

## ALTERATIONS IN CELLULAR AND TISSUE FUNCTION

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### CELLULAR ADAPTATION

**Atrophy** - decrease or shrinkage in cell size

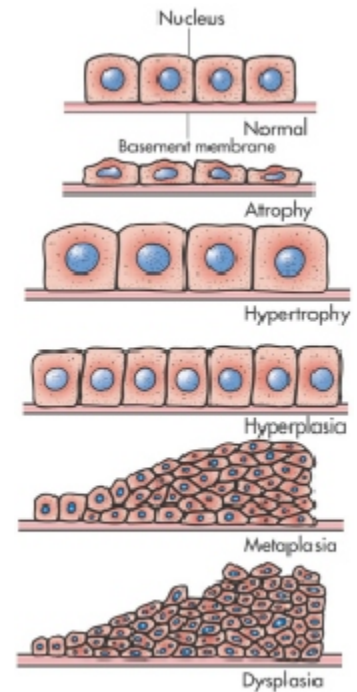
- Can (if sufficient numbers) result in shrinkage of entire organ  
Example: muscular atrophy after cast is removed  
Example: sports steroid abuse causes atrophy of penis

- **Physiologic atrophy** - normal process  
Example: atrophy of thymus during childhood
- **Pathologic atrophy** - disease process  
Example: Addison's disease -> atrophy adrenal glands
- **Disuse Atrophy**  
Example: Prolonged bed rest causes muscle atrophy  
Example: Casting limb causes atrophy

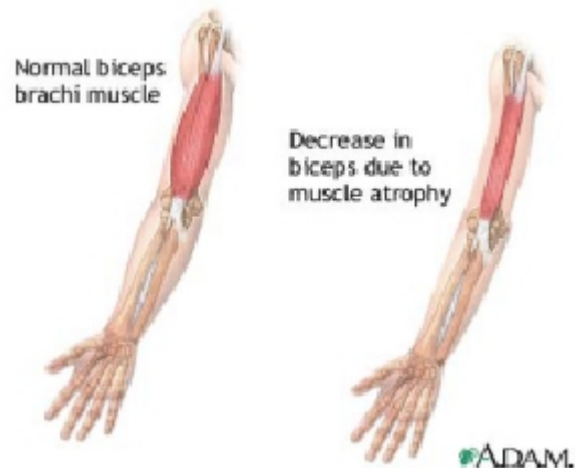
Atrophic cells have fewer mitochondria and myofilaments  
Autophagic vacuoles occurs with malnutrition

**Lipofuscin** - yellow-brown age pigment (may resist destruction)

- Persists as membrane-bound residue bodies
- Accumulates w age: liver, myocardial and atrophic cells
- Results in "age spots" to skin



"Age spots" Lipofuscin accumulation to skin



**Hypertrophy** - increase in cell size (vs cell number with hyperplasia)

Results in increased size of organ

Cardiac and kidney esp prone to hypertrophy

Increased size -> increased cellular protein and not increased fluid

**Physiologic hypertrophy** - normal process

Example: muscle increase with exercise

Example: genital size increase with hormones of puberty

**Pathologic hypertrophy** - disease process

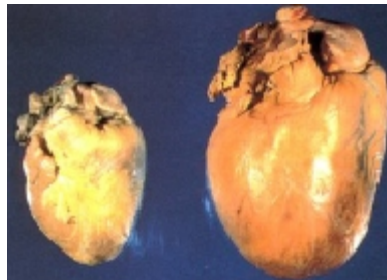
Example - Left ventricular hypertrophy from hypertension -> congestive heart failure

Triggers for hypertrophy

Mechanical: stretch, exercise

Trophic: growth factors, hormones, vasoactive agents

### CELLULAR HYPERTROPY



Left: dependent edema in CHF  
Right: dilated cardiomyopathy



Left ventricular  
hypertrophy (bottom)  
vs normal (top)

**Hyperplasia** - increase in number of cells (increased rate of cell division)

- Can occur in response to injury esp with cell death
- Can occur together with hypertrophy

note: if organ with non-dividing cells (e.g. myocardial fibers) only hypertrophy can place

**Compensatory hyperplasia** - adaptive mechanism allowing for organ regeneration

- Liver can regenerate from a 70% loss after 2 weeks (hepatocyte growth factor)
- Non-regenerative cells: nerve, skeletal muscle, myocardial cells, ocular lens

- Compensatory-capable cells

Epidermal and intestinal epithelium, hepatocytes, bone marrow, fibroblasts, bone, cartilage and smooth muscle

- Example: callus on foot from mechanical stimulation (hyperplasia of epidermal cells)

**Hormonal hyperplasia** - estrogen-dependent organs (breast, uterus)

Example: pregnancy (both hyperplasia and hypertrophy of uterus),

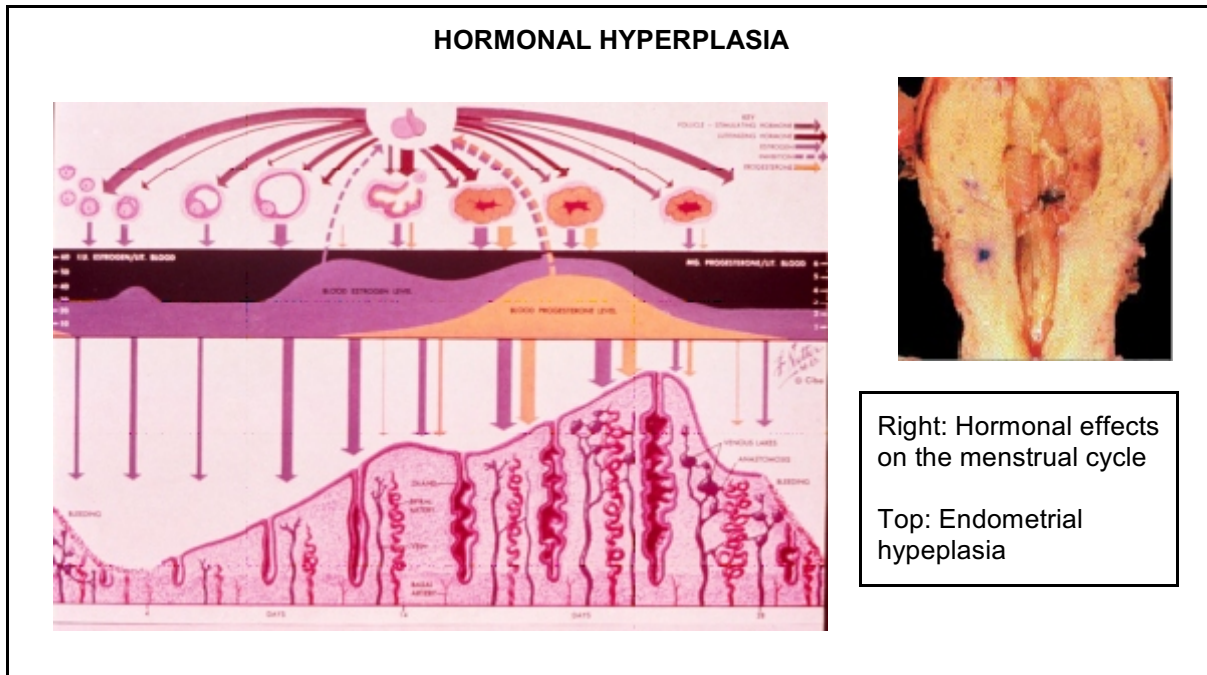
Example: thickening of endometrium (uterine lining) thickening in response to estrogen/progesterone

**Pathological hyperplasia** - abnormal proliferation of normal cells

- Usually in response to excessive hormonal stimulation
- Example: endometrial proliferation with “unopposed” estrogens (no progestins)
  - Excessive and dysfunctional vaginal bleed
  - Can lead to endometrial cancer

Example: failure to prescribe progestin with estrogen in menopause

Example: non-ovulatory cycles -> no progestins -> proliferation



**Dysplasia** - (not true adaptive change) abnormal changes in size, shape or organization of mature cells

- **Atypical hyperplasia**

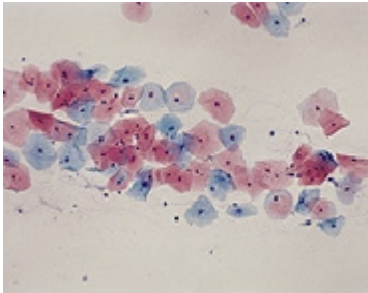
- Most commonly occur in epithelium of cervix, respiratory tract
- Commonly associated with neoplasia - often adjacent to malignant cells
- May be classed as high-grade or low grade

Example: Bethesda Pap classification

-HSIL high grades squamous intraepithelial lesion

-LSIL - low grade squamous intraepithelial lesion

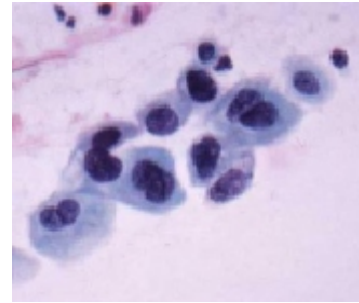
**NORMAL AND ABNORMAL PAP CYTOLOGY**



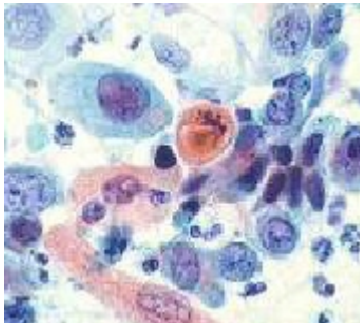
Normal Pap



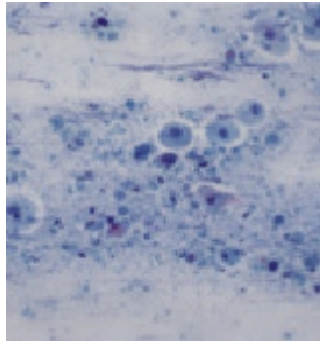
LSIL



HSIL



Squamous Cell CA  
Cervix



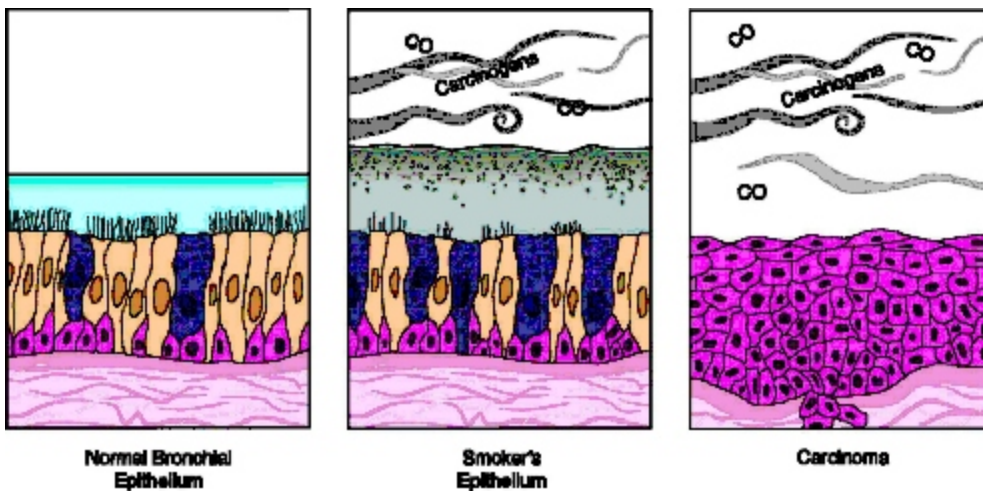
Atrophic pap

**Metaplasia** - reversible replacement of one mature cell type by another

- Replacement cells are sometimes less differentiated than original
- Thought to be the result of reprogramming of certain cell types
  - Stem cells existing most epithelium
  - Undifferentiated mesencymal cells on connective tissue
- Reprogrammed cells mature along a new pathway mediated by cytokines and growth factors

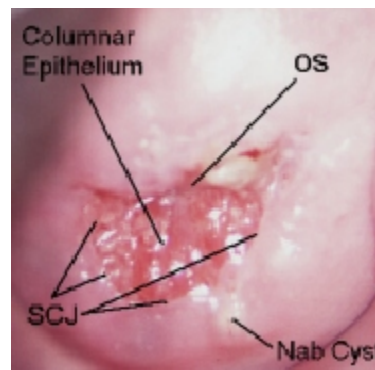
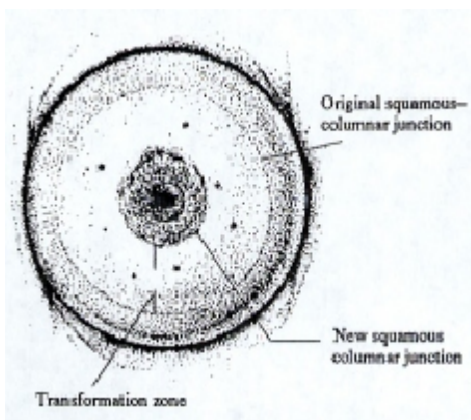
Example: **Lungs** - pathological change

- Smoking causes replacement of normal columnar ciliated epithelial cells of bronchi with stratified squamous epithelium
- New cells have no cilia and do not secrete mucus -> loss of protective mechanism
- Cease smoking -> reversal of changes; prolonged smoking -> cancerous transformation



Example: **Cervical metaplasia** - transformation - physiologic (normal) change

Estrogen-induced acid environment in vagina cause original columnar epithelium to transform into squamous epithelium on face of cervix -> transformation zone



## COMMON ETIOLOGIES OF CELL INJURY

### HYPOXIA - Lack of sufficient oxygen

- Most common cause cell injury
- Arises from inadequate O<sub>2</sub> in blood or decreased tissue perfusion
- Causes disturbed metabolism or excess lactic acid release
- **Anaerobic metabolism** results in **metabolic acidosis**
- **Ischemia**: reduced blood supply - most common cause of hypoxia  
Example: angina (chest pain often preceding an MI)  
Example: peripheral vascular disease
- **Anoxia** - total lack of oxygen - usually caused by acute obstruction  
Example: myocardial infarction  
Example: CVA, pulmonary embolism, gangrene
- **Reperfusion injury** - restoration of oxygen resulting in high-reactive intermediates (radicals)  
Radicals: (OH<sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, superoxide) can damage membranes  
Damaged decreased by **antioxidants** (block synthesis or inactivate radicals)  
Vitamin E, vitamin C, cysteine, glutathione, albumin, ceruloplasmin, transferrin

**HYPOXEMIA**

**Anoxia** - Gangrene in toes of a diabetic

**Ischemia**: Levine's sign in angina (above) due to plaques obstructing coronary arteries (below)

**Chronic ischemia** from compromised circulation (PVD). Note also changes from chronic lack of O<sub>2</sub>

Acute ischemia from thrombus

## MECHANICAL INJURIES

- Mechanical trauma, temperature gradients, electrical stimulation
- Atmospheric pressure gradients, irradiation
- Types of damage: rupture of membrane/walls, disruption reproduction
- Local swelling may impair microcirculation and predispose to hypoxia

**Blunt force:** application of mechanical force to body resulting in tearing, shearing or crushing of tissues

**Contusion** (bruise) bleeding into skin or underlying tissue secondary to blow which crushes soft tissue and ruptures blood vessels without breaking skin

- Several hours may ensue before injury is apparent (change in skin color)
- **Ecchymosis:** discoloration (lay term is "black and blue")
- May occur in internal organs

**Hematoma** - collection of blood in soft tissues or enclosed space

- Example: Subdural h. - blood between inner surface of dura mater and surface of brain
- Epidural h. - blood between inner surface of skull and dura

**Abrasion** (scrape) removal of superficial layer of skin secondary to friction between skin and injuring object

- Variable: fine thin scratch to large areas of denudation
- May mirror patterning of injuring object
- May have ecchymosis as with a contusion



- Laceration** - tear or rip when tensile secondary to injuring force exceeding tensile strength of skin
- Edges jagged and irregular (vs incision where skin is cleanly divided)
  - Portions may have small vessels and nerves which are stretched not broken
  - Underlying structure may be undermined with pocket formation
  - **Avulsion** - extreme laceration where wide area of tissue pulled away -> flap
  - Lacerations of underlying organs common with blunt trauma
  - Severe trauma may lacerate major vessels -> hemorrhaging

**Fractures:** breaking or shattering of bones - see Ortho Handout

## SHARP FORCE INJURIES

**Incision wounds:** a cut which is longer than it is deep

- Wound may be straight or jagged
- No tissue or undermining
- May be thin and narrow or gaping
- Significant external bleed with minimal internal hemorrhage

Example: surgical incision or knife slash wounds

“Hesitation marks” common if self-inflicted: multiple grouped superficial wounds in same area

Example: accidental injury with sharp object e.g. sheet metal or glass shard

**Stab wounds** - penetrating sharp force which is deeper than it is long - sharp edge instrument

- Created by knife or other instrument with sharp edge
- Sharp instrument thus no underlying crushing injury
- Edges usually clean but may be associated with blunt injury e.g. handle of knife
- External bleed may be quite small (tissue pressure) with extensive internal bleed

**Puncture wounds** - instruments or objects with sharp points but without sharp edge

- Example: stepping on a nail
- Can be deep in spite of benign appearance
- Very prone to infection esp with anaerobes eg tetanus, gangrene





### **Chopping wounds - heavy, edged instruments**

- Example: axes, hatchets, propeller blades
- Combines sharp and blunt force characteristics
- Cutting, crushing injuries to superficial and underlying tissues
- Can result in amputation

## **CHEMICAL INJURIES**

Poisons, drugs/therapeutic agents (disrupt cellular balance)

Chemicals (structural damage, metabolic damage, disrupt energy production, toxic metabolites)

Mechanism:

- Direct toxicity
- Formation of reactive free radicals and lipid peroxidation

Example: carbon tetrachloride injury (agent in dry cleaning)

Converted by liver into CCl<sub>3</sub> (highly toxic radical) -> destroys liver

**Poisons:** highly toxic substances which cause cellular injury

- Some are lethal (kill cells) rapidly with minute exposure (example: cyanide)
- Some cause injury with chronic exposure (example: ETOH, carbontetrachloride)

Lead and other heavy metals

- Common cause of childhood poisonings (esp old plumbing and lead paint)
- Affects CNS, hematopoieic

## **Microorganisms**

**Endotoxins** - secrete directly or liberate when bacteria is destroyed

**Virus-** commandeering cell metabolism and function

## **Genetic defects**

Inborn errors of metabolism or gross malformations

Mechanism are widely variable

## **Nutritional imbalances**

Includes protein and vitamin deficiencies - disrupt cellular function

Significant problem in third world countries

Caloric excesses lead to production of excessive lipids

Excessive fat intake associated with cancer and other disorders

## **Immunologic reactions**

**Hypersensitivity** reactions - release of histamines/other substances

Cellular response is inflammation, scar tissue and tissue death

Renal nephrons are particularly susceptible

Immunodeficiencies allow for opportunistic infections

## CELLULAR CHANGES FROM ADAPTATION OR INJURY

### Cellular swelling

- **Hydropic cellular swelling** is initial response to disruption of cellular metabolism
- Occurs most frequently with cellular hypoxia - impairs ability to synthesize DNA
- Results in increased permeability
- Death occurs when large molecules and enzymes leak out
- Vacuoles often give clue to continued accumulation of water within cell
- **Ischemia/hypoxic model** - primary target is oxidative phosphorylation
  - Decreased generation of ATP
  - Glycolysis stimulated - anaerobic metabolism - pyruvate, lactic acid production
  - Events reversible to a point - lethally injured after "point of no return"
  - Hyper permeable membrane causes protein leakage - useful marker of cell death

### Lipid accumulation

**Fatty deposits** in cytoplasm of parenchymal cells of certain organs

Most commonly occurs in **liver** - "**fatty liver**" (liver looks enlarged, yellow, greasy)

Also: heart and kidneys

**Cellular fatty accumulation** - leads to functional impairment of organ esp liver

Predominant lipid involved is triglycerides

**Alcohol** initiates initial hepatic changes

Protein-calorie malnutrition causes decrease in lipid transport proteins

Other organic molecules can cause toxicity (**carbon tetrachloride, benzene**, etc)

Fibrous scarring of cirrhosis results from reaction to lipid infiltration into hepatocytes

Cells of heart and kidneys undergo fatty change

Heart: most common stimulus is hypoxia

Liver: most common stimulus is toxins (also applies to kidney)

### Interstitial fatty infiltration

Occurs with **obesity**

Transformation of interstitial connective tissue cells to fat cells

Rarely affects function of organ - most common in heart and pancreas of obesity

Early formation of fat cells is critical - fat cells laid down during certain periods

- Gestation, 1<sup>st</sup> yr life

- Immediately after puberty

**Obese child**: implications for future health

- Develops increased fat cell numbers which remains for life

- Decrease in size with weight loss

Adult-onset obesity - caloric intake exceeds demands

- Excess converted to fat

- Fat distribution governed by hereditary

- Predisposes to **DM**

## Free radicals and reperfusion injury

- Arise as consequence of cellular oxidation-reduction
- Involves enzymatic-nonenzymatic reactions
- Damage to cells
  - Hydroxyl radical (-OH) is particularly reactive
  - Lipid peroxidation process is particularly - produce aldehydes and organic free radicals
  - Causes membrane/organelle damage eventually cell death

## Reperfusion injury - activated oxygen including **H<sub>2</sub>O<sub>2</sub>** and **hydroxyl radicals**

Ischemic tissue reperfused with activated oxygen

Macrophages and neutrophils generate superoxide anion during phagocytosis

Lethal injury ensues during extended ischemia from superoxide anions so generated

Free radicals so formed continue damage until removed

Endogenous **antioxidants** (Vitamin C, E, d-penicillamine, transferrin

**Vitamin C** protect other molecules via being oxidized in their place

**Vitamin E** (fat soluble) prevents oxidative attack on lipids esp in membrane

**Transferrin** binds free iron; catalase from peroxisomes decomposes H<sub>2</sub>O<sub>2</sub>

Tissue damage function of formation and termination of free radicals

## Glycogen depositions - excess

Storage form glucose

Normally quickly degraded to glucose for energy

**Glycogen storage disease** of glycogenosis - autosomal recessive disorder

- excess deposition of glycogen in organs and tissue
- glycogen accumulates in liver and kidneys

**Diabetes mellitus**: disturbance related to lack of insulin

Excess glycogen in proximal convoluted tubules (kidney) and liver

## Pigmentation abnormalities - colored substances accumulating within cell

ENDOGENOUS\_ - produced within body

### Melanin

- Imparts color to skin - protects fro UV radiation
- **Melanomas** arise from melanocytes
- **Addison's disease**: excessive pigmentation
- "Liver spots" or **lentigines**: decreased melanocyte activity with aging  
Skin becomes paler with areas of hyperpigmentation

**Hemosiderin** - derivative of hgb

- Pigment formed from excessive accumulation of iron
- Breakdown of hemoglobin - **ecchymosis**
- **Hemosiderosis** - excess absorbed dietary iron
- Accumulation does not interfere with organ function unless extreme

EXOGENOUS - produced outside the body

Inhalation of organic carbon from burning fossil fuels - "black lung" or **anthracosis**

**Lipofuscin** pigmentation with aging - golden brown granules

"Wear and tear" pigment gradually accumulates with age; no apparent harm

Predominant in atrophied or chronically injured cells

## Calcification

Normally calcium deposited only in bones and teeth - process under hormonal influence

Pathological calcification - skin - soft tissue - blood vessels, heart, kidney

May precipitate in areas of chronic inflammation or dead/degenerating tissue

**Metastatic calcification** - circulating calcium from metastatic bone resorption or destruction

Calcification from **immobilization** e.g. fractures or spinal cord injury

**Dystrophic calcification:** calcium precipitates into areas of unresolved healing

Intracellular - extracellular or both

Localizes in mitochondria and propagates

Results in organ dysfunction: **atherosclerotic vessels** or calcified **cardiac valves**

Increased uptake of calcium into mitochondria is characteristic of injured cells

## Hyaline infiltration

Characteristic alteration within cells or extracellular space

Appears as homogeneous, glassy, pink inclusion on stained histologic section

Different mechanisms responsible for its formation - no one pattern of accumulation

Intracellular: excessive protein, immunoglobulin aggregates, viral nucleoproteins,

Extracellular: precipitated plasma proteins, other cell proteins

Common around arterioles and renal glomeruli

Variety of mechanisms - implication varies with process