Cell Types
Introduction

- The human body is made up of many **specialised** cells that perform **specific functions**.

- Specialised cells arise from the **differentiation** of unspecialised cells during embryological development.
Cell Types

- There are over 200 different types of cells within the human body.
- These cells all vary in size, shape and diameter.
- Most cells range between ten and fifteen micrometers in diameter, however, some cells, such as the human egg cell, are much larger than this, with a diameter of roughly 100 micrometers.
- The human egg cell is just barely visible to the naked eye.
- Some of the longest cells include nerve cells, which can be as long as a meter, but are so thin, they are invisible to the naked eye.
- Cells, although they range in size and shape, cannot become too large, or they may become unable to support their own functions, or could burst.
Somatic cells

Somatic cells are the differentiated cells that form the different types of body tissue that exist.
Somatic cells

B Lymphocyte

Smooth muscle

Hyaline cartilage
Somatic cells

Ciliated epithelial cell

Platelets

Neutrophil

Red blood cell
Somatic cells

Cardiac muscle

Squamous epithelial cells

Nerve cells

T lymphocyte
Germline cells

Germline cells include the gametes and the cells that produce the gametes.
Different Cell Types in the Body
Squamous Cells

- A squamous cell is a type of epithelial cell that is found in many locations of the body.
  - Aorta
  - Vessels
- Squamous cells are thin and flat, with a slight bulge where the flat nucleus lies.
Cuboidal Cells

- Tyroid
- Ducts of many glands
- Kidney tubules
- Cubelike cells with large, spherical central nuclei.
- Cuboidal cells are square-like in shape and are typically as tall as they are wide.
Columnar Cells

- Columnar cells are similar to cuboidal cells, however, they are taller than they are wide.
- This type of cell is commonly found in the lining of the intestines.
- Nuclei is in the basal part and oval.
Spheroid cells

- Ovary
  - 200 micron

- Ganglional cells

- Spheroid cells, sometimes referred to as ovoid cells, range from circular to ovular.
Flagellated cell

- Sperm
- Head: 5µ  
  - Nucleus  
  - Acrosomal cap  
- Neck:  
  - Mitochondria  
- Tail: 45-50µ  
  - Flagella
Pyramidal cells

- Cerebral cortex

- Pyramidal cells are a type of neuron found in areas of the brain including cerebral cortex.
- Includes euchromatic nuclei and Nissl granules
- Pyramidal neuron is the triangular shaped soma or cell body,
- Structural features of the pyramidal cell are a single axon, a large apical dendrite, multiple basal dendrites, and the presence of dendritic spines.
Multipolar cells

- **Medulla spinalis, Ant. horn**
- The extensions (also called processes) project out of the cell body.
- Have many "dendrites" that extend from the cell body.
- Includes euchromatic nuclei and Nissl granul.
Fusiform Cells

- Smooth muscle cells
- Each cell is spindle-shaped, 20-500 micrometers in length, thick in the center and tapered at the ends.
Adipose tissue

Polygonal cells, much like their name implies, are polygonal in shape, with five or more sides.

Sometimes these sides are elongated in such a manner that they form a stellate, or star-like shape.
Polygonal Cell

- Skin

- Epidermisin Stratum spinosum layer

- Oval nuclei
Priform Cells (Purkinje Cells)

- Cerebellum
- Stratum gangliosum tabakasında bulunur.
- Big nuclei
- Nissl granulles
Stem Cell – Definition

• A cell that has the ability to continuously divide and differentiate (develop) into various other kind(s) of cells/tissues
Stem Cell Characteristics

- ‘Blank cells’ (unspecialized)
- Capable of dividing and renewing themselves for long periods of time (proliferation and renewal)
- Have the potential to give rise to specialized cell types (differentiation)
What are stem cells?

Stem cells are *unspecialised* cells that have the ability to reproduce and *differentiate* into a diverse range of specialised cells.
Why Stem Cells

• The purpose of cellular therapy, which damaged a cell / tissue or organs to replace its biological function, to repair or to expand.

• Regenerative medicine
• Reparative medicine
Advantage?

- To obtain stem cells which can be proliferate in laboratory conditions
- The cells can be stock and in any case they can be thaw and culture, proliferate and differentiate
- **Self renewable**: a cell that has the ability to continuously divide
- **Pluripotent**: ability to develop into several different kinds of cells/tissues
- **Repair**: ability to return function to damaged cells in the living organism
Stem Cell

- Stem cells which are differentiated during embryonic life, identified in adult tissues.
- They can be duplicate and proliferate in appropriate culture condition.
- Whereas the different culture media is provided them differentiated, when they transfer in to tissues, they can proliferate.
- Stem cells according them differentiation ability are classified as:
  - Totipotent
  - Multipotent
  - Pluripotent
# Kinds of Stem Cells

<table>
<thead>
<tr>
<th>Stem cell type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totipotent</td>
<td>Each cell can develop into a new individual</td>
<td>Cells from early (1-3 days) embryos</td>
</tr>
<tr>
<td>Pluripotent</td>
<td>Cells can form any (over 200) cell types</td>
<td>Some cells of blastocyst (5 to 14 days)</td>
</tr>
<tr>
<td>Multipotent</td>
<td>Cells differentiated, but can form a number of other tissues</td>
<td>Fetal tissue, cord blood, and adult stem cells</td>
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</table>
**Stem Cell Differentiation**

**Totipotent Stem Cell**
These cells have unlimited capability, and have the ability to form extraembryonic membranes and tissues, the embryo itself, and all postembryonic tissues and organs. An example is an embryo.

**Pluripotent Stem Cell**
These cells are capable of giving rise to most, but not all, tissues of an organism. An example is inner mass cells.

**Multipotent Stem Cell**
These cells are committed to give rise to cells that have a specific function. An example is blood stem cells.
Kinds of Stem Cells

- **Embryonic stem cells** come from a five to six-day-old embryo. They have the ability to form virtually any type of cell found in the human body.

- **Adult stem cells** are undifferentiated cells found among specialised or differentiated cells in a tissue or organ after birth. Based on current research they appear to have a more restricted ability to produce different cell types and to self-renew.
Types of stem cells

Embryonic

Adult
Blastocyst Diagram

- fertilized egg → Totipotent cells → Blastocyst
- inner cell mass (pluripotent cells)
- cultured pluripotent stem cells
- cells isolated from the ICM
Embryonic stem cells

- Embryonic stem cells are derived from an embryo about 4–5 days old (blastocyst).

- These cells have the ability to differentiate into all of the cell types that make up an organism.
Derivation and Use of Embryonic Stem Cell Lines

- Isolate inner cell mass (destroys embryo)
- Outer cells (forms placenta)
- Inner cells (forms fetus)
- Culture cells
- “Special sauce” (largely unknown)
- Day 5-6 Blastocyst

Kidney
Heart muscle
Heart repaired
- Isolate individual stem cell populations
- Characterize & track stem cell populations
- Ensure that cells retain their functionality and potential to differentiate
- Ensure that cells are “transplant” ready

- Culture stem cell lines in a stable, multi- or pluripotent state, free from mutations & to sufficient quantity
- Control & activate stem cell differentiation to desired lineages
- Functionally active differentiated cells
- Enable Economical expansion to make cell-therapy a reality
Sources of adult stem cells in the oral and maxillofacial region.
In 2000, adult human dental stem cells were first identified in the dental pulp (dental pulp stem cells; DPSCs), and these cells had phenotypic characteristics similar to those of BMSCs.

- **BMSCs**: bone marrow-derived MSCs from orofacial bone; **DPSCs**: dental pulp stem cells; **SHED**: stem cells from human exfoliated deciduous teeth; **PDLSCs**: periodontal ligament stem cells; **DFSCs**: dental follicle stem cells; **TGPCs**: tooth germ progenitor cells; **SCAP**: stem cells from the apical papilla; **OESCs**: oral epithelial progenitor/stem cells; **GMSCs**: gingiva-derived MSCs, **PSCs**: periosteum-derived stem cells; **SGSCs**: salivary gland-derived stem cells.
Applications

➤ Disease
  • Diabetes, Spinal cord injury, Parkinson’s disease, heart disease

➤ Genetic based Disease
  • Cystic fibrosis, Huntington’s
How they could treat certain types of diseases?

- Tissue repair
- Heart Disease
- Cancer
- Arthritis
- Parkisons disease
- Diabetes
Tissue Repair

• Regenerate spinal cord, heart tissue or any other major tissue in the body.
Heart Disease

- Adult bone marrow stem cells injected into the hearts arteries are believed to improve cardiac function in victims of heart failure or heart attack.
Mouse adult stem cells are injected into the muscle of the damaged left ventricular wall of the mouse heart.

Human adult bone marrow stem cells are injected into the tail vasculature of a rat.

The stem cells induce new blood vessel formation in the damaged heart muscle and proliferation of existing vasculature.

Stem cells help regenerate damaged heart muscle.

New blood vessels

Adult stem cells

Damaged heart muscle cells

Adult stem cells

Damaged heart muscle cells
Leukemia and Cancer

- Studies show leukemia patients treated with stem cells emerge free of disease.
- Injections of stem cells have also reduced pancreatic cancers in some patients.
Rheumatoid Arthritis

- Adult stem cells may be helpful in jumpstarting repair of eroded cartilage.
Type I Diabetes

- Pancreatic cells do not produce insulin.
- Basic research focused on understanding how embryonic stem cells might be trained to become pancreatic islets cells needed to secrete insulin.
The Promise of Stem Cell Research

- Test new drugs on tissues generated from stem cells in vitro.
- Faster drug development.

- What is the genetic program that controls cell differentiation?
- Faster gain in knowledge.

Bone Marrow  Nerve Cells  Heart Muscle Cells  Pancreatic Islet Cells

www.stemcells.nih.gov
Blood Cell Production is a Critical Life-Long Process

Stem cells are unique in their ability to self-renew

Adapted from Reya et al. Nature
Mutations in Stem Cells can Lead to Leukemia
Unknowns in Stem Cell/Cloning Research

• It is uncertain that human embryonic stem cells *in vitro* can give rise to all the different cell types of the adult body.

• It is unknown if stem cells cultured *in vitro* (apart from the embryo) will function as the cells do when they are part of the developing embryo.
Challenges to Stem Cell/Cloning Research

• Stem cells need to be differentiated to the appropriate cell type(s) before they can be used clinically.

• Recently, abnormalities in chromosome number and structure were found in three human ESC lines.
Challenges to Stem Cell/Cloning Research

• Stem cell development or proliferation must be controlled once placed into patients.
• Possibility of rejection of stem cell transplants as foreign tissues is very high.
Challenges to Stem Cell/Cloning Research

- Contamination by viruses, bacteria, fungi, and Mycoplasma possible.
- The use of mouse “feeder” cells to grow ESC could result in problems due to xenotransplantation (complicating FDA requirements for clinical use).
Other countries stands on Stem cell research

- The UK in 2001 made it legal to create cloned human embryos for use in medical research.
- Research is using therapeutic cloning to help disease.
- Scientists can only use eggs from fertility clinics that did not fertilize when mixed with sperm. Therefore, the eggs are not as good as they could be.
Asia and Sweden

- South Korea, Sweden, and Singapore are all moving forward on stem cell research.
- Singapore is becoming the biggest competition in the international race because they allow therapeutic cloning but banned reproductive cloning. Therefore, scientists worldwide are going to Singapore to work.
Adult (tissue) stem cells

- Adult or tissue stem cells are found in small numbers in the tissues and organs of adults and children, including the brain, bone marrow, skeletal muscle and skin.

- These cells give rise to a much more limited range of cell types and will tend to develop into cell types that are closely related to the tissue in which they are found.

- These cells replenish differentiated cells that need replaced in the tissues in which they are found.
Other types of stem cells

• Stem cells can also be taken from the umbilical cord of new babies.

• Like adult stem cells, these cells can differentiate into a limited range of specialised cells.
Induced pluripotent stem cells are adult cells that have been genetically reprogrammed to an embryonic stem cell-like state.
Stem cell research

Stem cell research provides us with a wealth of information and can be studied in a variety of ways, including:

- how cell processes such as growth, differentiation and gene regulation work
- the study of diseases and their development
- drug testing
- therapeutic uses in the treatment of diseases such as leukaemia (bone marrow transplant), Hunter’s disease and heart disease
- therapeutic uses in medicine, including skin grafts for burns and stem cell grafts for cornea repair.
For example, stem cells could be turned into new bone cells and then injected into weak or broken bones.

Or they could become nerve cells that could heal spinal cord injuries.

Skin cells could replace burnt skin, and brain cells could help people who have suffered brain damage.

Stem cells could be taken from someone with heart disease and be turned into heart cells, which can gather in a dish and throb! They could then be injected back into the patient to rebuild their heart tissue and combat heart disease.
Parkinson's disease

Parkinson's is a very common disease starting with mild symptoms, a mask-like face, stiffness and tremors until sufferers eventually become immobile. It is caused by a slow deterioration of certain brain cells (neurons) and there's no cure.

Replacing the affected brain cells seems more hopeful than finding better drugs. Many people think that stem cells could be grown into new brain cells that could help to treat or even cure Parkinson's.
1. Trachea is removed from dead donor patient.
2. It is flushed with chemicals to remove all existing cells.
3. Donor trachea "scaffold" coated with stem cells from the patient's hip bone marrow. Cells from the airway lining added.
4. Once cells have grown (after about four days) donor trachea is inserted into patient's bronchus.
Therapeutic stem cell cloning
Cancer cells

Cancer cells have many characteristics that make them different from normal cells:

- Cancer cells **continue to reproduce** to produce a mass of abnormal cells (a benign tumour).
- They **do not respond to normal regulatory signals** that would instruct them to stop dividing when necessary.
- They lose the molecules on their surface that would normally hold them in place and can therefore be detached from their neighbours, causing the **cells to spread** (malignant tumour).
Cell Death

normal WBC

apoptotic WBC
**Etiology of cell death**

**Major Factors**

- Accidental
  - Necrosis
- Genetic
  - Apoptosis

**Necrosis:**
The sum of the morphologic changes that follow cell death in a living tissue or organ.

**Apoptosis:**
a physiological process that includes specific suicide signals leading to cell death.
### Forms of cell death

<table>
<thead>
<tr>
<th></th>
<th>Necrosis</th>
<th>Apoptosis</th>
<th>Mitotic catastrophe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive</td>
<td></td>
<td>Active</td>
<td>Passive</td>
</tr>
<tr>
<td>Pathological</td>
<td>Physiological or</td>
<td>Physiological or pathological</td>
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<tr>
<td></td>
<td>pathological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling, lysis</td>
<td>Condensation, cross-linking</td>
<td></td>
<td>Swelling, lysis</td>
</tr>
<tr>
<td>Dissipates</td>
<td></td>
<td>Phagocytosed</td>
<td>Dissipates</td>
</tr>
<tr>
<td>Inflammation</td>
<td>No inflammation</td>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td>Externally induced</td>
<td>Internally or externally induced</td>
<td></td>
<td>Internally induced</td>
</tr>
</tbody>
</table>
**Pre-Apoptotic Cell**

- **Early Apoptotic Cell**
  - Membrane blebs

- **Late Apoptotic Cell**
  - Apoptotic bodies
  - Nuclear fragments

**Normal cell**

- **Small blebs form; the structure of the nucleus changes.**

**The blebs fuse and become larger; no organelles are located in the blebs.**

**The cell membrane ruptures and releases the cell's content; the organelles are not functional.**

**Necrosis**

**Apoptosis**

- **The nucleus begins to break apart, and the DNA breaks into small pieces. The organelles are also located in the blebs.**

- **The cell breaks into several apoptotic bodies; the organelles are still functional.**

**NECROSIS**

**APOPTOSIS**
**Necrosis:** a pathological response to cellular injury

- Chromatin clumps
- Mitochondria swell and rupture
- Plasma membrane lyses
- Cell contents spill out
- General inflammatory response is triggered

**Apoptosis:** a physiological response to specific suicide signals, or lack of survival signals

- Chromatin condenses and migrates to nuclear membrane. Internucleosomal cleavage leads to laddering of DNA at the nucleosomal repeat length, ca. 200 bp.
- Cytoplasm shrinks without membrane rupture
- Blebbing of plasma and nuclear membranes
- Cell contents are packaged in membrane bounded bodies, internal organelles still functioning, to be engulfed by neighbours.
- Epitopes appear on plasma membrane marking cell as a phagocytic target.
  No spillage, no inflammation
The road to necrosis

Homeostatic 'steady state'

Cellular adaptations

Reversible cell injury

Irreversible cell injury

Cell death → Necrosis

Cell death ↔ Necrosis
Pathogenesis of necrosis

**REVERSIBLE INJURY**

- Ischemia
  - ↓ Oxidative phosphorylation (mitochondria)
    - ↓ Na pump → ↑ Influx of, Ca$^{++}$ and H$_2$O
    - ↑ Efflux of K$^+$
  - ↓ ATP
    - ↑ Glycolysis
    - ↓ Glycogen
    - ↓ pH
  - Other effects
    - e.g. Detachment of ribosomes
      - ↓ Protein synthesis → Lipid deposition

**IRREVERSIBLE INJURY (Cell Death)**

- Membrane injury
  - ↑ Exit of enzymes (CPK, LDH)
  - ↑ ↑ Ca$^{++}$ influx → ↑ ↑ Ca$^{++}$
  - in mitochondria
  - Cellular swelling
  - Loss of microvilli
  - Blebs
  - ER swelling
  - Myelin figures

- Intracellular release of lysosomal enzymes
  - ↓ Basophilia (↓ RNP)
  - Nuclear changes
  - Protein digestion
Necrosis: consequences of cell injury

NORMAL

REVERSIBLE CHANGES
- Disaggregated polysomes
- Focal chromatin margination
- Mild mitochondrial swelling

IRREVERSIBLE CHANGES
- High amplitude mitochondrial swelling
- Mitochondrial matrix densities
- Progressive dilatation of endoplasmic reticulum
- Lysosomal rupture
- Plasma membrane rupture
- Nuclear dissolution
- Loss of recognisable organelles
APOPTOSIS

• Where?

  - Everywhere.............................

  - Apoptosis or programmed cell death is very important mechanism in the embryonic development and tissue homoeostasis.
APOPTOSIS AS A PHYSIOLOGICALLY IMPORTANT PROCESS

In embryonic and fetal development:
- Tissue developmental programs which control sculpting of embryonic form
- Developmental organization of the nervous system
- Elimination of self-reactive components of the immune system

In the adult:
- On stimulation by T-lymphocytes
- In response to DNA damage or abnormality, e.g. by radiation, viral infection or transformation
- In certain organs and tissues, on withdrawal of supporting hormones

In addition, there are often apoptotic centers in tumors, accounting for the paradox of slow gross enlargement in the face of rapid cell proliferation, and the rare spontaneous remission.
STAGES OF CLASSIC APOPTOSIS

Genetically controlled: Caenorhabditis elegans
soil nematode (worm)

Healthy cell

Committed cell

Dead cell

ces2 → ces1 → ced9 → ced3,4

BCL2

Caspases (proteases)

C. elegans genes == mammalian genes
Apoptosis
(Programmed Cell Death)

Normal cell → Cell shrinkage → Chromatin Condensation → Membrane Blebbing → Apoptotic Body Formation → Lysis of Apoptotic Bodies → Nuclear Collapse → Continued Blebbing
Apoptosis is responsible for balancing cell proliferation and maintaining constant cell numbers in tissues undergoing turnover.
Cells are balanced between life and death.

- Damage
- Physiological death signals

Death signal:
- Proapoptotic proteins (dozens!)
- Antiapoptotic proteins (dozens!)

Result: Death
Extrinsic Pathway

- death ligand
- death receptor
- adaptors
- disc formation
- caspase 8 activation

Intrinsic Pathway

- mitochondrial changes (MPT)
- apoptosome forms
- caspase 9 activation
- caspase 3 activation (Execution Pathway)

- endonuclease activation → degradation of chromosomal DNA
- protease activation → degradation of nuclear and cytoskeletal proteins → cytoskeletal reorganization
- cytomorphological changes:
  - chromatin and cytoplasmic condensation, nuclear fragmentation, etc.
- formation of apoptotic bodies

Perforin/Granzyme Pathway

- Cytotoxic T cells
- perforin
- granzyme B
- granzyme A
- caspase 10 activation
- SET complex
- DNA cleavage
Mitochondria play a central role in mediating the apoptotic signal

Mitochondria-free cytoplasm would not induce apoptosis *in vitro*

Cytochrome c-neutralizing antibodies block apoptosis

Cytochrome c is an abundant protein of the mitochondrial inner membrane, and acts as an electron transport intermediate.

*a* and *b* type cytochromes are inaccessible components of large complexes, but cytochrome c is monomeric, freely diffusible in the inner membrane, and in equilibrium between inner membrane, inter-membrane space and cristae.

The events of apoptotic activation lead to alterations in permeability of the mitochondrial membrane pore proteins and release of cytochrome c.

Initial release of cytochrome c occurs by a highly specific process, involving proteins of the Bcl-2 family.
Signaling pathways leading to Mitochondria Permeability Transition

Death receptors of the TNFR family, as well as various oxidants, detergents and chemotherapeutic drugs, induce the release of active cathepsins from the lysosomal compartment. These cathepsins cleave Bid, which can then mediate cathepsin-induced MPT. Disruption of the cytoskeleton leads to the release of the BH3 domain–only proteins Bim and Bmf. DNA damage induced by radiation or various chemotherapeutic drugs induces the p53-mediated transcription of genes encoding Bax, BH3 domain–only proteins (Noxa or Puma), proteins involved in ROS generation and cathepsin D. ER stress results in the release of calcium, which may cause direct mitochondrial damage or activate Bax through calpain-mediated cleavage. Various death stimuli, mediated through death receptors, trigger the production of lipid second messengers (such as ganglioside (GD3), arachidonic acid (AA) and ceramide) that are involved in MPT and mitochondrial damage. Depending on the stimulus and the type of cell, as well as the metabolic status of the cell, MPT leads to either caspase-mediated apoptosis or caspase-independent PCD.
Bcl-2 family: Pro-Life and Pro-Death factions

Vertebrate Apaf-1 activation occurs through cytochrome c binding. Bcl-2 and Bcl-X<sub>L</sub> appears to act by dimerizing with pro-apoptotic agonists such as Bax or Bak.

Normally, the balance is in favor of Bcl-2 or Bcl-X<sub>L</sub>, but the BH3-only factors appear to act to titrate out the Bcl2/Bcl-X<sub>L</sub>, tipping the balance in favor of Bax/Bak.

Bax can oligomerize in the membrane to form a permeability channel able to transport cytochrome c.

BH3-only factors have been reported to induce reorganization of the cristae. Alternative models suggest that Bid/Bad/Bak like factors act to open permeability channels such as the permeability transition pore, by disrupting the membrane potential, and affecting the voltage-dependent anion channel VDAC and ATP/ADP exchange transporter.
DEATH RECEPTORS:
Pathways linking external signal receptors to caspase-8

A variety of cell surface receptors related to TNF-R (tumor necrosis factor receptor) interact with the apoptotic activation system. The intracellular portion of the receptor carries a specific protein interaction domain called the death domain, DD. The DD is activated by proximity, brought about when bound extracellular ligand induces receptor oligomerization. Activation can also be induced in absence of ligand by artificial cross-linking of the receptor.

Clustered receptor DDs recruit a variety of DD-containing adapters, of which FADD, Fas-associated death domain protein (also known as MORT1) bridges to a second protein interaction domain, DED, or death effector domain. The cluster of FADD-DEDs recruits procaspase-8, which also carries DEDs at its N-terminus (corresponding to the CARDs on Procaspsase-9).

Procaspsase-8 is activated to Caspase-8 by proximity-induced self-cleavage. Procaspsase-10 is the only other caspase with DED boxes, and may substitute for Caspase-8 in some cases.

In some cells, TNF receptors associate with adaptors linked to cell proliferation or inflammatory signalling pathways, and may induce anti-apoptotic c-IAPs.
APOPTOSIS: important in embryogenesis

Morphogenesis (eliminates excess cells):

Selection (eliminates non-functional cells):
APOPTOSIS: important in embryogenesis

Immunity (eliminates dangerous cells):

Organ size (eliminates excess cells):
APOPTOSIS: important in adults

Tissue remodeling (eliminates cells no longer needed):

Virgin mammary gland → Late pregnancy, lactation → Involution (non-pregnant, non-lactating)

Prostate gland → Apoptosis - Testosterone → Apoptosis
APOPTOSIS: important in adults

Tissue remodeling (eliminates cells no longer needed):

- Resting lymphocytes
- + antigen (e.g. infection) → Apoptosis → - antigen (e.g. recovery)

Steroid immunosuppressants: kill lymphocytes by apoptosis

Lymphocytes poised to die by apoptosis
APOPTOSIS: important in adults

Maintains organ size and function:

Cells lost by apoptosis are replaced by cell division

(remember limited replicative potential of normal cells restricts how many times this can occur before tissue renewal declines)
APOPTOSIS: control

Receptor pathway (physiological):
APOPTOSIS: control

Intrinsic pathway (damage):

Mitochondria

Cytochrome c release

Pro-caspase 9 cleavage

Pro-execution caspase (3) cleavage

Caspase (3) cleavage of cellular proteins, nuclease activation, etc.

Death

BAX  BAK  BOK  BCL-Xs  BAD  BID  BIK  BIM  NIP3  BNIP3

BCL-2  BCL-XL  BCL-W  MCL1  BFL1  DIVA  NR-13  Several viral proteins
APOPTOSIS: control

Physiological receptor pathway

Intrinsic damage pathway

MITOCHONDRIAL SIGNALS

Caspase cleavage cascade

Orderly cleavage of proteins and DNA

CROSSSLINKING OF CELL CORPSES; ENGULFMENT (no inflammation)
APOPTOSIS: Role in Disease

**TOO MUCH:** Tissue atrophy

- Neurodegeneration
- Thin skin
- etc

**TOO LITTLE:** Hyperplasia

- Cancer
- Atherosclerosis
- etc
APOPTOSIS: Role in Disease
Neurodegeneration

Neurons are post-mitotic (cannot replace themselves; neuronal stem cell replacement is inefficient)

Neuronal death caused by loss of proper connections, loss of proper growth factors (e.g. NGF), and/or damage (especially oxidative damage)

Neuronal dysfunction or damage results in loss of synapses or loss of cell bodies (synaptosis, can be reversible; apopsosis, irreversible)

PARKINSON'S DISEASE
ALZHEIMER'S DISEASE
HUNTINGTON'S DISEASE etc.
APOPTOSIS: Role in Disease
Cancer

Apoptosis eliminates damaged cells
(damage => mutations => cancer

Tumor suppressor p53 controls senescence
and apoptosis responses to damage

Most cancer cells are defective in apoptotic response
(damaged, mutant cells survive)

High levels of anti-apoptotic proteins
or
Low levels of pro-apoptotic proteins
===> CANCER
APOPTOSIS: Role in Disease
AGING

Aging --> both too much and too little apoptosis
(evidence for both)

Too much (accumulated oxidative damage?)
---> tissue degeneration

Too little (defective sensors, signals?
---> dysfunctional cells accumulate hyperplasia (precancerous lesions)