The Cellular Basis of Disease
Cell Injury 1

Adaptation and Reversible Injury
Patterns of Tissue Necrosis (Irreversible Injury)

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APPROVED

The Cellular Basis of Disease

Cell Injury 1: Adaptation and Reversible Injury
Patterns of Irreversible Injury (Necrosis)

Cell Injury 2: Mechanisms of Cell Injury

Cell Injury 3: Apoptosis and Necrosis
Cellular Aging

Cell Injury 4A: Sub lethal Cell Injury

John Shelburne MD PhD

Cell Injury 4B: Intracellular accumulations

Objectives

- **Understand the cellular response to injury and stress.**
- **Understand the differences between hyperplasia, hypertrophy, atrophy and metaplasia at the cellular and organ level.**
- **List and understand the causes of cell injury and death including oxygen deprivation; physical and chemical agents including drugs; infections and immunologic reactions; genetic derangements and nutritional imbalances**
- **Discriminate cell adaptation, reversible cell injury and irreversible cell injury (cell death) based on etiology, pathogenesis and histological and ultrastructural appearance.**
- **Define and understand the morphologic patterns of lethal cell injury and the clinical settings in which they occur.**

Cellular Adaptation to Injury or Stress

Injury or Stress

- Increased demand
- Decreased stimulation or nutrients
- Chronic irritation

Adaptation

- Hyperplasia or hypertrophy
- Atrophy
- Metaplasia

increase in cell number

increase in size

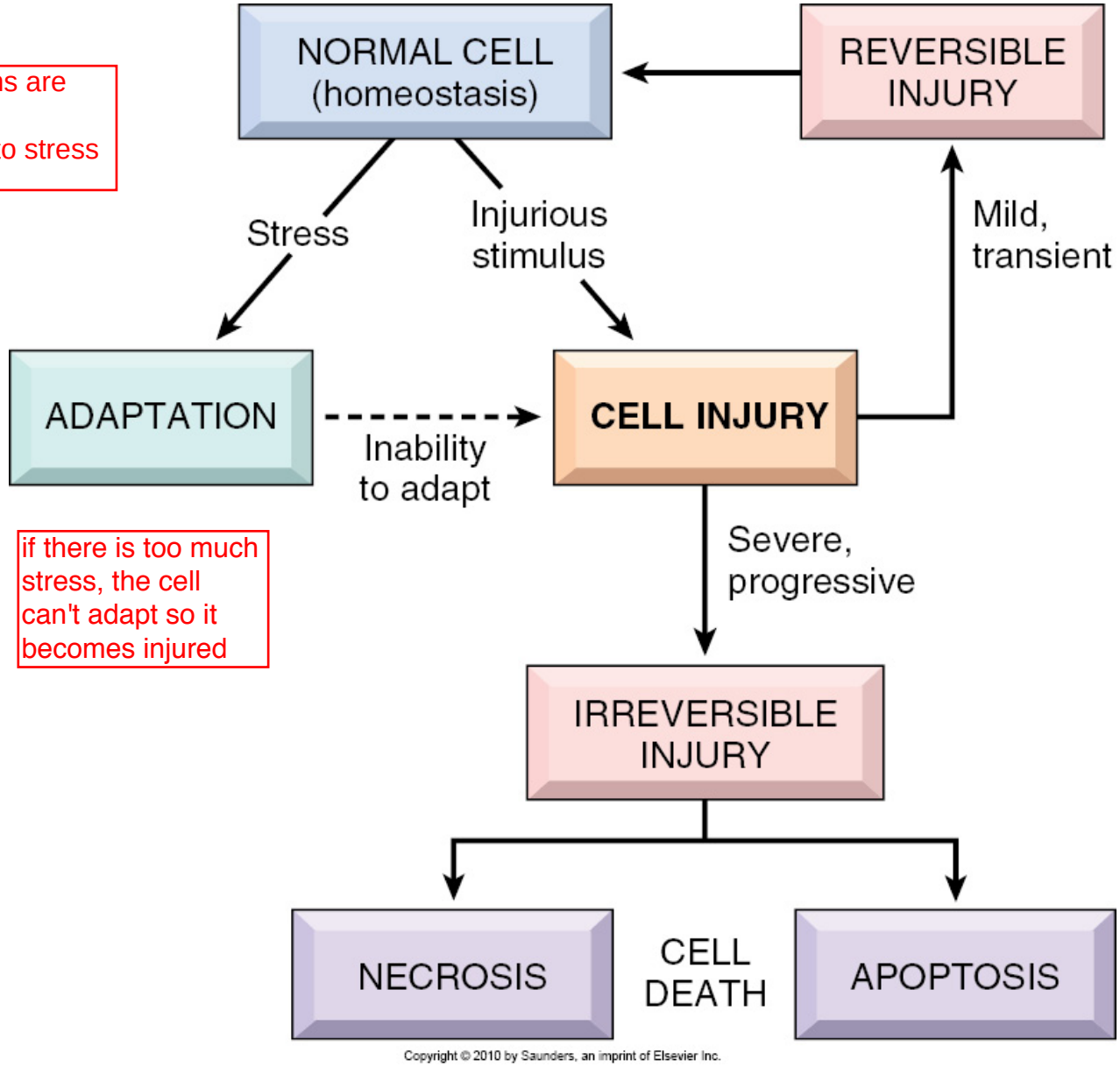
replacement of one cell type with another

This process is important for neoplastic transformation (abnormal growth)

abnormal growth

CELLULAR RESPONSE TO STRESS

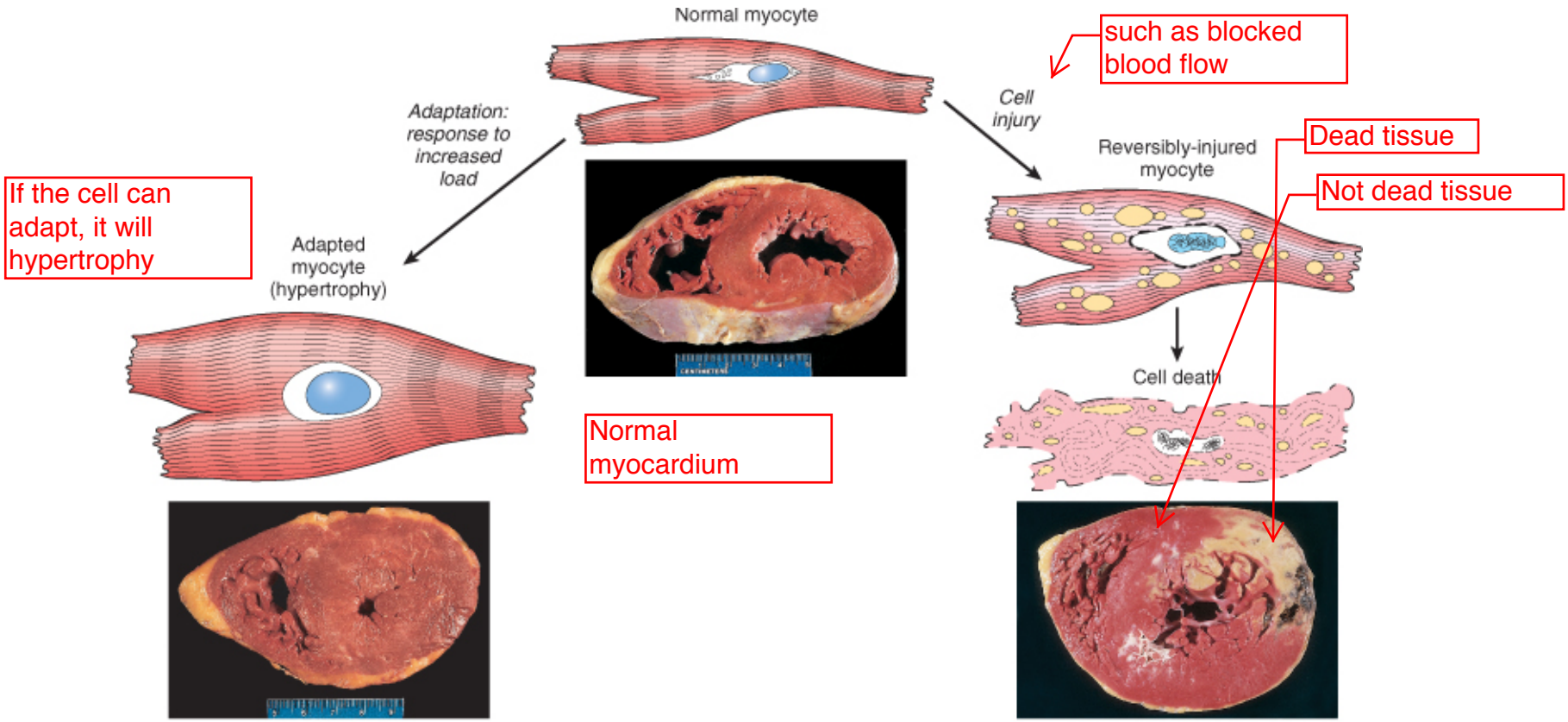
Adaptations are reversible reponses to stress



if there is too much stress, the cell can't adapt so it becomes injured

Adapted - Normal - Injured Cells

Cardiac



Adaptations

- **Hypertrophy**
- Hyperplasia
- Atrophy
- Metaplasia

Hypertrophy

Increase in the size of cells results in increased size of the organ

May be Physiologic or Pathologic

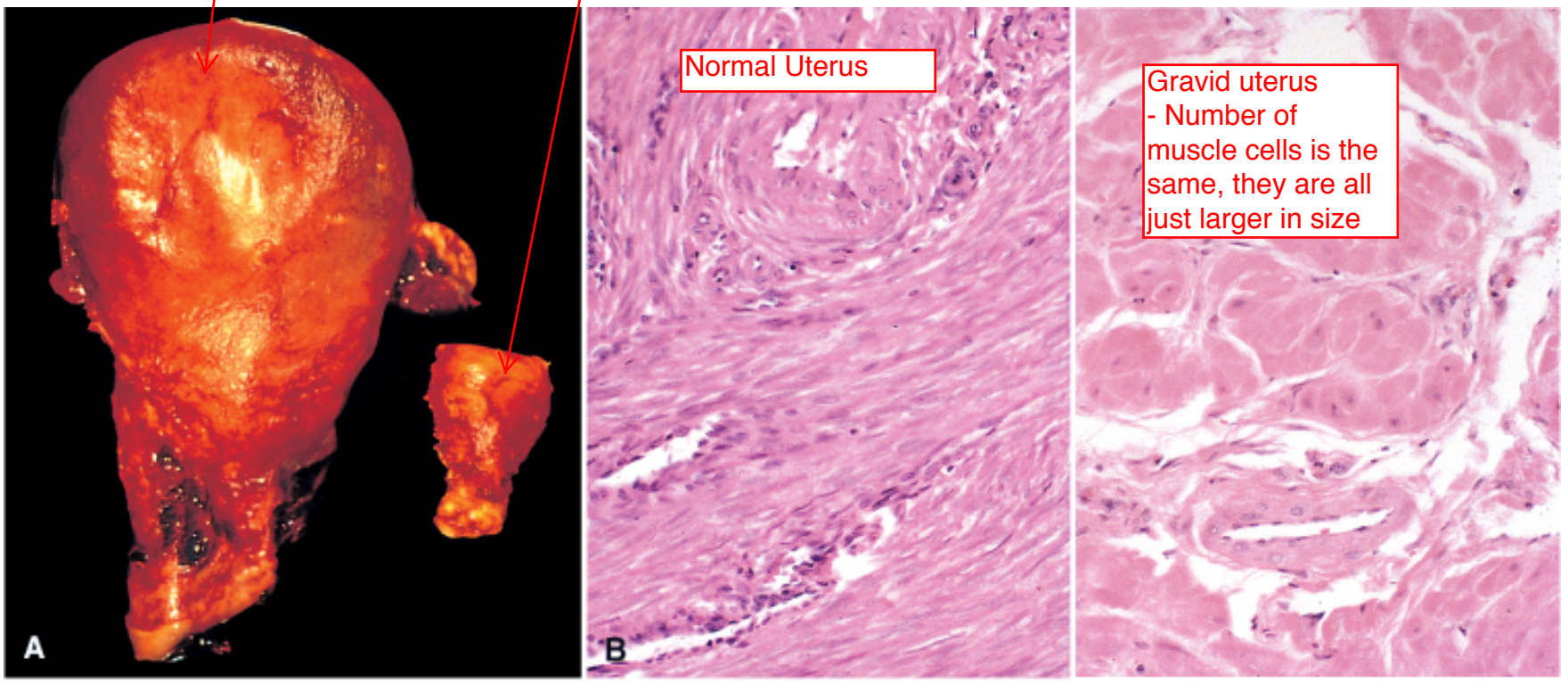
Examples of Physiologic Hypertrophy

Increased workload - skeletal muscle

cardiac muscle

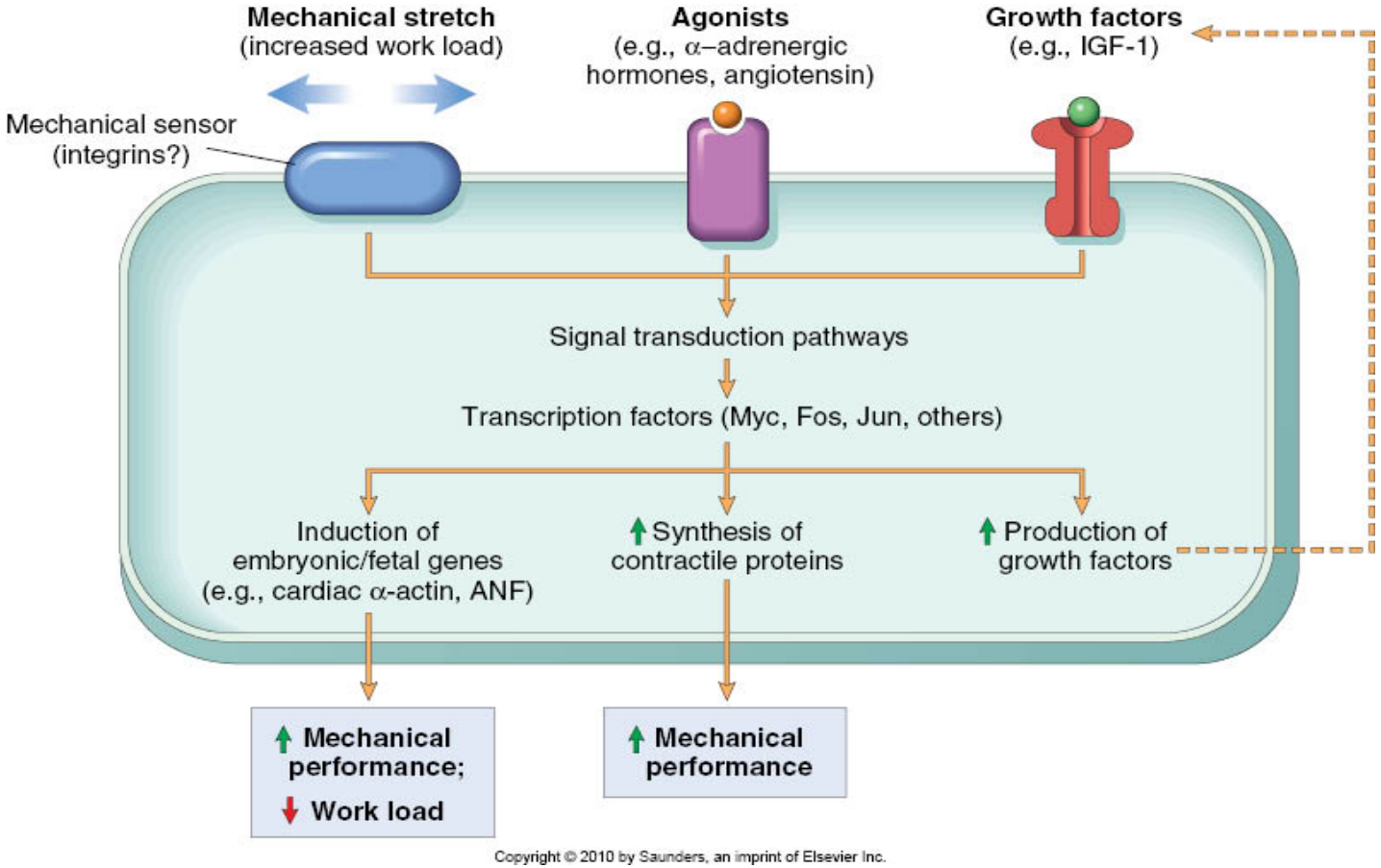
Hormone induced –pregnant uterus

Physiologic hypertrophy Gravid uterus and Normal uterus



How physiological hypertrophy happens

Biochemical Mechanisms of Myocardial Hypertrophy



Adaptations

- Hypertrophy
- **Hyperplasia**
- Atrophy
- Metaplasia

Hyperplasia

vs hypertrophy where the cells just get bigger; both will result in overall bigger organs

Increase in the number of cells results in increase in size of the organ.

May be Physiologic or Pathologic.

Physiologic Hyperplasia

- **Hormonal hyperplasia**
  - **Female breast; puberty and pregnancy**
- **Compensatory hyperplasia**
  - **Prometheus**
  - **Unilateral nephrectomy** if you lose a kidney for whatever reason, your other one will undergo hyperplasia
  - **Erythroid hyperplasia of bone marrow in chronic hypoxia (mountain climbers).**

Pathologic Hyperplasia

- **Excessive hormone stimulation**
  - **Endometrial hyperplasia** common during menopause
  - **Prostatic hyperplasia**
- **Viral infections**
  - **Papilloma virus (warts)**

Adaptations

- Hypertrophy
- Hyperplasia
- **Atrophy**
- Metaplasia

Atrophy

- **Reduced size of an organ due to a decrease in cell size and number.**
- **Physiologic atrophy – notochord, post partum uterus**
- **Pathologic atrophy – local or generalized**

Causes and Examples of Atrophy

- Decreased workload (disuse atrophy)
- Loss of innervation (denervation atrophy)
- Diminished blood supply (ischemia)
- Inadequate nutrition (marasmus, cachexia)
- Loss of endocrine stimulation (menopause)
- Aging (senile atrophy)
- Pressure (enlarging benign tumor)

very severe peripheral atherosclerosis can cause legs to get smaller

protein malnutrition

terminal stages in many kinds of cancer

old people shrink

Mechanisms of Atrophy

- Decreased protein synthesis
- Increased protein degradation
- Ubiquitin-proteasome pathway- degrades cytosolic and nuclear proteins
- Autophagic vacuoles
- Lipofuscin granules
- Brown atrophy

These two normally occur together

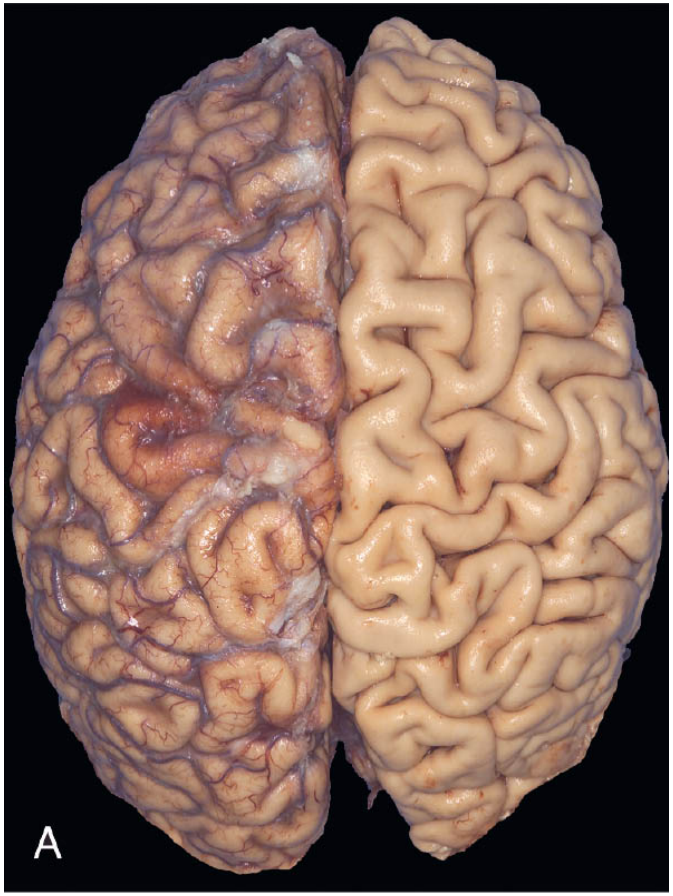
These vacuoles contain the remnants of the degraded proteins. The remnants coalesce to form the lipfuscin granules

Lipofuscin is the name given to finely granular yellow-brown pigment granules[1] composed of lipid-containing residues of lysosomal digestion. It is considered one of the aging or "wear and tear" pigments, found in the liver, kidney, heart muscle, adrenals, nerve cells, and ganglion cells. It is specifically arranged around the nucleus, and is a type of Lipochrome.

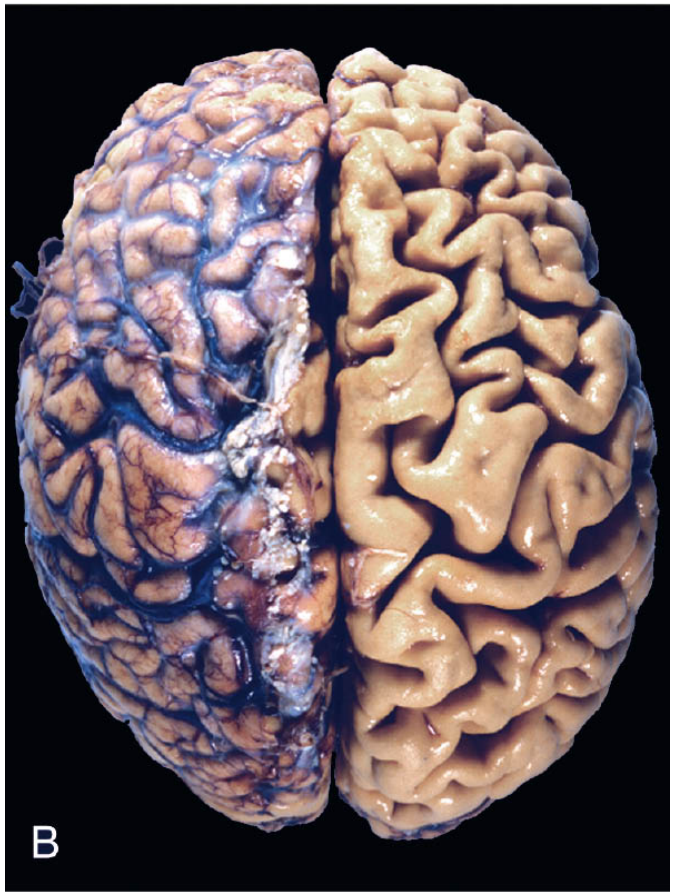
When the above three happen to a whole organ we call it Brown atrophy

You do get normal physiological atrophy as you age but compare to alzheimer patient with increased atrophy

Normal



Atrophy



Adaptations

- Hypertrophy
- Hyperplasia
- Atrophy
- **Metaplasia**

Metaplasia

Reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type.

Usually occurs in response to stress or chronic irritation.

Causes and Examples of Metaplasia

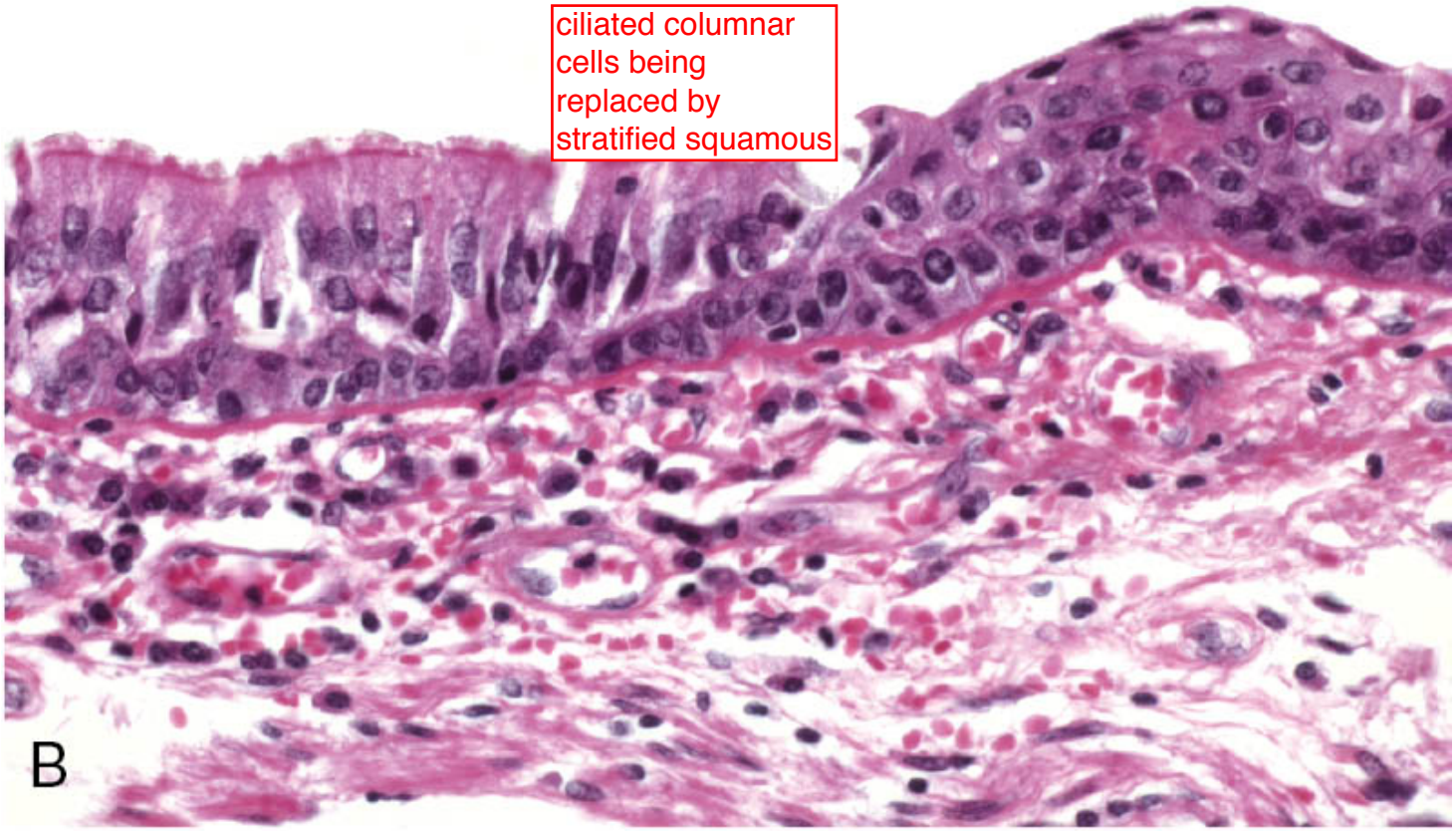
common

fertile ground for lung cancer

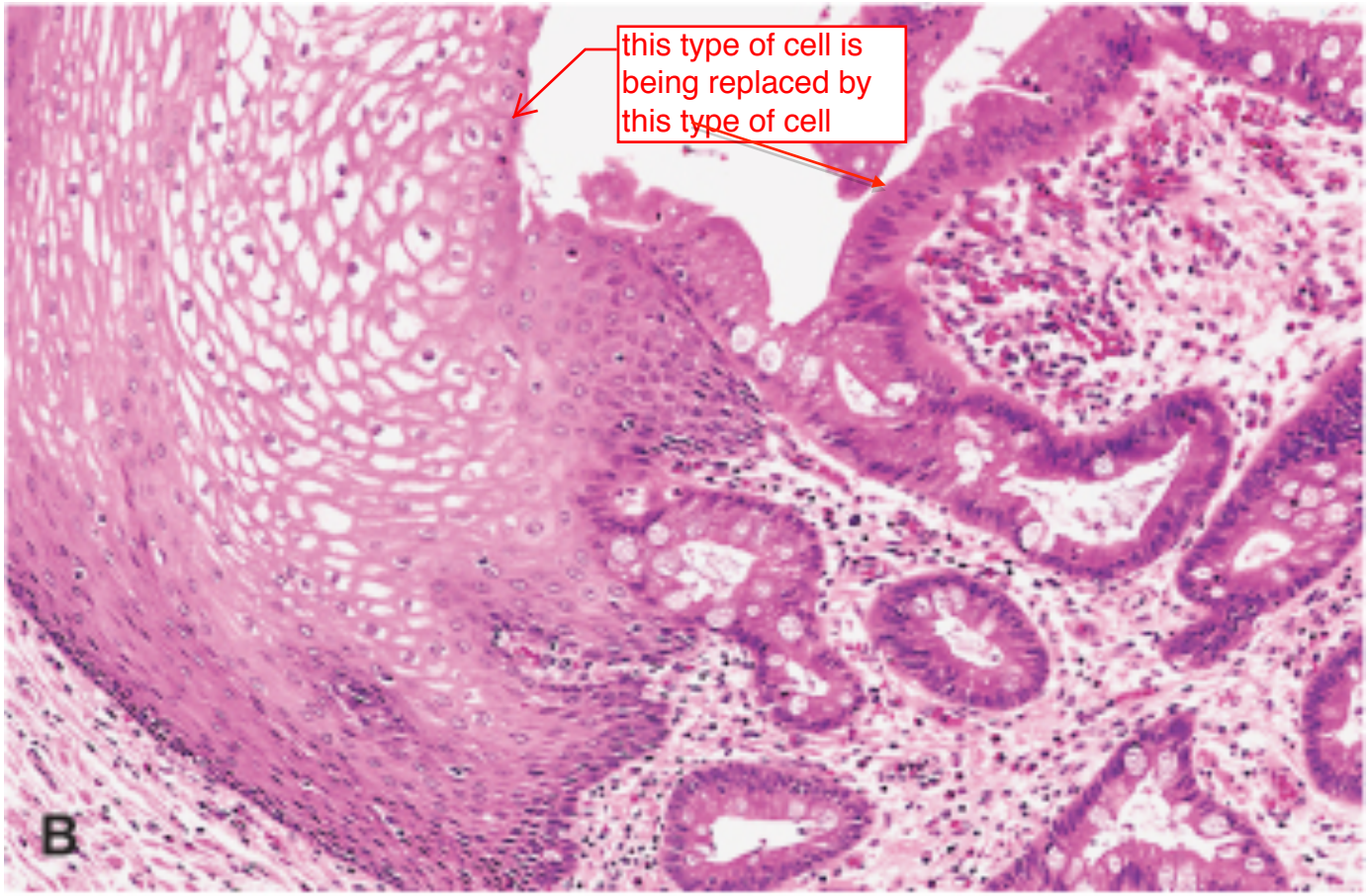
- **Tobacco smoke - Squamous metaplasia in the respiratory tract, most common.**
- **Gastric acid reflux - Gastric metaplasia of distal esophagus; Barrett esophagus.**
- **Repeated skeletal muscle injury with hemorrhage- muscle replaced by bone; myositis ossificans.**

uncommon

Bronchus with Columnar to Squamous Metaplasia



Esophagus with Squamous to Columnar metaplasia



Mechanisms of Metaplasia

- Re-programing of stem cells that exist in normal tissue.
- Induced by cytokines, growth factors and other environmental signals
- Retinoic acid may play a role.
- Exact mechanism is unknown.

Under the influence of cytokines and growth factors, stem cell differentiation can be altered to result in an epithelial cell type other than what normally lines a tissue surface. What is the name of this process?

Cytokines and growth factors change the niche in which the stem cell exists

A. Atrophy

B. Hyperplasia

C. Hypertrophy

D. Metaplasia

E. Neoplasia

cancer

You have been working out and lifting weights. The increase in the size of your skeletal muscles induced by weight lifting is an example of

A. Atrophy

B. Hyperplasia

C. Hypertrophy

D. Metaplasia

E. Neoplasia

Cell Injury and Death

- **Reversible – reduced ATP, cellular swelling**
- **Irreversible – two types of cell death**

  Necrosis – always pathologic

  Apoptosis – may be physiologic or pathologic (Cell Injury 3)

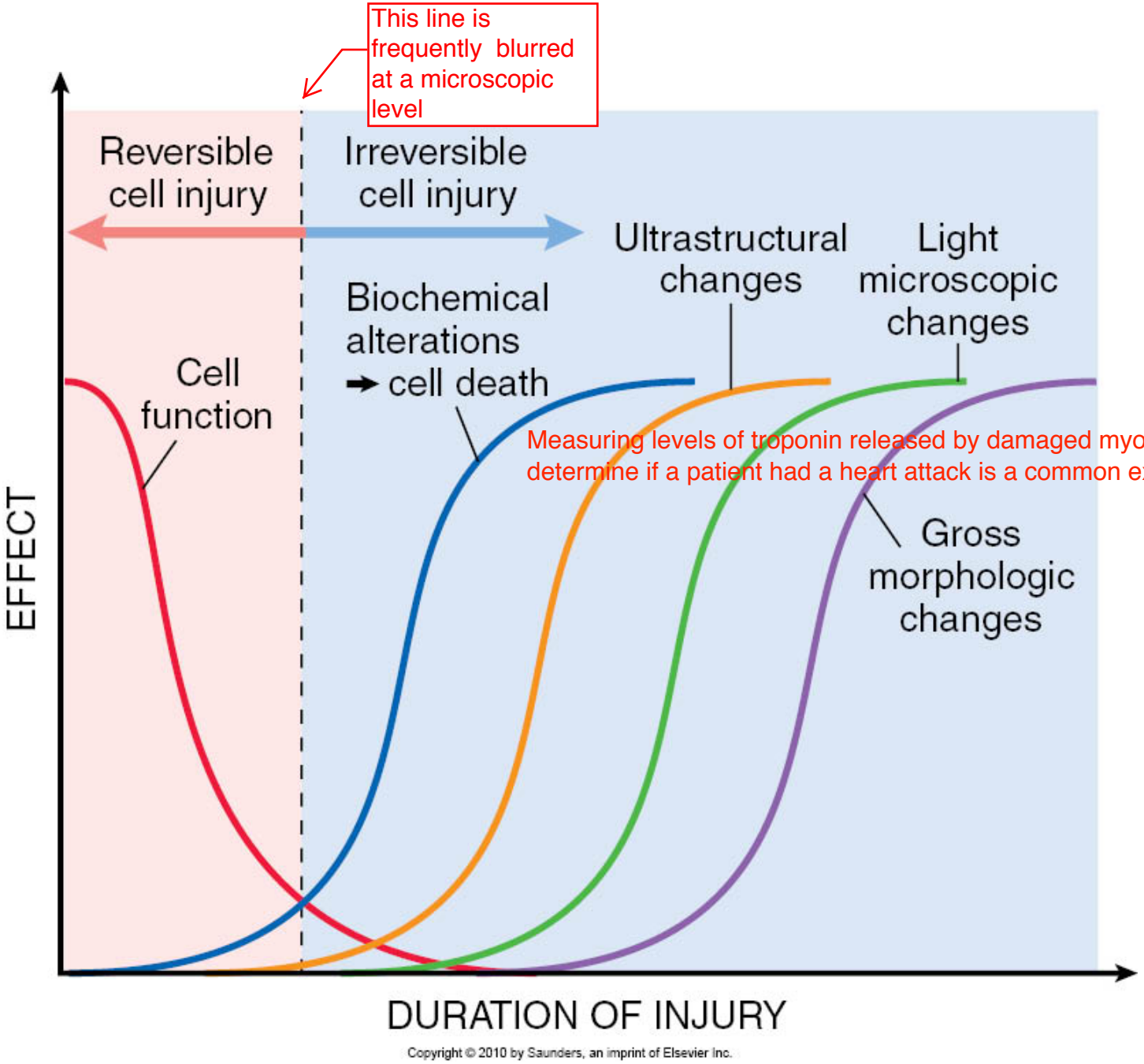
not enough blood

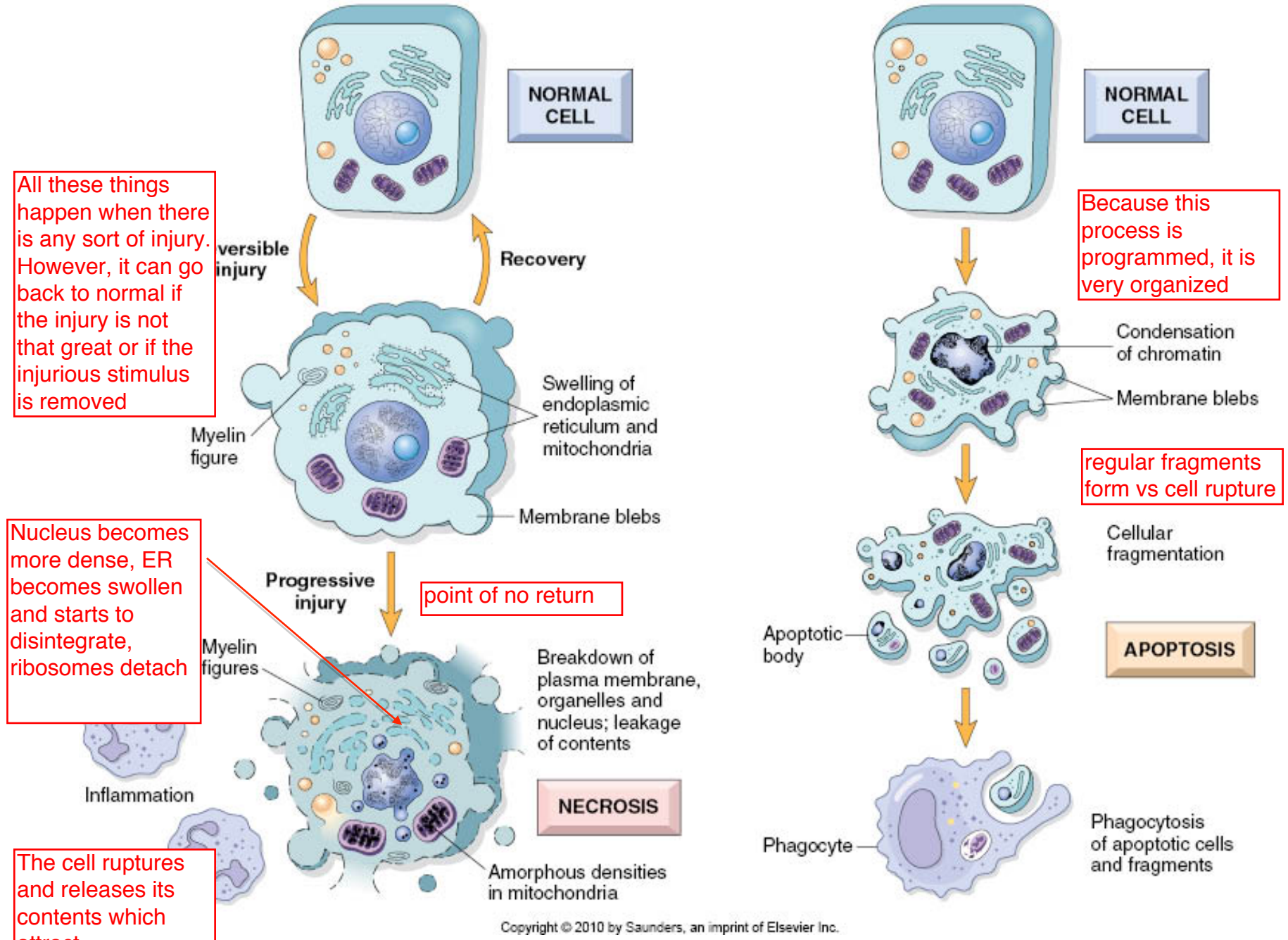
Causes of Cell Injury

- Oxygen deprivation (hypoxia or ischemia)

decreased levels of O2 in blood

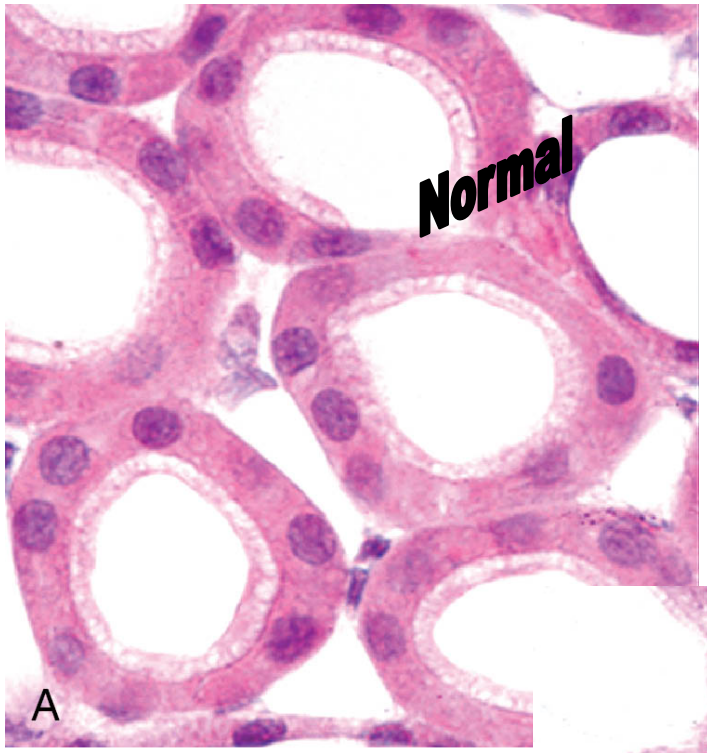
- Physical Agents (trauma)
- Chemical agents and Drugs
- Infectious Agents
- Immunologic Reactions
- Genetic Derangements
- Nutritional Imbalances



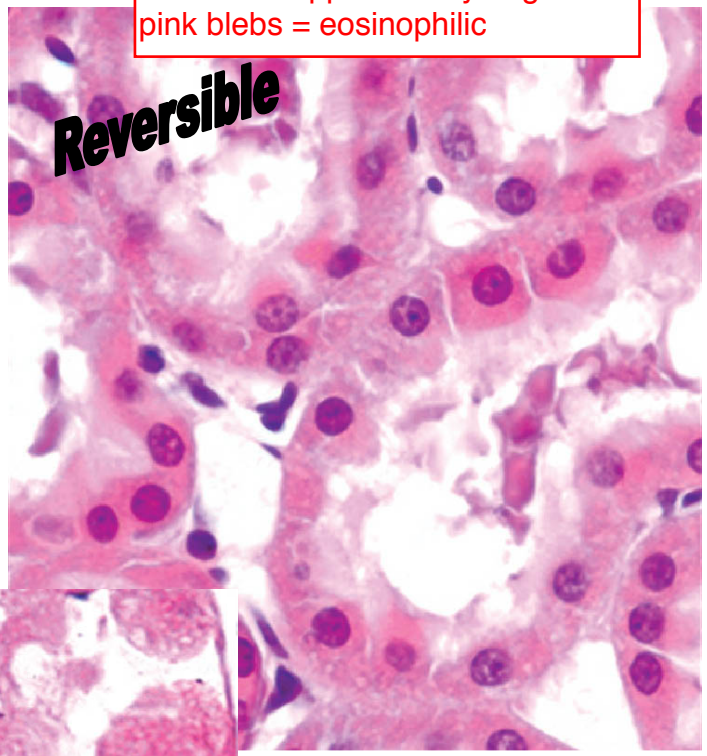


Kidney cells

nucleus starts to shrink, but doesn't disappear and you get the pink blebs = eosinophilic



(Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San A



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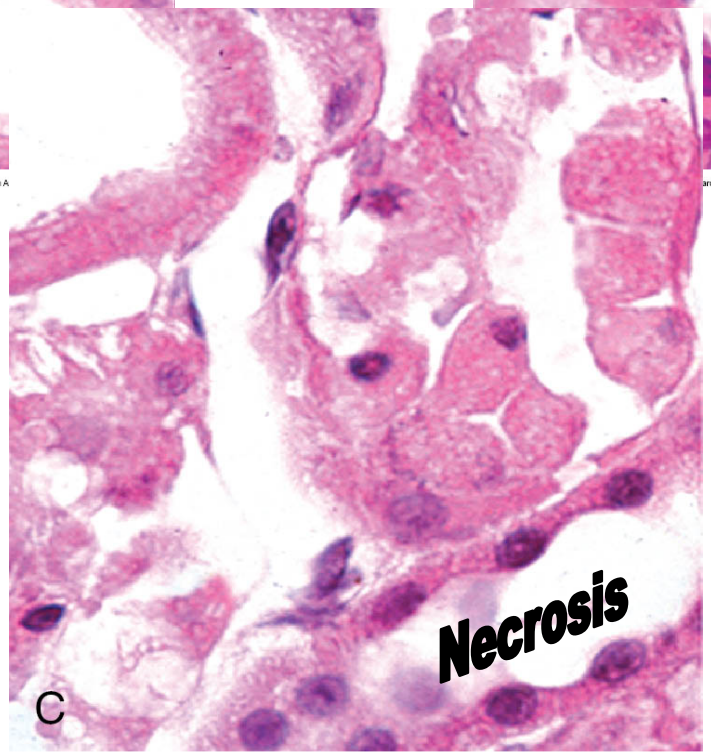


here the nucleus disappears entirely

(Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)

Morphologic Alterations in Reversible Cell Injury

- **Cellular swelling**
- **Fatty change**

really characteristic in the liver

Morphologic Alterations in Irreversible Injury (Necrosis)

all these things occur in various combinations

Cytoplasmic eosinophilia

Karyolysis - nucleus becomes pale and eventually disappears

Pyknosis - nucleus shrinks, chromatin condenses, becomes deeply basophilic

Karyorrhexis – nucleus undergoes fragmentation

Patterns of Tissue Necrosis

Coagulative Necrosis

Liquefactive Necrosis

Fat Necrosis

Caseous Necrosis

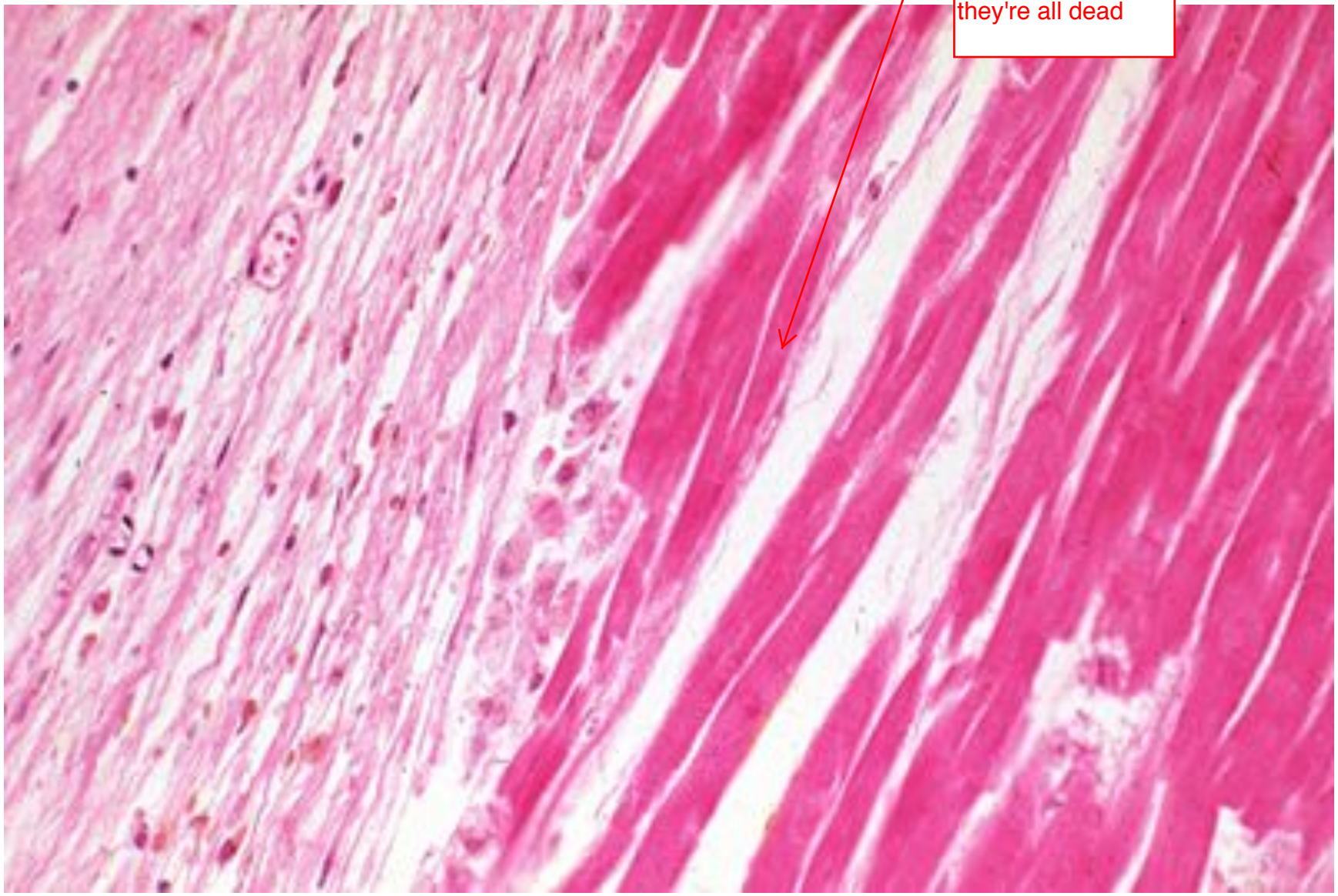
Fibrinoid Necrosis

Coagulative Necrosis

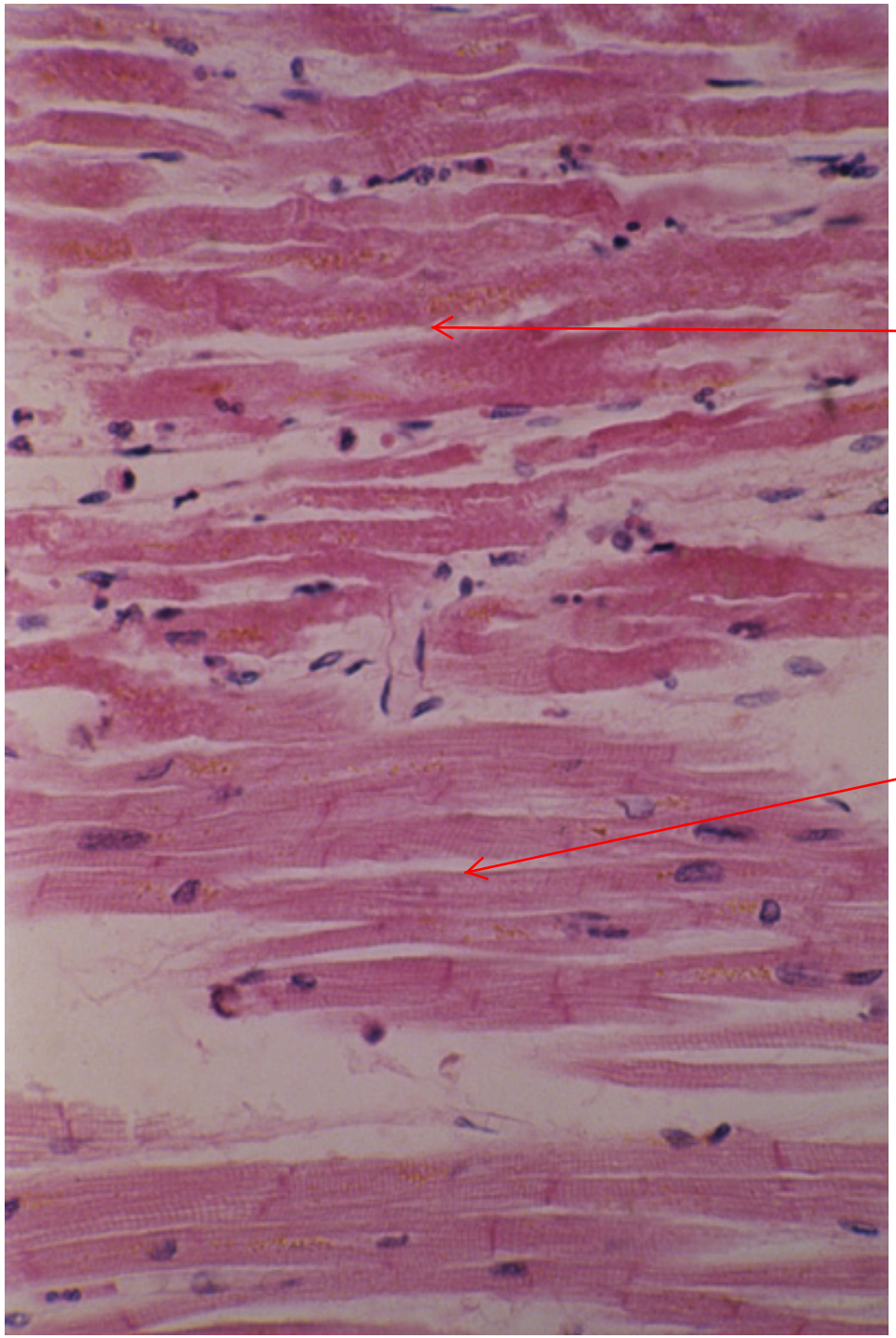
Pattern of cell death characterized by progressive loss of cell structure, with coagulation of cellular constituents and persistence of cellular outlines for a period of time, often until inflammatory cells arrive and degrade the remnants.

coagulative necrosis in the myocarium

myocytes
- you don't see any nuclei because they're all dead



more coagulative necrosis



dead
-notice absence of zbands and nuclei

normal

Coagulative Necrosis

Similar in many respects to autolysis.

Autolysis is self digestion and does not require the participation of inflammatory cells.

common in bodies before autopsy

Autolysis occurs in tissue incubated for a period of time in the absence of blood flow or oxygen (very common in autopsy material).

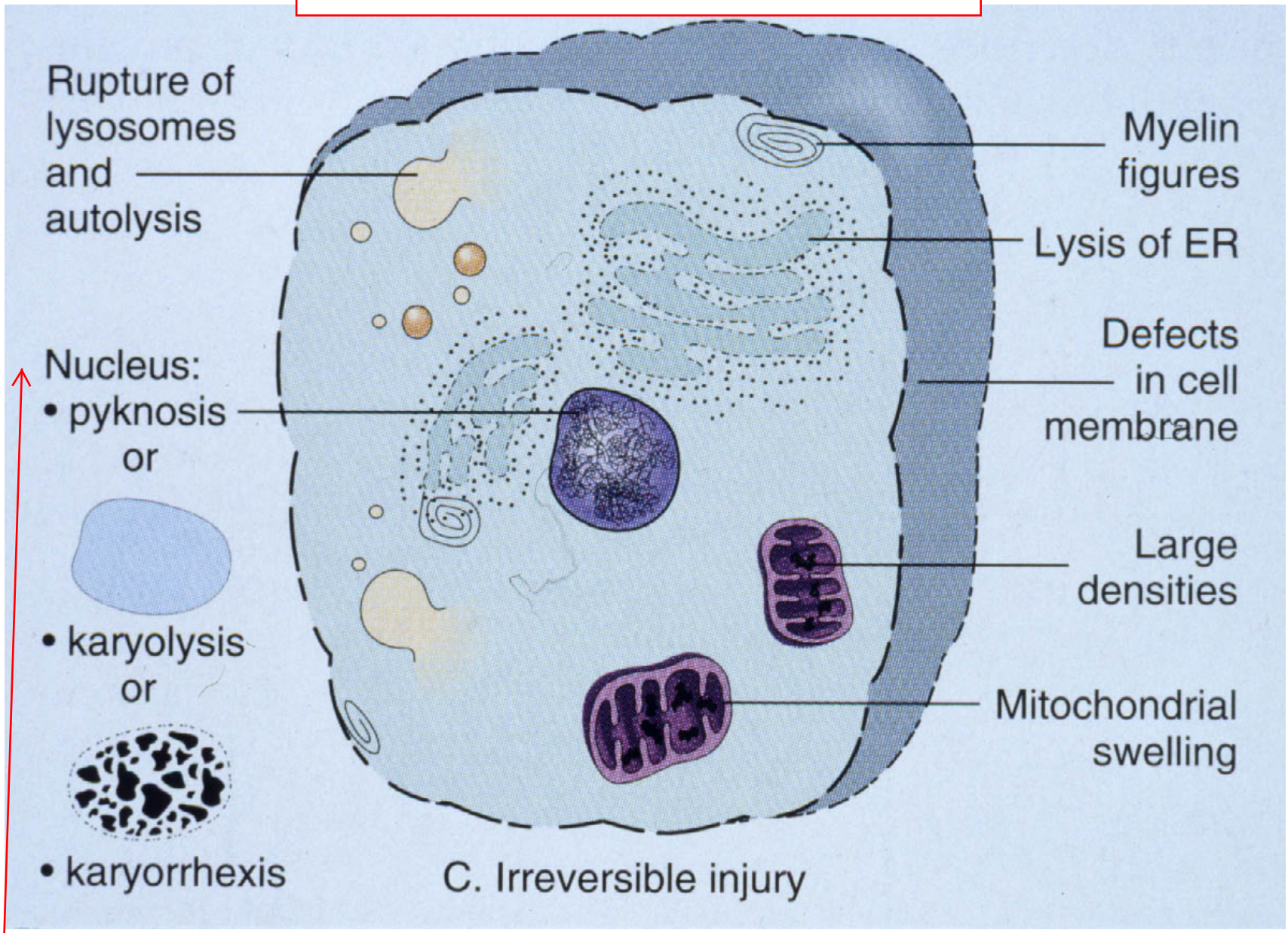
Coagulative Necrosis

Characterized by changes in cytoplasmic staining in routine histology sections and changes in nuclear morphology and/or staining characteristics

Cytoplasm becomes more eosinophilic

Several patterns of nuclear change

These are all signs of irreversible injury



Process is dependant on what the injury is

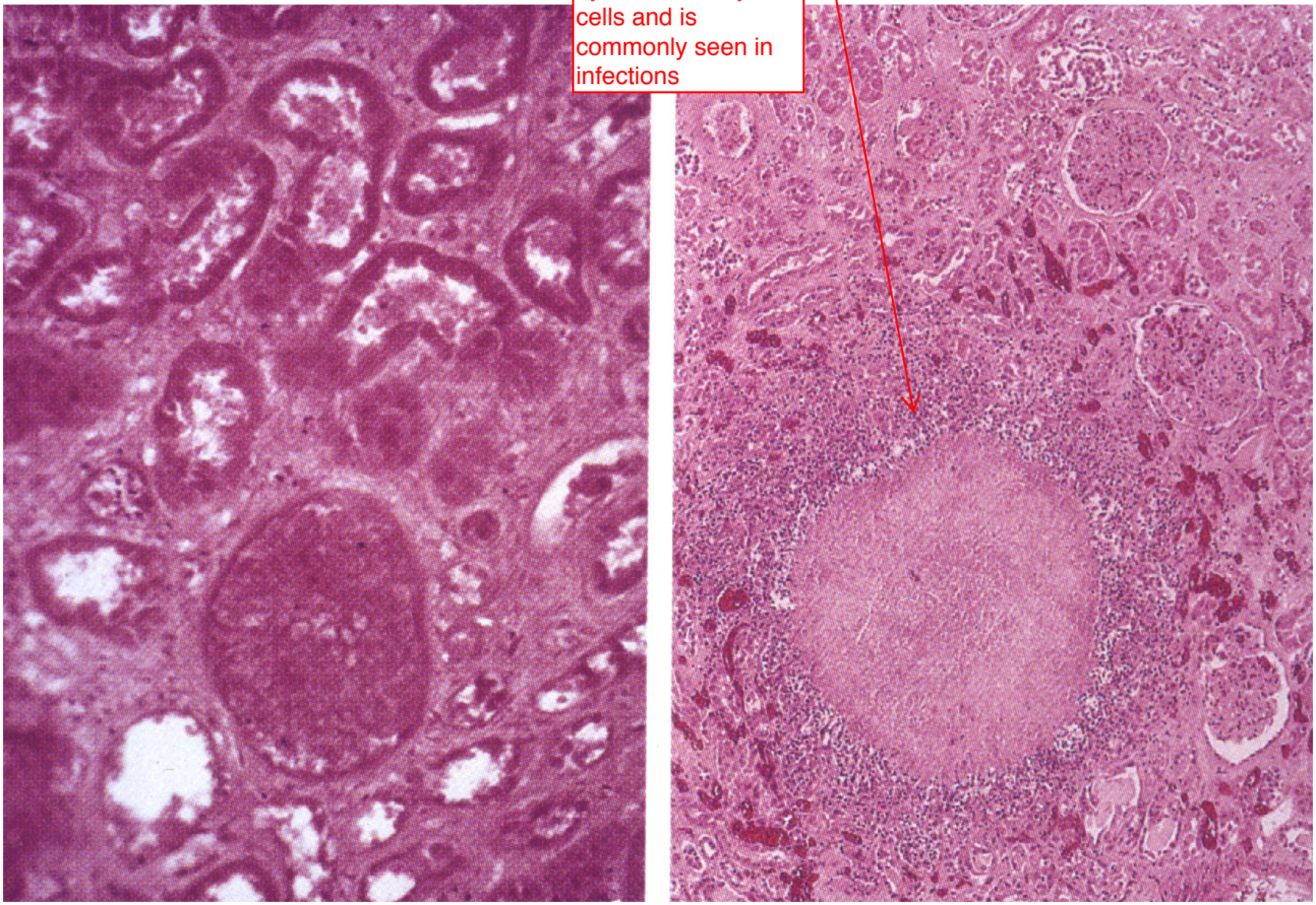
Liquefactive Necrosis

Common in the CNS mostly because there is a lot of lipid in myelin

Pattern of cell death characterized by dissolution of necrotic cells.

Typically seen in an abscess where there are large numbers of neutrophils present, which release hydrolytic enzymes that break down the dead cells so rapidly that pus forms.

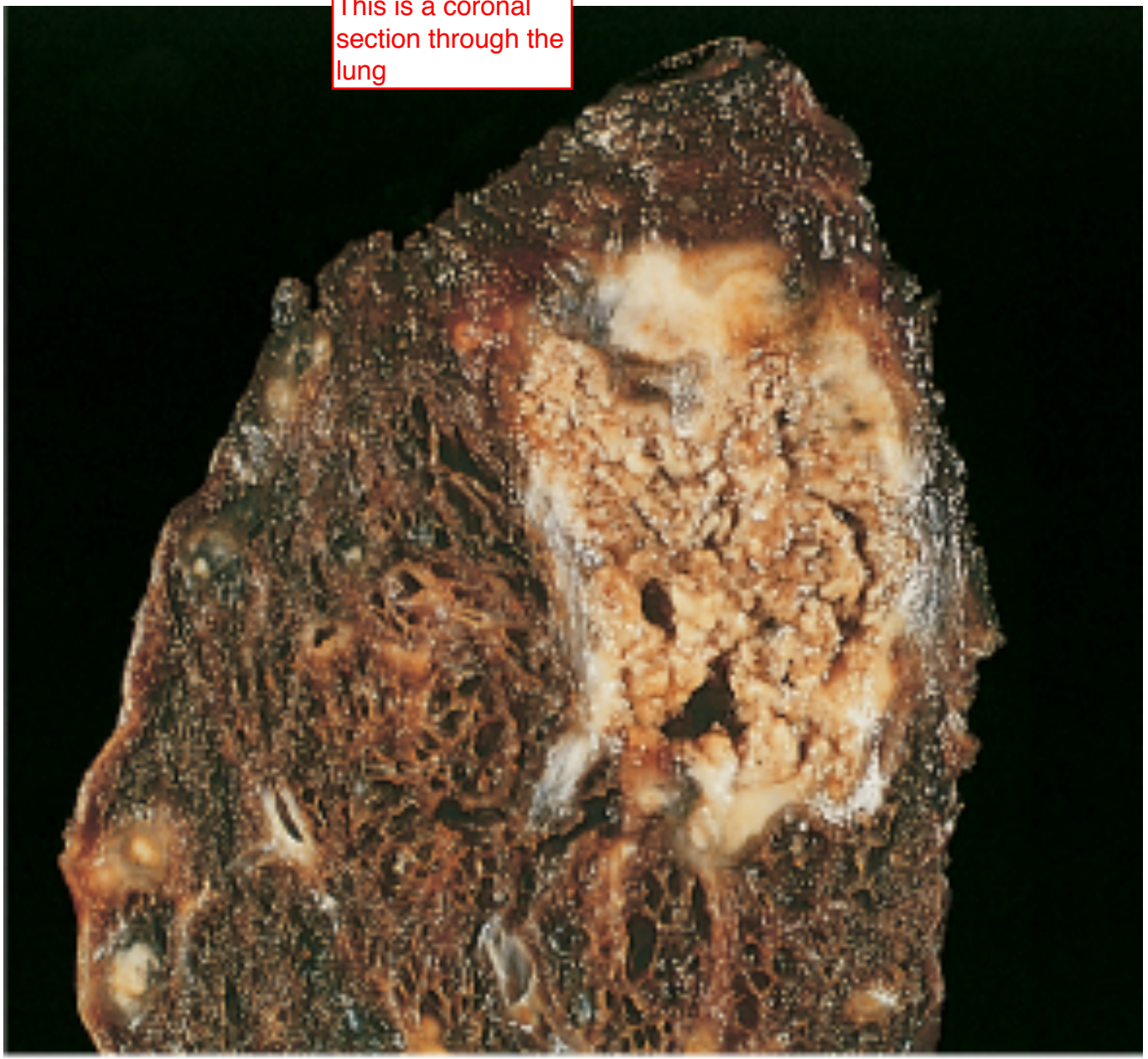
Pus is the liquefied remnants of dead cells, including dead neutrophils.



Coagulative Necrosis **Liquefactive Necrosis**

Caseous Necrosis

The pattern of cell injury that occurs with granulomatous inflammation in response to certain microorganisms (tuberculosis). The host response to the organisms is a chronic inflammatory response and in the center of the caseating granuloma there is an area of cellular debris with the appearance and consistency of cottage cheese.

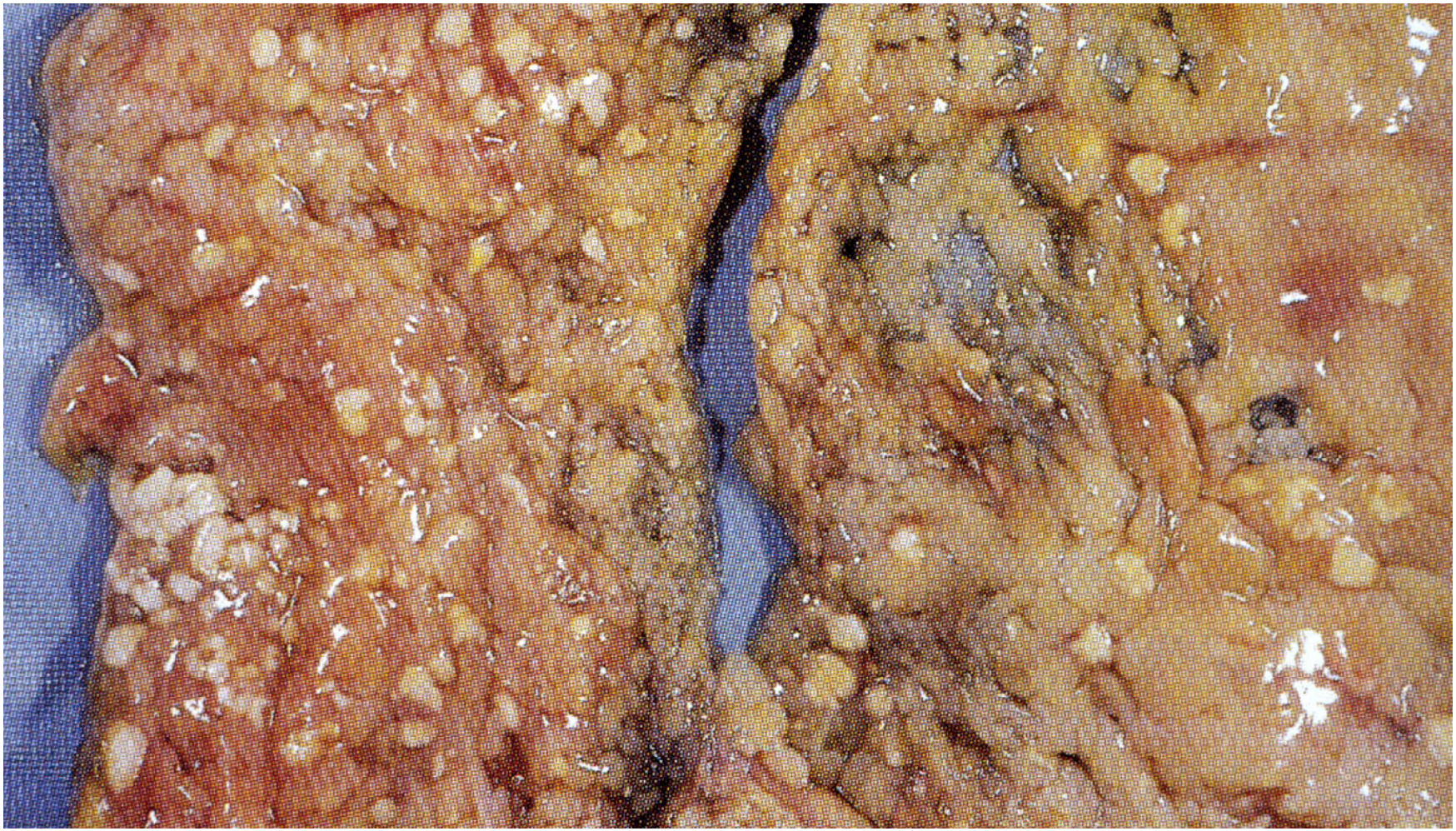


Fat Necrosis

When lipases are released into adipose tissue, triglycerides are cleaved into fatty acids, which bind and precipitate calcium ions, forming insoluble salts.

These salts look chalky white on gross examination and are basophilic in histological sections stained with H&E.

omentum from a person who died of pancreatitis; pancreatic enzymes including lipases were released into the peritoneum



Fibrinoid Necrosis

not very common but has a very specific environment in which in occurs (vasculitis)

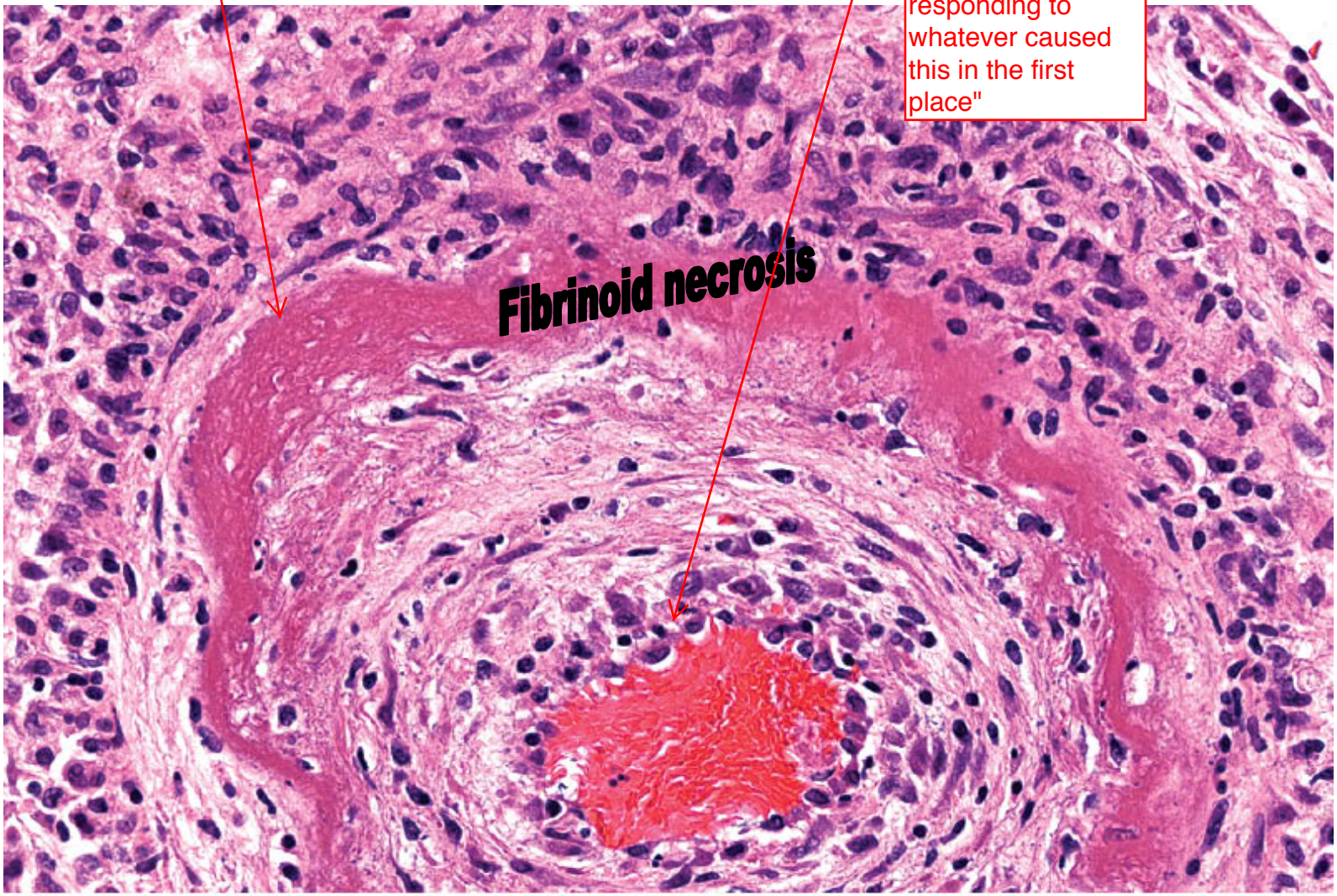
The pattern of cell injury that occurs in the wall of arteries in cases of vasculitis. There is necrosis of smooth muscle cells of the tunica media and endothelial damage which allows plasma proteins, (primarily fibrin) to be deposited in the area of medial necrosis.

The descriptor "especially" may be a better word, but fibrin is the major protein deposited because the coagulation cascade starts when an arterial wall injured.

eosinophilic ribbon of necrotic tissue

ARTERY

endothelial cells are enlarged because "they're responding to whatever caused this in the first place"



Your patient has experienced an acute myocardial infarct and expired due ventricular rupture seven days later. You ask for an autopsy and examine a section of the heart under the microscope. What type of necrosis do you see?

A. Caseous necrosis

B. Liquefactive necrosis

C. Fibrinoid necrosis

D. Fat Necrosis

E. Coagulative necrosis

seen in cases of TB

abscesses and also seen in cerebral infarcts

vasculitis

heart should not be fatty

Summary

Cellular Adaptation to Injury or Stress

- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia

Patterns of Tissue Necrosis

- Coagulative Necrosis
- Liquefactive Necrosis
- Caseous Necrosis
- Fat Necrosis
- Fibrinoid Necrosis