mice indicating that adult stem cells from brain can grow into a wide variety of organs, including heart, lung, intestine, kidney, liver, nervous system, muscle, and other tissues).
Magavi *et al*.; "Induction of neurogenesis in the neocortex of adult mice"; Nature 405, 951-955; June 22, 2000 (reporting that adult stem cells in brain stimulated to grow and replace damaged brain tissue).
Bjorklund, A and Lindvall, O; "Self-repair in the brain"; Nature 405, 892-893, June 22, 2000 (same).
Kondo, T and Raff, M; "Oligodendrocyte precursor cells reprogrammed to become multipotent CNS stem cells"; Science 289, 1754-1757; Sept. 8, 2000.
Johansson, CB *et al*.; "Neural stem cells in the adult human brain"; Exp. Cell Res. 253, 733-736; Dec. 1999.
Johansson, CB *et al*.; "Identification of a neural stem cell in the adult mammalian central nervous system"; Cell 96, 25-34; Jan. 1999
Bjornson *et al*.; "Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells in vivo"; Science 283, 534-537; Jan. 22, 1999.
Barnett *et al*.; "Identification of a human olfactory ensheathing cell that can effect transplantmediated remyelination of demyelinated CNS axons"; Brain 123, 1581-1588, Aug. 2000 (reporting on the isolation of the human adult stem cell that has been able to repair nerve axons in rat spinal cords).
Pagano, S *et al*.; "Isolation and Characterization of Neural Stem Cells from the Adult Human Olfactory Bulb"; Stem Cells 18, 295-300; July 2000.
Schwarz EJ *et al.*; "Multipotential marrow stromal cells transduced to produce L-DOPA: engraftment in a rat model of Parkinson disease"; Hum Gene Ther 10, 2539-2549; Oct 10, 1999
Kopen, GC *et al*.; "Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains"; Proc. Natl. Acad. Sci. USA 96, 10711-10716; Sept. 14, 1999 (injected stem cells show the ability to migrate throughout the hosts brain without damaging it).
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Foster, GA and Stringer, BM; "Genetic regulatory elements introduced into neural stem and progenitor cell populations"; Brain Pathol. 9, 547-567; July 1999 (review of methods tha t enable cell immortalization, purification and safety mechanisms, and genetic therapy using neural stem cells).
Yandava, BD *et al*.; " 'Global' cell replacement is feasible via neural stem cell transplantation: evidence from the dysmyelinated shiverer mouse brain"; Proc. Natl. Acad. Sci. USA 96, 7029-7034; June 8, 1999 (adult neural stem cell transplantation repairing tissue damage caused by a condition similar to Parkison's).

Ramer, MS *et al.*; "Functional regeneration of sensory axons into the adult spinal cord"; Nature 403, 312-316; Jan. 20, 2000.
Young, MJ *et al.*; "Neuronal differentiation and morphological integration of hippocampal progenitor cells transplanted to the retina of immature and mature dystrophic rats"; Molecular and Cellular Neurosciences 16, 197-205; Sept. 2000 (reporting that injected adult neural stem cells migrate to damaged retina in rats and take on the characteristics of retinal cells).
Flax, JD *et al.*; "Engraftable human neural stem cells respond to developmental cues, replace neurons, and express foreign genes"; Nature Biotechnol. 16, 1033; Nov. 1998.
Przyborski, SA *et al.*; "Developmental regulation of neurogenesis in the pluripotent human embryonal carcinoma cell line NTERA-2"; Eur. J. Neurosci. 12, 3521-3528; Oct. 2000.
Tuszynski, MH; "Intraparenchymal NGF infusions rescue degenerating cholinergic neurons"; Cell Transplant 9; 629-636; Sept.-Oct. 2000.
Smith, DE *et al.*; "Age-associated neuronal atrophy occurs in the primate brain and is reversible by growth factor gene therapy"; Proc Natl Acad Sci USA 96, 10893-10898; Sept. 14, 1999.
Raymon, HK *et al.*; "Immortalized human dorsal root ganglion cells differentiate into neurons with nociceptive properties"; J. Neurosci 19, 5420; July 1, 1999 (reporting the establishment of human neural cell lines, the establishment of immortalized human CNS cell lines, and their ability to differentiate into functional sensory neurons).

RETINAL STEM CELLS

Ahmad, I *et al.*; "Identification of neural progenitors in the adult mammalian eye"; Biochem. Biophys. Res. Commun. 270, 517-521; April 13, 2000
Tropepe *et al.*; "Retinal stem cells in the adult mammalian eye"; Science 287, 2032-2036, March 17, 2000 (isolation of retinal stem cell in humans, as well as other animals).
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

MUSCLE STEM CELLS

Lee, J-Y *et al.*; "Effect of Bone Morphogenetic Protein-2-Expressing Muscle-Derived Cells on Healing of Critical-Sized Bone Defects in Mice"; The Journal of Bone and Joint Surgery 83-A, 1032-1039; July 2001
(describing gene therapy with muscle-derived cells that have been genetically engineered to express growth factor BMP-2; used to treat nonhealing bone defects. The muscle-derived cells appear to include stem cells, which are easily obtained with muscle biopsy and could be used in gene therapy.)
U. of Pittsburgh researchers successfully used stem cell tissue engineering to restore deficient urethral sphincter muscles in animal models. Used muscle stem cells. Reported at 96th annual meeting of the American urological association. Researchers include Steven Chung, Michael Chancellor.
Menasché P *et al.*; [Autologous skeletal myoblast transplantation for cardiac insufficiency. First clinical case] [Article in French] Arch. Mal. Coeur Vaiss 94(3):180-182; March 2001
Pouzet B *et al.*; "Factors affecting functional outcome after autologous skeletal myoblast transplantation." Ann. Thorac. Surg. 71(3):844-850; March 2001 (study noting that ability of animal adult stem cells to repair damaged heart tissue).
Menasché P *et al.*; "Myoblast transplantation for heart failure"; Lancet 357(9252):279-280; Jan. 27, 2001 (evidence of improved function human heart after myoblast transplantation).
El Oakley, RM *et al.*; "Myocyte transplantation for cardiac repair: A few good cells can mend a broken heart"; Ann. Thorac. Surg. 71, 1724 –1733; 2001.
Torrente, Y *et al.*; "Intraarterial injection of muscle-derived CD34+Sca-1+ stem cells restores dystrophin in *mdx* mice"; J. of Cell Biology 152, 335-348; Jan. 22, 2001
Scorsin M *et al.*; "Comparison of the effects of fetal cardiomyocyte and skeletal myoblast transplantation on postinfarction left ventricular function"; J. Thorac. Cardiovasc. Surg. 119; 1169-1175; June 2000.
Pouzet B *et al.*; "Intramyocardial transplantation of autologous myoblasts : can tissue processing Be

optimized?"; Circulation 102; III210-215; Nov. 7, 2000 (reporting that autologous skeletal myoblast (SM) transplantation improves function of infarcted myocardium in rats).
Jackson, K *et al.*; "Hematopoietic potential of stem cells isolated from murine skeletal muscle"; Proceedings National Academy of Sciences USA 96, 14482-14486; Dec. 7, 1999. [NOTE: may have been due to hematopoietic stem cell contamination! personal communication, M. Goodell]
Lee, JY *et al.*; "Clonal isolation of muscle-derived cells capable of enhancing muscle regeneration and bone healing"; J. Cell Biology 150, 1085-1100; Sept. 4, 2000 (reporting that intravenous

injection of muscle-derived adult stem cells back into the mice resulted in muscle regeneration and partial restoration of dystrophin expression in the mice, and that the transplantation of these cells engineered to secrete a bone protein results in their differentiation into bone cells and acceleration of healing of a skull defect in immunodeficient mice).
Gussoni, E *et al.*; "Dystrophin expression in the mdx mouse restored by stem cell transplantation"; Nature 401, 390-394; Sept. 23, 1999 (similar findings as ref. 146, additionally finding that normal haematopoietic cells partially restored dystrophin expression in the affected muscle and that the inherent developmental potential of adult stem cells isolated from diverse tissues is greater than previously anticipated).
Williams, JT *et al.*; "Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes"; Am. Surg. 65, 22; Jan. 1999.
Kessler, PD and Byrne, BJ; "Myoblast cell grafting into heart muscle: cellular biology and potential applications"; Ann. Rev. Physiol. 61, 219; 1999.
Ray, C.J. Chiu *et al.*; "Cellular Cardiomyoplasty: Myocardial Regene ration With Satellite Cell Implantation"; Ann. Thorac. Surg. 60:12-18; 1995.
Dorfman, J *et al.*; "Myocardial tissue engineering with autologous myoblast implantation"; J. Of Thorac. And Cardio. Surg. 116, 744-751; Nov. 1998.
Atkins, B *et al.*; "Intracardiac Transplantation of Skeletal Myoblasts Yields Two Populations of Striated Cells In Situ"; Ann. Thorac. Surg. 67, 124-129; 1999.

SKIN STEM CELLS

Stem Cells from skin develop into brain cells and other tissues

Researchers in Montreal, Canada report in Nature Cell Biology that they have taken adult stem cells from the skin of mice and transformed them into brain cells, including neurons, as well as glial cells, smooth muscle cells, and fat cells. The development points to the potential of creating a "vast and accessible supply" of neurons. The researchers' work also suggests that similarly versatile adult stem cells can be found in the human scalp.

" 'They are beautiful neurons,' said molecular biologist and co-author Freda Miller. 'You kind of look at them and say, this can't be true. But then you go back and do it 10 times, and you realize it is true.' "

Ronald Worton, head of Canada's Stem Cell Network, said "Two years ago, I would have said this is a big surprise and I wouldn't have believed it unless it could be widely reproduced. But then the dogma used to be that if you were a stem cell in [adult] bone marrow, you could only make blood cells, or if you were a stem cell in skin, you could only make skin. There's now enough lab work to say the dogma was wrong."

References

Carolyn Abraham, "McGill team harvest stem cells from skin," The Globe and Mail, August, 13, 2001.
J.G. Toma *et al.*; "Isolation of multipotent adult stem cells from the dermis of mammalian skin"; Nature Cell Biology 3, 778-784; Sept 2001
Oshima, H *et al.*; "Morphogenesis and renewal of hair follicles from adult multipotent stem cells"; Cell 104, 233-245; Jan. 2001.

Taylor, G; “Involvement of follicular stem cells in forming not only the follicle but also the epidermis”; Cell 102, 451-461; Aug. 2000.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

PANCREATIC STEM CELLS

Retraining Lymphocytes to Overcome Diabetes

Scientists have implanted encapsulated pancreatic islet cells and retrained lymphocytes to reverse diabetes in mice. The autoimmunity that was previously directed against insulin-secreting cells was reversed, and the implants restored pancreatic function to such an extent that normal blood glucose levels were maintained in up to 75% of the animals after discontinuation of treatment and removal of the islet transplant s. “A therapy aimed at the selective elimination of autoreactive cells and the reeducation of T cells, when combined with control of glycemia [blood glucose levels], is thus able to effect an apparent cure of established type 1 diabetes in the [diabetic] mouse.)

Reference:

Ryu S *et al.*; “Reversal of established autoimmune diabetes by restoration of endogenous ß cell function”; J. Clin. Invest. 108, 63–72; July 2001

Gene Therapy Corrects Diabetes In Mice

Use of gene therapy has been successful in restoring normal blood glucose and insulin levels in mice. A team from Novartis in Summit, New Jersey, reported that “this study provides an entirely novel approach to treat type 2 diabetes.” The team treated mice with a gene therapy vector for glucose kinase regulatory protein, which plays a central role in control of glucose levels in the body. To their surprise, the vector completely corrected the diabetic symptoms of the animals.

Reference:

Slosberg ED *et al.,* “Treatment of type 2 diabetes by adenoviral-mediated overexpression of the glucokinase regulatory protein”, Diabetes 50, 1813-1820; Aug 2001
de la Tour D *et al.*; “Beta-cell differentiation from a human pancreatic cell line in vitro and in vivo”; Mol Endocrinol 15, 476-483, Mar 2001
Itkin-Ansari P *et al.*; “PDX-1 and cell-cell contact act in synergy to promote delta-cell development in a human pancreatic endocrine precursor cell line”; Mol Endocrinol 14, 814-822; June 2000.
Serup, P *et al.*; “Islet and stem cell transplantation for treating diabetes”; British Medical J. 322, 29-32; Jan. 6, 2001 (review of possible stem cell treatments for diabetes, suggesting that adult stem cells show more promise).
Cheung, AT *et al.*; “Glucose-dependent insulin release from genetically engineered K cells”; Science 290; 1959-1962; Dec. 8, 2000.
Gmyr, V *et al.*, “Adult human cytokeratin 19-positive cells reexpress insulin promo ter factor 1 in vitro: Further evidence for pluripotent pancreatic stem cells in humans”; Diabetes 49, 1671-1680; Oct. 2000.
Bonner-Weir, S *et al.*; “In vitro cultivation of human islets from expanded ductal tissue”; Proc. Natl. Acad. Sci. USA 97, 7999-8004; July 5, 2000 (reporting that cultured human pancreatic ductal cells formed islet buds and secreted insulin).
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
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.

BONE MARROW and PERIPHERAL BLOOD STEM CELLS

Adult Stem Cells Can “Be Cultured and Expand Indefinitely”

Confirming numerous previous published reports, a new report in the journal *Blood* shows that human adult bone marrow stem cells can be grown in culture for extended periods of time and still retain the ability to differentiate into multiple cell types. Even after extensive time in culture, the cells maintained their ability to grow as well as their plasticity at forming different cell types. The results provide further evidence that sufficient numbers of adult stem cells can be generated for clinical treatments.

References:

Reyes M *et al.*; "Purification and ex vivo expansion of postnatal human marrow mesodermal progenitor cells"; *Blood* 98, 2615-2625; Nov 1, 2001

Krause DS; "Multipotent human cells expand indefinitely", *Blood* 98, 2595; Nov 1, 2001

Adult stem cells repair heart damage

Scientists at New York Medical College in Valhalla and the National Institutes of Health report that stimulating the production of stem cells in bone marrow has repaired heart damage in mice. Mice were first injected with immune system chemicals called cytokines to stimulate production of stem cells in bone marrow. Seventy-three percent of the mice receiving this treatment were alive a month after the heart attack, compared to only 20 percent of those untreated. Autopsies showed signs of heart repair, and the researchers report "a remarkable recovery" in the heart's pumping ability. The findings are reported in the Proceedings of the National Academy of Sciences Early Edition, August, 2001.

Reference

D. Orlic *et al.*; "Mobilized bone marrow cells repair the infarcted heart, improving function and survival"; Proceedings of the National Academy of Sciences USA www.pnas.orgycgiydoiy10.1073ypnas.181177898 (PNAS Early Edition published online)

"Bone Marrow Cell Repair Heart Damage in Mice," Reuters Health, August 14, 2001

Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

Human Adult Bone Marrow Stem Cells Can Form Kidney Tissue

Researchers in Great Britain have found that human adult bone marrow stem cells can form kidney tissue. The work, published in the Journal of Pathology, highlights another possibility for use of adult stem cells to treat human disease. ``In people whose kidneys are failing, we might be able to generate more functional kidney cells. That is something that has not been known before," said Dr. Richard Poulsom, lead scientist on the report.

Reference:

Poulsom R *et al.*; "Bone marrow contributes to renal parenchymal turnover and regeneration"; The Journal of Pathology 195, 229-235; Sept 2001 (published online July 25, 2001; DOI: http://dx.doi.org/10.1002/path.976)

Bone marrow implantation enhanced angiogenesis (blood vessel formation) in a rat heart attack model system. Three weeks after bone marrow stem cell implantation, regional blood flow was significantly higher and cardiac function was improved. There was a marked increase in number of vessels nourishing the heart.

Reference:

Kamihata H *et al.*, "Implantation of Bone Marrow Mononuclear Cells Into Ischemic Myocardium Enhances Collateral Perfusion and Regional Function via Side Supply of Angioblasts, Angiogenic Ligands, and Cytokines," Circulation 104, 1046; 2001

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

Jackson, KA *et al.*; "Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells"; J. of Clinical Investigation 107, 1395-1402; June 2001 (reporting that adult bone marrow stem cells could form functional heart muscle and blood vessels in mice which had heart damage).

Orlic, D *et al.*; "Bone marrow cells regenerate infarcted myocardium"; Nature 410, 701-705; April 5, 2001 (reporting that that locally delivered bone marrow cells can generate de Nov.o myocardium, ameliorating the outcome of coronary artery disease).

Kocher, AA *et al.*; "Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function"; Nature Medicine 7, 430-436; April 2001.

Chen, J *et al.*; "Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats"; Stroke 32, 1005-1011; April 2001 (study indicates that bone marrow stem cells may be able to be used to reverse the effects of strokes).

Li, Y *et al.*; "Adult bone marrow transplantation after stroke in adult rats"; Cell Transplant 10(1), 31-40; Jan.-Feb. 2001.
Cooper, LF *et al.*; Incipient analysis of mesenchymal stem-cell-derived osteogenesis"; J. Dent. Res. 80(1), 314-320; Jan. 2001.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Moutsatsos, IK *et al.*; "Exogenously regulated stem cell- mediated gene therapy for bone regeneration"; Mol Ther 3(4), 449-461; April 2001.
Glimm, H *et al.*; "Previously undetected human hematopoietic cell populations with short-term repopulating activity selectively engraft NOD/SCID-beta2 microglobulin- null mice"; J. Clin. Invest. 107, 199-206; Jan. 2001.
Wang, J-S *et al.*; "Marrow stromal cells for cellular cardiomyoplasty: Feasibility and potential clinical advantages"; The J. of Thorac. And Cardio. Surg. 120, 999-1006; Nov. 2000.
Bhardwaj, G *et al.*; "Sonic hedgehog induces the proliferation of primitive human hematopoietic cells via BMP regulation"; Nature Immun. 2, 172-180; 2001 (reporting that human and animal adult stem cells were shown to be able of extensive proliferation in culture, providing potentially unlimited supplies of adult stem cells for clinical treatments).
Brazelton, TR *et al*.; "From marrow to brain: expression of neuronal phenotypes in adult mice"; Science 290, 1775-1779; Dec. 1, 2000 (reporting that adult stem cells from mouse bone marrow injected into mouse blood stream could be found developing neuron characteristics in brain, "demonstrat[ing] a remarkable plasticity of adult tissues with potential clinical applications").
Mezey, E *et al*.; "Turning blood into brain: Cells bearing neuronal antigens generated in vivo from bone marrow"; Science 290, 1779-1782; Dec. 1, 2000 (same).
Cashman, JD and Eaves, CJ; "High marrow seeding efficiency of human lymphomyeloid repopulating cells in irradiated NOD/SCID mice"; Blood 96, 3979-3981; Dec. 1, 2000 (finding that previously reported human stem cell frequencies and their in vivo self-renewal activity have been markedly underestimated).
Goan *et al*.; "Donor stromal cells from human blood engraft in NOD/SCID mice"; Blood 96, 3971-3978; Dec. 1, 2000.
Liechty, KW *et al.*; "Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep"; Nature Medicine 6, 1282-1286; Nov. 2000.
Lagasse, E *et al.*; "Purified hematopoietic stem cells can differentiate into hepatocytes in vivo"; Nature Medicine 6, 1229-1234; Nov. 2000 (reporting that the intravenous injection of adult bone marrow stem cells in a mouse model of tyrosinemia type I rescued the mouse and restored biochemical function of its liver).
Kirzner, RP *et al.*; "Prevention of coronary vascular disease by transplantation of T-cell-depleted bone marrow and hematopoietic stem cell preparation in autoimmune-prone w/BF(1) mice"; Biol. Blood Marrow Transplant 6, 513-522; 2000.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Varnum-Finney, B *et al.*; "Pluripotent, cytokine-dependent, hematopoietic stem cells are immortalized by constitutive Notch1 signaling"; Nature Medicine 6, 1278-1281; Nov. 2000
Sharma, AK *et al*.; "Human CD34(+) stem cells express the hiwi gene, a human homologue of the Drosophila gene piwi"; Blood 97, 426-434; Jan. 15, 2001.
Ema, H *et al.*; "In vitro self- renewal division of hematopoietic stem cells"; J. Exp. Med. 192, 1281-1288; Nov. 6, 2000.
Huss, R; "Isolation of primary and immortalized CD34- hematopoietic and mesenchymal stem cells from various sources"; Stem Cells 18, 1-9; 2000 (review of techniques to isolate hematopoietic and mesenchymal stem cells from various sources, and expansion and differentiation in culture for potential clinical uses).
Sanchez-Ramos, J *et al*.; "Adult bone marrow stromal cells differentiate into neural cells in vitro"; Experimental Neurology 164, 247-256; Aug. 2000 (stud y showing that human and mouse

bone marrow stem cells able to form nerve cells).
Woodbury, D *et al*.; "Adult rat and human bone marrow stromal cells differentiate into neurons"; J. Neuroscience Research 61, 364-370; Aug. 15, 2000 (reporting that adult human bone marrow stem cells can create a "virtually limitless supply" of nerve cells, and that the adult stem cells "grow rapidly in culture, precluding the need for immortalization, and differentiate into neurons exclusively with use of a simple protocol").
Cao, H *et al.*; "In vitro generation of dendritic cells from human blood monocytes in experimental conditions compatible for in vivo cell therapy"; J. Hematother. Stem Cell Res. 9, 183-194; April 2000.
Theise, N *et al*.; "Liver from bone marrow in humans"; Hepatology 32, 11-16; July 2000 (reporting that human bone marrow stem cells can form liver).
Alison, M *et al*.; "Cell differentiation: hepatocytes from non-hepatic adult stem cells"; Nature 406, 257; July 20, 2000.
Theise, N *et al*.; "Derivation of hepatocytes from bone marrow cells in mice after radiation- induced myeloablation"; Hepatology 31, 235-240; Jan. 2000
Schwarz EJ *et al.*; "Multipotential marrow stromal cells transduced to produce L-DOPA: engraftment in a rat model of Parkinson disease"; Hum Gene Ther 10, 2539-2549; Oct 10, 1999
Petersen, B *et al*.; "Bone marrow as a potential source of hepatic oval cells"; Science 284, 1168-1170; May 14, 1999.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Lian, JB *et al.*; "Marrow transplantation and targeted gene therapy to the skeleton"; Clin. Orthop. 379 Supp., S146-155; Oct. 2000 (review of bone marrow as a source of cells for nervous system).
Mezey, E and Chandross, KJ; "Bone marrow: a possible alternative source of cells in the adult nervous system"; Eur. J. Pharmacol. 405, 297-302; Sept.. 29, 2000.
Colter, D *et al*.; "Rapid Expansion of recycling stem cells in cultures of plastic-adherent cells from human bone marrow"; Proc. Natl. Acad. Sci. USA 97, 3213-3218; March 28, 2000 (reporting identified conditions that allow large-scale expansion of human adult stem cells in culture, making these cells an almost unlimited source).
Ueda, T *et al*.; "Expansion of human NOD/SCID-repopulating cells by stem cell factor, Flk2/Flt3 ligand, thrombopoietin, IL-6, and soluble IL-6 receptor"; J. Clin. Invest. 105, 1013-1021; April 2000.
Jaiswal, RK *et al.*; "Adult human mesenchymal stem cell differentiation to the osteogenic or adipogenic lineage is regulated by mitogen-activated protein kinase"; J. Biol. Chem. 275, 9645-9652; March 31, 2000.
Pittenger, MF *et al*.; "Multilineage potential of adult human mesenchymal stem cells"; Science 284, 143-147; April 2, 1999 (reporting that adult stem cells could be stimulated to form either bone, cartilage, or fat cells, and that these cells appear to have the potential to form other tissues as well, including tendon and muscle).
Kopen, GC *et al*.; "Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains"; Proc. Natl. Acad. Sci. USA 96, 10711-10716; Sept. 14, 1999.
Makino S *et al*.; "Cardiomyocytes can be generated from marrow stromal cells in vitro"; J. Clin. Invest. 103, 697–705; March 1999
Pereira RF *et al.*; "Marrow stromal cells as a source of progenitor cells for nonhematopoietic tissues in transgenic mice with a phenotype of osteogenesis imperfecta"; Proc. Natl. Acad. Sci. USA 95, 1142–1147; February 1998
Asahara, T *et* al.; "Isolation of Putative Progenitor Endothelial Cells for Angiogenesis"; Science 275, 964-967; Feb. 14, 1997.
Shi, Q *et al.*; "Evidence for Circulating Bone Marrow-Derived Endothelial Cells"; Blood 92, 362-367; July 15, 1998.

Yagi, M *et al*.; “Sustained ex vivo expansion of hematopoietic stem cells mediated by thrombopoietin”; Proc. Natl. Acad. Sci. USA 96, 8126–8131; July 1999.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Bhatia, M *et al*.; “Purification of primitive human hematopoietic cells capable of repopulating immune-deficient mice”; Proc. Natl. Acad. Sci. USA 94, 5320–5325; May 1997 (reporting that a single human marrow stromal cell has the ability to repopulate bone marrow of mice).
Huss, R *et al*.; “Evidence of Peripheral Blood-Derived, Plastic-Adherent CD34 –/low Hematopoietic Stem Cell Clones with Mesenchymal Stem Cell Characteristics”; Stem Cells 18, 252-260; 2000.
Eglitis, MA *et al*.; “Targeting of marrow-derived astrocytes to the ischemic brain”; Neuroreport 10, 1289; April 26, 1999 .
Deans, RJ and Moseley, AB, “Mesenchymal stem cells. Biology and potential clinical uses”, Experimental Hematology 28, 875-884; Aug., 2000 (reporting that multiple tissue types can be derived from bone marrow stem cells, with many potential clinical uses).
Azizi, SA *et al.*; "Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats-similarities to astrocyte grafts"; Proc. Natl. Acad. Sci. USA 95, 3908; March 1998 (reporting that human bone marrow stromal cells had the ability to repair damaged rat brain tissue without inflammatory response or rejection).
Bruder, SP *et al.*; "Bone regeneration by implantation of purified, culture-expanded human mesenchymal stem cells"; J. Orthop. Res. 16, 155; 1998.
Ringden, O *et al.*, “Peripheral blood stem cell transplantation from unrelated donors: a comparison with marrow transplantation”; Blood 94, 455; July 15, 1999.
Jaiswal, N *et al.*; "Osteoge nic differentiation of purified, culture-expanded human mesenchymal stem cells in vitro"; J. Cell Biochem. 64:295-312; 1997 (reporting that human bone marrow cells induced to form bone in culture).
Bruder, SP *et al.*; "Growth kinetics, self- renewal, and the osteogenic potential of purified human mesenchymal stem cells during extensive subcultivation and following cryopreservation", J Cell Biochem 64, 278; 1997 (reporting that bone marrow cells maintain potential after longterm cryopreservation).
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

LIVER STEM CELLS

Malouf, NN *et al.*; “Adult-derived stem cells from the liver become myocytes in the heart in vivo”; American J. of Pathology 158, 1929-1935; June 2001 (reporting that adult stem cells from liver could transform into heart tissue when injected into mice, demonstrating “that adultderived stem cells, like their embryonic counterparts, are pluripotent”).
Suzuki, A *et al*.; “Flow-cytometric separation and enrichment of hepatic progenitor cells in the developing mouse liver”; Hepatology 32, 1230-1239; Dec. 2000.
Shafritz, DA; “Rat liver stem cells: Prospects for the future”; Hepatology 32, 1399-1400; Dec. 2000 (commentary on future prospects of liver stem cell research for therapeutic application).
Lagasse, E *et al.*; “Purified hematopoietic stem cells can differentiate into hepatocytes in vivo”; Nature Medicine 6, 1229-1234; Nov. 2000.
Kubota, H and Reid, LM; “Clonogenic hepatoblasts, common precursors for hepatocytic and biliary lineages, are lacking classical major histocompatibility complex class I antigen”; Proc. Natl. Acad. Sci. USA 97, 12132-12137; Oct. 24, 2000.
Strain, AJ and Crosby, HA; “Hepatic stem cells”; Gut 46, 743-745; 2000 (general reference collecting research regarding liver stem cells).

STEM CELLS FROM HEART, BLOOD VESSELS, and HEART VALVES

Beltrami, AP *et al.*; “Evidence That Human Cardiac Myocytes Divide after Myocardial Infarction”; *New England J. of Medicine* 344, 1750-1757; June 7, 2001 (research indicating that the human heart contains its own adult stem cell, which could possibly be stimulated to grow and repair damage after a heart attack).
Shum-Tim, D *et al*.; “Tissue engineering of autologous aorta using a new biodegradable polymer”;

Ann. Thorac. Surg. 68, 2298-2304; Dec. 1999.
Asahara, T *et* al.; "Isolation of Putative Proge nitor Endothelial Cells for Angiogenesis"; Science 275, 964-967; Feb. 14, 1997.
Shi, Q *et al.*; "Evidence for Circulating Bone Marrow-Derived Endothelial Cells"; Blood 92, 362-367; July 15, 1998.
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

STEM CELLS FROM FAT

Zuk, PA *et al.*; "Multilineage cells from human adipose tissue: Implications for cell-based therapies"; Tissue Engineering 7, 211-228; 2001 (reporting that human adult fat stem cells could be expanded and maintained in culture for extended periods, and could be differentiated into fat, cartilage, muscle, and bone).
Norton, A; "Stem cells from body fat—limitless supply"; Reuters Health; Oct. 18, 2000 (press report discussing recent findings that fat stem cells can transform into bone).

LUNG STEM CELLS

Emura, M; "Stem cells of the respiratory epithelium and their in vitro cultivation"; In Vitro Cell Dev. Biol. Anim. 33, 3; Jan. 1997.

DENTAL STEM CELLS

Gronthos, S *et al*.; "Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*"; Proc Natl Acad Sci USA 97, 13625-13630; Dec. 5, 2000 (identification and isolation of stem cells from human dental pulp that could be induced to differentiate into tooth structures).

MAMMARY GLAND

Kim, ND *et al.*; "Stem cell characteristics of transplanted rat mammary clonogens"; Exp. Cell Res. 260, 146-159; Oct. 10, 2000.

SPERMATOGONIAL STEM CELLS

Izadyar, F *et al.*; "Spermatogonial stem cell transplantation"; Mol Cell Endocrinol 169, 21-26; Nov. 27, 2000.
Johnston, DS *et al.*; "Advances in spermatogonial stem cell transplantation"; Rev. Reprod. 5, 183-188; Sept.. 2000 (review).

GASTROINTESTINAL STEM CELLS

Booth, C, Potten, CS; "Gut instincts: thoughts on intestinal epithelial stem cells"; Journal of Clinical Investigation 105, 1493-1499; June 2000
Pageot LP *et al.*; "Human cell models to study small intestinal functions: recapitulation of the cryptvillus axis"; Microsc Res Tech 49, 394-406; May 15, 2000
(The intestinal epithelium is continuously and rapidly renewed by a process involving cell generation, migration, and differentiation, from the stem cell population located at the bottom of the crypt. Important advances have been achieved over recent years in the generation of normal human intestinal cell models.)
Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice
Wright NA; "Epithelial stem cell repertoire in the gut: clues to the origin of cell lineages, proliferative units and cancer"; Int J Exp Pathol;81, 117-143; April 2000
(Gastrointestinal stem cells are shown to be pluripotential and to give rise to all cell lineages in the epithelium.)
Bach SP *et al.*; "Stem cells: the intestinal stem cell as a paradigm"; Carcinogenesis 121, 469-476; 2000
Wong, WM, Wright NA; "Cell proliferation in gastrointestinal mucosa"; J. Clin. Pathol. 52, 321-333; 1999
Booth C *et al.*; "Maintenance of Functional Stem Cells in Isolated and Cultured Adult Intestinal Epithelium"; Experimental Cell Research 249, 359–366; 1999

STEM CELLS FROM PLACENTA

Anthrogen, in a press release, reports that they can isolate stem cells from placenta after delivery, and that these stem cells so far have been induced to form bone, nerve, cartilage, bone marrow, muscle, tendon, and blood vessel. This press release is available at

<http://www.mcpf.org/AnthroGen%20Discovery.htm>. AnthroGen has also posted articles based on that press release at <http://www.anthrogenesis.com/page411559.htm>.

OTHER SIGNIFICANT RESEARCH INVOLVING ADULT STEM CELLS

Asahara, T *et al.*; "Stem cell therapy and gene transfer for regeneration"; Gene Ther. 7; 451-457; March 2000.

Wei, G *et al.*; "Stem cell plasticity in mammals and transdetermination in Drosophila: Common themes?"; Stem Cells 18, 409-414; Nov. 2000.

STEM CELLS FROM UMBILICAL CORDS

Researchers at the University of South Florida have reported at the meeting of the American Association for the Advancement of Science (Jan. 2001) and the American Academy of Neurology meeting (May 2001) that human cord blood stem cells can be induced to form neurons. When injected into the bloodstream of rats which had suffered stroke, the adult stem cells found their way to the brain and repaired much of the damage. Rats which were previously paralyzed showed 80% recovery. (From Meetings press releases).

Lu S, Ende N; "Potential for clinical use of viable pluripotent progenitor cells in blood bank stored human umbilical cord blood"; Life Sciences 61, 1113-1123; 1997

Ende N *et al.*; "Potential effectiveness of stored cord blood (non- frozen) for emergency use"; The Journal of Emergency Medicine 14, 673-677; 1996

Updated November 18, 2001 Treatments with Adult Stem Cells David A. Prentice

Ende N *et al.*; "Effect of Human cord blood transfer on survival and disease activity in MRL-*lpr/lpr* mice"; Clinical Immunology and immunopathology 75, 190-195; 1995 (mouse lupus)

Ende N, Chen R; "Human umbilical cord blood cells ameliorate Huntington's disease in transgeneic mice"; Journal of Medicine *in press*; 2001

Ende N *et al.*; "The effect of megadose of human umbilical cord blood mononuclear cells on Alzheimer's disease mice"; Modern Pathology 14, 207A; Jan 2001

Ende N, Chen R; "The effect of megadose of human umbilical cord blood mononuclear cells on Huntington disease mice"; Am. J. Clinical Pathology 114, #4, abst 89; Oct 2000

Chen R, Ende N; "The potential for the use of mononuclear cells from human umbilical cord blood in the treatment of amyotrophic lateral sclerosis in SOD1 mice"; Journal of Medicine 31, 21-31; 2000

Ende N *et al.*; "NOD/LtJ type I diabetes mice and stem cells (Berashis) derived from human umbilical cord blood"; *submitted*.

Ende N *et al.*; "Human umbilical cord blood cells ameliorate Alzheimer's disease in transgenic mice"; Journal of Medicine *in press*; 2001

Ende N, Chen R; "Parkinson's disease mice and human umbilical cord blood"; abstract submitted to USCAP

Ende N; "The Berashis cell: a review. Is it similar to the embryonic stem cell?"; Journal of Medicine 31, 113-130; 2000