Spinal Cord Injuries: Where are We?

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Calgary, Alberta
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We need to be humble in the face of Nature.

(Nature is often complex, powerful and mysterious, we see all of these aspects in the nervous system).

Knowledge Translation

- This talk is an example of knowledge translation (KT).
- KT is an important new tool in medical research.
- KT involves making a bridge of understanding between researchers, doctors and patients.
- Complex messages are lost if they are not easily understood. Our goal is to present information in a way that is understandable to all interested parties:
  - Patients can better understand research findings and judge information pertaining to them.
  - Health care providers and researchers can better understand patients and their needs.

Introduction

- This presentation will provide an overview of the basic concepts and some of the background issues involved in the science of spinal cord injuries (SCI) and their treatment, with an emphasis on stem cells.
- Research on SCIs has greatly advanced over the years, but is still in the early stages.
- The research on spinal cord injuries is very complex and is largely done on animals. Understanding is increasing about how we may someday repair nerve cells, but it is a big step from animals to humans. This research involves many complex areas of biology, for example, the use of stem cells as therapy.

A Long History

- By 1664 Descartes saw the neural connection between the toe and the brain.

(But he thought that the fiber from the toe is pulled by the heat, releasing a fluid from the head that made the muscles contract and pull back.)

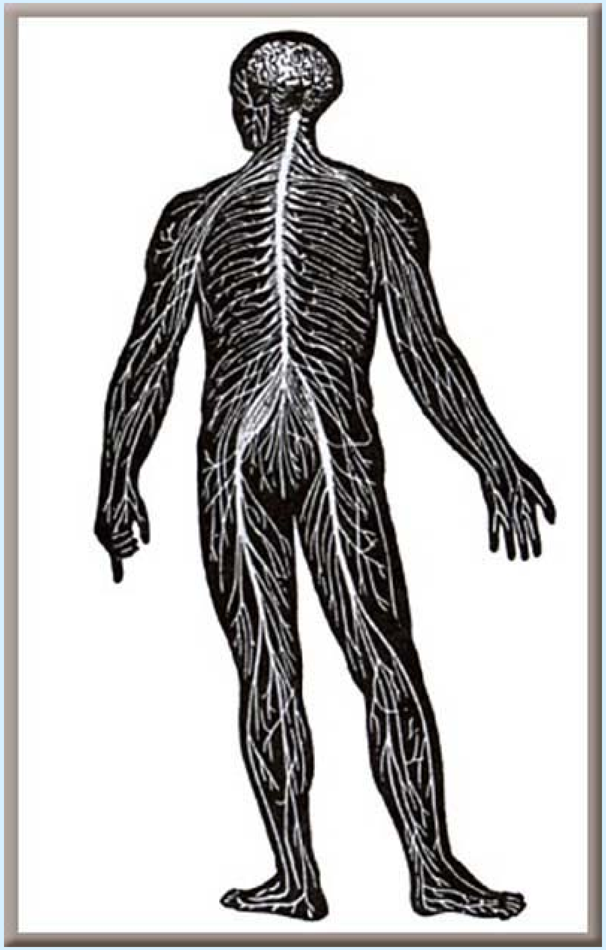
From: ocw.mit.edu

What is the Spinal Cord?

- The spinal cord is a jelly-like cable of nerves that carries electrical signals to and from the brain and connects the brain with the rest of the body.
- The cord also plays an active role, e.g., through spinal reflexes and in helping to control, coordinate, interpret & integrate the body's movement & sensation signals.
- The spinal cord runs down through the center of 33 vertebrae – bones that protect the cord from damage:
  - The spine is robust, but if the vertebrae become unstable, the cord becomes very vulnerable.
- The brain and the spinal cord make up the Central Nervous System (CNS).

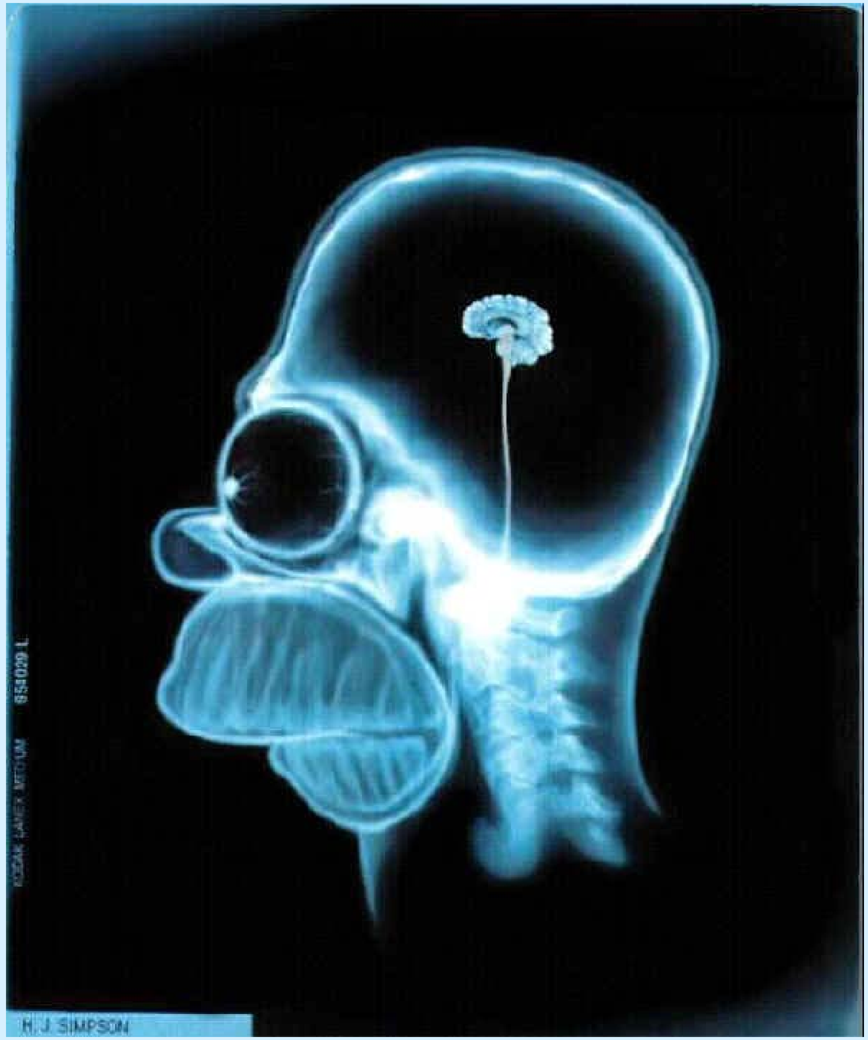
The Nerves of the Spinal Cord

- The cord connects the brain with the Peripheral Nervous System (PNS), a complex series of nerves radiating out from the cord to the rest of the body:
  - Sensation messages from sensory neurons in all parts of the body go to the cord and then up to the brain (afferent - up).
  - Action messages from the brain go down the cord and out to motor neurons that then connect to muscles and glands (efferent - down).



- zemlin.shs.uiuc.edu/CNS/slides/cns_01.jpg

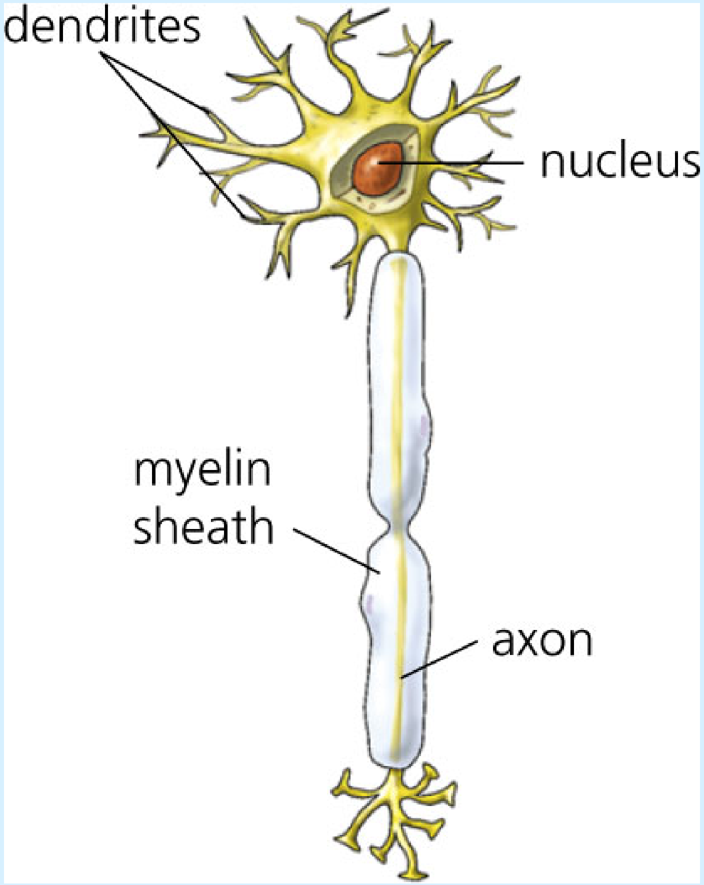
X-ray View of the Brain and Cord



www.theomnivore.com/ photos/homer_x-ray.JPG

Patient: Simpson, H. J.

The Nerve Cell (Neuron)



From The American Heritage Dictionary

- A neuron has a). a cell body (with a center nucleus), b). an axon – a long "cord" that carries an electrical signal & c). dendrites – extensions that end in synapses.
  - Axons can extent up to 3 feet from a single nerve.
  - Axons are wrapped in a myelin sheath of insulation.
  - SCIs often affect axons and their myelin sheaths.

What is a Spinal Cord Injury (SCI)?

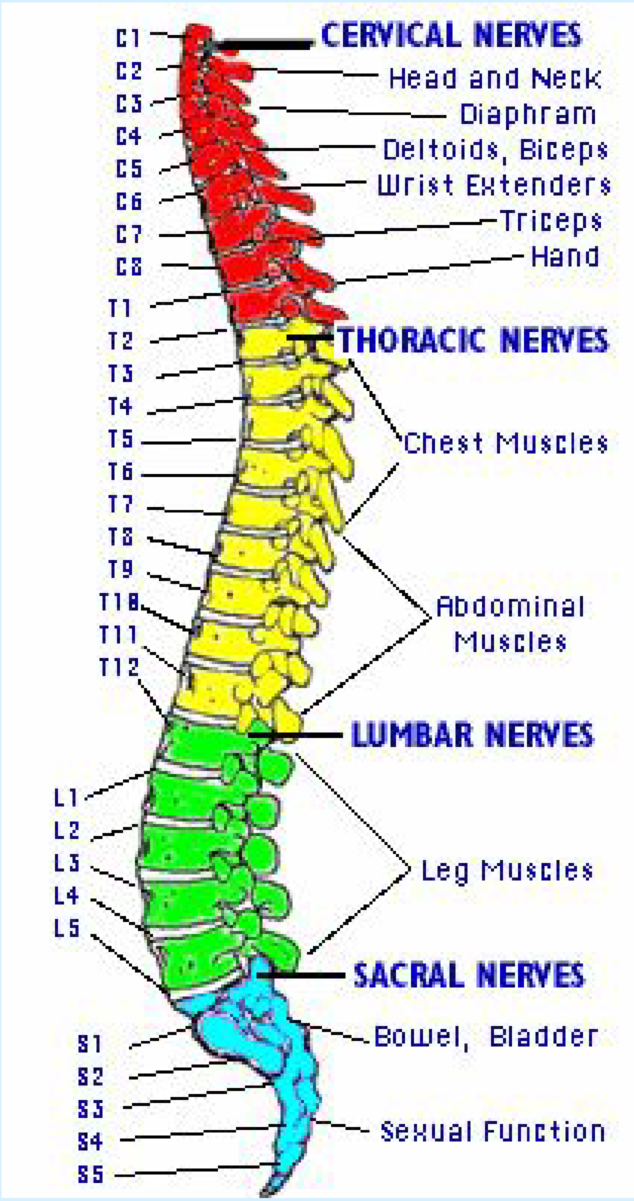
- About 35 people per million suffer a SCI every year.[1]
- SCIs usually result from severe trauma that results in a loss of function – usually a loss of mobility and/or a loss of feeling (causes: vehicle accidents ~50%, falls ~23%, violence ~14%, sports 9%, etc.).[2]
- Each case is considered unique because no two injuries are exactly alike & each has a unique impact.
- Other common causes of spinal cord damage are birth defects and diseases, for example; spina bifida, polio, Friedreich's Ataxia, and Motor Neuron Diseases like Amyotrophic Lateral Sclerosis (ALS).

Spinal Injuries – Where?

- A major factor in SCI is where the damage occurs – there are four main zones of vertebrae identified:
  - Injuries at the cervical level (neck) may impair breathing and usually cause loss of function in the arms & legs, resulting in quadriplegia (tetraplegia).
  - Injuries in the thoracic region (chest) usually affect the chest and the legs and result in paraplegia.
  - Injuries involving a lumbar vertebra (lower back) or a sacral (pelvic) vertebra (“tail bone”) generally result in some loss of function in the hips and legs and/or in the bladder and genitals.

Spinal Nerves

http://www.spinalinjury.net/html/_spinal_cord_101.html



- There are 31 pairs of spinal nerves passing out through the vertebrae and linking with the PNS.

- Injuries impact functions at and below the level of the damage.

Spinal Injuries – How Severe?

- The second major factor is the extent of the injury – complete, discomplete or incomplete:
  - The most severe type is a complete injury: no voluntary movement or conscious sensory function (no sensation) below the level of the injury on either side of the body. [Complete Tetra. 18%; C. Para. 23%] [2]
  - The cord is seldom cut completely, it is usually compressed or bruised and nerve channels are damaged. More nerves are damaged in the days following the trauma as the cord swells.

Spinal Injuries – How Severe?

- Discomplete: loss of all functions below the injury but with physiological or anatomical continuity of CNS tracts across the lesion. Signals transmitted across the lesion are too few to allow voluntary function or sensation but they represent a residual function and the **potential** for further enhancement.
- An incomplete injury means that there is some functioning below the level of the damage. The person may be able to move one limb more than another, may be able to feel some parts of the body that cannot be moved, or may have more function on one side of the body than the other.

[Incomplete tetra. 34.5%; Incomplete para. 17.5%] [2]

The First Few Hours Are Critical

- The first hours & days after the injury are critical. A lot of “extra” damage results from swelling, inflammation & other complex effects of trauma. The initial goal is to save as many neurons as possible:
  - The steroid methylprednisolone [methyl-pred-NISS-alone] (Medrol) has been widely used to reduce swelling – a major cause of secondary damage.[3]
  - Other changes occur upon injury, (e.g., changes in blood supply & in cellular calcium levels) and other drugs being studied to address these factors.
- This critical window is the first major opportunity to mitigate the damages from SCIs.

Complex and Ongoing Issues

- Loss of mobility is the most obvious symptom but loss of sensation and feeling is often just as serious.
- Other major clinical problems include: spasms, painful burning sensations and phantom limb sensations as well as secondary issues.
- 50 years ago, SCIs were usually fatal, mostly due to kidney failure. With better care, life expectancy has greatly improved (but sadly, complications still claim many).

- http://news.bbc.co.uk/1/hi/in_pictures/3732504.stm

Secondary Issues

- Many SCI patients still succumb to secondary issues.
  - #1: Complications and infections caused by pressure sores (ulcers) are the costliest and most common issue and they can be fatal (Chris Reeve). Several issues contribute; reduced skin sensation, circulation problems, limited mobility and a reduced immune response. The incidence of sores is increasing (from 23% in 1990 to 33% in 2003).[4]
  - #2: Urinary tract infections and complications.
  - #3: Respiratory complications like pneumococcal pneumonia (today, respiratory impairments are the leading cause of death in SCI).

Not Just The Initial Cord Injury

- People tend to think only in terms of the initial injury to the cord, but secondary damages are as big a factor.
- One of the major challenges is the complexity and interrelatedness of the secondary changes in the nervous system that occur well after the injury:
  - For example: as time passes, axons (the long "cables" of the neurons) above and below the injury degenerate and their myelin sheaths disintegrate:
    - This feature, known as Wallerian [WALL-ear-eee-in] degeneration, appears about twelve months post injury.

Brain Reorganization

- Some CNS injuries (and some SCIs?) may cause a secondary reorganization of the CNS (often seen in trauma in children). This effect is poorly understood and could have positive and/or negative effects.[5]
- If this turns out to be a major factor in SCI, then:
  - Research must discover any negative effects and block them & any positive effects & enhance them.
  - Little is understood about how this reorganization may be influenced by the type and level of activity after the injury or the use of movement in therapy.
  - Learning to stimulate and control reorganization may be an important part of an eventual treatment.

Restoration of Lost Function

- There are three general strategies to restore function:
- 1). Adaptation to the loss of function (example: using an orthosis – a brace) and compensation: trying to get undamaged, existing pathways and muscles to learn to do the jobs needed.
- 2). Reorganization of neuronal circuits by repetitive training sessions that aim to optimize the neural inputs and to improve complex limb movements.
- 3). Regeneration and repair of neuronal tissues.

Regeneration of Neuronal Tissues

- Ultimately, a successful treatment for SCIs will involve nerve regeneration, reestablishing physiological connections, and, ideally, restoring proper function.
- One major thrust of regeneration is to develop drugs that will create a “positive atmosphere” for new cells:
  - Chemicals normally present in the spinal cord inhibit the growth of new neurons. These chemicals must be temporarily neutralized before re-growth is possible.
- There is an emerging appreciation that several approaches will need to be combined to lead to practical solutions (called combination therapy).

Five Potential Treatment Opportunities

- 1). Protection of cells undamaged in the initial injury.
- 2). Stimulating axonal growth:
  - by enhancing intrinsic growth capacity, and/or
  - by blocking natural inhibitors of neural growth.
- 3). Building bridges ("bridging") across damaged and scarred areas to provide a positive environment for axon growth and to replace lost tissue.
- 4). Enhancing axonal transmission (restoring the correct chemical balance of the nerve cells).
- 5). Rehabilitation to improve function in surviving circuits and to consolidate repairs.[6]

Two Steps Toward Combination Therapy

- 1). Identify the best individual methods to address each of the five treatment opportunities (this is the state of the art today; tomorrow, there may be a sixth or seventh treatment opportunity to consider).

- 2). Where and When? Once identified, the best individual treatments will have to be arranged in the optimal spatial and temporal sequence to be given in combination. This balance will ensure the best results possible.

Example of a Simple Combination Therapy

- A new study shows that combining partially differentiated stem cells with gene therapy can promote the growth of new myelin around nerve fibers in the damaged spinal cords of rats.
- Researchers injected genetically enhanced precursor cells into the damaged spinal cords of rats. Studies of the cord tissue showed that many transplanted cells survived and migrated within the cord and that about 30% developed into myelin-producing cells. (oligodendrocytes) [OH-glee-OH-den-drow-sights]
- The study also shows that producing myelin can lead to functional improvements in animals with SCI.[7]

First Major Steps: Drugs and Stem Cells

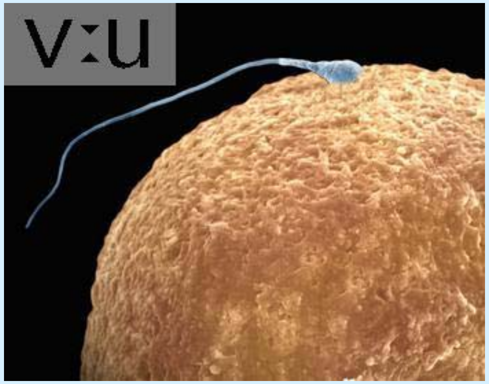
- Several strategies are being researched but won't be discussed here, for example; using computer chip and electrode implants, using artificial (silicon) neurons to form bridges and the use of nerve tissue grafting.
- Two of the major aspects in a combination therapy will be drug therapy ("pharmacotherapy") and the use of stem cell derived therapies:
  - It is beyond the scope of this talk to cover drug therapies.
- Because of the potential of stem cell therapies, the rest of this talk will outline the basic principles of stem cells.

Cells

- Humans are a multicellular organism made up of trillions of cells. A cell is our smallest living subunit.
- About 220 types of cells are found in humans.
- Cells nourish themselves, produce energy, exchange information with other cells, multiply, and eventually die – most are continually being replaced in the body.
- Cells work individually to do many biological tasks.
- Cells also work together to build larger units, for example, to form different types of tissue and organs.
- How do we develop from just one cell and how do we maintain our cells over our lifetime?
  - Stem cells are part of the answer.

Fertilization

- To understand stem cells, we need to look at development.
- An ovum (egg) is the largest cell in the human body.
- A single sperm is the smallest cell found in the body.
- Fertilization takes place inside the fallopian tube.



- Upon fertilization, one egg cell and one sperm cell join together to form one new cell, beginning the development of an individual.
- This first cell formed is called a zygote [ZYE-goat].

Early Cell Division

- The zygote begins a series of cell divisions going through 2-cell, 4-cell, 6-cell, 8-cell (day 3), 16-cell stages, and so on.

Six cell blastocyst.

- These divisions create a hollow ball of cells called a blastocyst [BLAST-oh-cyst].

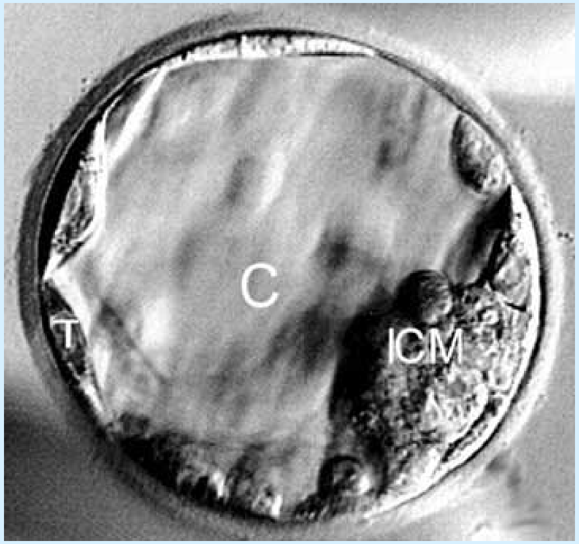
- The blastocyst travels down the fallopian tube, reaching the uterus in 3 or 4 days.

The First Few Cells Are Special

- All of the different cells of the body are derived from the zygote's single cell and its first few divisions.
- The first 8 or so cells are very special because each one is identical and each has the ability to create <u>any type</u> of cell found in the human body – in fact, any one of these early cells could go on to develop into an individual. If all 8 cells were removed & implanted individually, we would get octuplets – 8 identical siblings.
- Removal of a cell or two here does not affect development (this is how preimplantation genetic testing is done).

Inner and Outer Layers

- By about day 4 or 5, the cells of the blastocyst have differentiated into two distinct cell types:
  - An outer wall of cells that will form the extraembryonic membranes (e.g., the placenta) These cells also produce the hormone measured by pregnancy tests and they are responsible for implantation of the embryo into the uterus.
  - An inner cell mass – a core of cells that will form the embryo. These cells are the primary source of embryonic stem cells.
- By day 5, the blastocyst has about 200-300 cells.



Pregnancy Begins

- As development moves ahead and more cell divisions occur, the cells continue to differentiate.
- About 7 – 9 days after fertilization, the blastocyst (embryo) embeds itself into the wall of the uterus – a process called implantation, and the pregnancy is established.
- Cell division and differentiation explodes as the embryo rapidly develops (after 8 weeks it is called a fetus).

Definition of a Stem Cell

- A stem cell is basically an immature cell:
  - These cells are undifferentiated and can develop into the various types of specialized cells found in the body.
  - Stem cells can also renew themselves by dividing indefinitely and creating more stem cells.
- In summary, each stem cell keeps on dividing to form:
  - one daughter cell that goes on to differentiate, and
  - one daughter cell that remains a stem-cell.

Two Basic Types of Stem Cells

- There are two basic types of stem cells:
  - Embryonic stem cells:
    - Found in the very early blastocyst (and they have also been recovered from fetal tissues after 8 weeks growth).
  - Adult stem cells:
    - Found in the umbilical cord and in differentiated tissues.
    - By birth, these cells are present in various tissues (although they are called “adult”, they are present as soon as cells begin to specialize, that is, when cells differentiate to become nerve cells, muscle cells, etc.).
- These two types of stem cells have different functions and characteristics that we need to understand.

All Stem Cells are Undifferentiated

- A stem cell is undifferentiated, it does not yet have any tissue-specific identity – it is not yet a blood cell, or a nerve cell, or a muscle cell:
  - This is the “stemness” of the cell: the degree of stemness is a measure of the cell’s potential to become one of the various different types of cells.
- When called upon, stem cells can form specialized (differentiated) cells. All of the specialized cells in the body are formed by stem cells.

Totipotent Cells

- In mammals, the zygote and the first 8 or so cells produced by division are totipotent [TOE-tea-potent]:
  - Each of these cells can become any type of cell in the body (including the extraembryonic membranes, e.g., the placenta, amniotic fluid, and the umbilical cord).
- Think of totipotent as stem cells with TOTAL potency – these cells can make any cell needed by the developing individual (with one of these cells, you could theoretically reproduce an individual).
- These are one type of "embryonic stem cells."

Development Limits Potential

- As cells become more specialized, they quickly lose their totipotency and they become pluripotent [PLUR-eee-potent]:
  - Each pluripotent cell has the potential to make any differentiated cell in the body, but it can no longer make the extraembryonic membranes. (one of these cells could not reproduce an individual).
  - Think of pluripotent as cells with SEVERAL potencies.
- Pluripotent stem cells are primarily found in the inner cell mass of the blastocyst and are a second type of embryonic stem cells.

Further Limits on Potential

- As pluripotent stem cells further specialize, they become multipotent (or unipotent) stem cells.
- These stem cells are found in various body tissues.
- The view has been that multipotent cells can only become the type of tissue they are found in, e.g., blood stem cells can give rise only to red blood cells.
- Think of multipotent as cells with SINGLE potency.
- These cells have several names:
  - Adult stem cells.
  - Postnatal stem cells (postnatal means after birth).
  - Umbilical stem cells (the umbilical cord is rich with them).
  - Somatic stem cells (somatic means found in the body).

Summary

- The single cell zygote and the first 8 or so cells produced by its division are totipotent:
  - Totipotent cells can become any type of cell in the body, including the extraembryonic membranes.
- Pluripotent cells can make any differentiated cell in the body, but not the extraembryonic membranes.
- Totipotent & pluripotent cells are primarily found in the embryo and are called embryonic stem cells.
- As cells differentiate, they become multipotent:
  - “Adult” stem cells are found in specialized tissues and in the umbilical cord. Until recently, their stemness (potency) has been seen as very limited.

In Vitro Fertilization (IVF)

- Infertility affects about 10% of men & women of reproductive age in the United States. Just less than 5% of them use *in vitro* fertilization (IVF).
- *In vitro* fertilization involves first stimulating a woman's egg production and collecting several eggs.
- The eggs are fertilized with sperm in the laboratory resulting in zygotes (this is what *in vitro* means).
- The zygotes are grown for a few days becoming blastocysts, then several are transferred into the woman's uterus. Ideally, a normal pregnancy will result.

How Scientists Obtain ESCs

- Most embryonic stem cells (ESCs) used in stem cell research are obtained from four or five day old blastocysts created through *in vitro* fertilization.
- There are usually “extra” blastocysts left over after the couple has had the children they want. These extra “embryos” are usually either simply discarded or are frozen and stored indefinitely.
- With informed consent, many couples donate these extra embryos for use in stem cell research.
- The use of ESCs is controversial because the procedure destroys the unimplanted blastocysts.

Embryonic Stem Cells

- In the laboratory, ESCs can be grown in special conditions & remain undifferentiated (unspecialized).
- If cells are allowed to clump together, they spontaneously begin to differentiate: they begin to form muscle cells, nerve cells, and other types of cells.

- Scientists are struggling to learn how to control the differentiation of ESCs into specific cell types:
  - If they can reliably control this process, they may someday be able to produce differentiated cells in the laboratory to treat certain diseases.

Embryonic Stem Cell Lines

- Researchers remove a cell (or several) from a blastocyst before the cells differentiate, and grow the cells in a dish in the laboratory:
  - The undifferentiated stem cells keep dividing (for years), creating millions of identical cells. This is called a cell line. These cells are used in research.
- Each of these millions of cells is pluripotent – they can go on to grow into any type of cell in the body.
- One major challenge is that conditions must be perfect – one mistake here would be repeated over & over and multiplied – e.g., just one skin cell in a batch of a million muscle cells would create a cancer.

ESCs From Cloning

- Scientists are developing a type of cloning (often called therapeutic cloning) to create ESCs:
  - Also called somatic nuclear transfer, this creates stem cells genetically matched with the patient.
- The nucleus (center) of a cell contains its DNA.
- The nucleus is removed from a donated, “fresh,” unfertilized (human) egg. This “hollow” egg now cannot be fertilized or develop normally.
- The nucleus is taken out of a somatic cell (e.g., a skin cell) obtained from a patient & is inserted into the egg:
  - Nuclear transfer: transfer of a nucleus [NEW-cue-luss] (a cell’s center) from one cell to another.

Somatic Nuclear Transplant

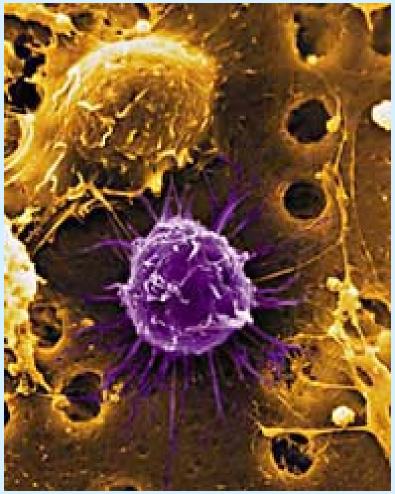
- The cell reverts to a totipotent state and the new "egg" starts to develop into a normal blastocyst.
- Embryonic stem cells are removed at day 5 or 6.
- The stem cells are grown in the laboratory and are allowed to differentiate into different types of cells.
- These differentiated cells – whatever tissue or organ is needed to treat the patient – are now transplanted back into the patient, ideally curing his or her disease.
- This procedure is controversial as it destroys human genetic material (the DNA in the unfertilized egg).
- This method is being used to clone animals (Dolly).
- This procedure is still in the very early stages.

Adult Stem Cells

- Adult stem cells are undifferentiated cells found along with the differentiated cells in a tissue or organ.
- An adult stem cell can renew itself, and can differentiate to yield the specialized cell type of the tissue or organ it is found in (multipotent).
- The primary roles of adult stem cells are to maintain and repair the tissue in which they are found:
  - Example, adult stem cells in the blood help to maintain and repair the blood.
- Only a fraction of the cells are adult stem cells: e.g., 1 in every 15,000 bone marrow cells is a blood stem cell. Scientists have had a hard time isolating them.

Types of Adult Stem Cells

- Adult stem cells are thought to stay in a specific area of each tissue where they may remain silent (non-dividing) for many years until they are activated by disease or tissue injury.
- About 20 types of adult stem cells have been found – here is a picture of an adult bone marrow cell.



- Tissues reported to contain stem cells include; brain, bone marrow, blood, blood vessels, skeletal muscle, heart, fat, teeth, skin and the liver.

Pluripotent Adult Stem Cells?

- There have now been many reports that some adult cells may be more pluripotent than once thought:
  - Some adult stem cells may not be totally specialized, they may be "semi-specialized" and have some flexibility to become one of several different cell types – not limited to just the tissue they are found in.
    - Example: Recently (2005), researchers have been able to manipulate adult skin stem cells into developing into bone, fat and muscle cells.[8]
- This holds promise that some (all?) adult stem cells may have the pluripotency of ESCs. Researchers are trying to discover the potentials of these stem cells.

Another New Type of Stem Cells?

- A new type of stem cell has recently been discovered in umbilical cord blood.
- The newly discovered human cells, named “cord-blood-derived embryonic-like stem cells” (CBEs), are not quite as totipotent as embryonic stem cells, but they appear to hold similar clinical potential to ESCs and are much more versatile than adult stem cells.[9]
- The new cells avoid the controversies associated with the use of embryonic stem cells.

A Tantalizing Theory

- Theory: any cell can become any other type of cell.
- Most of the cells in the body contain a full set of DNA.
- Cells are different because in different environments, different genes are turned on inside them. For example, in skin, a certain set of genes switches on to tell the cell to be a skin cell, in nerve tissue, a different set of genes are activated to form a nerve cell.
- By manipulating the environment of cells in the laboratory, it may be possible to make somatic cells dedifferentiate back to totipotency and then trigger them to redifferentiate into different kinds of cells.[10]

Autologous (self-to-self) Transplantation

- Autologous [awe-TAH-la-gus] transplantation avoids the major problems associated with tissue rejection and the need for immunosuppression. Because the cells belong to the patient to begin with, the body accepts them as its own and there should be no immune response to them.
- Adult stem cells are taken from a patient (at any age) grown & differentiated in the laboratory creating healthy cells that are then reintroduced back into the patient to treat or repair his or her disorder.
- This is perhaps the ideal scenario – using autologous cells, possibly with genetic enhancements or repairs, to repair or replace a patient's damaged tissues.

Embryonic Neural Stem Cells

- Neurons do not divide and show little capacity to regenerate after injury to the central nervous system.
- Research has shown that human embryonic stem cells can develop into precursor CNS cells and then further differentiate into neurons and astrocytes, the cell types that populate the different regions of the brain and spinal cord.
- Scientists have recently (2005) learned how to coax human embryonic stem cells to become spinal motor neurons, capable of surviving in the lab.[11]
- This creates a laboratory model that will allow drugs to be screened and will help move research ahead.

Adult Neural Stem Cells

- Human neural stem cells (hNSCs) as well as neuronal precursors (neuroblasts) that divide to give rise to nerve cells (neurons), can be isolated from the adult central nervous system:
  - These neural stem cells can generate several types of nerve cells.
  - Neuroblasts spontaneously multiply and move toward areas of brain damage, but, for some reason, natural regeneration and repair of tissues is not very efficient in the CNS.
- Neural stem cells, present in the adult brain, may someday be controlled and used to serve as replacement cells for CNS repair.

An Important Step

- Adult human neural stem cells have just been used to successfully regenerate damaged spinal cord tissue and improve mobility in spinally injured mice:
  - Researchers injected neural stem cells into mice with limited mobility due to spinal cord injuries.
    - These cells differentiated into new oligodendrocyte cells that created new myelin around damaged mouse axons. Transplanted cells also differentiated into new neurons that formed synaptic connections with mouse neurons.
    - Mice that received the cells nine days after spinal cord injury showed improvements in walking ability. Later the transplanted human cells were selectively killed and the improvements in walking disappeared.[12]

Stem Cell Controversy

- Much of the controversy over the use of different types of cells and procedures relates to the terminology and definitions used.
- For example, is a blastocyst (a scientific term) also an embryo? Do these early few cells represent a life, even before implantation takes place?
- The moral, philosophical and Religious aspects of science are one important consideration in planning and conducting research.
- Today, scientists are struggling to achieve a balance between these complex issues and the potential advances offered by these new areas of science.

Summary: How Can Stem Cells Help?

- By studying stem cells, we gain a basic understanding of the genetic controls of development – this should help us learn how to treat diseases.
- Human stem cells may be used to test new drugs.
- Human stem cells may be used to generate new cells and tissues that can potentially be used for treating disease.

We can’t always control life.

Life can be confusing.

Life often challenges us.

Life can seem hopeless.

But we can't give up! 13

Notes

- 1 (Slide # 10) This figure is 40 per million in the United States, likely due to their higher rate of violent crime. About 500,000 people in N. America and Europe have a SCI (see: Guertin).
- 2 (Slides 10, 13,14) Statistics from June 2005, Spinal Cord Injury Information Network (USA), http://www.spinalcord.uab.edu/show.asp?durki=19679
- 3 (slide # 15) In 1990, 23% of patients with SCI developed sores – in 2003, 33% of patients with SCI developed sores. (Ravary, *Total Access*, Winter 2004, p. 2)
- 4 (slide # 17) "Administration of this steroid is no longer a standard treatment, nor even a guideline for treatment of acute SCI in Canada and many other countries have adopted similar policies." see: Hugenholtz H. Methylprednisolone for acute spinal cord injury: not a standard of care. *CMAJ,* 2003; *168*: 1145–1146.
- 5 (slide # 19) The research is not clear on how or how often the brain may reorganize after injury or what may influence this reorganization over time. This is an ongoing question.
- 6 (slide # 22) This is from Ramer, *Spinal Cord*, 2005, *43*,134-161.

Notes

- 7 (Slide # 24) See: Cao*, Journal of Neuroscience*, July 27, 2005, Vol. 25, No. 30, pp. 6947-6957.
- 8 (Slide # 47) See: Bartsch, *Stem Cells and Development* 2005, 14: 337-348.
- 9 (Slide # 48) See: Forraz, *Cell Proliferation 38*, p. 245 (2005).
- 10 (Slide # 49) See: Cowan *Science* 26 August 2005, 309 1369-1373.
- 11 (Slide # 51) See: summary by Kuehn, *JAMA*, March 2, 2005, *293*,1047.
- 12 (Slide # 53) See: Cummings *PNAS* September 27, 2005, vol. 102 no. 39 14069–14074.
- 13 (Slide # 60) Keegan Reilly and members of his Strong Arm Expeditions team reach the summit of Mount Fuji after a four-day climb.
- Photo Credits: Slide 13: http://www.themiamiproject.org/x188.xml
- slide 27: http://www.visualsunlimited.com/browse/vu167/vu167105.html
- Slide 28: www.ohiorepromed.com/ images/6c.gif
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