Cell Injury

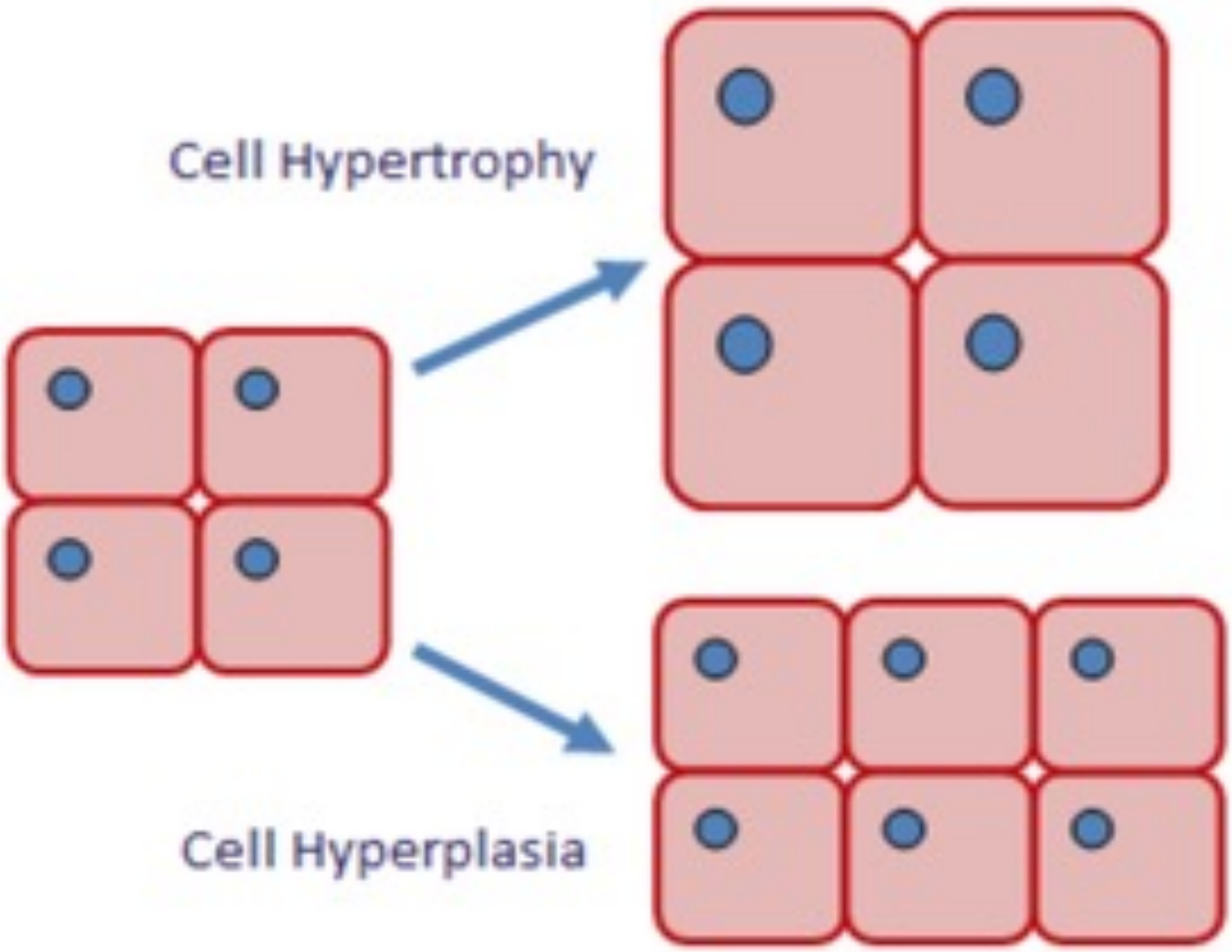
Dr. Gary Mumaugh

Cellular Adaptation

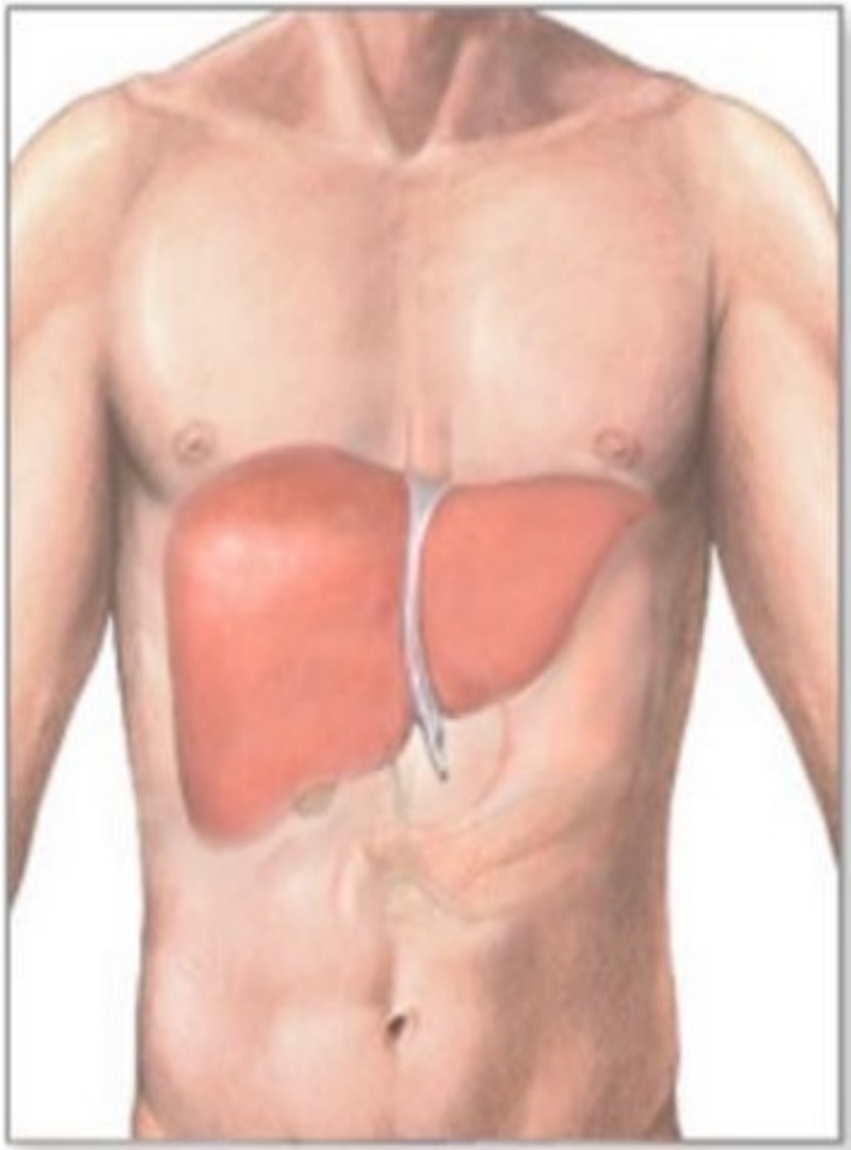
- Altered cell biology can happen with injury, aging, neoplasia, adaptations, deficiencies, poisoning
- Adaptations can be physiologic or pathogenic
- For example the normal change of the size of the uterus in pregnancy.
- Injuries can be reversible (sublethal) or irreversible (lethal)

- Cells adapt to the environment all the time, usually to protect themselves
- Cellular adaptations are a common part of most disease states
- **Atrophy** is decrease or shrinkage of cell size
  - Can affect any organ, but usually seen in skeletal muscle
  - Physiologic atrophy (Shrinking thymus in childhood)
  - Pathologic atrophy (decreased blood or nerve supply or nutrition, etc.)
  - Disuse atrophy (Immobilized muscles)

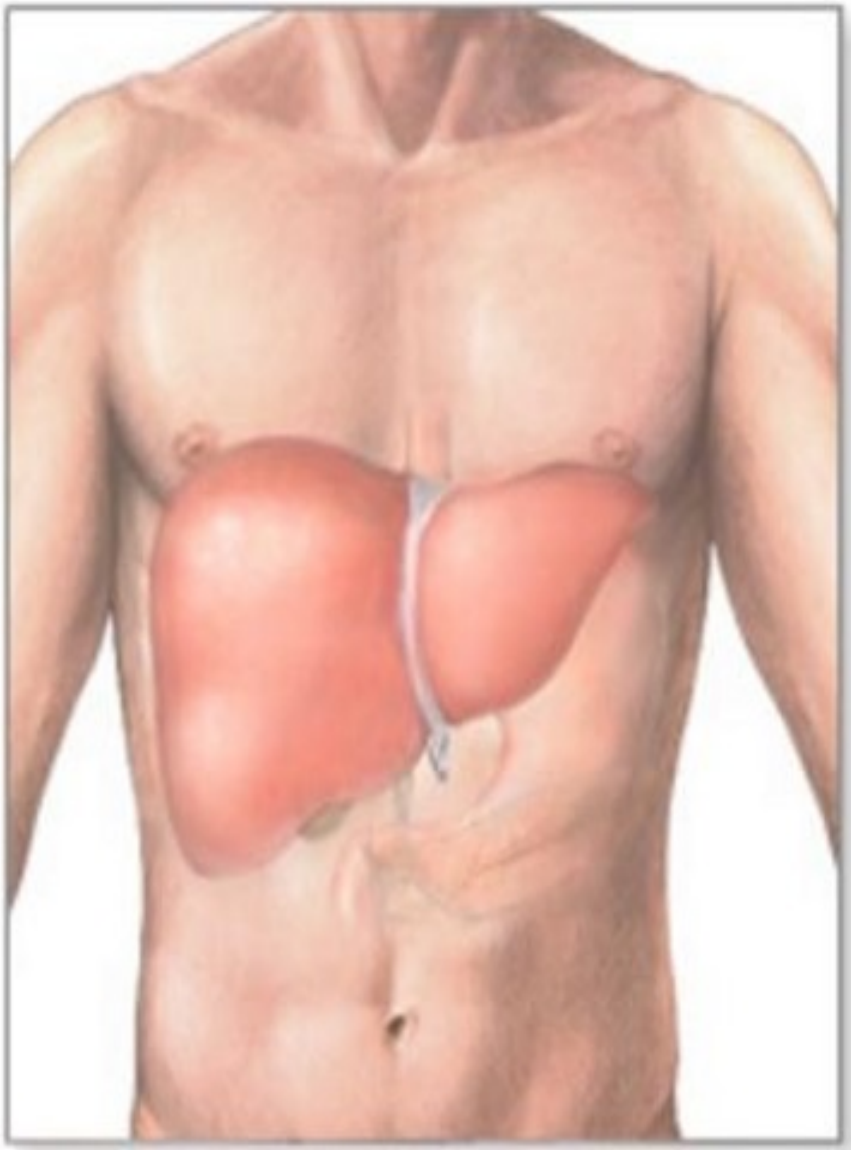
- **Hypertrophy** is increase in size of cells and ultimately the organ
  - Heart, liver, spleen, etc
  - The increased cell size is an accumulation of protein in the plasma membrane, myofilaments, endoplasmic reticulum and mitochondria and NOT with increased cell fluid.


Cell Hypertrophy
Cell Hyperplasia

Normal liver



Enlarged liver due to hepatomegaly



- **Hyperplasia** is an increase in the number of cells because of increased cell division
  - Compensatory hyperplasia is when organs regenerate (spleen and liver)
  - Hormonal hyperplasia occurs as a result of estrogen
  - Pathologic hyperplasia is usually caused by hormonal or growth factors

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Compensatory Hyperplasia is common in the liver and spleen

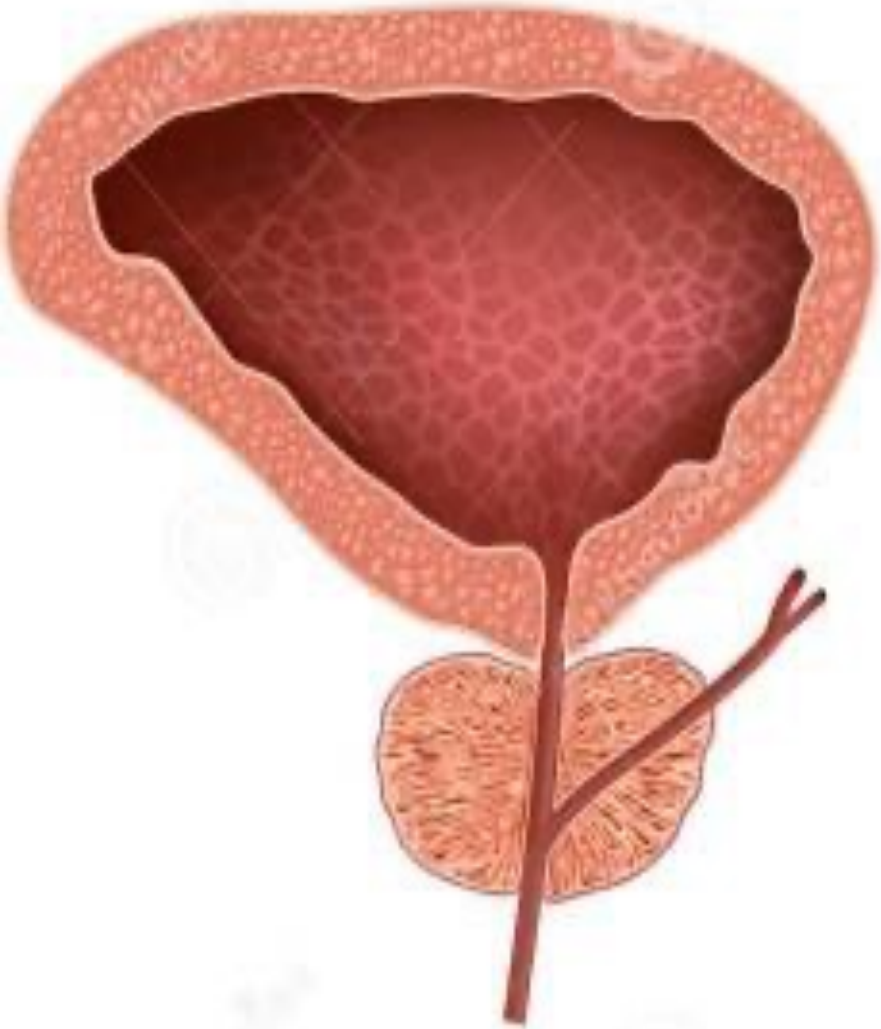
- The liver, however, is able to replace damaged tissue with new cells.
- The growth can be from increased cell size or cell division or both
- If up to 50 - 60 percent of the liver cells may be killed within **3 - 4 days** in an extreme case like a Tylenol overdose, the liver will repair completely after 30 days if no complications arise.

- Complications of liver disease occur when regeneration is either incomplete or prevented by progressive development of scar tissue within the liver.
- This occurs when the damaging agent such as a virus, a drug, alcohol, etc., continues to attack the liver and prevents complete regeneration.

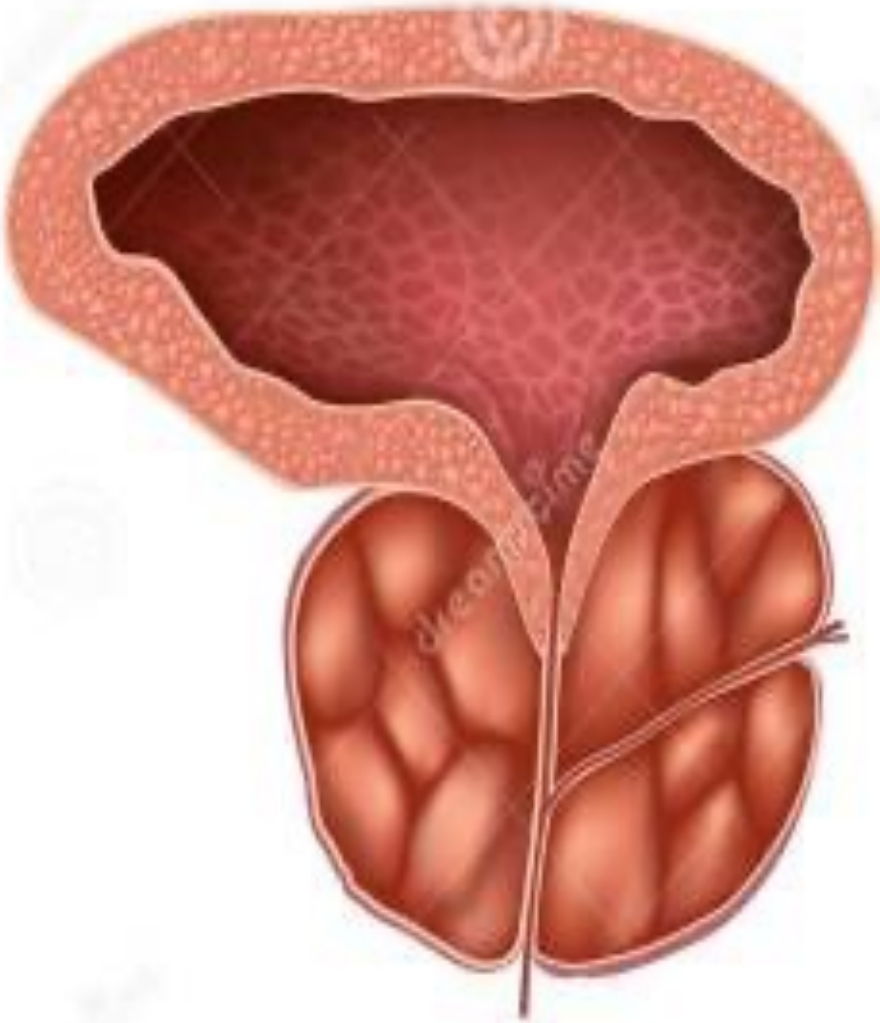
- The growth can be the result of increased cell size (**compensatory hypertrophy**) or an increase in cell division (**compensatory hyperplasia**) or both.
- **Compensatory Hyperplasia** also occurs when one kidney is removed, the other kidney grows to pick up the difference.
- Eventually, the remaining kidney can grow until it's mass is similar to the combined mass of two kidneys.
- Bone marrow hyperplasia occurs after massive hemorrhage


40 mm

Benign Prostatic Hyperplasia

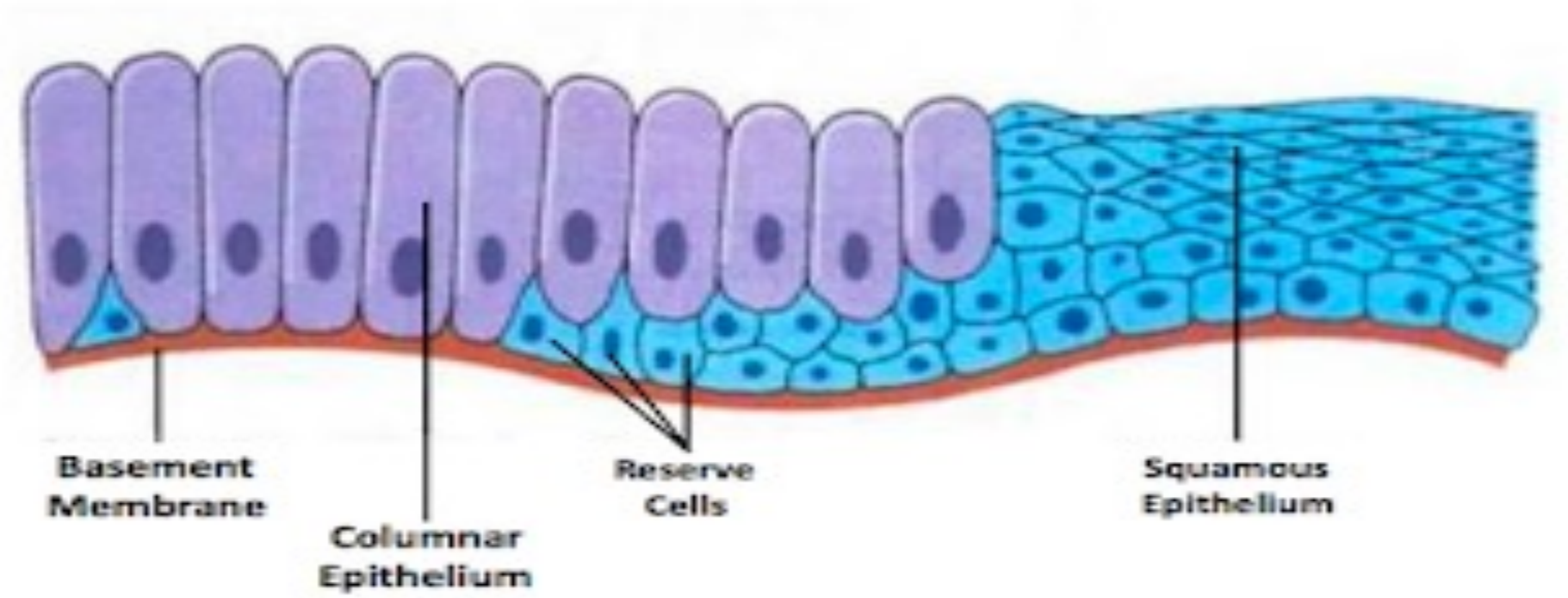


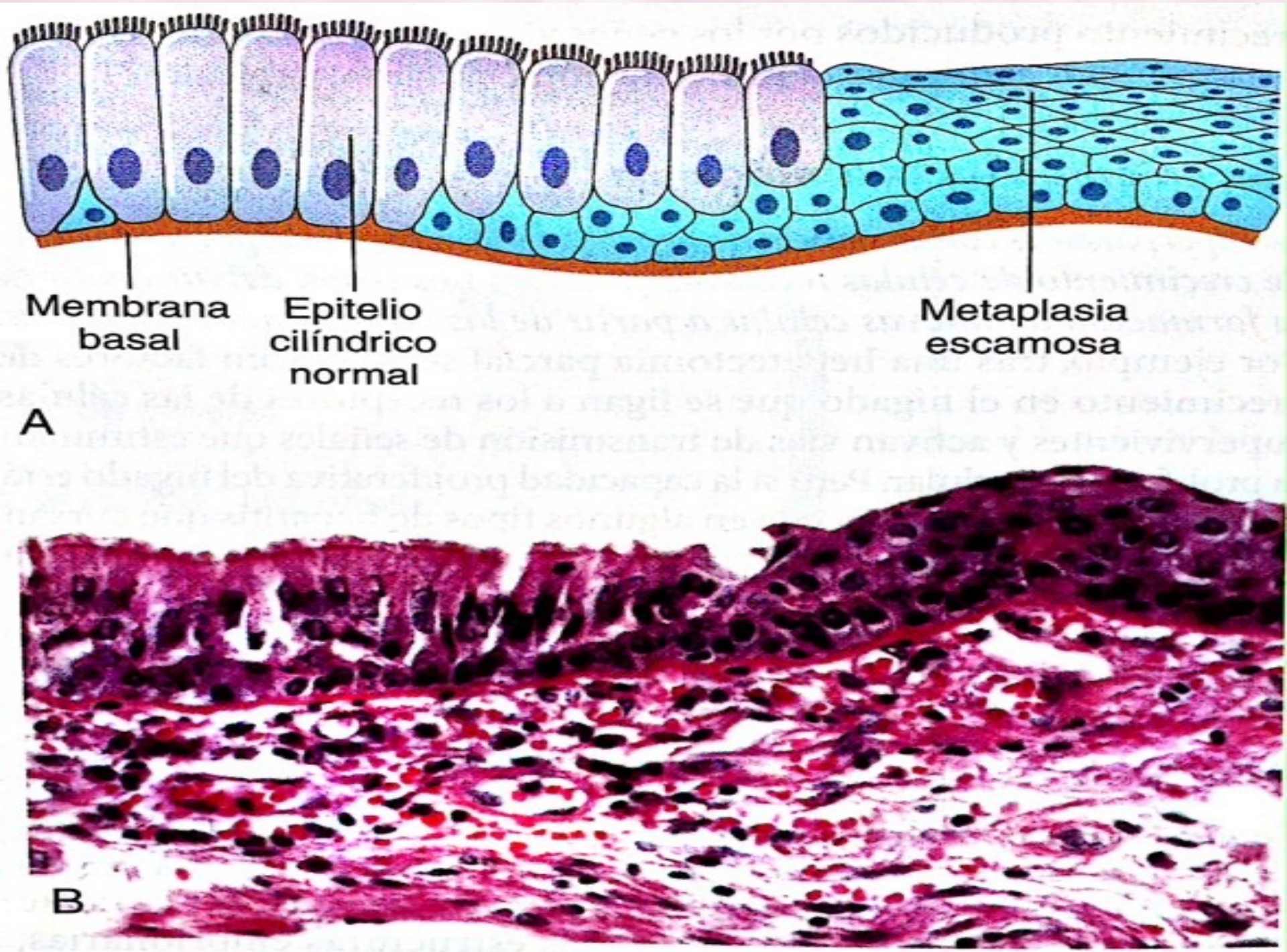
Normal prostate



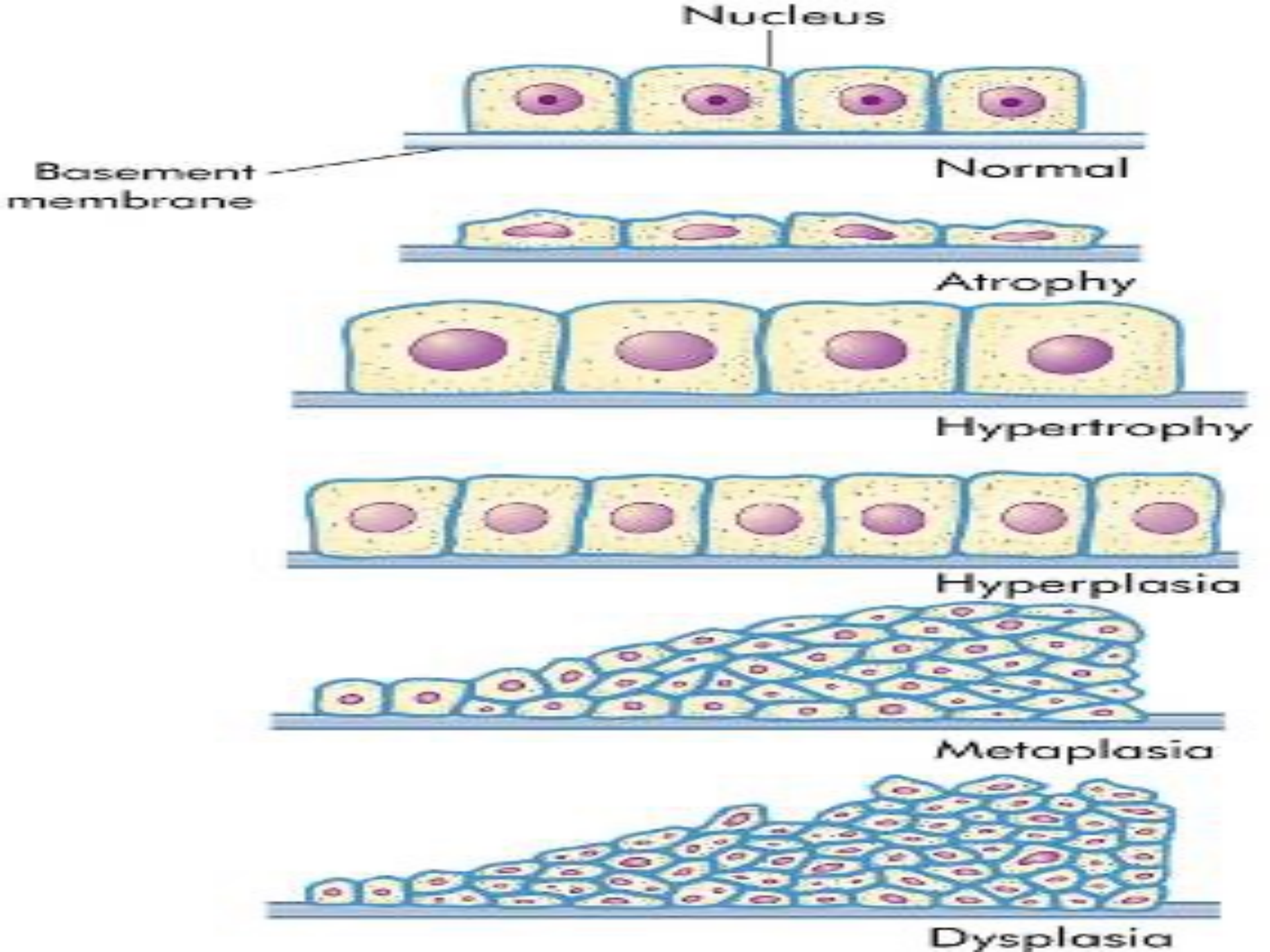
Enlarged prostate

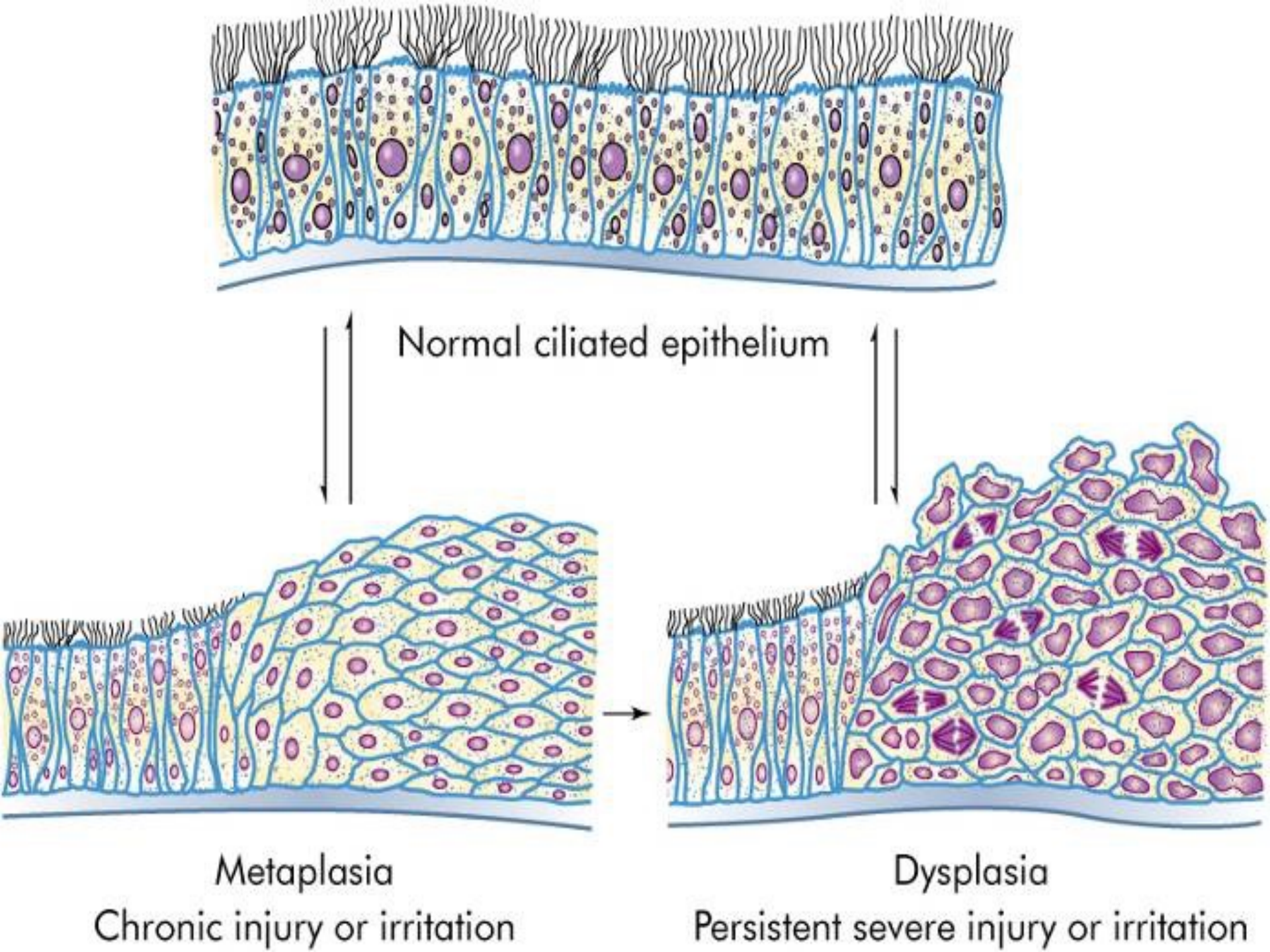
- **Metaplasia** is a reversible of a mature cell to a less differentiated cell
  - Smoking and Epithelial cells
    - Pseudostratified columnar epithelium before smoking and squamous epithelium after smoking



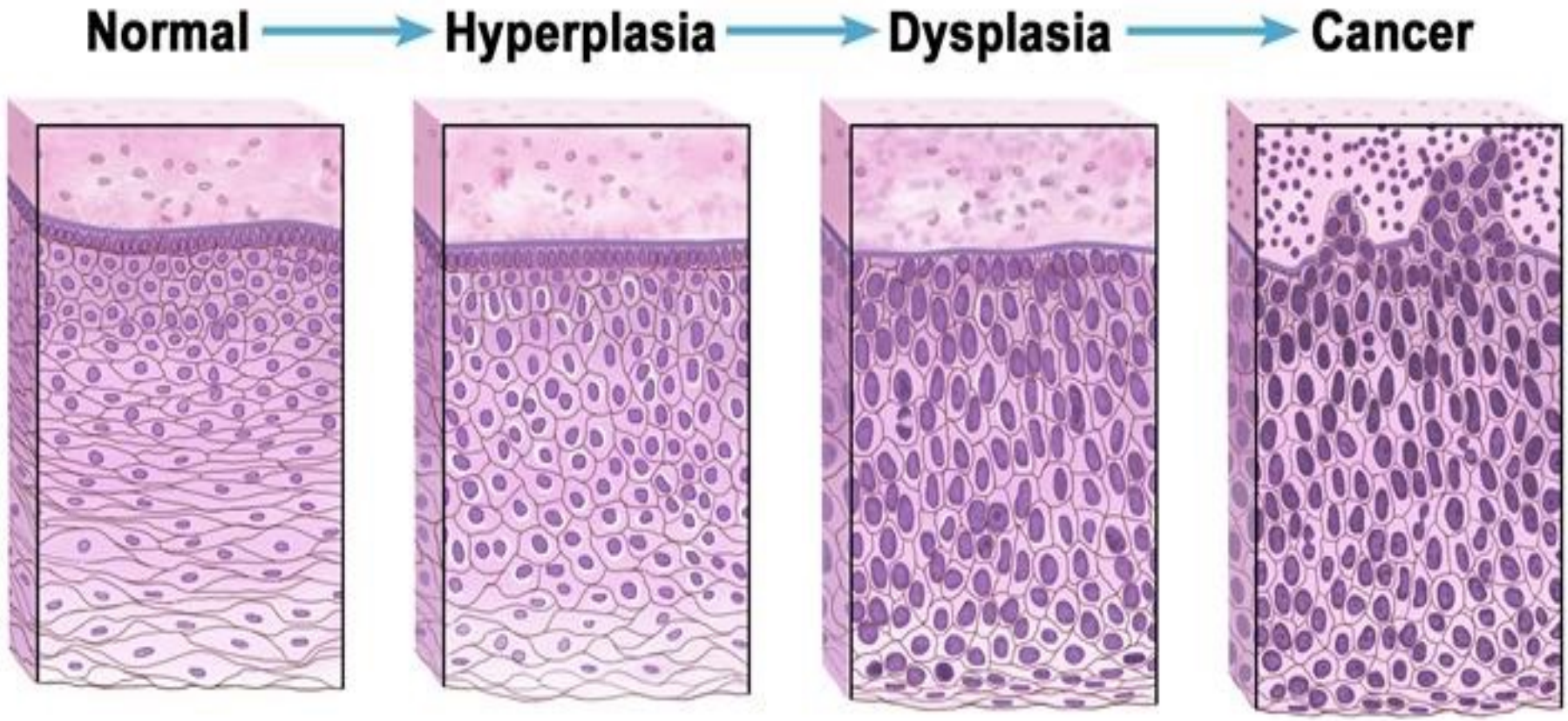

Membrana basal
Epitelio cilíndrico normal
Metaplasia escamosa
A
B

- **Dysplasia** is abnormal changes in the size and shape of cells
  - Dys = bad or difficult
  - Plasia = formation
- Not a true adaptive process but is like hyperplasia and is often called atypical hyperplasia
  - Seen often in breast cancer development


Nucleus
Basement membrane
Normal
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia


Normal ciliated epithelium
Metaplasia
Chronic injury or irritation
Dysplasia
Persistent severe injury or irritation

Normal Cells May Become Cancer Cells



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- Most diseases start with cell injury which messes with cell homeostasis
  - Reversible
  - Irreversible
- The extent of the injury depends on the type, and state of the cells, the adaptive process of the cells, the severity of the injury and duration of the injury

Causes of Cellular Injury Deficiency

- **Deficiency**- Lack of substance(s) necessary for cell's "health"
  - **Primary Nutrient Deficiency**- Cell doesn't get needed materials
  - **Secondary Nutrient Deficiency**- Nutrients are present in diet, but cannot be absorbed
  - May also be caused by…
    - Genetic Errors
    - Infections
    - Lack of adequate precursors of needed materials

Causes of Cellular Injury
Intoxication

- **Intoxication**- Cell is exposed to a substance that interferes with normal function (a "**toxin**") a.k.a. "poisoning"
  - **Exogenous Toxin**- Comes from outside source
    - Pathogenic Microbes
    - Physical or Chemical Means (e.g. radiation, toxic chemicals, etc.)
  - **Endogenous Toxin**- Cell is producing something toxic to itself and/or other cells
    - Defective Genes

Examples of defective genes:

- Huntington's- neurological dysfunction due to toxic substances
- PKU- phenylketones build up due to malfunctioning enzyme

Causes of Cellular Injury
Trauma

- **Trauma** - Physical damage to the cell's structural integrity
  - Trauma may also have many sources
    - Pathogenic Microbes
    - Defective Genes
    - Physical or Chemical Means
    - Mechanical Pressure
    - Oxygen Loss - hypoxia and ischemia

- **Temperature changes can affect cells:**
  - **Hypothermia**- Cell gets too cold -- ice crystals forming in cytoplasm can physically damage cells
  - **Hyperthermia**- Cell gets too hot -- many important molecules will denature

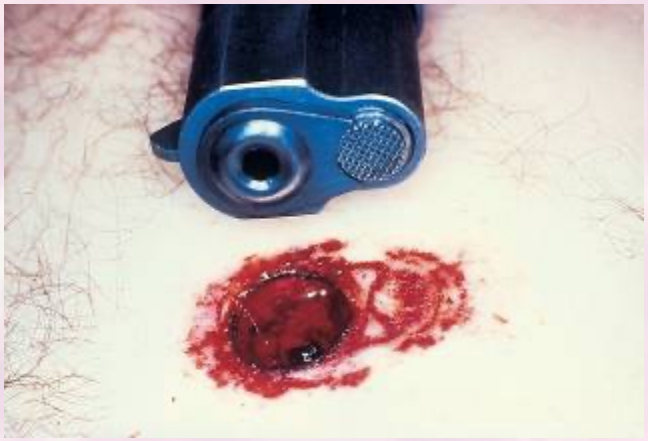
Unintentional and Intentional Injuries

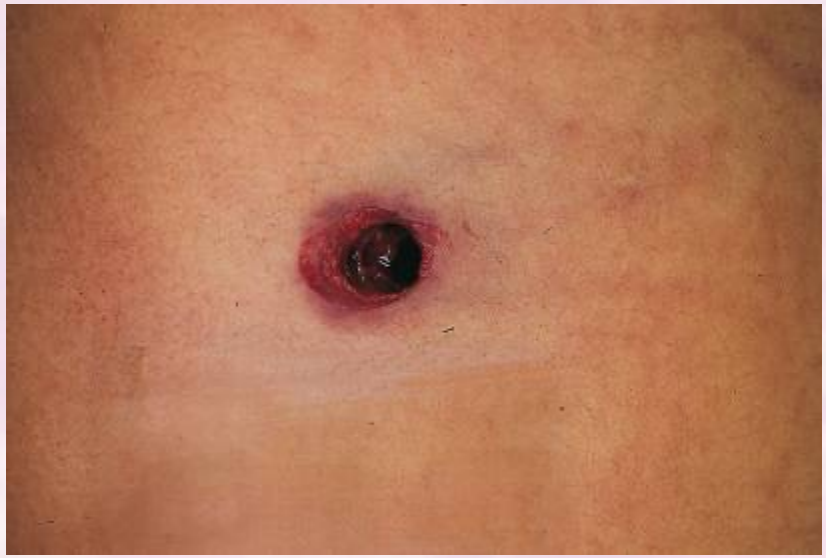
- Blunt force injuries
  - Application of mechanical energy to the body resulting in the tearing, shearing, or crushing of tissues
  - Contusion *(bruise)* vs. hematoma *(Blood in an enclosed space)*
  - Abrasion
  - Laceration
  - Fractures

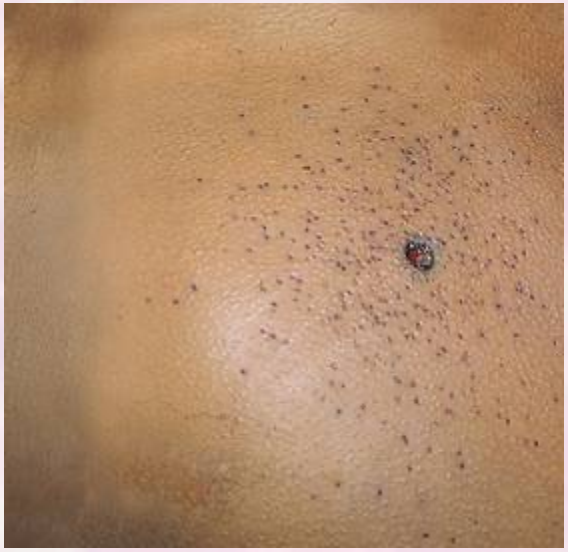
Unintentional and Intentional Injuries

- Sharp injuries
  - Incised wounds – *cut is longer than it is deep*
  - Stab wounds – *penetration is deeper than it is long*
  - Puncture wounds
  - Chopping wounds

Gunshot Wounds







Unintentional and Intentional Injuries

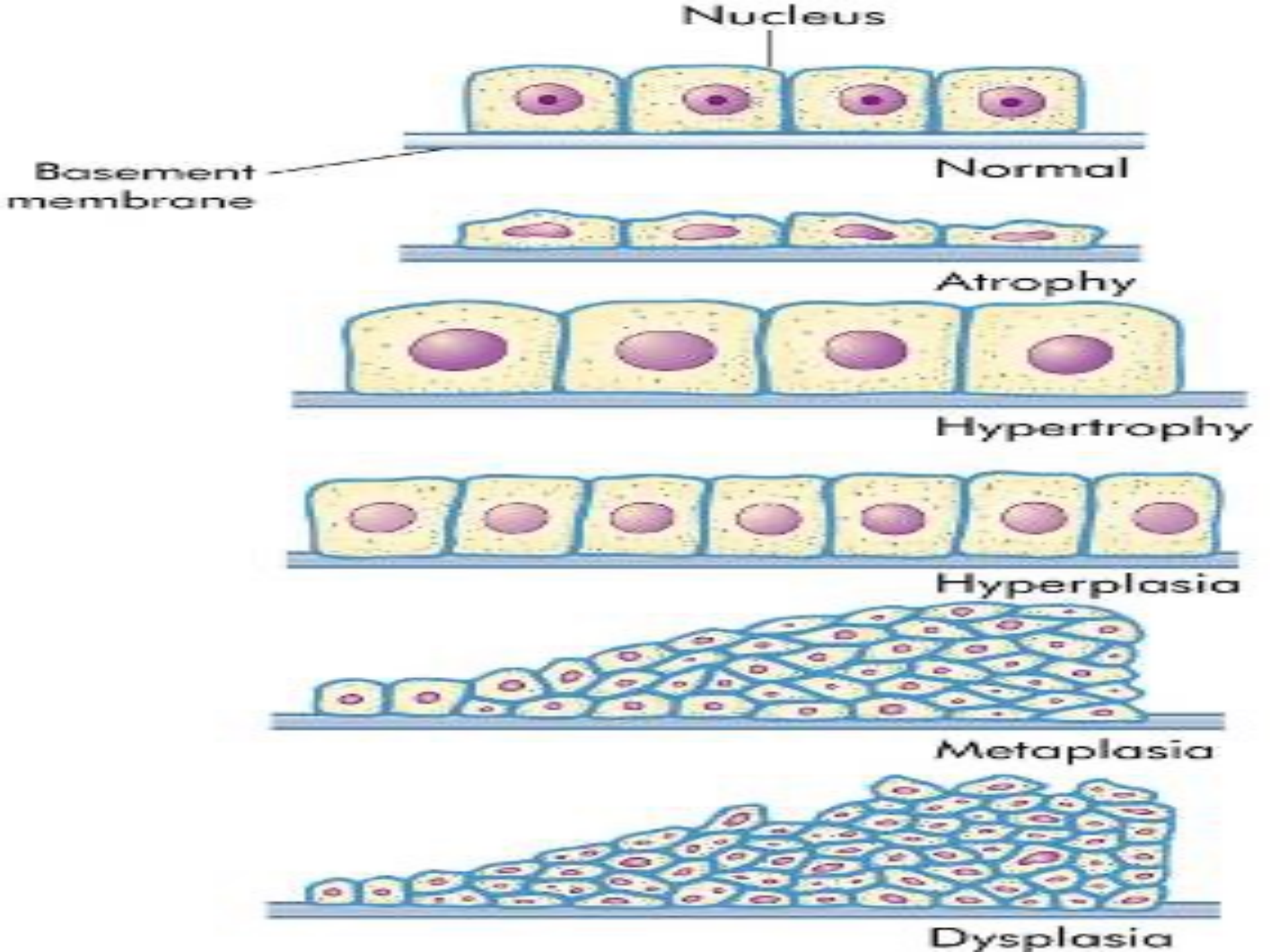
- Asphyxial injuries
  - Caused by a failure of cells to receive or use oxygen
    - Suffocation
      - Choking asphyxiation
    - Strangulation
      - Hanging, ligature, and manual strangulation
        - *Blocking of carotids 15 seconds= unconsciousness*
    - Chemical asphyxiants
      - Cyanide and hydrogen sulfide
    - Drowning

Effects of Cellular Injury

- Effects may be **reversible** or **irreversible**
- Usually affect cell's…
  - Function
  - Structure
- Effects of and response to injury determined by:
  - Nature of causing agent
  - Intensity of causing agent
  - Duration of causing agent
  - Number of exposures to causing agent

Reversible Changes: Functional

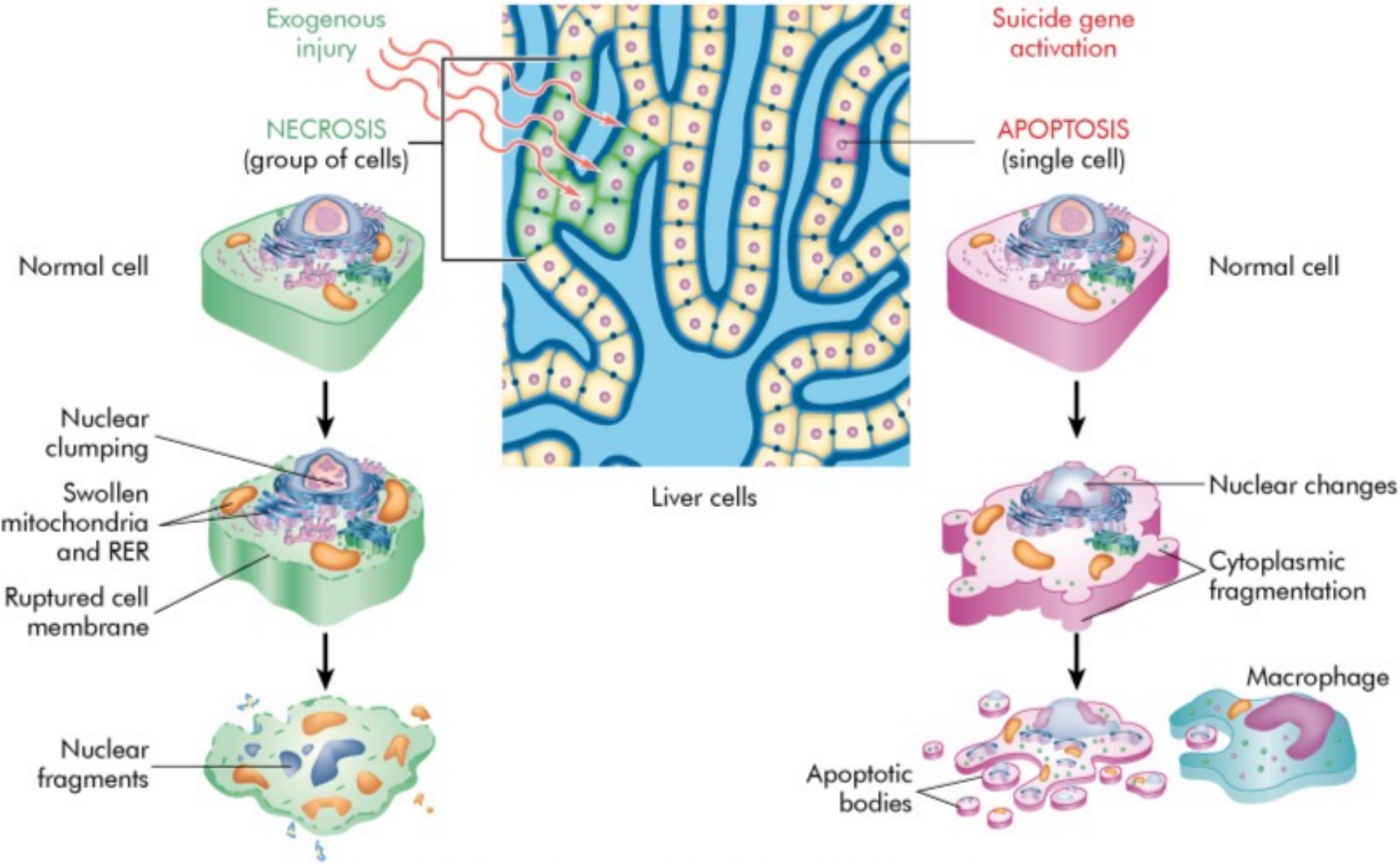
- **Adaptive Responses**
  - **Alternative Metabolism**
    - Allow cell to adjust to conditions
    - i.e. aerobic → anaerobic cellular respiration


Nucleus
Basement membrane
Normal
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia

Reversible Changes: Functional

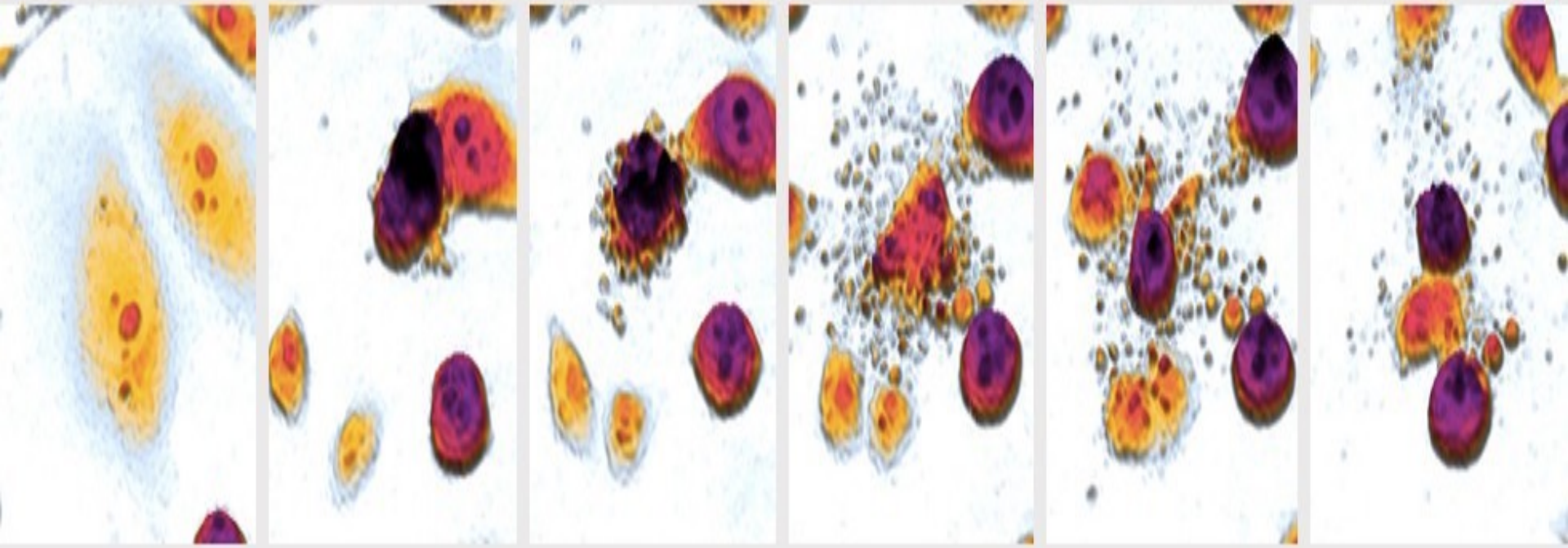
- **Adaptive Responses** (cont.)
  - **Apoptosis-** Programmed cell death
    - Programmed cellular death
    - Every day we can produce 10 billion new cells and kill off the same number
  - Physiologic
    - Is important in body tissue development
  - vs. Pathologic
    - The result of intracellular events or exogenous stimuli
- Absence of apoptosis can cause pathologic change and gene mutation

Apoptosis vs. Necrosis

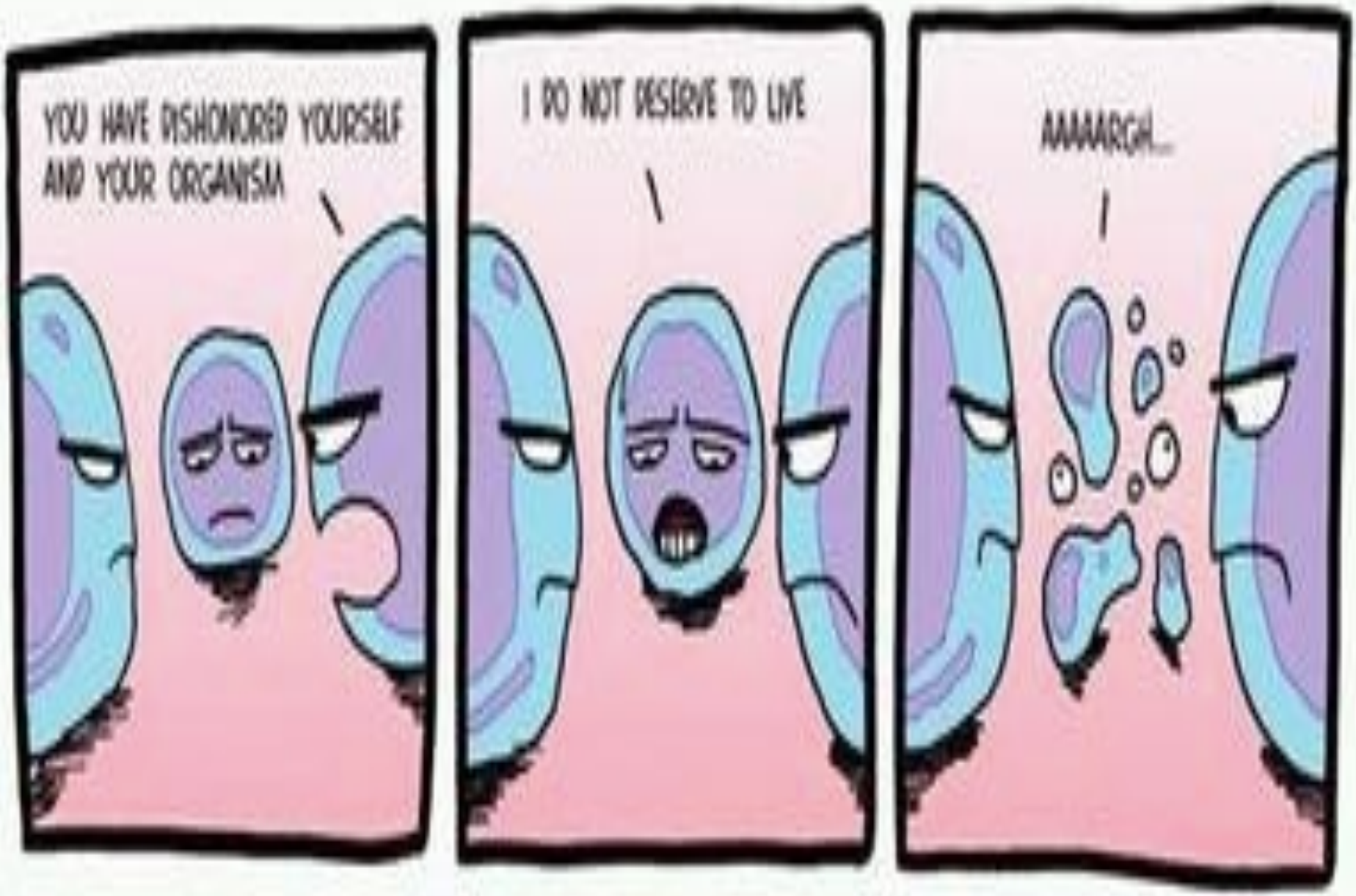


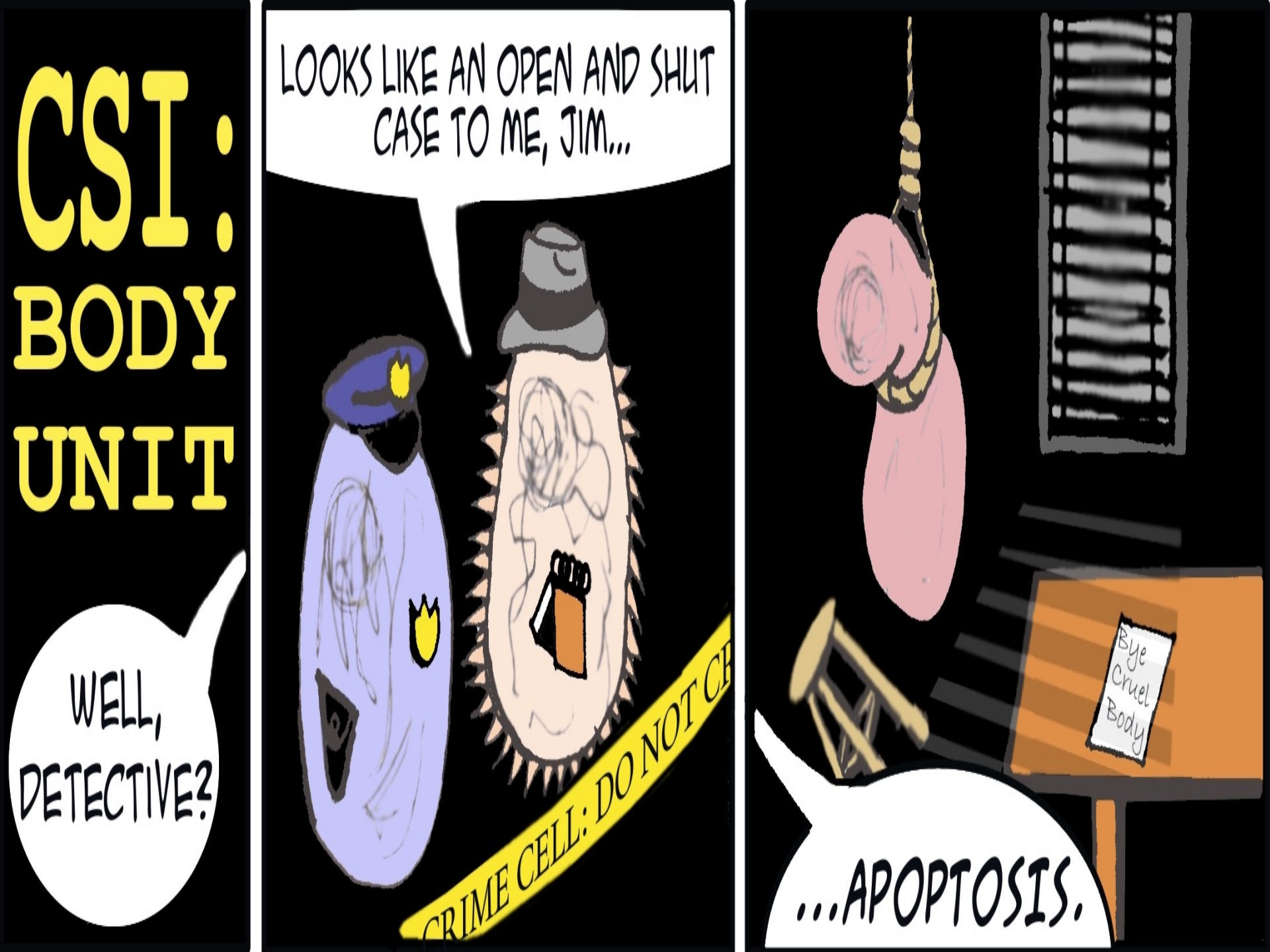
Redrawn from Damjanov I: *Pathology for the health professions*, ed 3, St Louis, 2006, Saunders.

Apoptosis: It's a Good Thing It Happens



Every day billions of cells commit suicide to make room for other new, healthy cells.


YOU HAVE DISHONORED YOURSELF AND YOUR ORGANISM
I DO NOT DESERVE TO LIVE
AAAAARGH...
APOPTOSIS


CSI: BODY UNIT
WELL, DETECTIVE?
LOOKS LIKE AN OPEN AND SHUT CASE TO ME, JIM...
CRIME CELL: DO NOT CR
Bye Cruel Body
...APOPTOSIS.

- **Cell Stress Proteins**
  - Formed when cell exposed to adverse conditions
    - Trauma, temp/pH changes, toxins, nutrient depletion
  - Prevent damaged proteins from clumping and forming insoluble tangles
  - Cell stress proteins - help in 3 ways:
    1. Bind to damaged proteins- easier to destroy
    2. Stabilize and enable to refold damaged proteins
    3. Easier to pass through cell membrane and be expelled

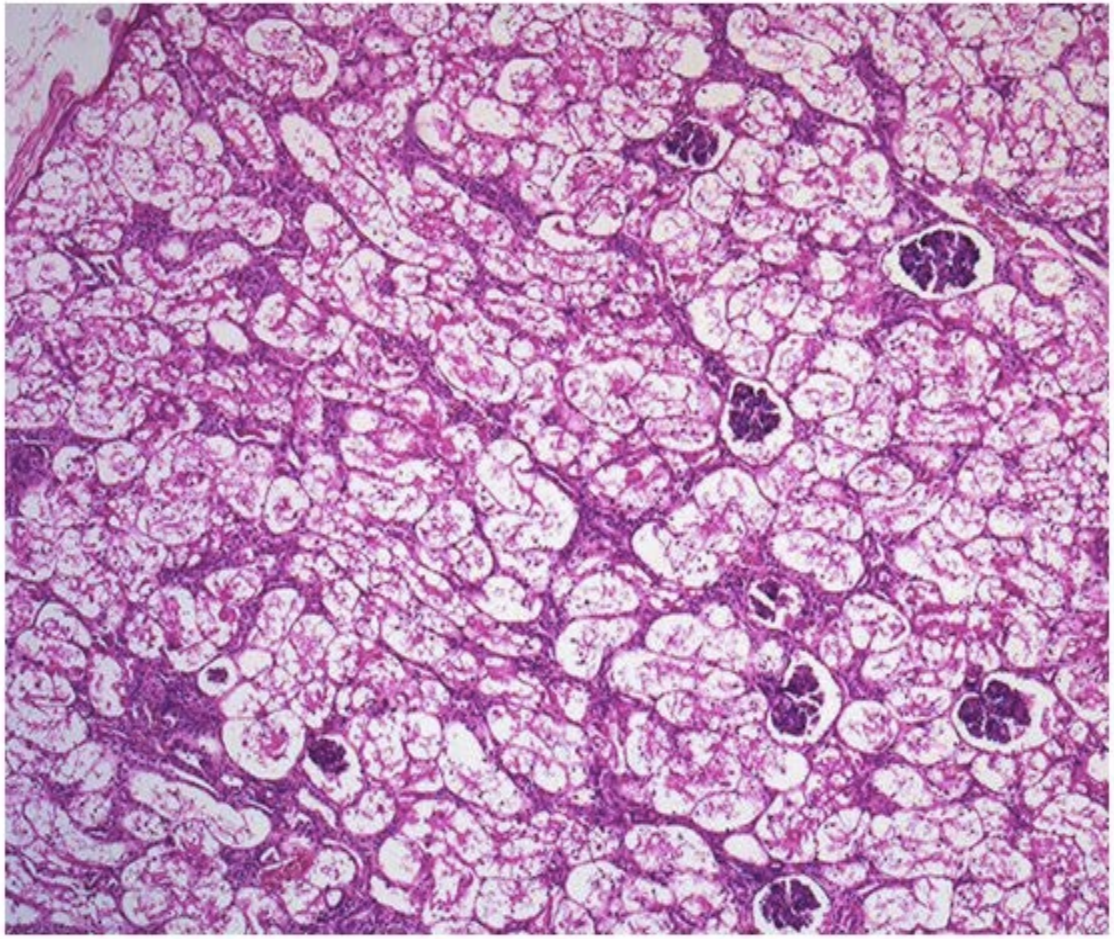
Other Adaptive Changes

- **Organelle Changes**
  - Make or destroy organelles depending on demand

Reversible Changes: Functional

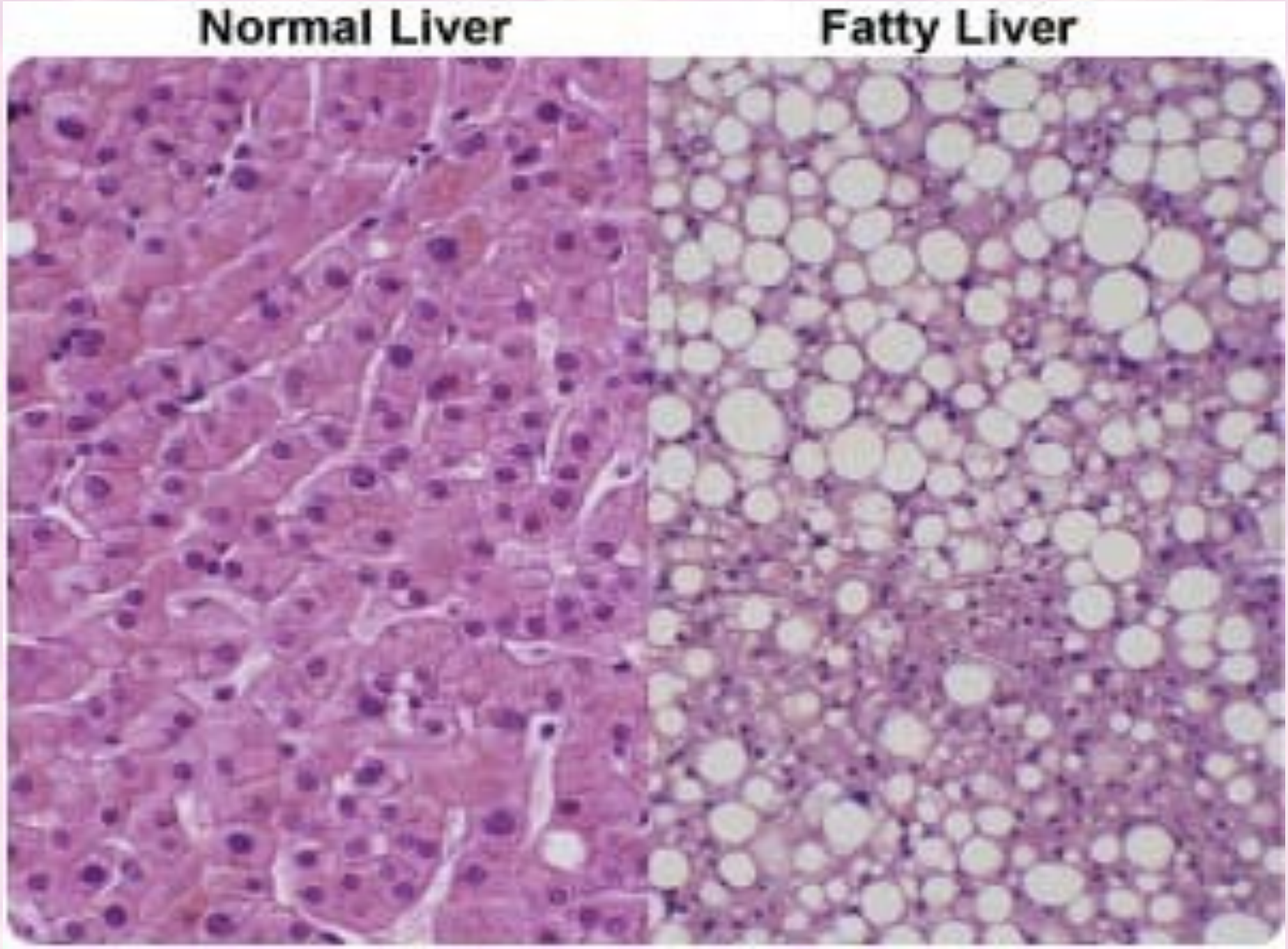
- **Cell and Tissue Accumulations**
  - **Hydropic Changes**
    - Reduced ATP production decreases ion pump activity
    - Affect cell's ability to keep osmotic balance
    - Water accumulation in vacuoles of cells- becomes pale

Hydropic Change



- Hydropic change is one of the early signs of cellular degeneration in response to injury.
- refers to the accumulation of water in the cell. This is clearly seen in this slide.
- The accumulation of water in the tubular cells is usually due to hypoxia of the tissue with a resultant decrease in aerobic respiration in the mitochondria and a decreased production ATP.

- **Fatty Changes**
  - Injury causes fats to accumulate in cells
    - Most often in kidneys, heart, liver
  - FFAs (free fatty acids) accumulate in vacuoles of cells
  - Can be caused by toxin damage or anoxia
  - May cause cells to rupture
  - Fatty changes occur in cells that metabolize a large amount of fat


Normal Liver
Fatty Liver

Reversible Changes: Functional

- **Cell and Tissue Accumulations** (cont.)
  - **Residual Body Accumulation**
    - Happens when materials (bacteria, damaged organelles) are not properly digested by the cell
    - **Lipofuscin Granules** – Residual bodies that contain undigested cell membrane lipids
      - Most often in neurons, liver, and myocardium
  - **Hyaline Changes**
    - a.k.a. "**hyalinization**"
    - Deposition of hyaline around cells
    - Usually a good indication of cell damage elsewhere

Irreversible Changes: Structural

- More extreme structural changes
  - Plasma membrane distortion and increased permeability
  - Mitochondrial and ER breakdown
  - Fewer lysosome- released into cytoplasm
  - Altered nucleus most significant indicator of irreversible cell injury

- Altered nucleus
  - **Karyolysis**- Nucleus fragments and disintegrates
  - **Pyknosis-** nucleus shrinks, condenses, or
  - **Karyorrhexis-** Nucleus breaks up into densely staining fragments that disperse into cytoplasm

Irreversible Changes: Mechanism

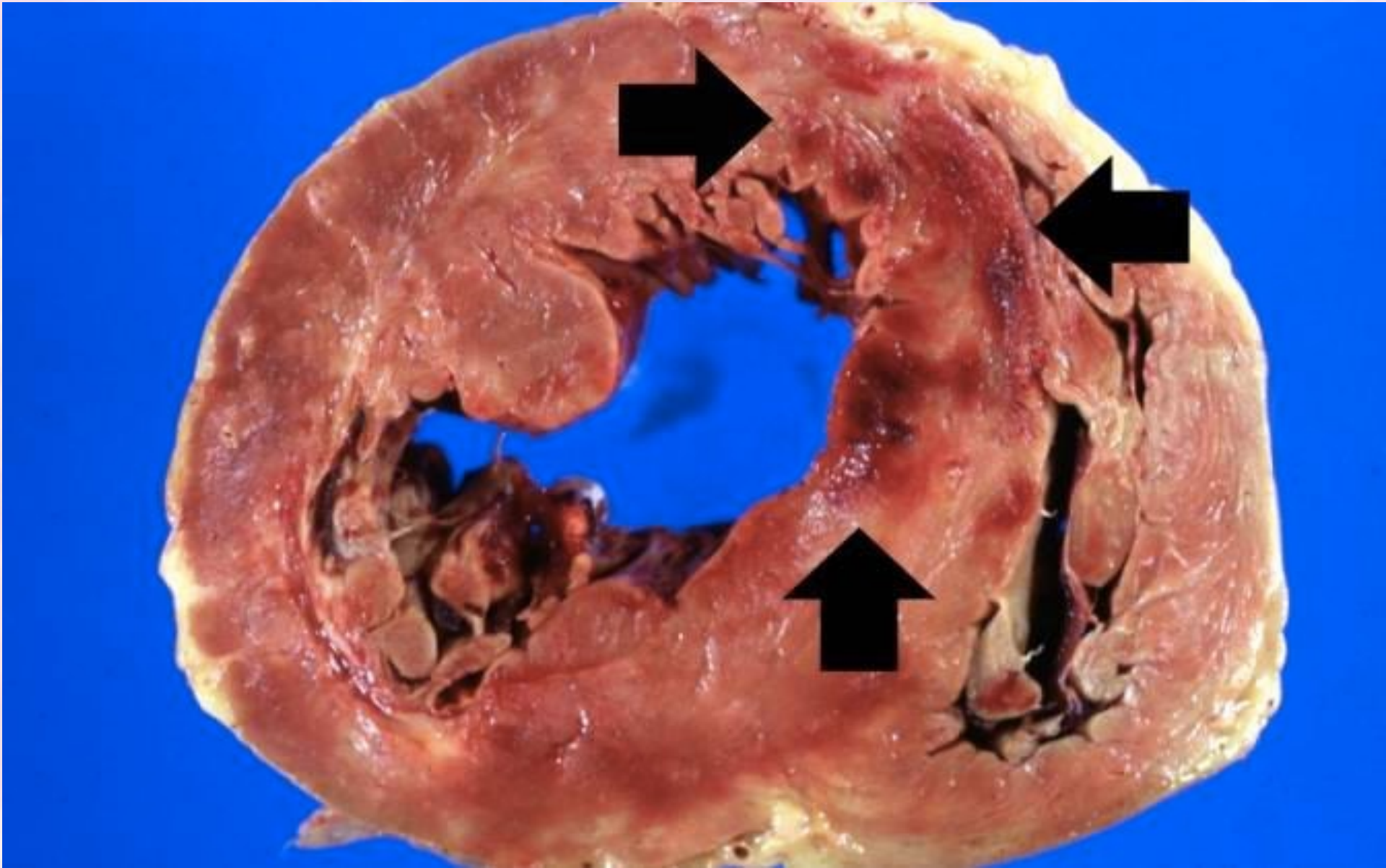
- Organelle and plasma membrane damage leads to compromised permeability and cytoplasm- organizing functions
  - Sodium influx and cell swelling
  - Protein denaturation by high calcium concentrations
  - Activate damage causing enzymes
  - Decreased ATP production → anaerobic
    - Lower pH
  - Flawed protein synthesis
  - Disruption of cytoskeleton- form blebs

Permanent Effects of Cellular Injury

- **Necrosis** - Cell death
  - Lysosomal enzymes released after lethal injury

- **Coagulative Necrosis**
  - Kidneys, heart, and adrenal glands
  - Protein denaturation occurs causing albumin to change from a gel to a firm fibrotic substance

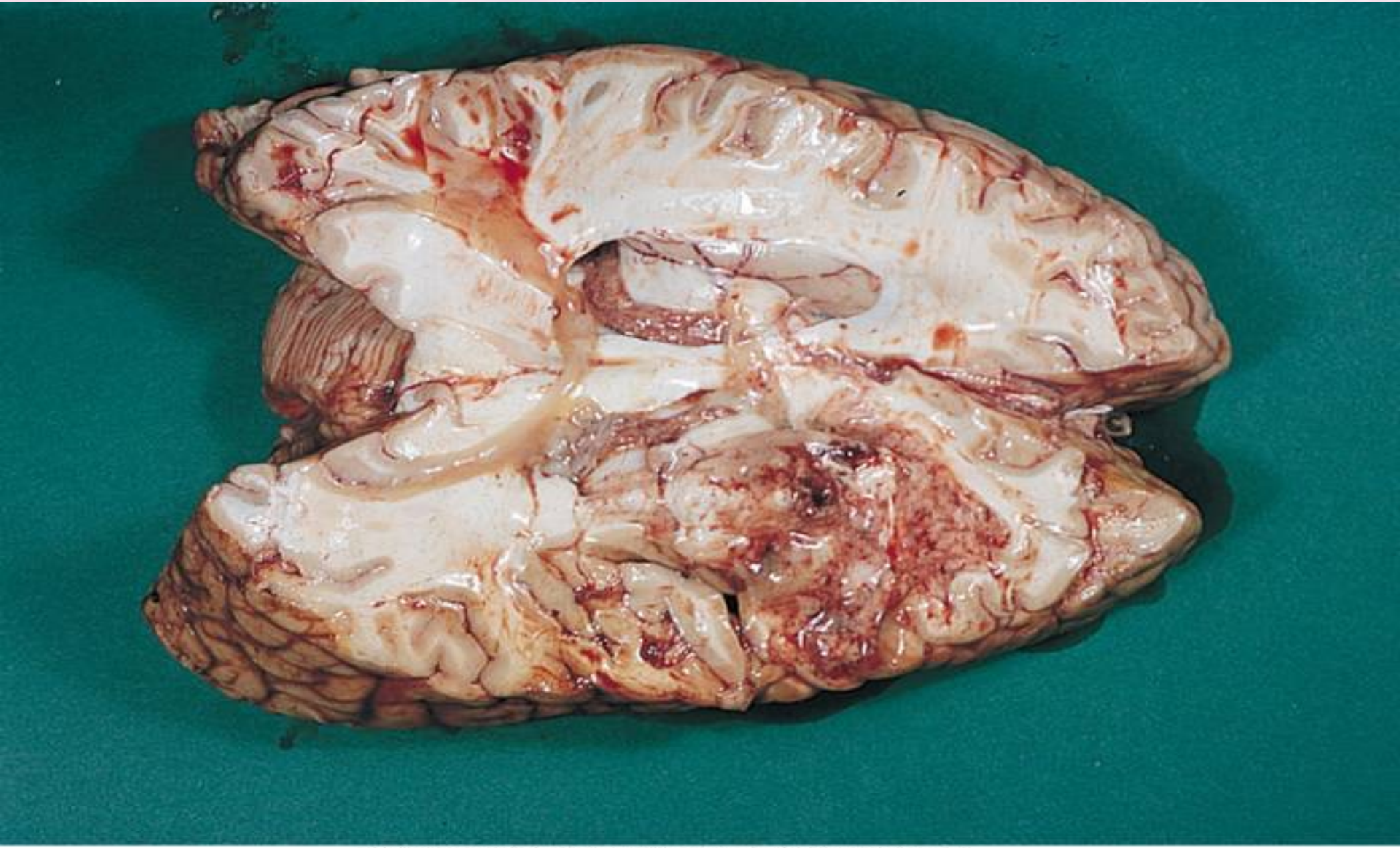
Coagulative Necrosis
Ventriclar Wall - Note Infarctions



Necrosis

- **Liquefactive necrosis**
  - Neurons and glial cells of the brain
    - usually from ischemia
  - Hydrolytic enzymes
  - Bacterial infection
    - Staphylococci, streptococci, and *Escherichia coli*

Liquefactive Necrosis



From Damjanov I: *Pathology for the health professions*, ed 3, St Louis, 2006, Saunders.

Necrosis

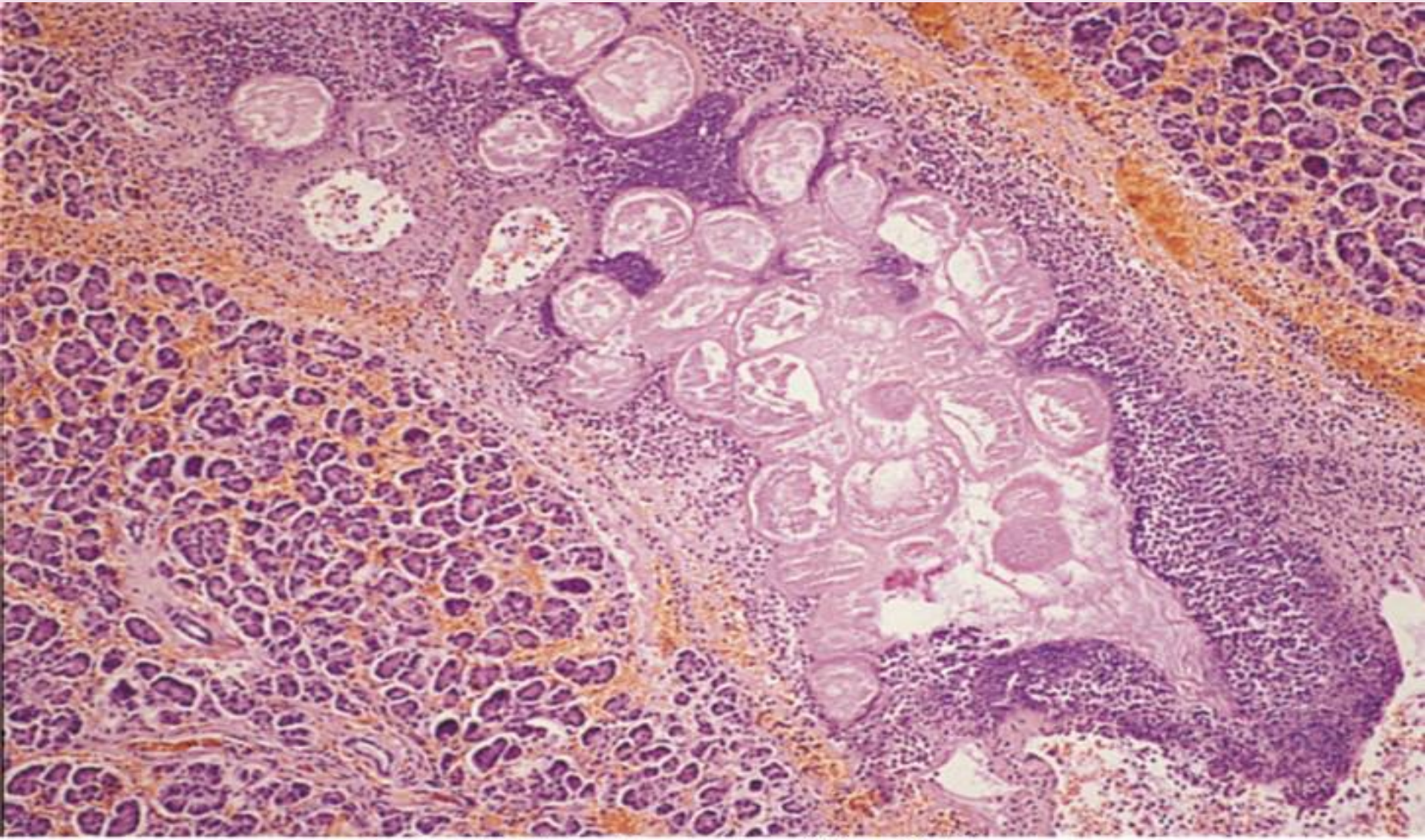
- **Caseous necrosis**
  - Tuberculous pulmonary infection
  - Combination of coagulative and liquefactive necrosis
  - The dead cells disintegrate but the debris is not completely destroyed leaving granular cheesy clumps behind

Caseous Necrosis

Necrosis

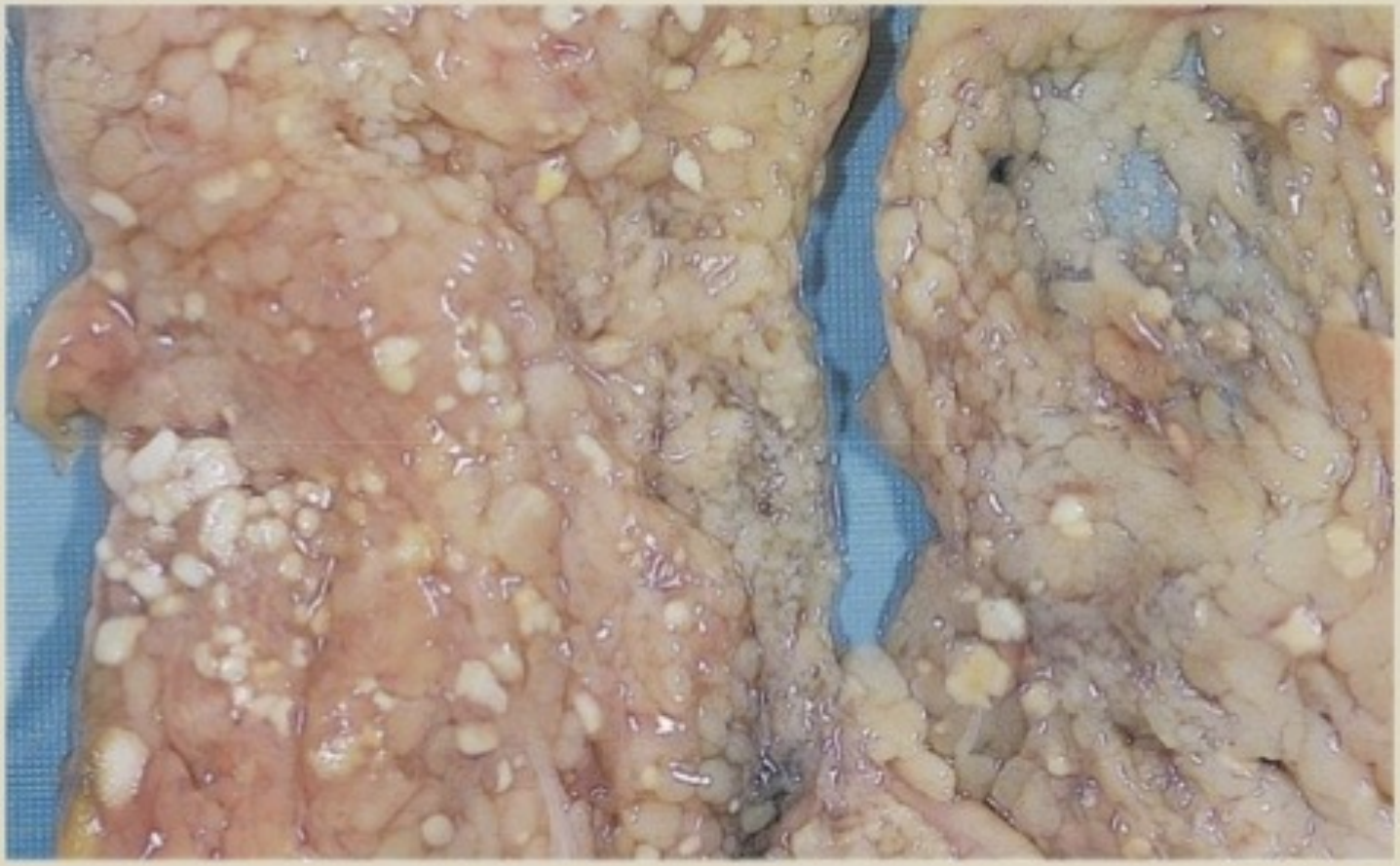
- **Fat necrosis**
  - Breast, pancreas, and other abdominal organs
  - Action of very powerful lipases which break down triglycerides and releases fatty acids which combine with calcium, magnesium and sodium and creates soaps (Saponification)

Fat Necrosis



From Damjanov I, Linder J, editors: *Anderson's pathology*, ed 10, St Louis, 1996, Mosby.

FAT NECROSIS



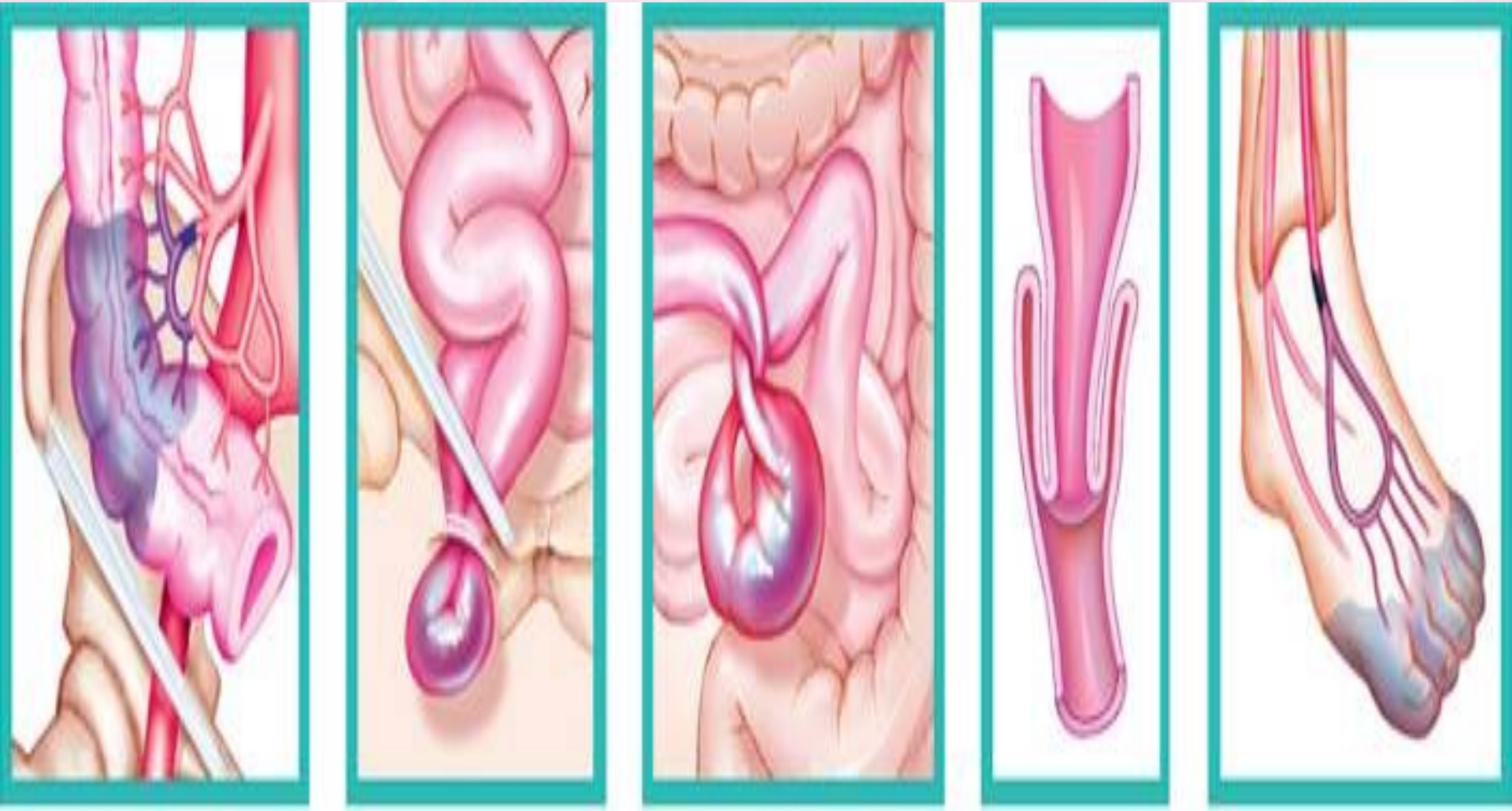
Fat necrosis in acute pancreatitis.
The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.

www.facebook.com/drvesdental

Necrosis

- **Gangrenous necrosis**
  - Characterized by noxious products of anaerobic bacterial metabolism
  - Death of tissue from severe hypoxic injury
    - **Putrefaction-** tissue damage due to reduced blood flow
  - Dry vs. wet gangrene
    - Dry is a result of coagulative necrosis and skin is dry and wrinkled
    - Wet is when massive neutrophils invade the site causing liquefactive necrosis
  - Gas gangrene
    - Clostridium

Gangrenous Necrosis



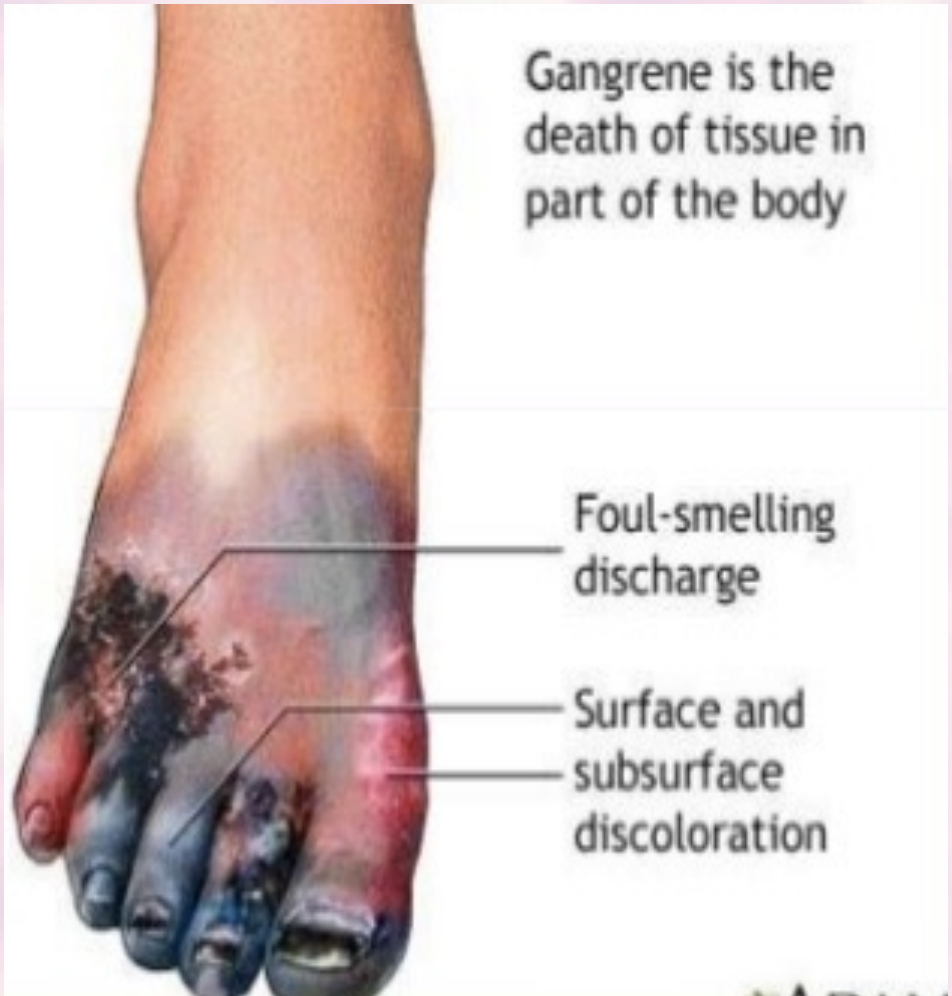
Review of Types of Necrosis

- Coagulative - think “coagulate”
  - Albumin change causes coagulation
  - Kidneys, heart, adrenals
- Liquefactive - think “liquid”
  - Usually in brain
- Caseous - think “cheesy”
  - Usually in lungs as with TB
- Fat - think “soapy” (saponification)
  - Usually in breast, pancreas and abdominal organs
- Gangrenous - think “hypoxic” tissues

Types of Gangrene
Dry vs. Wet

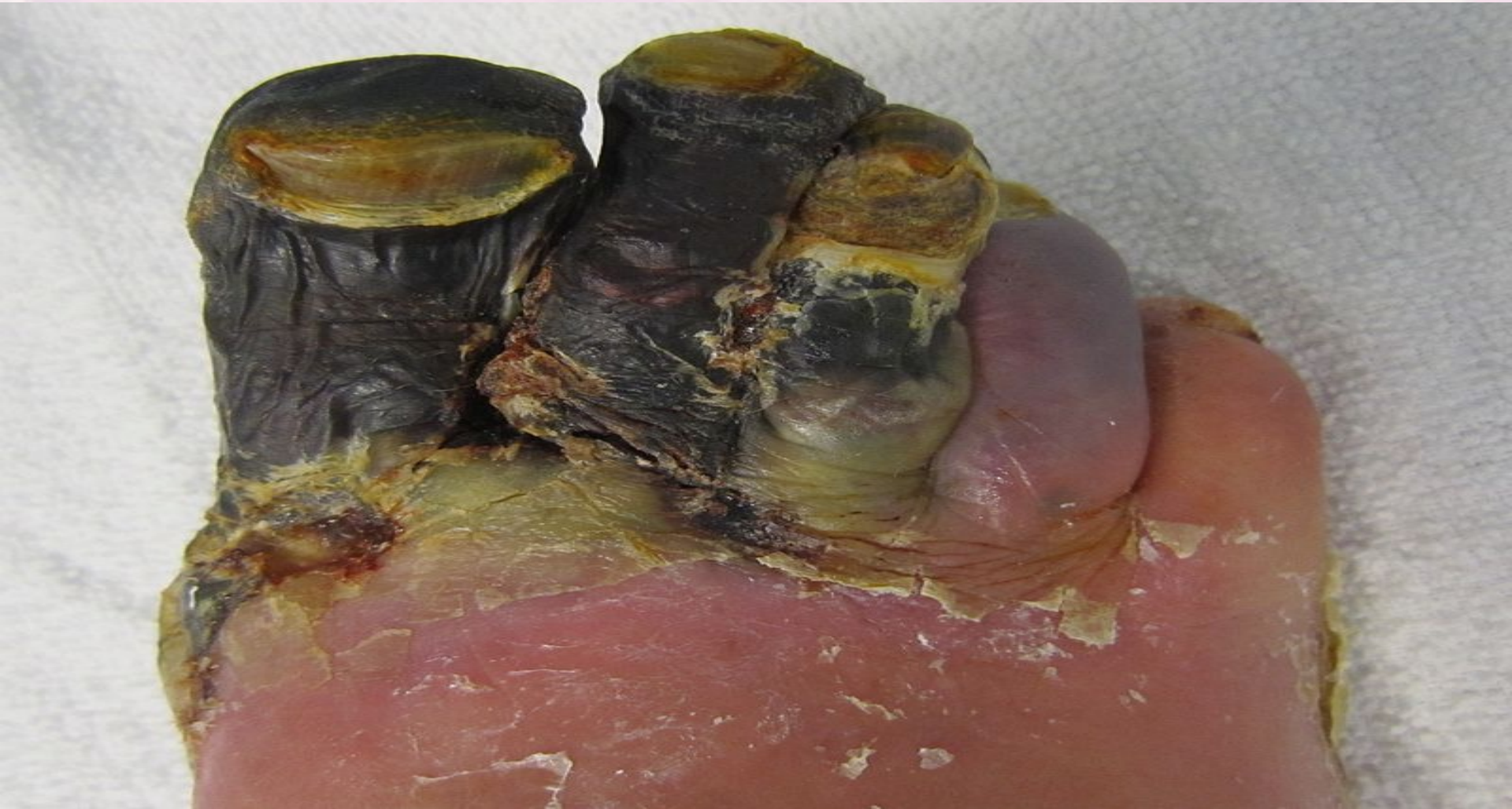
Dry Gangrene - the tissue is dying but there is no infection. Commonly seen in patients with vascular disease and in diabetics.

Wet Gangrene - the tissue is infected and wet and oozing pus and fluids



Diabetic Gangrene

Mr. Deeds Foot



Permanent Effects of Cellular Injury

- **Calcification-** may occur in necrotic cells/tissues
  - Calcium deposits form in mitochondria→ death
  - **Dystrophic Calcification** - deposits start small and grow which lead to stiff, brittle cells/tissues
  - **Metastatic Calcification**
    - May occur in normal cells (not JUST necrotic cells)
    - Deposition happens because of **hypercalcemia** in the body

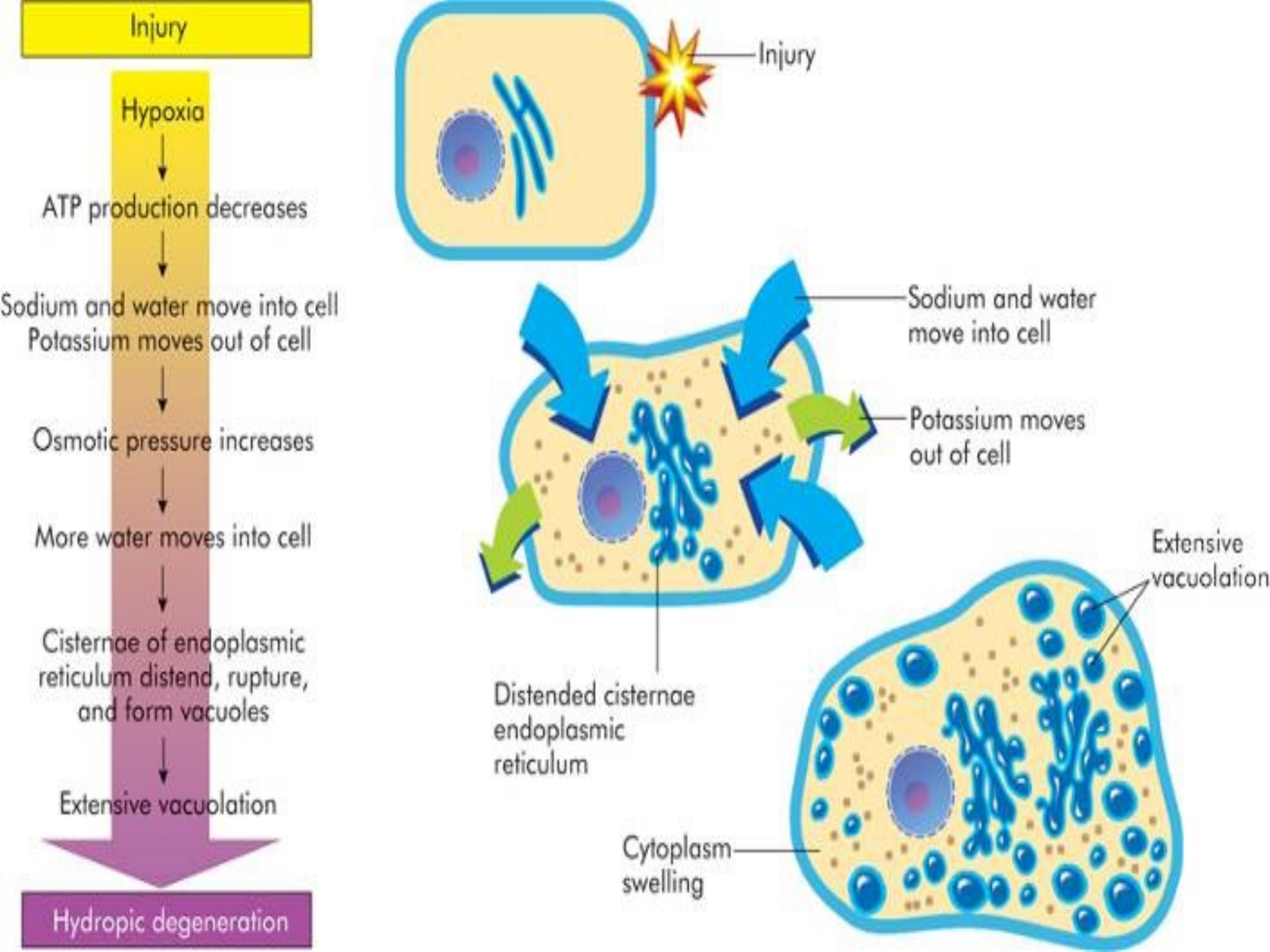
Vulnerability to Injury

- Tissues differ in vulnerability to injury depending on:
  - **Ischemia-** Loss of blood flow (oxygen) to a tissue/organ (e.g. stroke)
    - Some tissues/organs may tolerate ischemia for a period of time better than others
  - **Intoxication-** different toxins may affect and injure different tissue types
  - **Ionizing Radiation-** DNA highly sensitive
    - Tissues with high mitotic rate affected more
  - **Viral Infection-** each virus has specific target cell
    - Disrupt cell from within

Testing for Cellular Injury in a Patient

- **Functional Loss**
  - Test for a physical and/or biochemical defect(s) in the patient
- **Release of Cell Constituents**
  - Certain cell constituents may be released into the bloodstream by damaged cells/tissues/organs (e.g. ions, enzymes, amino acids)

- **Electrical activity**
  - Any change from normal electrical pattern can be interpreted by tests
    - EEG: brain, ECG: heart, EMG: muscle
- **Biopsy**
  - Direct microscopic examination of a section of tissue believed to be diseased or damaged
  - Look for evidence of any type of injury or tumor

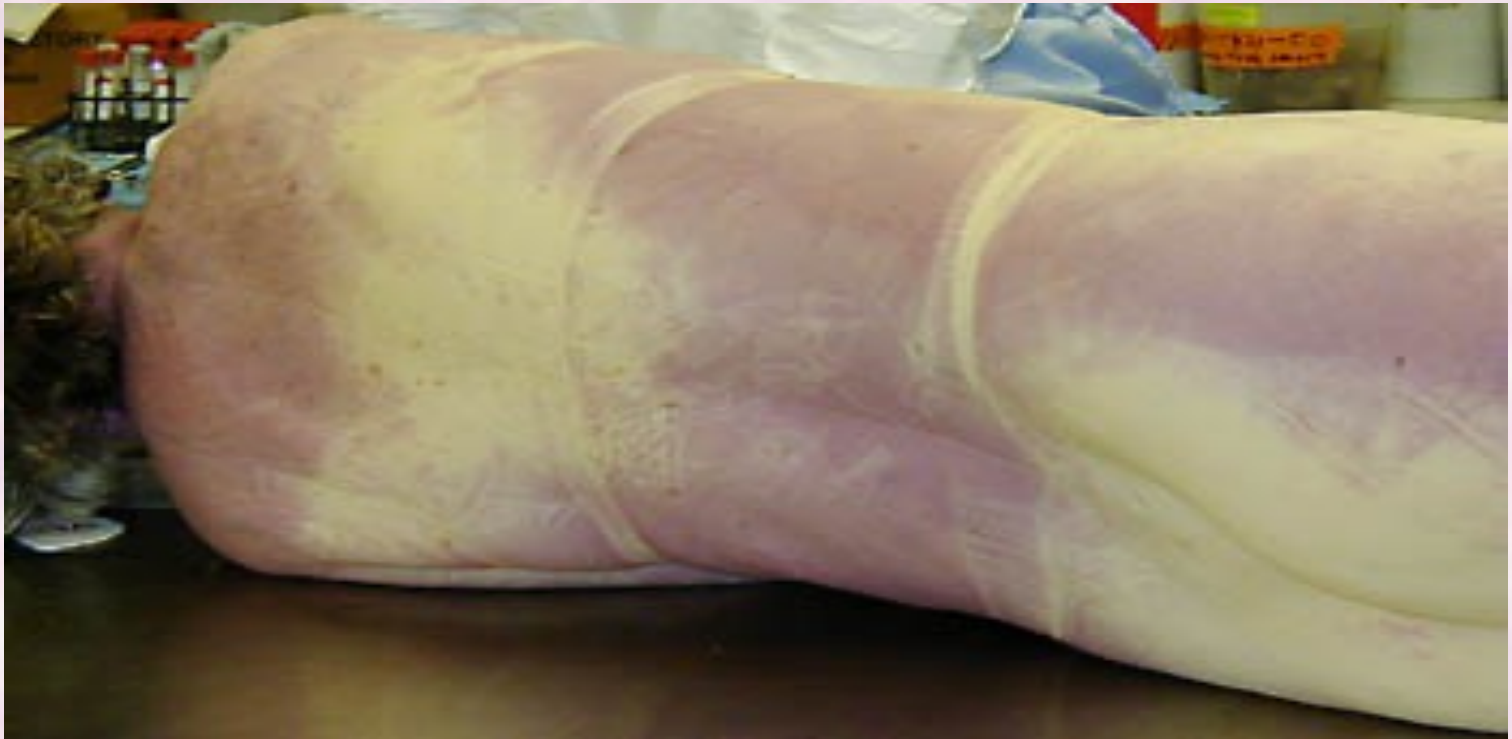

Injury
Hypoxia
ATP production decreases
Sodium and water move into cell
Potassium moves out of cell
Osmotic pressure increases
More water moves into cell
Cisternae of endoplasmic reticulum distend, rupture, and form vacuoles
Extensive vacuolation
Hydropic degeneration
Injury
Sodium and water move into cell
Potassium moves out of cell
Distended cisternae endoplasmic reticulum
Extensive vacuolation
Cytoplasm swelling

Somatic Death

- Death of an entire person is somatic death
- **Postmortem changes**
  - Algor mortis – lowered temperature
  - Livor mortis – gravity causes blood to pool in the lowest areas = purple
  - Rigor mortis – muscle stiffening
  - Postmortem autolysis – swelling and bloating of entire body with liquefactive changes

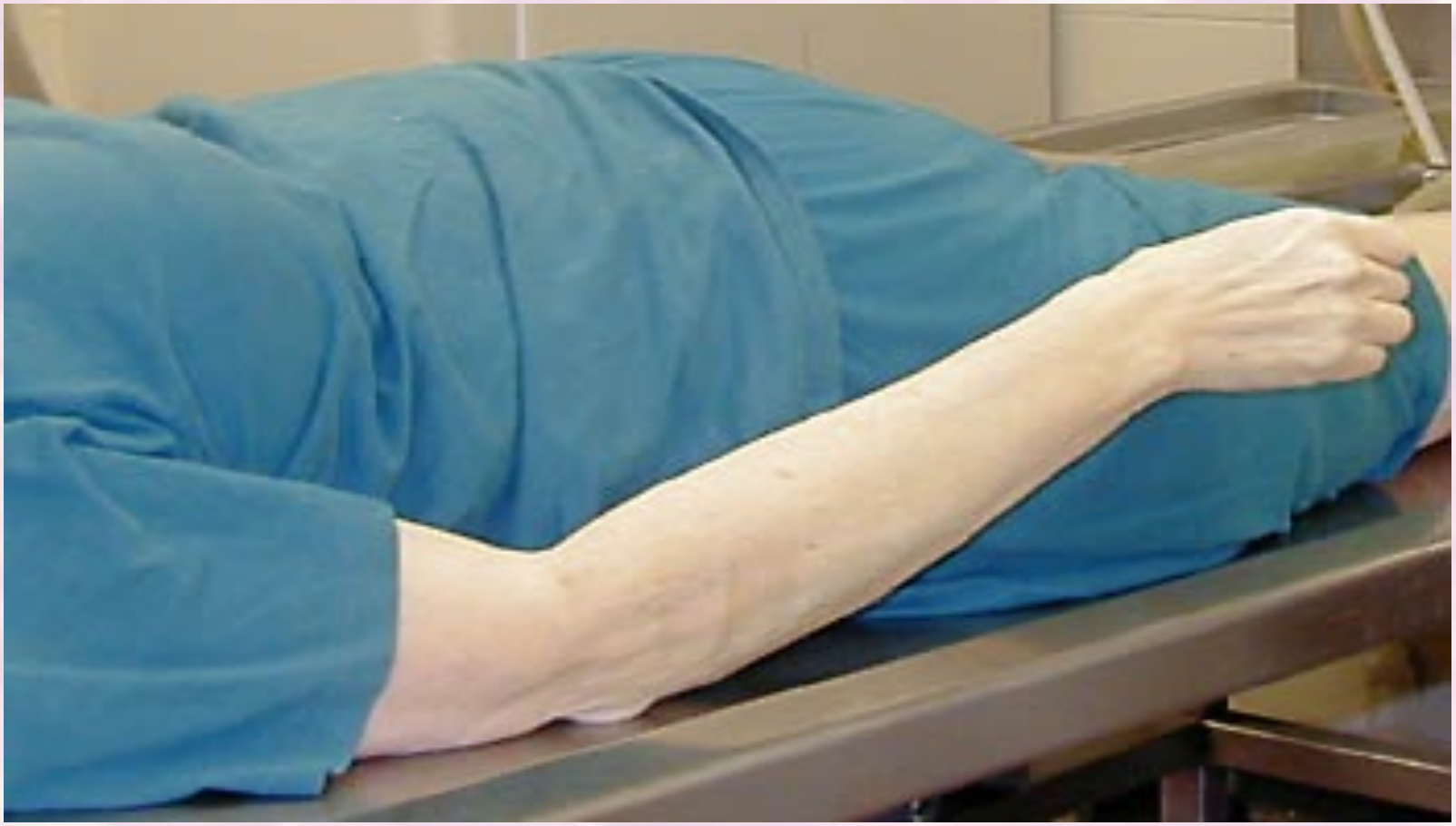
Livor Mortis – also Hypostasis

Discoloration of the skin due to the pooling of blood in the dependent parts of the body following death. The blood pools because the heart can no longer circulate the blood. Gravity will make the blood settle and the areas where it settles turns to a dark blue or purple color, which is termed 'lividity'. Occurs within a few hours.



Rigor Mortis

Can start within 10 minutes to a few hours



Rigor Mortis during Finals