UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
"NICOLAE TESTEMIȚANU" DIN REPUBLICA MOLDOVA

Introduction
General etiology. General pathology. Cell injury. Cellular pathological processes

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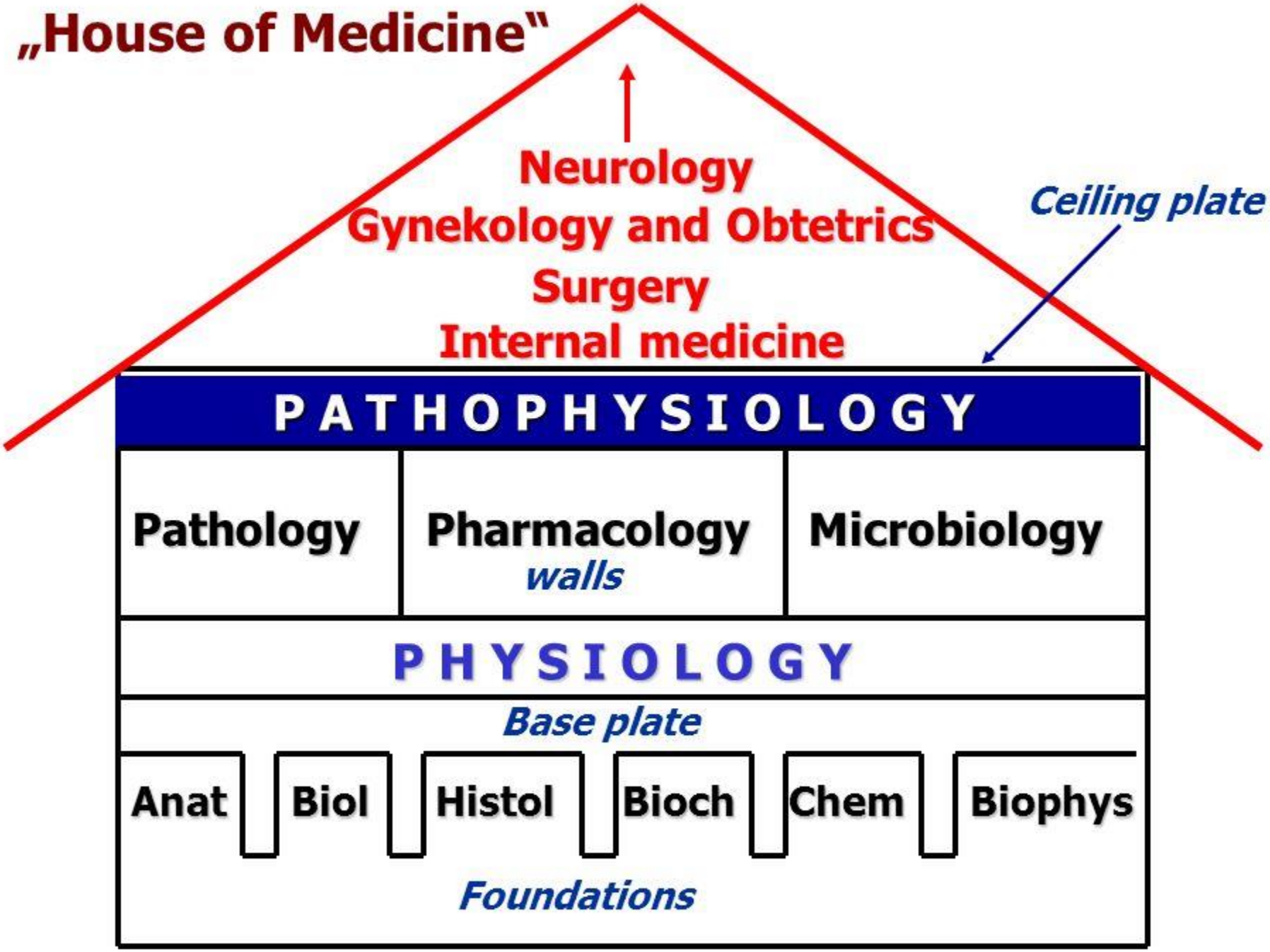
What is the pathophysiology?

- it is a science which study general laws of origin, onset, evolution and resolution of pathological processes and complex of biochemical, morphological and functional changes at the molecular, cellular, tissular, organ and system level.

- Pathophysiologia – gr. pathos = disease, pain, suffering; logos = science


„House of Medicine"
Neurology
Gynekology and Obtetrics
Surgery
Internal medicine
Ceiling plate
PATHOPHYSIOLOGY
Pathology
Pharmacology
walls
Microbiology
PHYSIOLOGY
Base plate
Anat
Biol
Histol
Bioch
Chem
Biophys
Foundations

COMPARTMENT OF PATHOPHYSIOLOGY

Pathophysiology

THEORETICAL

GENERAL NOSOLOGY
ETIOLOGY
PATHOGENY
SANOGENESIS
STRUCTURE OF DISESE
CLASSIFICATION OF DISEASE
DISEASE PERIODS

GENERAL

Typical pathological processes = the alphabet of pathology
CELLULAR (apoptosis, necrosis, cell dystrophy)
TISSULAR (hypertrophy, atrophy, fibrosis)
ORGAN (inflammation, allergy)
INTEGRAL (acid-base imbalance, hydroelectrolytic changes, metabolic disorders)

SPECIAL

Pathophysiological mechanisms of disorders with a characteristic localization.

CLINICAL

Pathophysiological mechanisms of every disease separately

ETIOLOGY= Cause of disease

A compartment of theoretical physiopathology which studies the cause and conditions of disease.

Cause of disease versus conditions ?

CAUSE OF DISEASE= ETIOLOGICAL FACTOR – any substance, energy or information which acting on the body structures induces functional, structural and biochemical dyshomeostasis.

CONDITION OF DISEASES
any substance, energy or information which doesn't induce disease but can favors or impede the action of the cause

FAVORABLE **UNFAVORABLE**

Etiological factors

ENDOGENOUS

EXOGENOUS

- **Mechanical** (mechanical energy, rupture – mechanical trauma);
- **Physical** (radiation, temperature: burns);
- **Chemical** (toxins; organic acids from bacterial carbohydrates fermentation in the mouth);
- **Biological** (bacteria, viruses, parasites etc…)
- **Informational** (mediators, hormones, antigens
- **Social** (human interrelation in society)

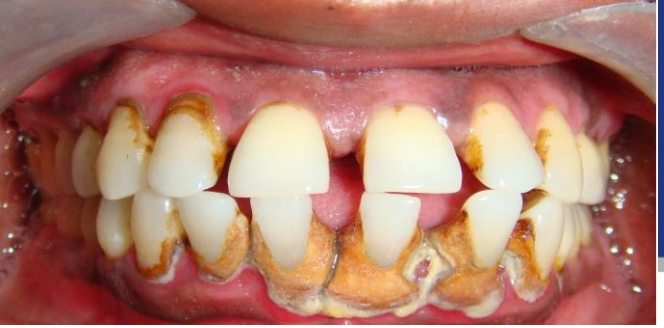
LOCAL **Isotropic action**

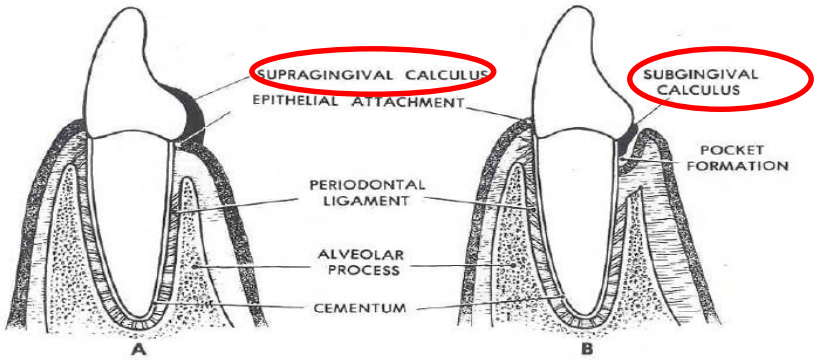
GENERAL **Anisotropic action**

Etiological factors in the mouth

Plaque is the sticky, colorless film that constantly forms on the teeth. Bacteria live in plaque and secrete acids that cause tooth decay and irritate gum tissue. This irritation causes an inflammatory reaction that can eventually lead to gingivitis and periodontal disease

60-70 species of bacteria. Bacteria secrete a sticky substance with adhesive properties. Bacterial colonies and their secretion form so-called "bacterial plaque". In the formation of these the most frequent involved bacteria are: Streptococcus mutans and Lactobacillus;





Odontolith = tartar = dental tophus.

caused by precipitation of minerals from saliva and gingival crevicular fluid in plaque on the teeth. This rough and hardened surface that is formed provides an ideal surface for further plaque formation. This leads to calculus buildup, which compromises the health of the gingiva (gums).

Calculus can form both along the gumline, where it is referred to as supragingival ("above the gum"), and within the narrow sulcus that exists between the teeth and the gingiva, where it is referred to as subgingival ("below the gum`)

PATHOGENY

from Greek pathos – suffering;
logos – science

How it appears, develops and ends the disease ?

Compartment of physiopathology which studies the mechanisms of onset, evolution, development and ending of disease.

PATHOGENIC CHAIN
PATHOGENIC FACTOR
MAIN LOOP OF PATHOGENY
VICIOUS CIRCLE
PATHOGENIC PROCESS

Hyposalivation

Colonization of the mouth with bacteria

Development of bacterial plaque

Mineralization of bacterial plaque

Development of dental calculus

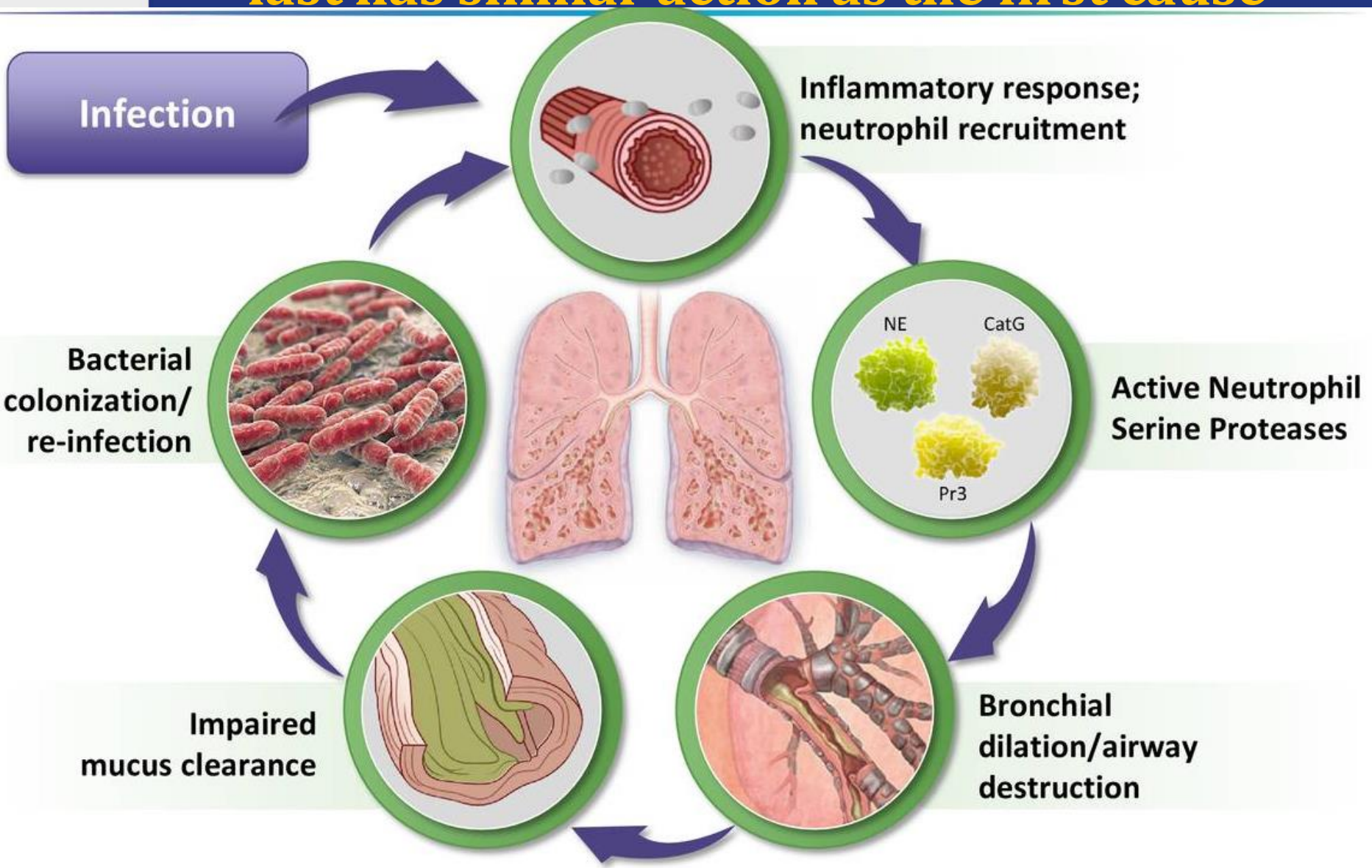
Chronic irritation of the gum

Inflammation of the gum

Gingivitis

Saliva: 1 -1,5 L/day
Lysosime
Lactopherin
pH – 6,8 -7
Secretory IgA

Closed pathogenic chain = vicious circle = relation between cause and effect, where the last has similar action as the first cause



ROLE OF BODY REACTIVITY IN DISEASE DEVELOPMENT

REACTIVITY - ability of the body to react to every change in order to maintain the functional, structural , biochemical and psychic homeostasis.

- ADAPTATIVE REACTIONS
- PROTECTIVE REACTIONS
- COMPENSATORY REACTIONS
- REPARATIVE REACTIONS

Definition of health

WHO

"a state of complete physical, mental, and social well-being, and not merely the absence of disease and infirmity"

- Criticisms of WHO definition: too ideal, too abstract, too broad, and not subject to scientific application
- Despite these criticisms, WHO definition of health is most popular and most comprehensive definition of health worldwide

• Much more useful is to define health through as a notion of *norm*;

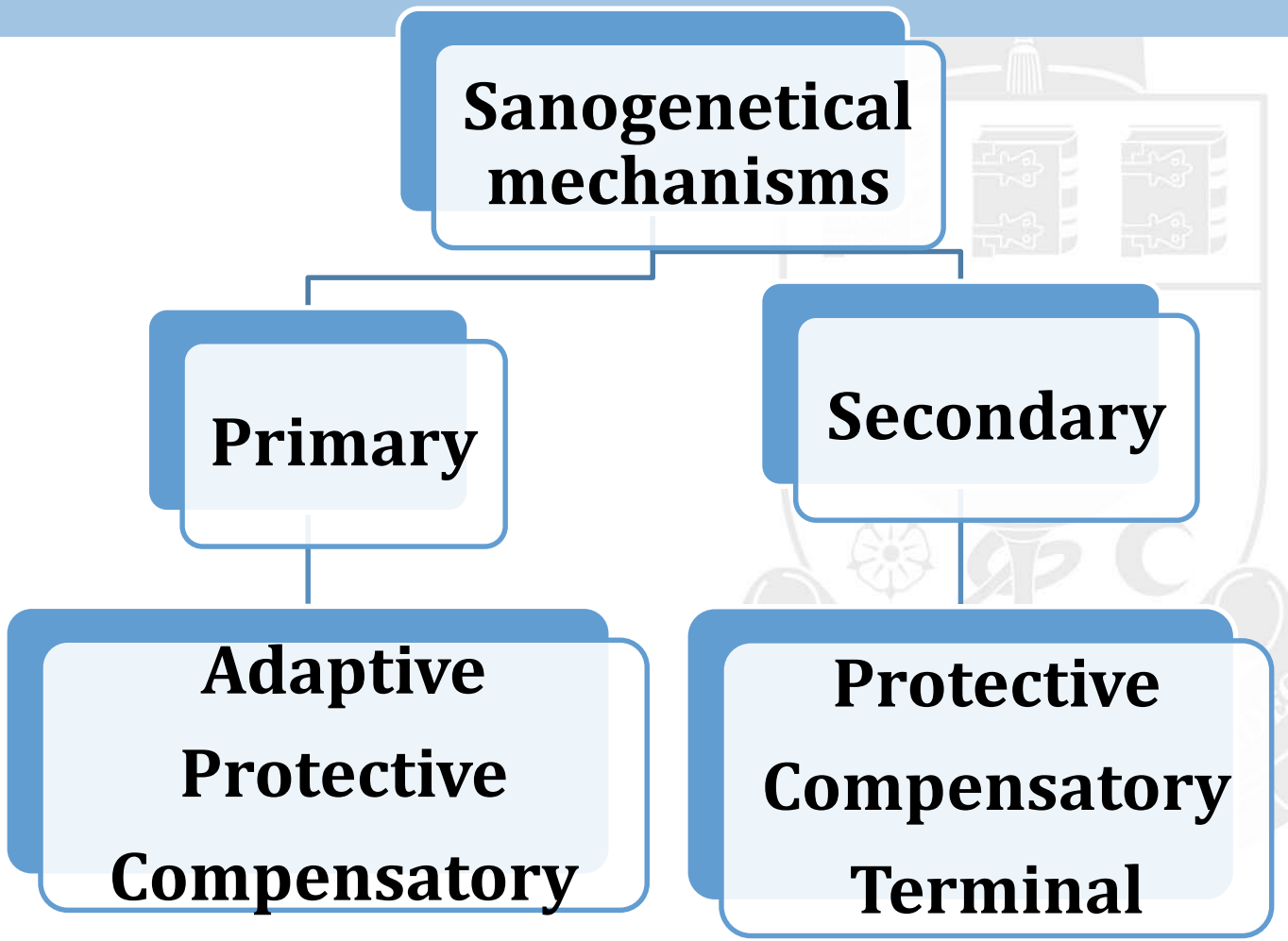
• The norm is the medium statistic value of morphologic, functional, biochemical and psychic parameters of the human body of a special race, sex, age and constitution in special existence.

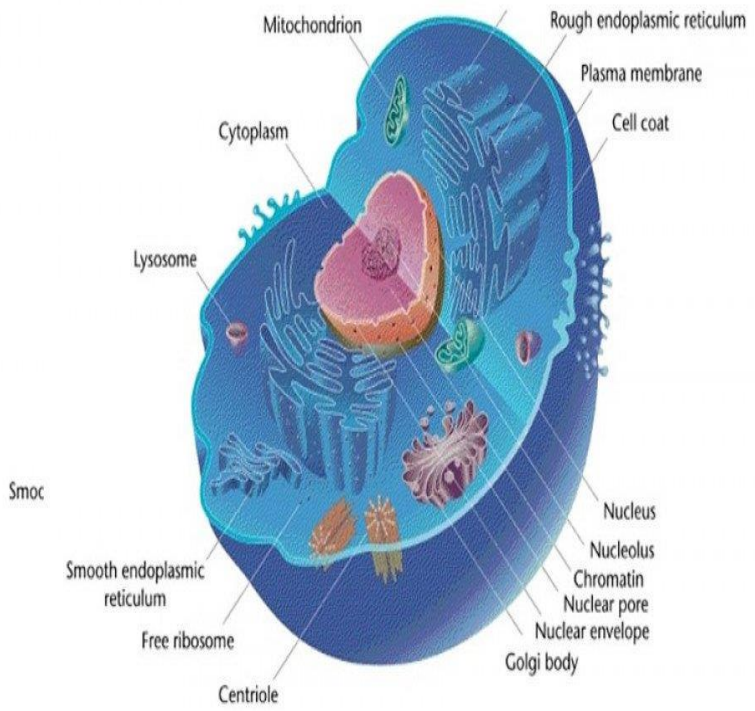
Definition of the disease

- **The disease *may be defined as a new qualitative state of the body that can appear under the action of harmful factors and is characterized through a homeostatic disequilibrium (morphological, functional, biochemical and psychic), inadaptability, social disequilibrium, loss of work capacity and social – economic values for a certain period of time.***

General sanogenesis

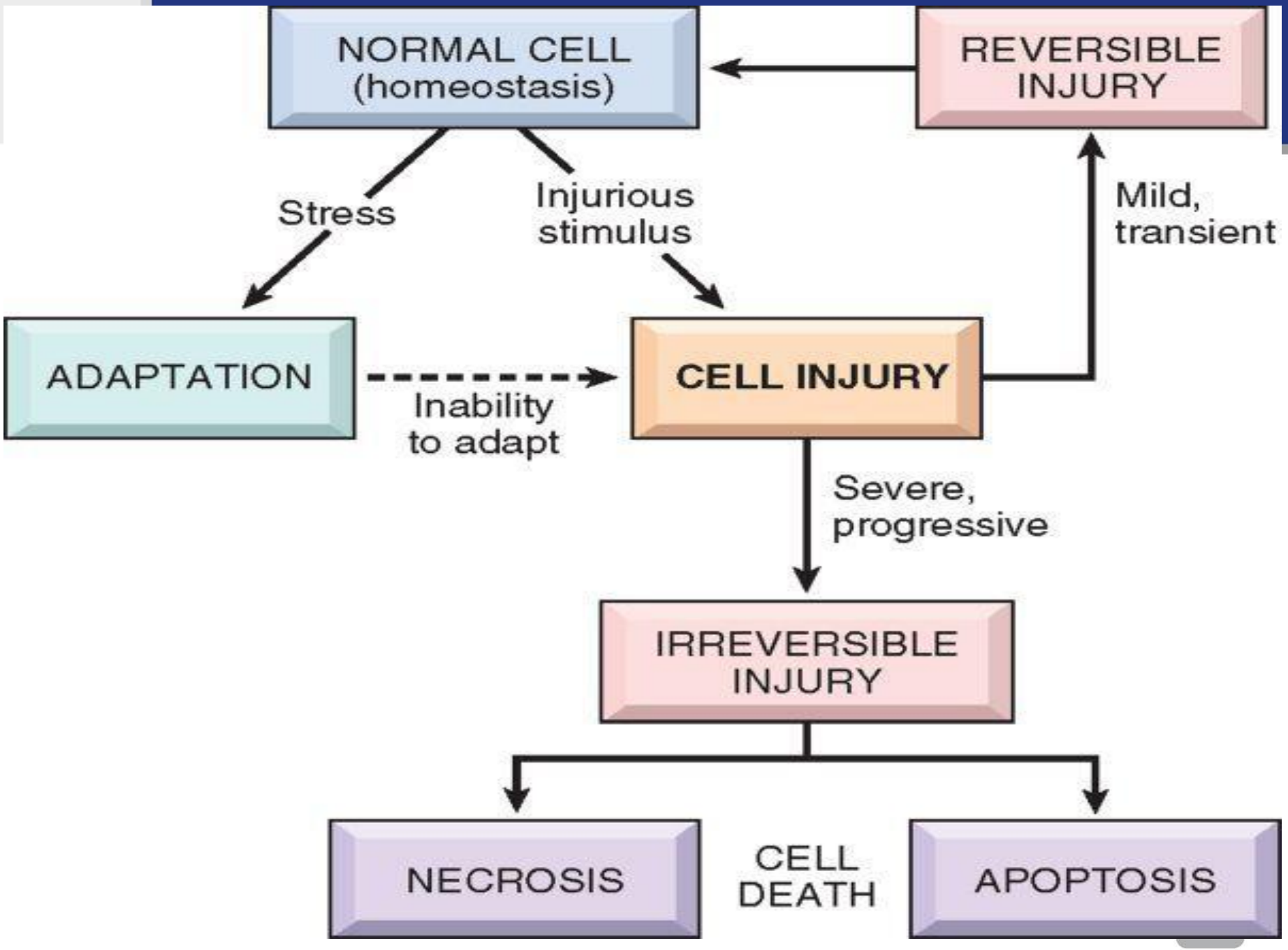
- **(*lat. sanitas – health, genesis-a birth*) is general compartment of nosology, studying general laws of healing and recovery - restoration of damaged structures and disordered function in disease outcome.**





Cell injury : mitochondrial, nucleus, RE injury; Apoptosis; Necrosis

"Virtually all forms of disease start with molecular or structural alterations in cells," **Rudolf Virchow**


NORMAL CELL
(homeostasis)
REVERSIBLE
INJURY
Stress
Injurious
stimulus
Mild,
transient
ADAPTATION
Inability
to adapt
CELL INJURY
Severe,
progressive
IRREVERSIBLE
INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

- ***Cell injury*** **is the persistent change of biochemical, structural and functional homeostasis of the cell under the action of harmful factor.**

Classification

- **By the sequence of appearance (primary, secondary)**
- **By the nature of lesions (specific, nonspecific)**
- **By the character of etiologic factor: mechanical damage; physical injuries (burns, frostbite, electrical); osmotic injury; lesions by lipid peroxidation; infectious lesions; immune (allergic) injury; toxic injury; enzymatic injury; hypoxic injury; damage of circulation; dysmetabolic damage; injury of homeostasis**
- **By location: membrane lesion; mitochondrial lesion, lysosomal injury; nucleus lesions (including lesions by mutations); endoplasmic reticulum damage and Golgi apparatus**
- **By degree of injury: reversible, irreversible.**

Etiology of cell injury

- Mechanical factors;
- Hypoxic injuries;
- Ischemic injuries;
- Oxidative stress;
- Biological factor (bacteria, viruses, fungi);
- Radiation (ionizing, ultraviolet radiation);
- Electrical injuries;
- Enzymatic injuries;
- Extreme of temperature (burns, frost bite);

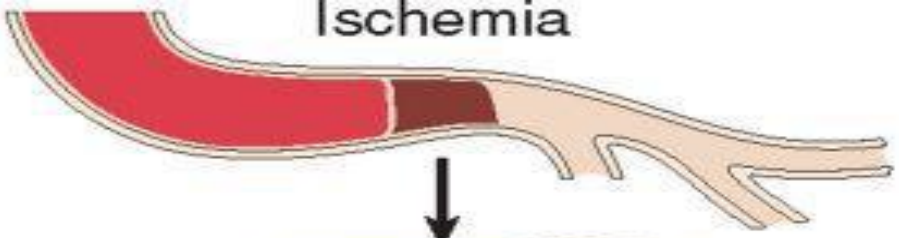
Mechanical injury

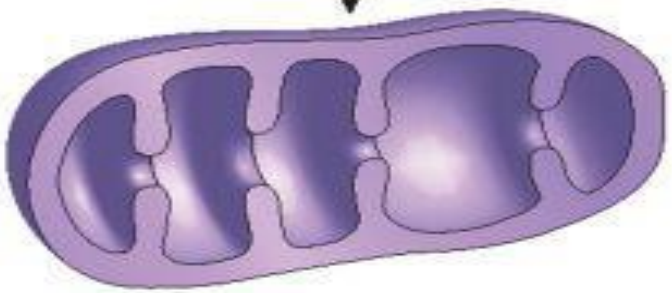
Graphical illustration of a damaged cell

- **Disintegration of membrane**
- **Open of mechanical barrier cell-interstitium**
- **Free passage of substances in both directions**
- **Influx of Na+, efflux of K+**

Hypoxic injury. Causes

- general hypoxia (hypoxic, respiratory, circulatory, anemic);
- regional blood flow and lymphatic disorders (venous hyperemia, ischemia, stasis);
- disorders of cellular processes of oxidative phosphorilation





↓ Oxidative phosphorylation

↓ ATP

↓ Na^+ pump

↑ Influx of Ca^{2+}, H_2O, and Na^+

↑ Efflux of K^+

ER swelling
Cellular swelling
Loss of microvilli
Blebs

↑ Anaerobic glycolysis

↓ Glycogen

↑ Lactic acid → ↓ pH

Clumping of nuclear chromatin

Detachment of ribosomes

↓ **Protein synthesis**

Lipid deposition

Depletion of ATP

↑Influx of Na+

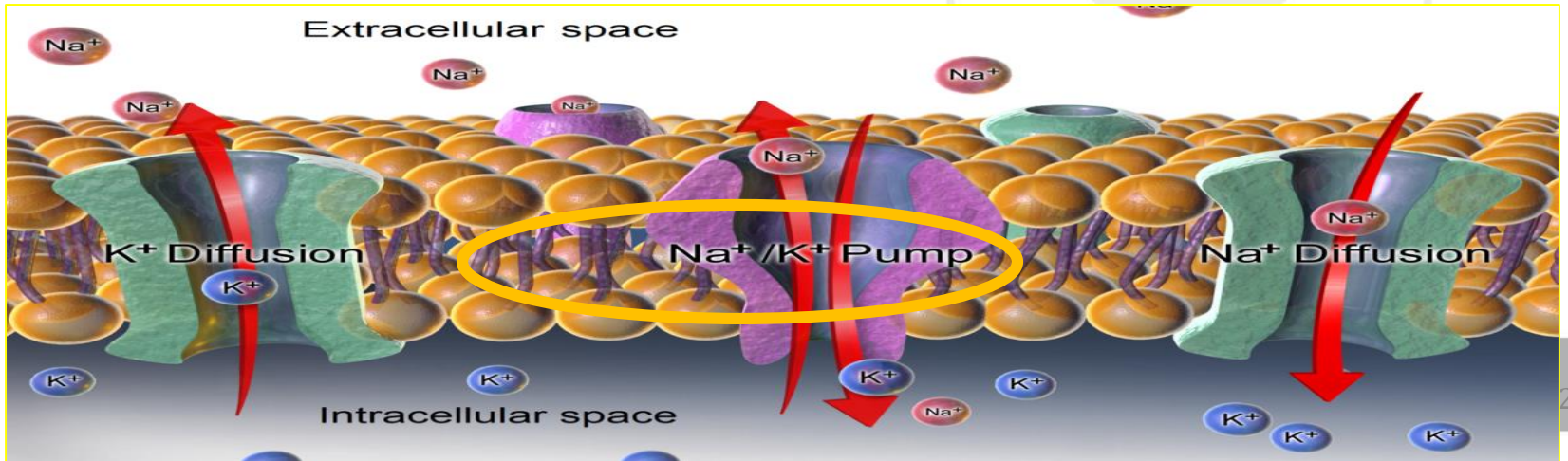
↑ **Intracellular osmolarity**

Cell swelling, dilation of ER

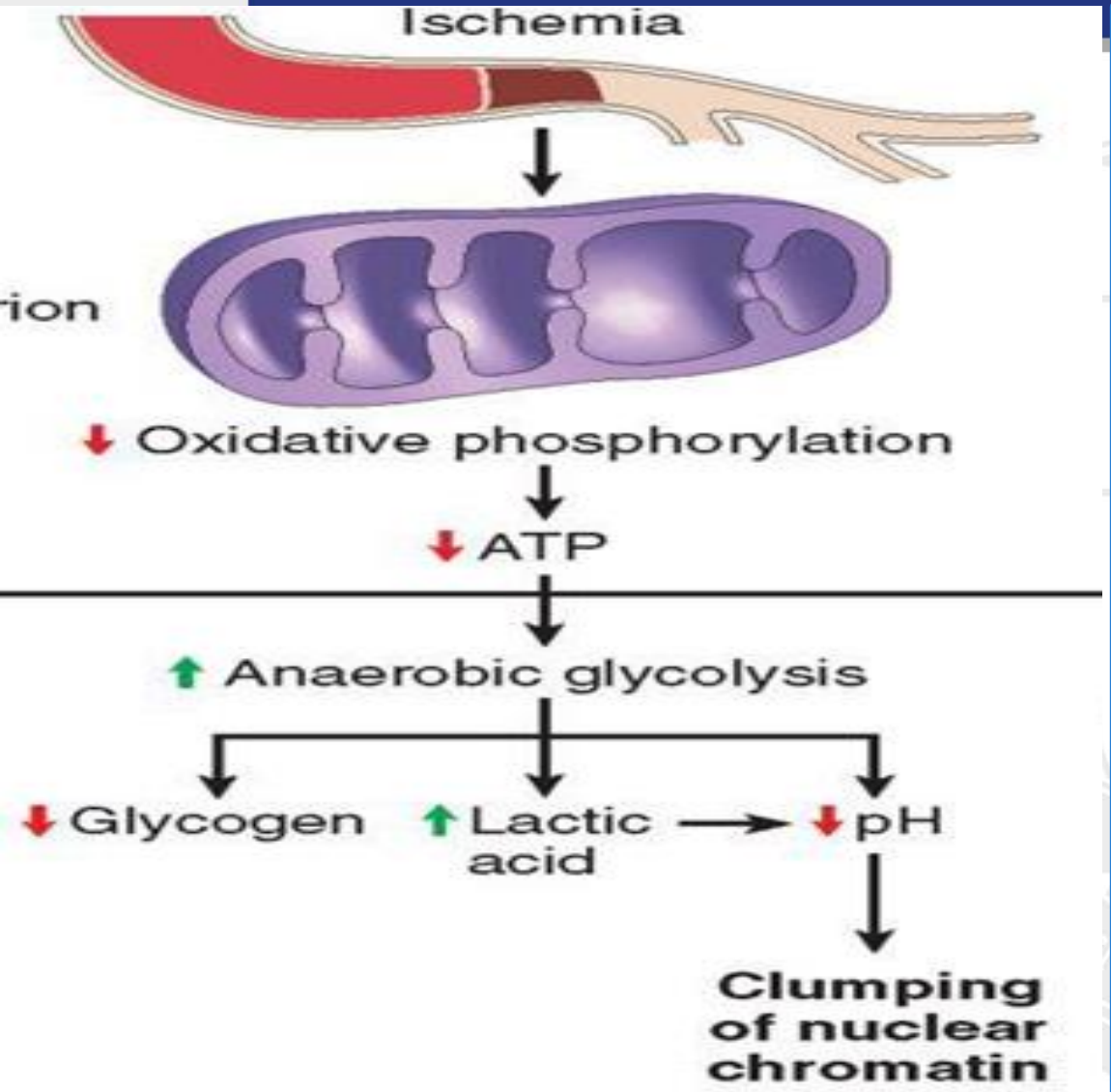
↑Efflux of K+

↓ **intracellular- resting potential- *inhibitory depolarization***

Increase extracellular – reduces transmembrane potential of adjacent cells – increase the excitability

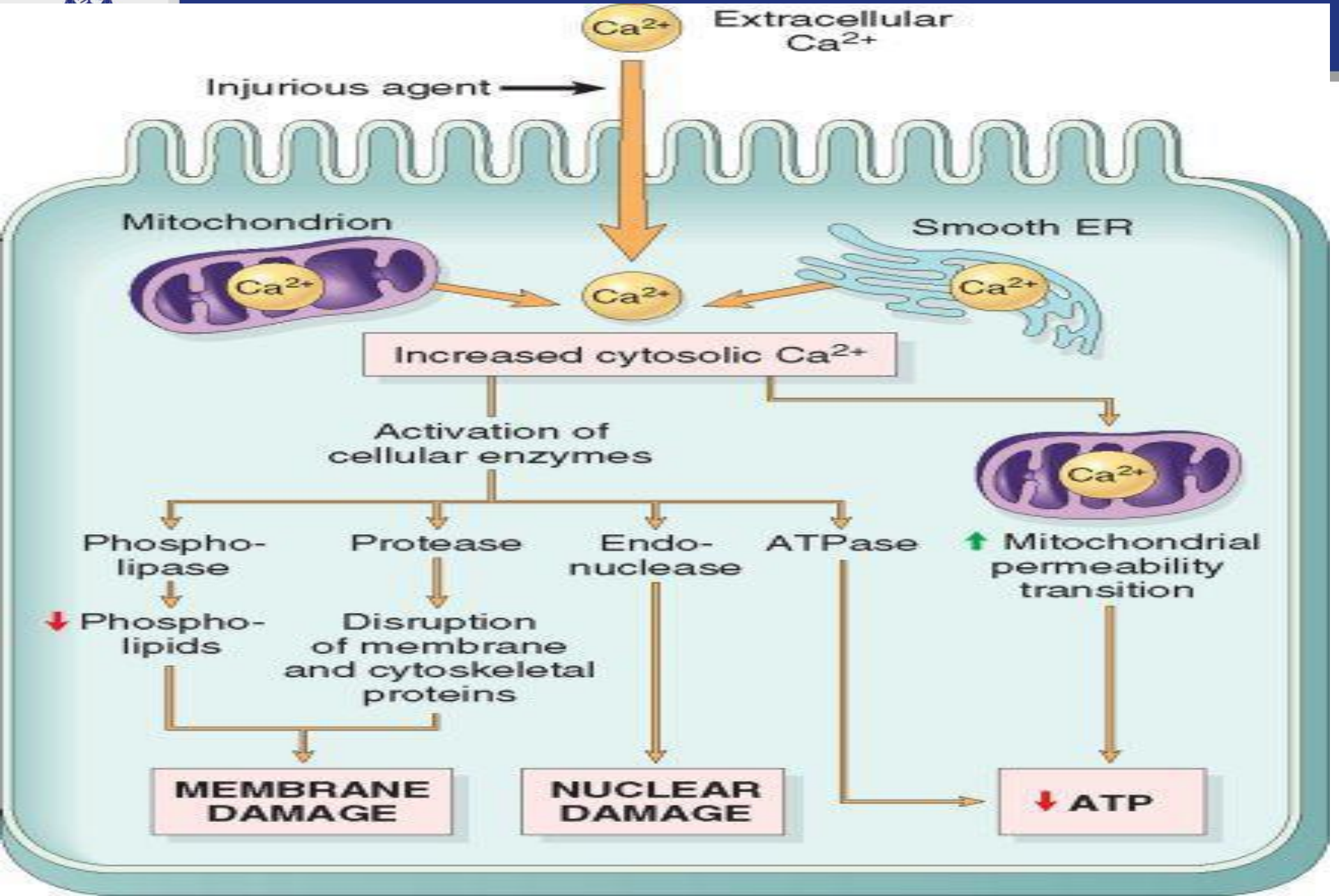


Depletion of ATP



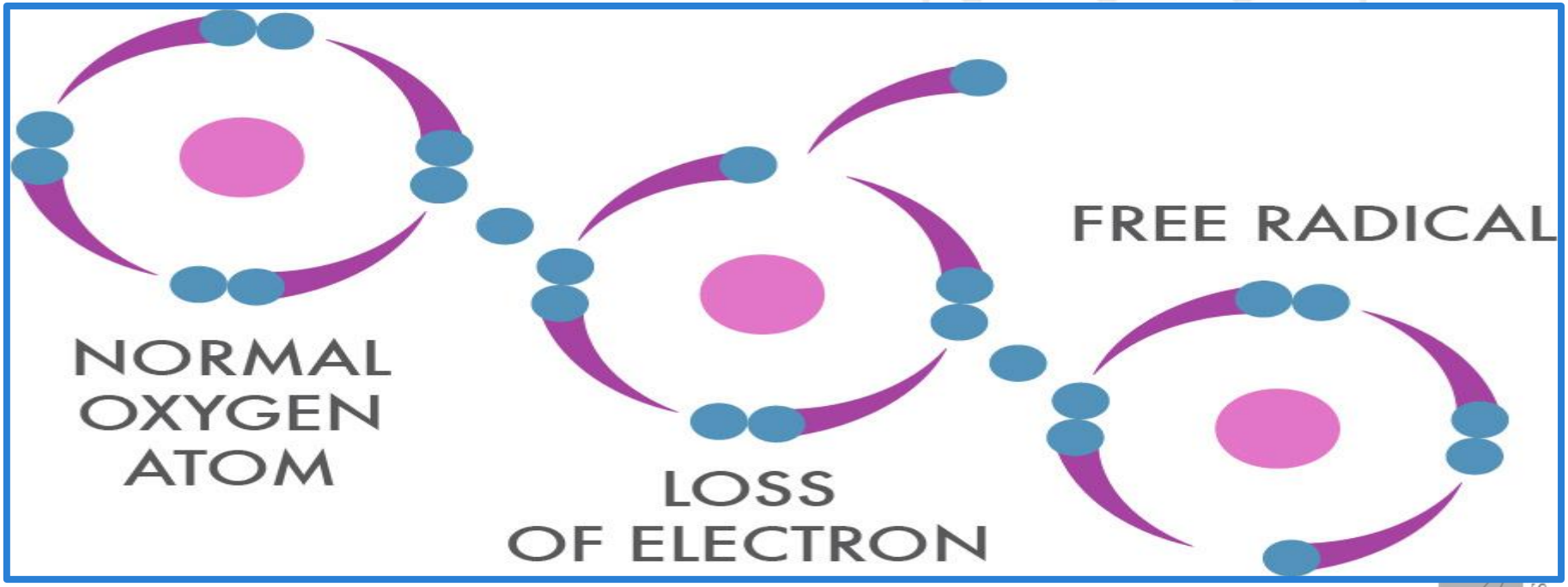
- **decrease ATP -- increase AMPc -- stimulate phosphofructokinase and phosphorilase activity -- lead to anaerobic glycolysis**
- **Cellular acidosis – changes of protein's functions, activation of lysosomal enzymes, increase permeability of the membrane lipid layer**

ATP depletion ➡ failure of Ca2+pump

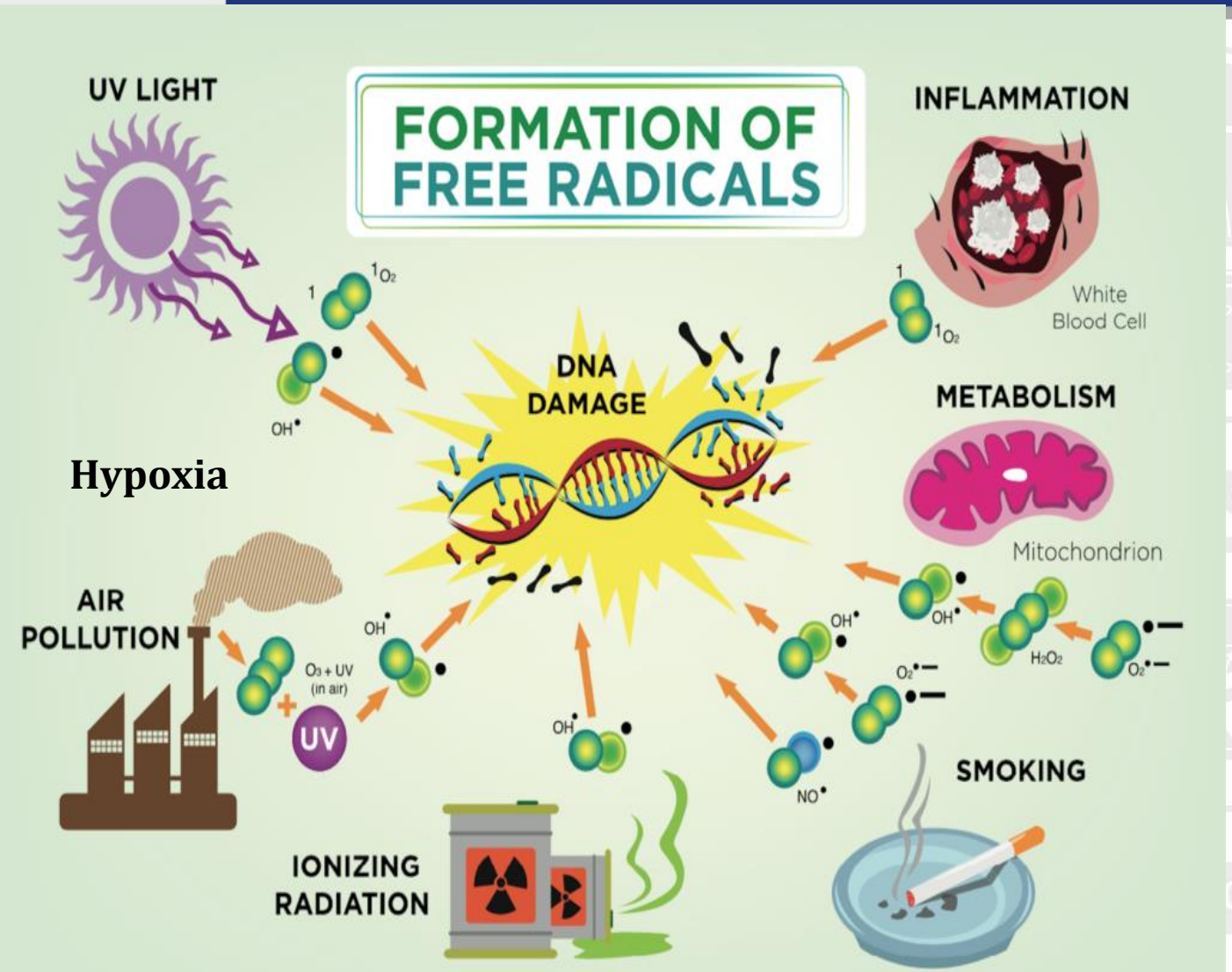


Oxidative stress= free radicals= reactive oxygen species (ROS)

It is called oxygen compound, which on the latest electronic layer has an unpaired electron, single electron, what gives an extremely higher chemical reactivity

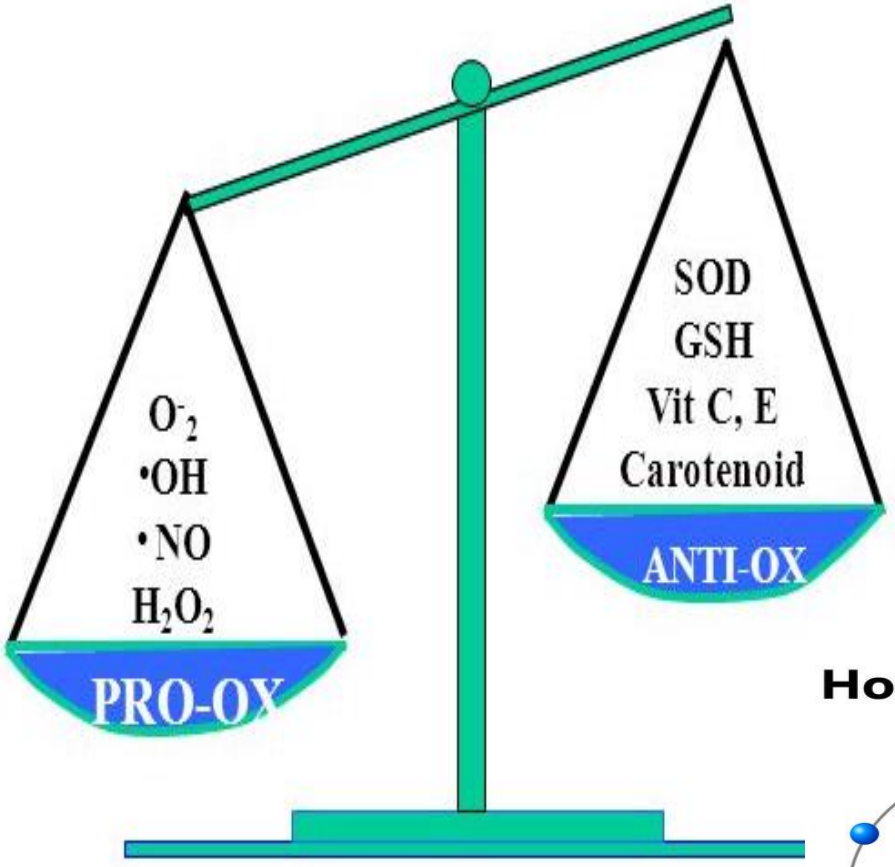


Types and causes of ROS



- $O_2^{\bullet}$ - oxygen superoxide
- $OH^{\bullet}$ - hydroxyl radical
- H_2O_2 - hydrogen peroxide

Oxidants vs Antioxidants

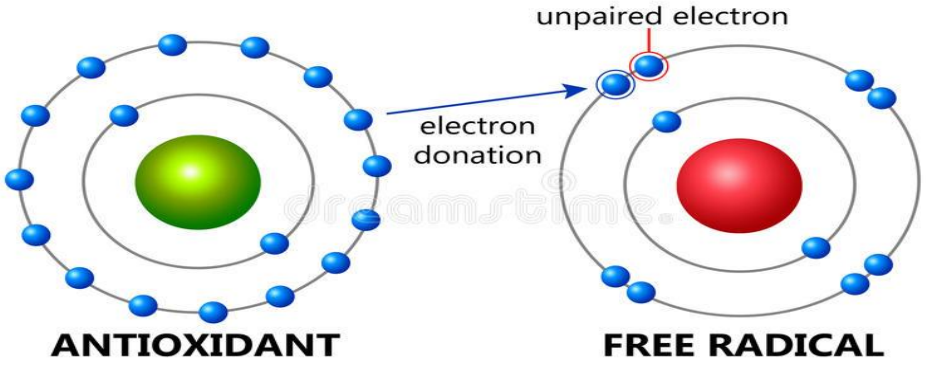


REMOVAL OF FREE RADICALS

Antioxidant mechanisms:

- SOD (in mitochondria)
  converts $O_2^{\cdot-} \rightarrow H_2O_2$
- Glutathione peroxidase
  (in mitochondria)
  converts $^{\cdot}OH \rightarrow H_2O_2 \rightarrow H_2O + O_2$
- Catalase (in peroxisomes)
  converts $H_2O_2 \rightarrow H_2O + O_2$

How antioxidants reduce free radicals



chemically reactive unpaired electron + electron donation:
stable electron pair is formed, free radical is neutralised

The most important effects of ROS

ROS react with:

1. **FA → oxidation → generation of lipid peroxidase → disruption of plasma membrane and organelles;**
2. **Proteins → oxidation → loss of enzymatic activity, abnormal folding;**
3. **DNA → oxidation → mutations, breaks.**

Enzymatic cellular injury

Endogenous

- phagocytic cells from the inflammatory foci,
- lysosomal enzymes (from lysosomal membrane destabilization),
- pancreatic digestive enzymes (pancreatitis or pancreonecrosis).

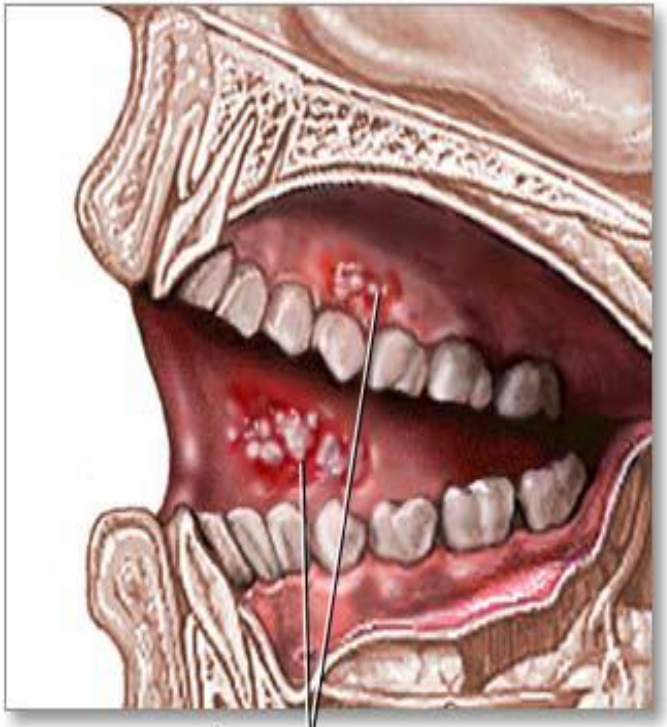
Exogenous

- microbial enzymes (for ex: streptococci lecithinase that splits membrane phospholipids).

Thermal cell injury

- **Exposure to heat (43ºC to 46ºC) - vascular injury, accelerate cell metabolism, inactivate temperature sensitive enzymes, and disintegration of the cell membrane.**
- **Exposure to cold - induces vasoconstriction by direct action and by activated SNS, increases blood viscosity - decreases blood flow - hypoxic tissue injury.**
- **Injury from freezing probably results from a combination of ice crystal formation and vasoconstriction - decreases blood - capillary and arteriolar stasis and capillary thrombosis.**

Thermal injury of the mouth mucosa



Sores on mucous membrane of inner cheek and gum

A.D.A.M.

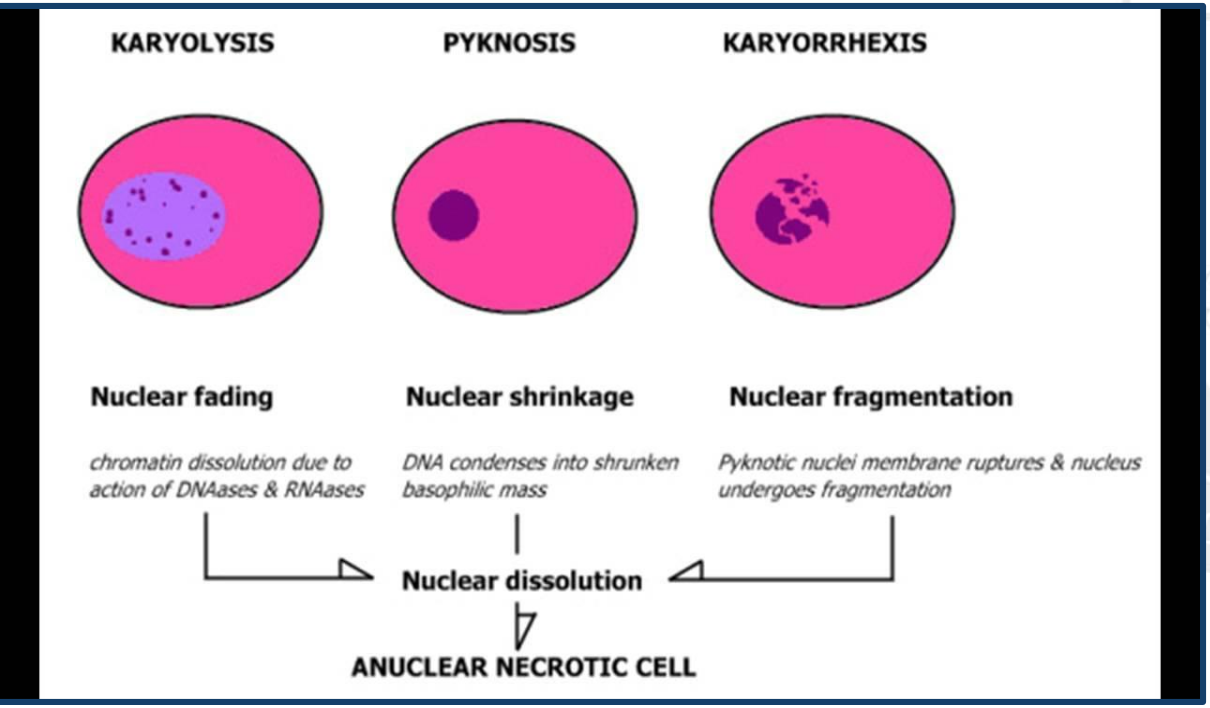
Burns with hot air or hot water start with *acute catharal stomatitis*, the epithelium being partly or totally macerated. In case of a severe burn epithelium detaches in flaps or forms blebs under which develop erosions or ulcerations.

Nuclear injuries

Karyopiknosis – margination and condensation of chromatin (action of ADNase and lysosomal enzymes)

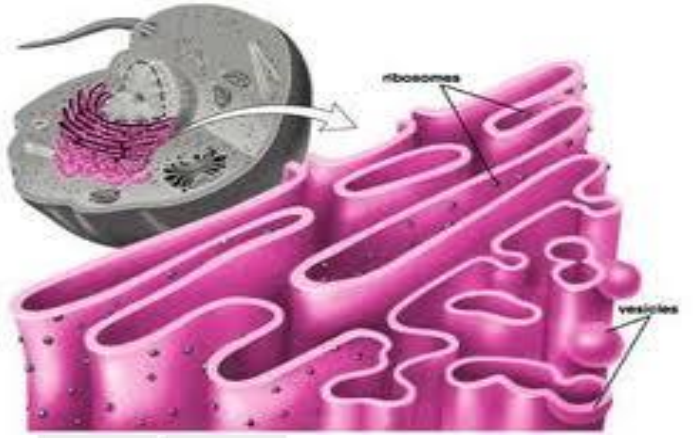
Karyorrhexis - fragmentation of chromatin: pyknotic nucleus undergo fragmentation

Karyolysis - total lysis of the nucleus of the cell.



Nucleus death

INJURY OF ENDOPLASMIC RETICULUM

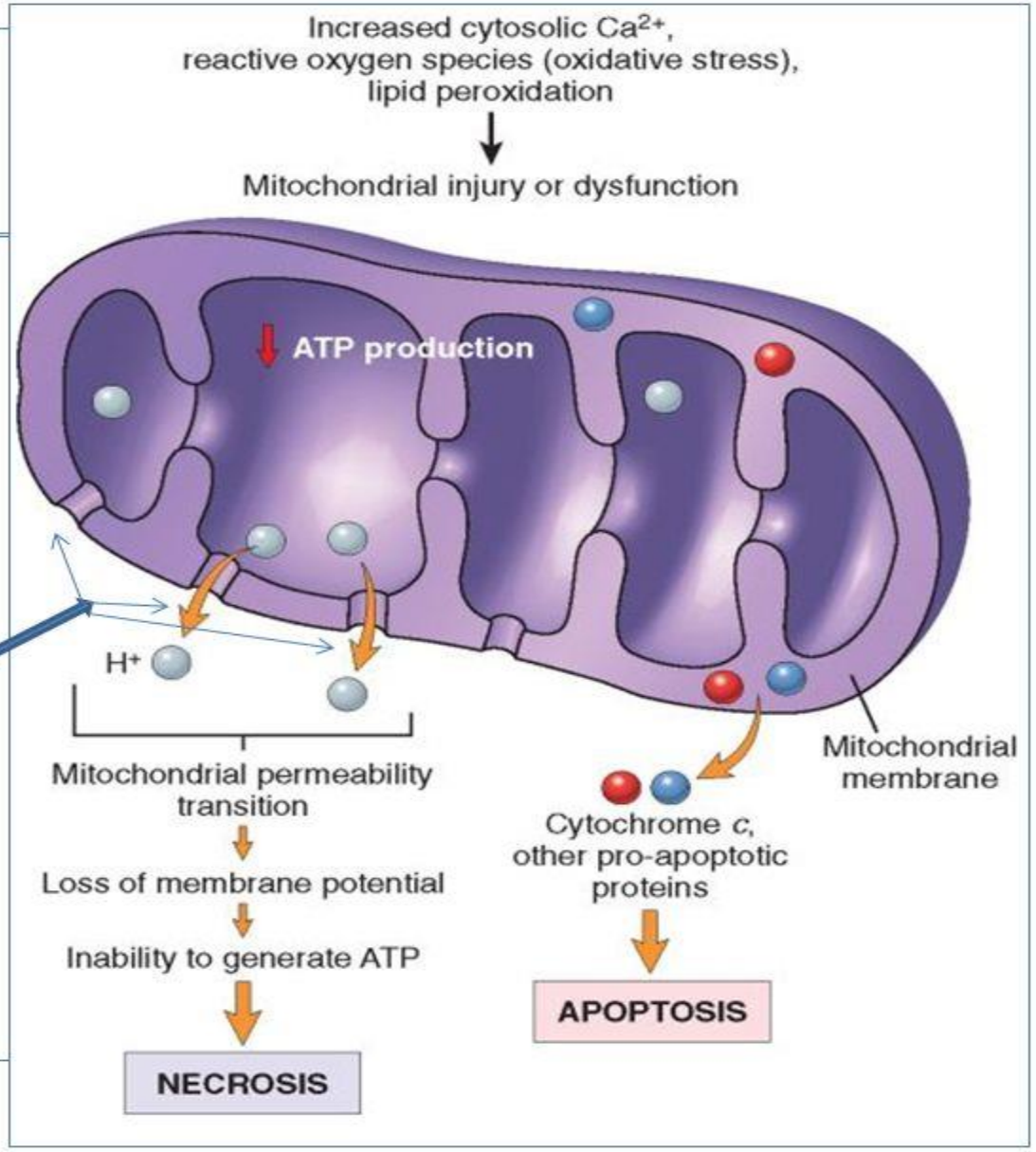


1. *Fragmentation of the ER* – a sign of unspecific cell injury (ischemia).
2. *Formation of vacuoles* - caused by interruption of energy metabolism in which the reaction chain involving Na+/K+-ATPase fails (hypoxia).
3. *Swelling of the ER* – "hydropic swelling" - final stage in the collapse of cellular energy metabolism (anoxia). Is due to cell hyperosmolarity . Swelling of the ER leads to detachment of ribosomes, desintegration of polysomes, finally leading to disturbances in protein synthesis (both needed for intracellular processes as well as for export)

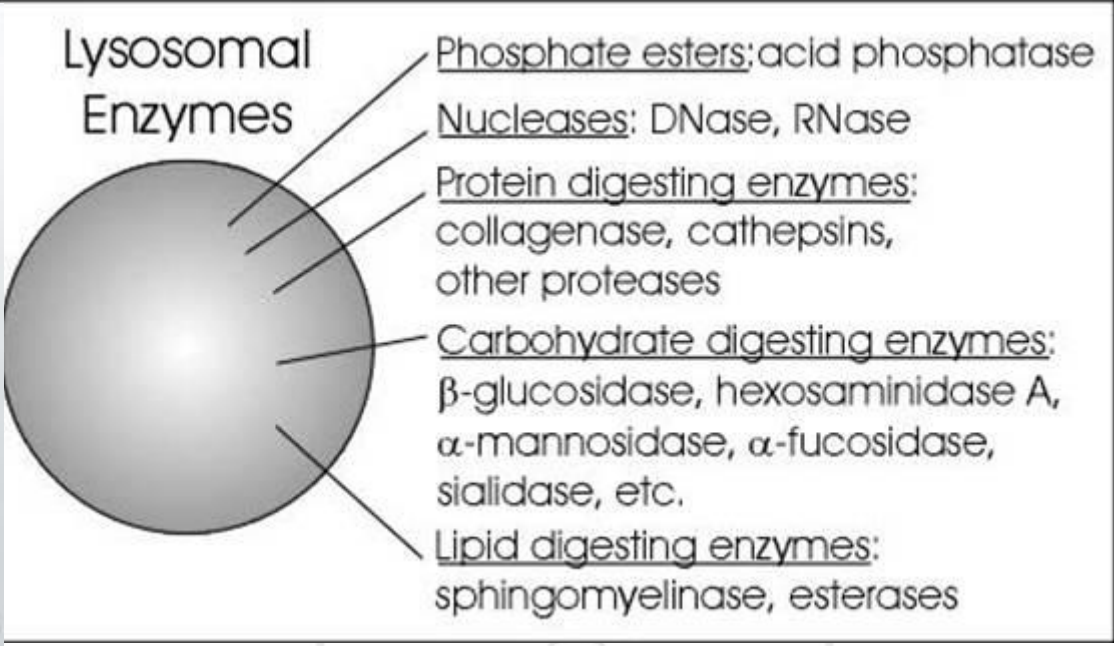
Injury of mitochondria

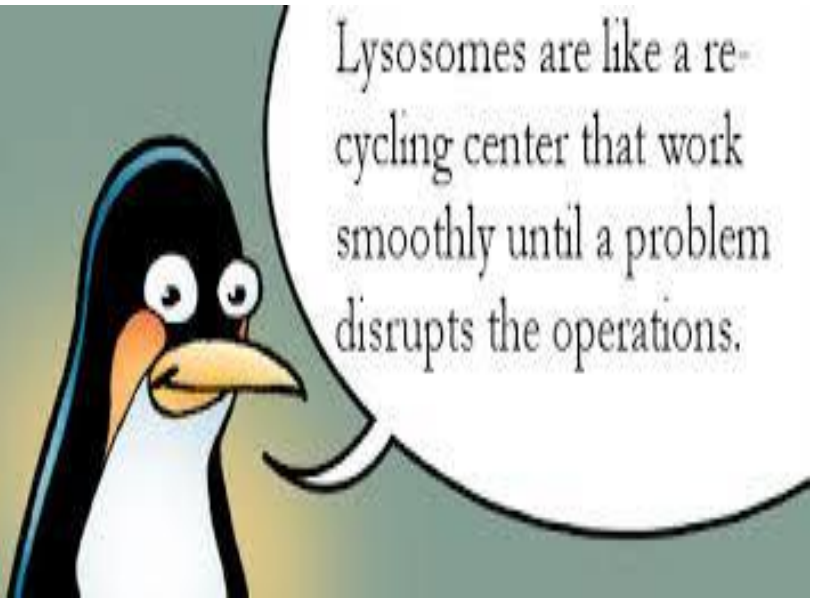
There are two major consequences of mitochondrial damage.

1- Mitochondrial damage often results in **the formation of a high-conductance channel** in the mitochondrial membrane, called **the mitochondrial permeability transition pore** **culminating in necrosis of the cell.**

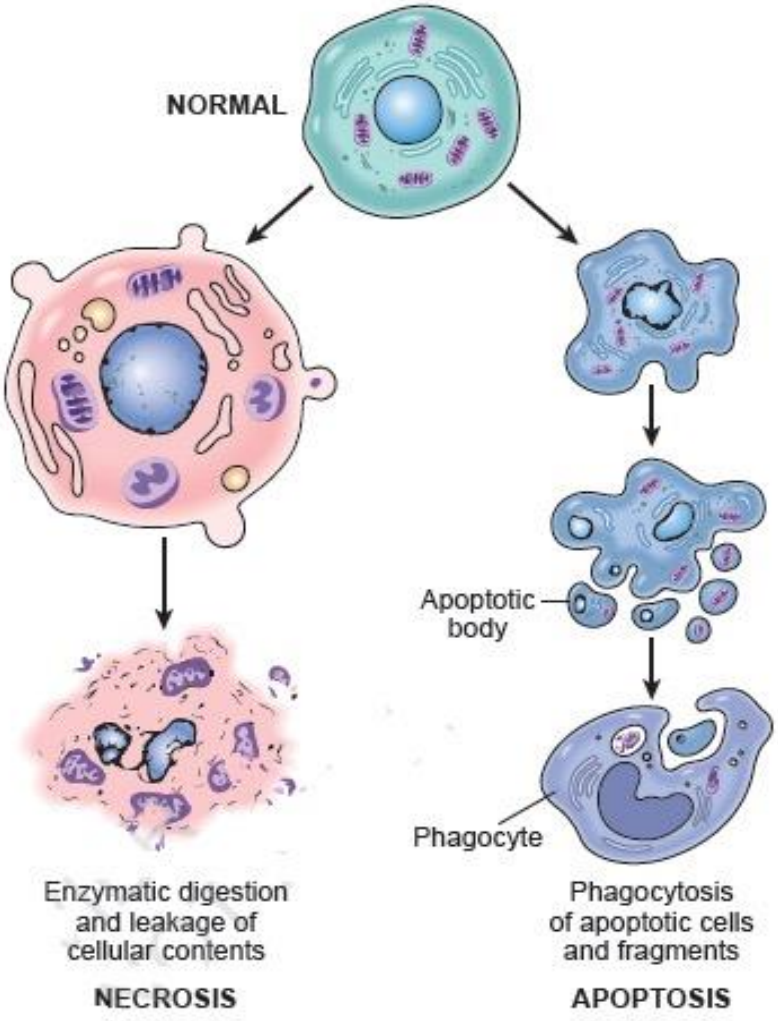


LYSOSOMAL INJURY

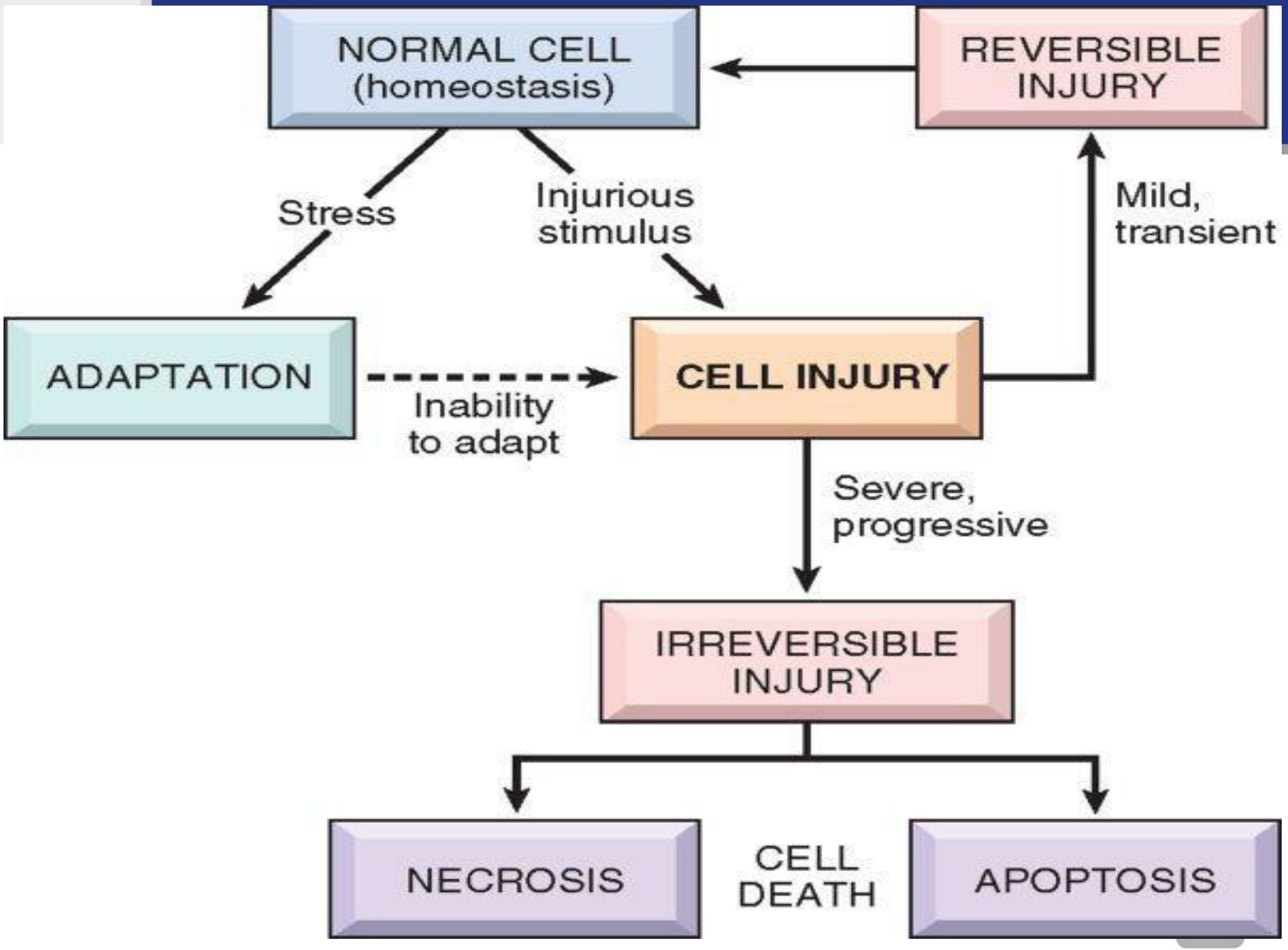




Hypoxia, peroxidation, acidosis etc… leads to tumefaction and destabilization of lysosomal enzymes



Cell dystrophy
Apoptosis
Necrosis


NORMAL CELL
(homeostasis)
REVERSIBLE
INJURY
Stress
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stimulus
Mild,
transient
ADAPTATION
Inability
to adapt
CELL INJURY
Severe,
progressive
IRREVERSIBLE
INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

Cell dystrophy

– typical pathological cellular process which develops in local or general metabolic dyshomeostasis and is characterized by functional and structural changes in the cells.

CELL DYSTROPHY = **INTRACELLULAR ACCUMULATIONS**

Is a result of cell injuries (acquired)
Enzymatic defect (congenital)

NORMAL CELL CONSTITUIENTS:
- **Water - hydropic dystrophy**
- **Minerals – mineral dystrophy**
- **Lipids – lipid dystrophy**
- **Carbohydrates – carbohydrates dystrophy**
- **Proteins – protein dystrophy**

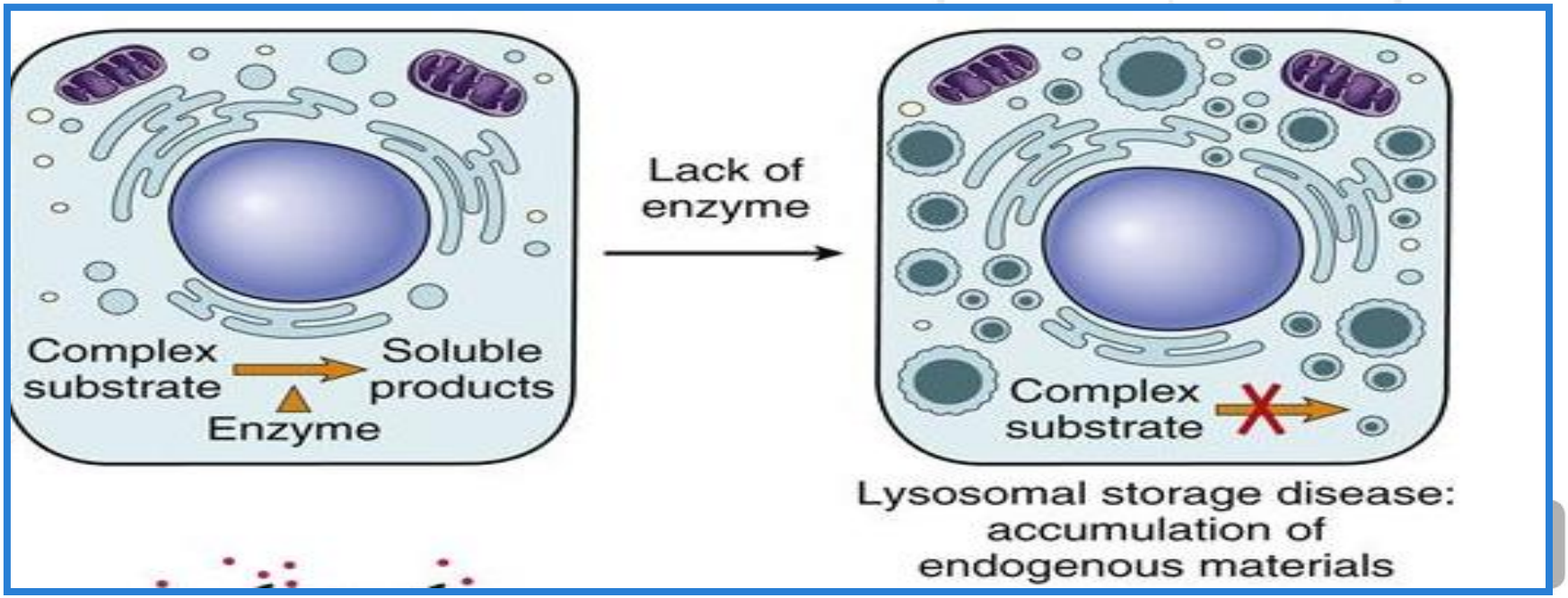
Abnormal substance

EXOGENOUS **ENDOGENOUS**

Products of abnormal synthesis or metabolism

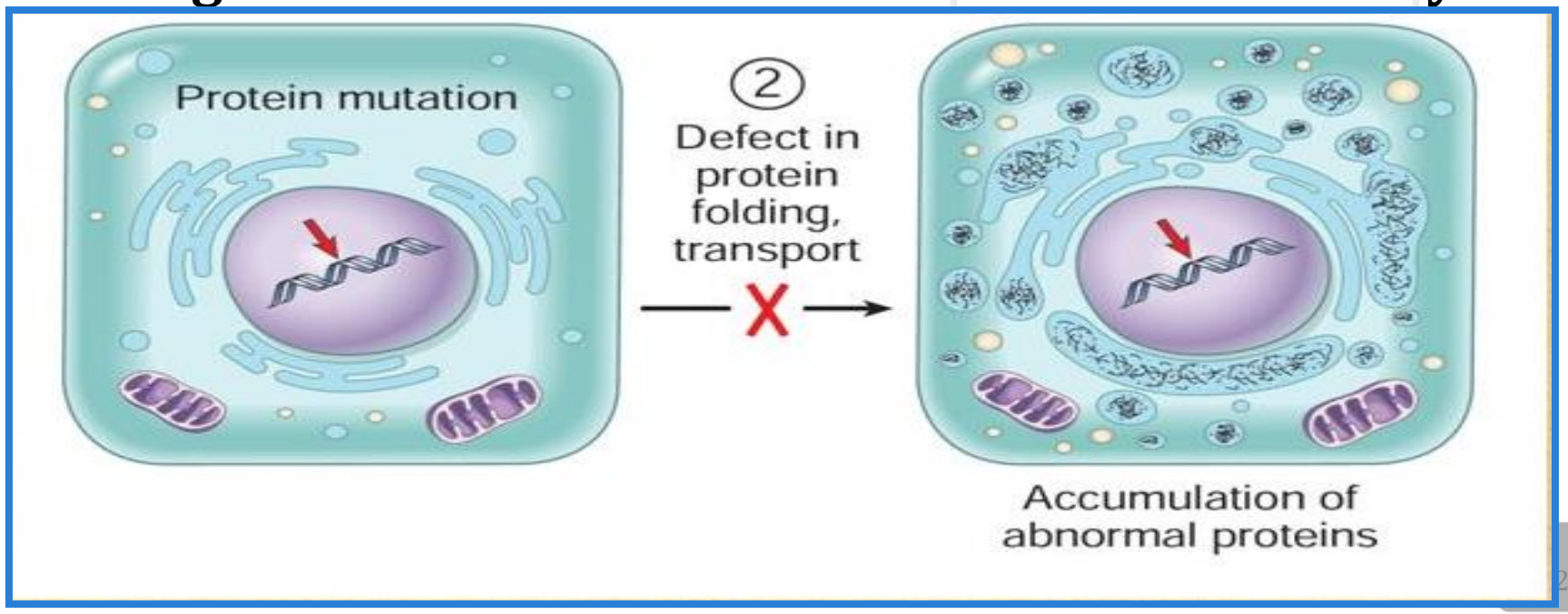
CONGENITAL CELL DYSTROPHY

- **A normal endogenous substance accumulates because of defects, usually inherited, in enzymes that are required for the metabolism of the substance.**
- **Examples: diseases caused by genetic defects in enzymes involved in the metabolism of lipid and carbohydrates, resulting in intracellular deposition of these substances, largely in lysosomes.**



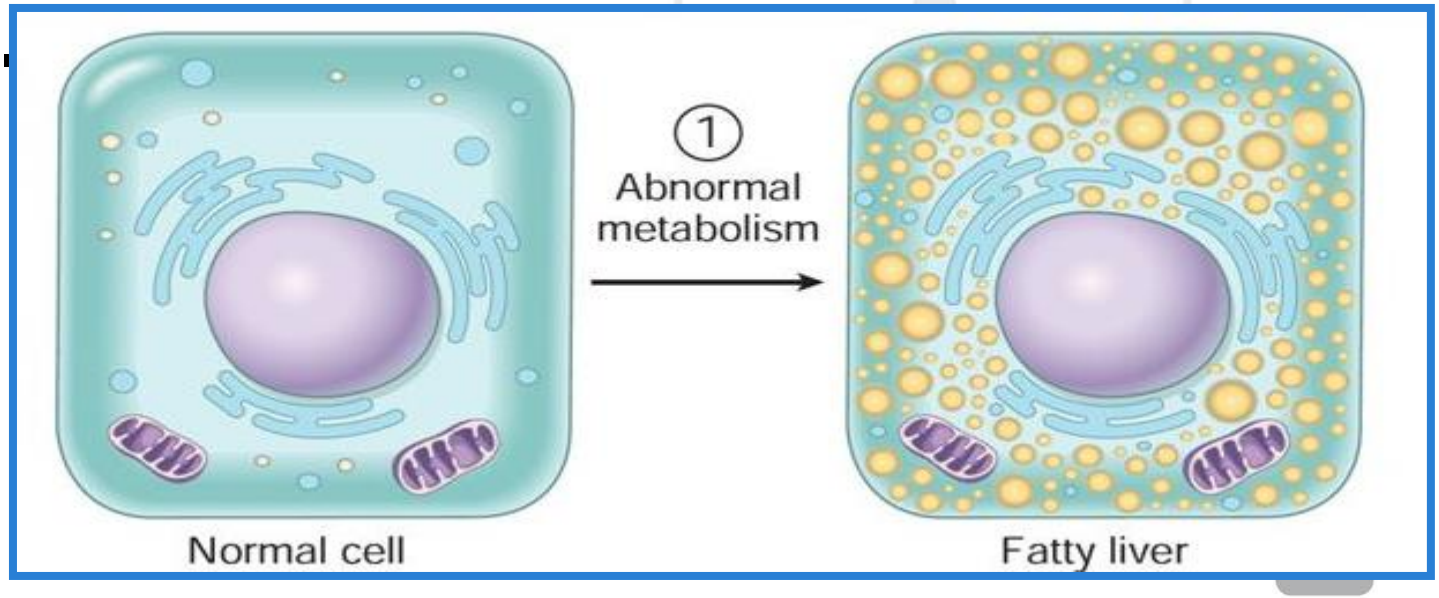
CONGENITAL CELL DYSTROPHY

- **An abnormal endogenous substance, typically the product of a mutated gene, accumulates because of defects in protein folding and transport and an inability to degrade the abnormal protein efficiently.**
- **Examples include the accumulation of mutated α1-antitrypsin in liver cells and various mutated proteins in degenerative disorders of the central nervous system**



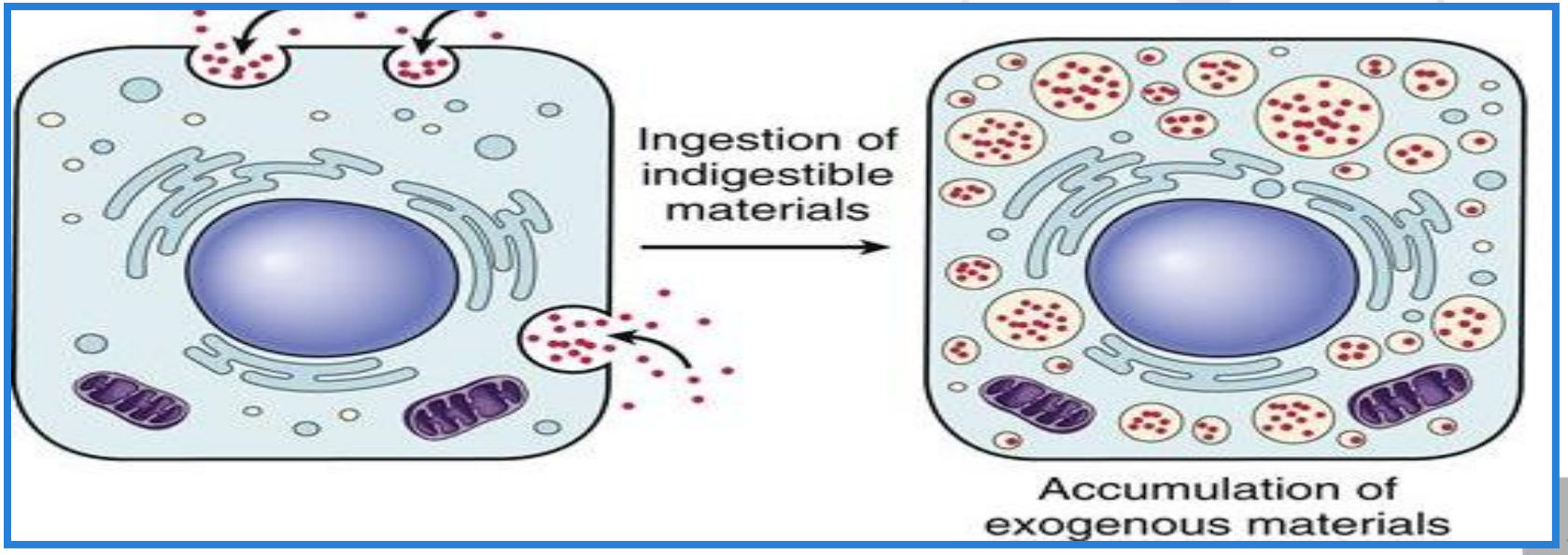
AQUIRED CELL DYSTROPHY

- **A normal endogenous substance is produced at a normal or increased rate, but the rate of metabolism is inadequate to remove it.**
- **Example of this type of process is fatty change in the liver (obesity, alcohol abuse, diabetes mellitus).**



AQUIRED CELL DYSTROPHY

- **An abnormal exogenous substance is deposited and accumulates because the cell has no the enzymatic machinery to degrade the substance or the ability to transport it to other sites.**
- **Accumulations of carbon particles and non-metabolizable chemicals such as silica, asbestos are examples of this type of alteration.**



APOPTOSIS

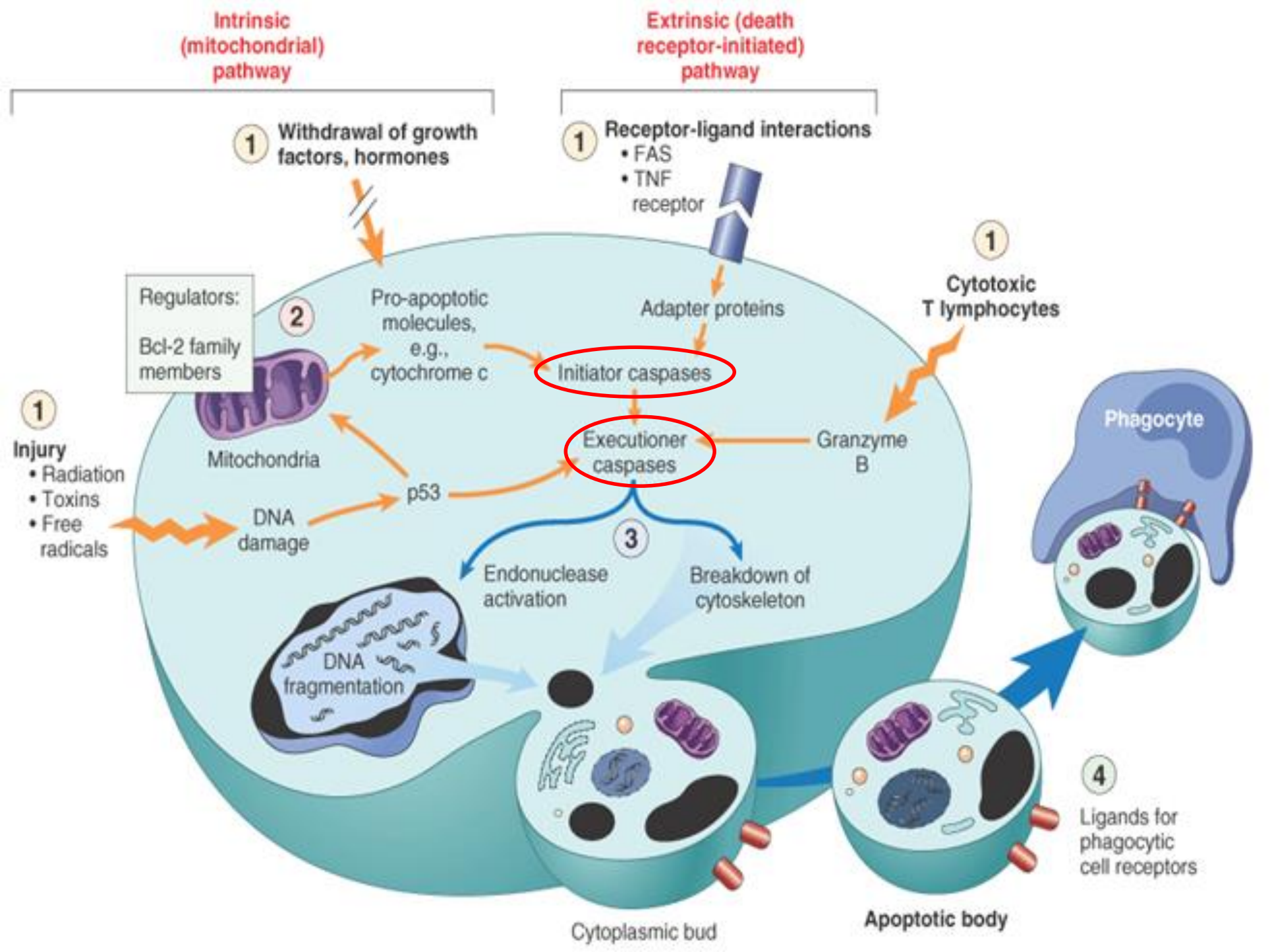
Apoptosis **is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die - activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.**

Apoptosis in physiologic situations

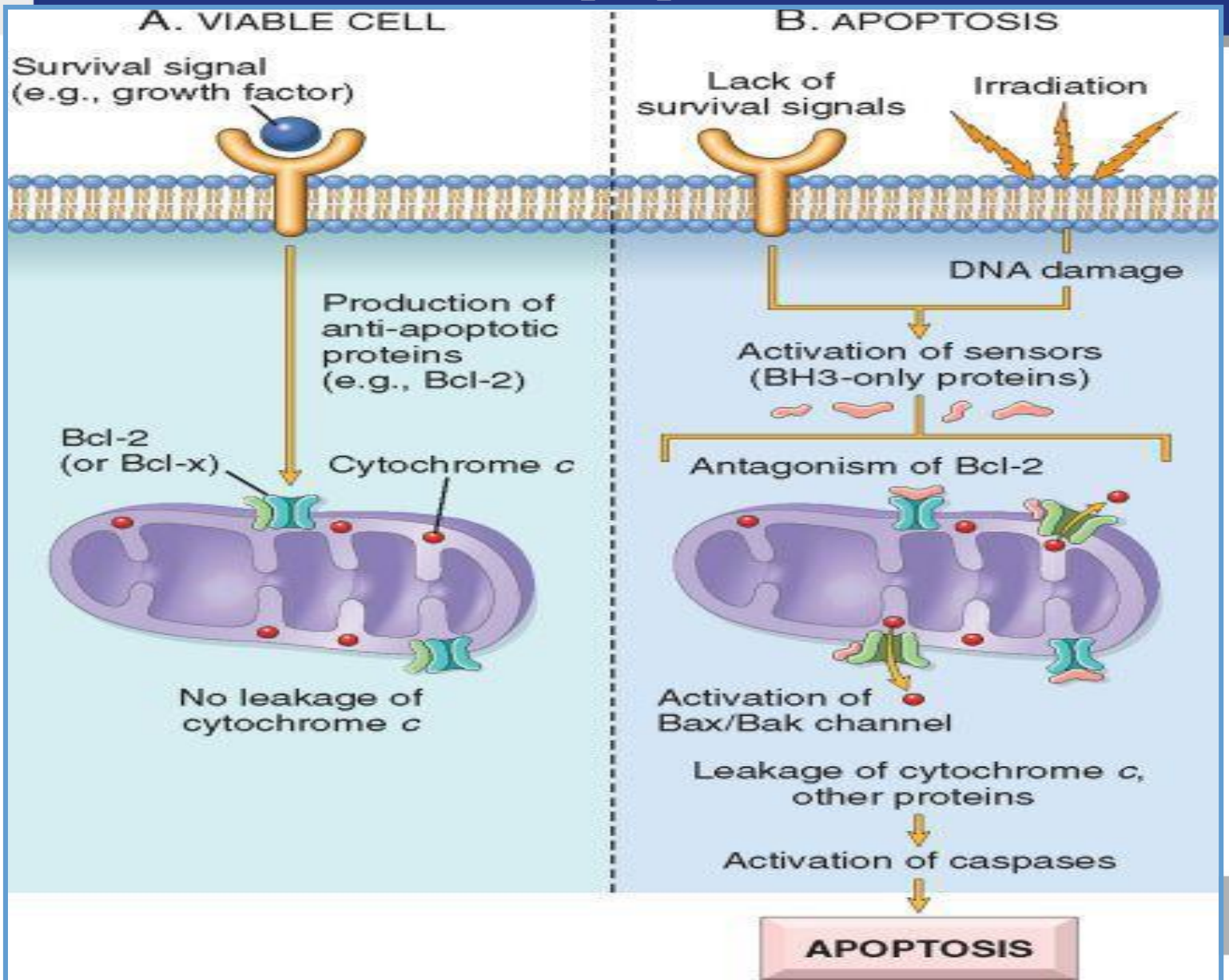
- ***The programmed destruction of cells during embryogenesis.***
- ***Involution of hormone-dependent tissues upon hormone withdrawal*** **(the regression of the lactating breast after weaning).**
- ***Elimination of potentially harmful self-reactive lymphocytes*****.**
- ***Death of host cells that have served their useful purpose,*** **cells undergo apoptosis because they are deprived of necessary survival signals, such as growth factors (neutrophils in acute inflammatory response).**

Apoptosis in pathological conditions

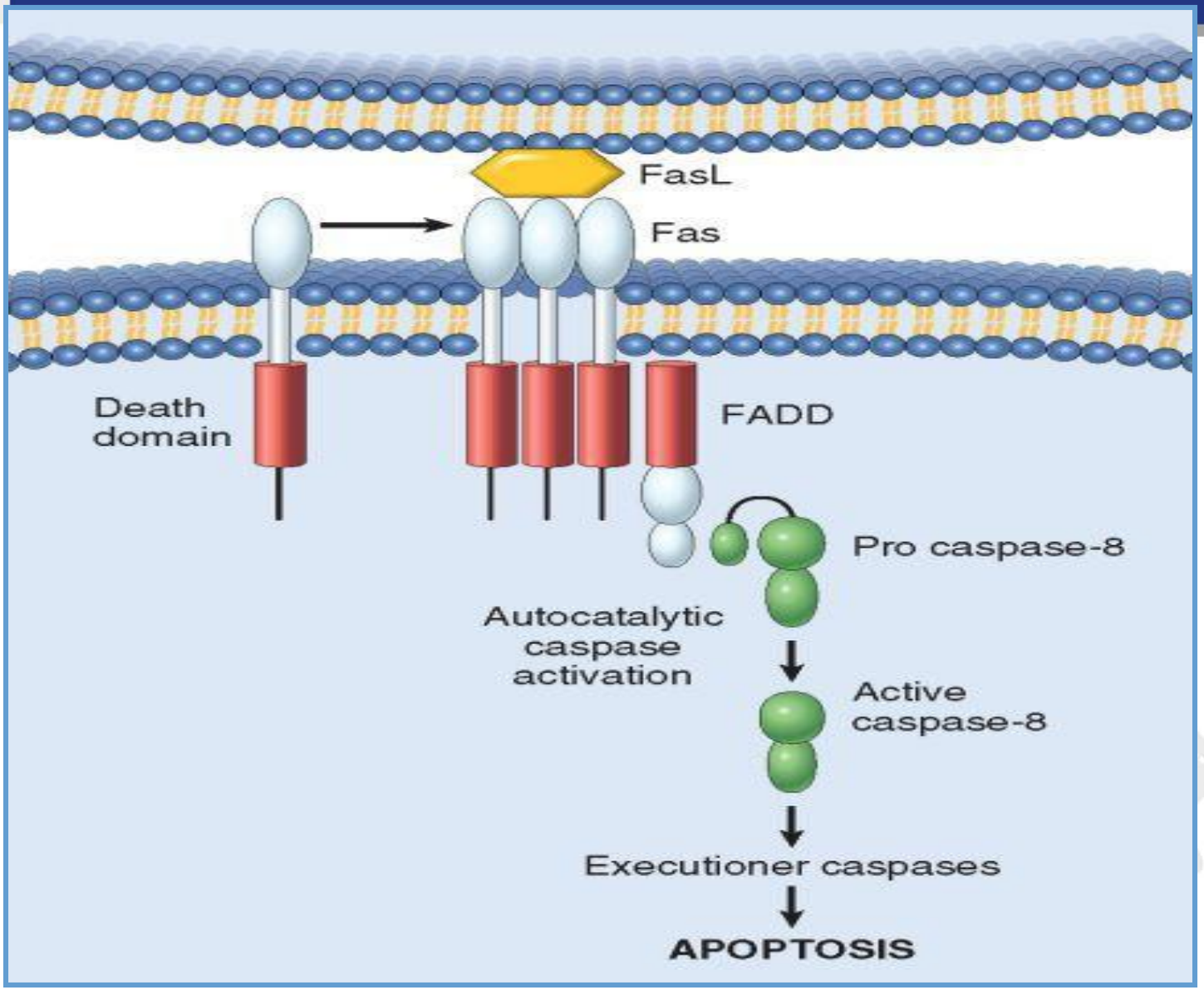
- ***DNA damage (cells undergo apoptosis)***
- ***Accumulation of misfolded proteins***
- ***Cell death in certain infections, particularly viral infections***
- ***Pathologic atrophy in parenchymal organs after duct obstruction, such as occurs in the pancreas, parotid gland, and kidney.***


Intrinsic (mitochondrial) pathway
Extrinsic (death receptor-initiated) pathway
1 Withdrawal of growth factors, hormones
1 Receptor-ligand interactions
• FAS
• TNF receptor
1 Cytotoxic T lymphocytes
Regulators:
Bcl-2 family members
2
Pro-apoptotic molecules, e.g., cytochrome c
Adapter proteins
Initiator caspases
1 Injury
• Radiation
• Toxins
• Free radicals
Mitochondria
DNA damage
p53
Executioner caspases
Granzyme B
3
Endonuclease activation
Breakdown of cytoskeleton
DNA fragmentation
Phagocyte
4 Ligands for phagocytic cell receptors
Cytoplasmic bud
Apoptotic body

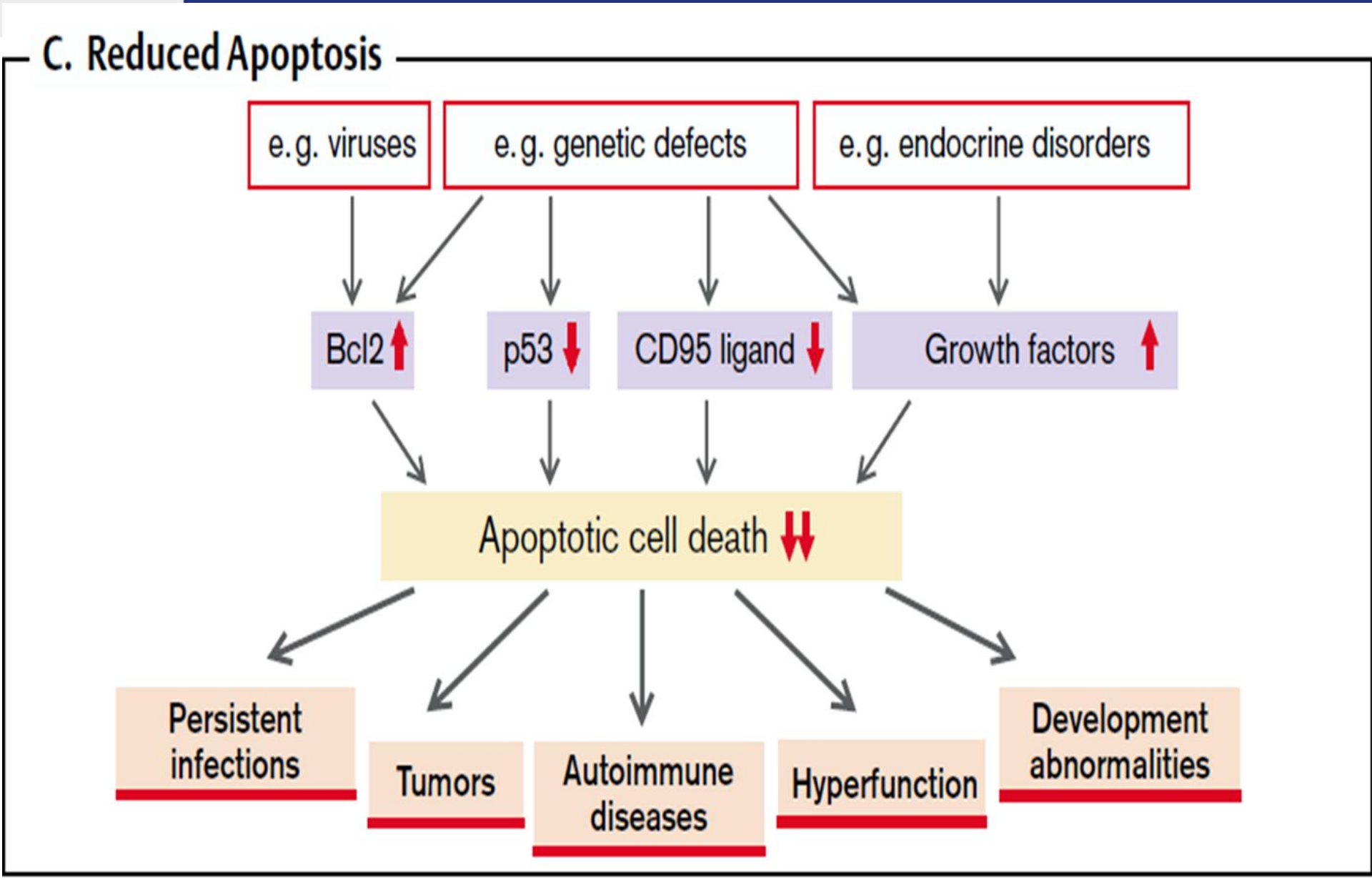
The intrinsic (mitochondrial) pathway of apoptosis



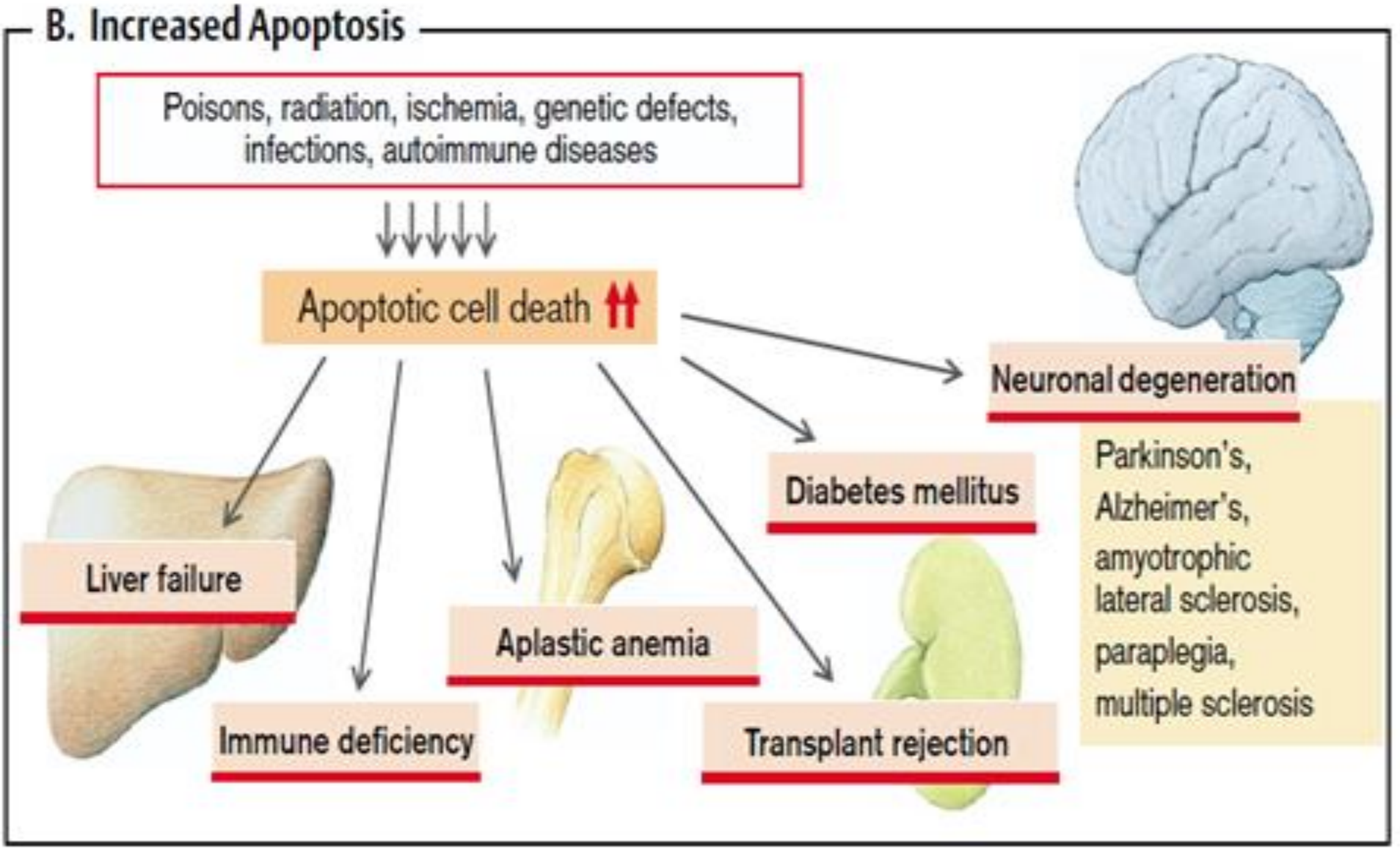
The extrinsic pathway of apoptosis



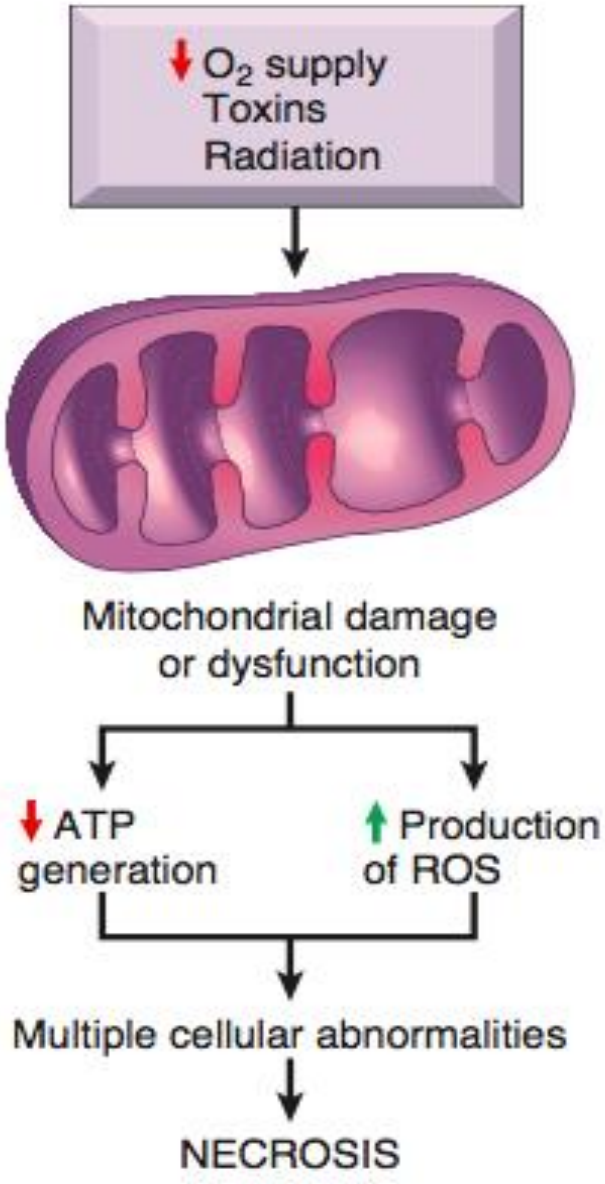
Too little or too much ?



Too little or too much?

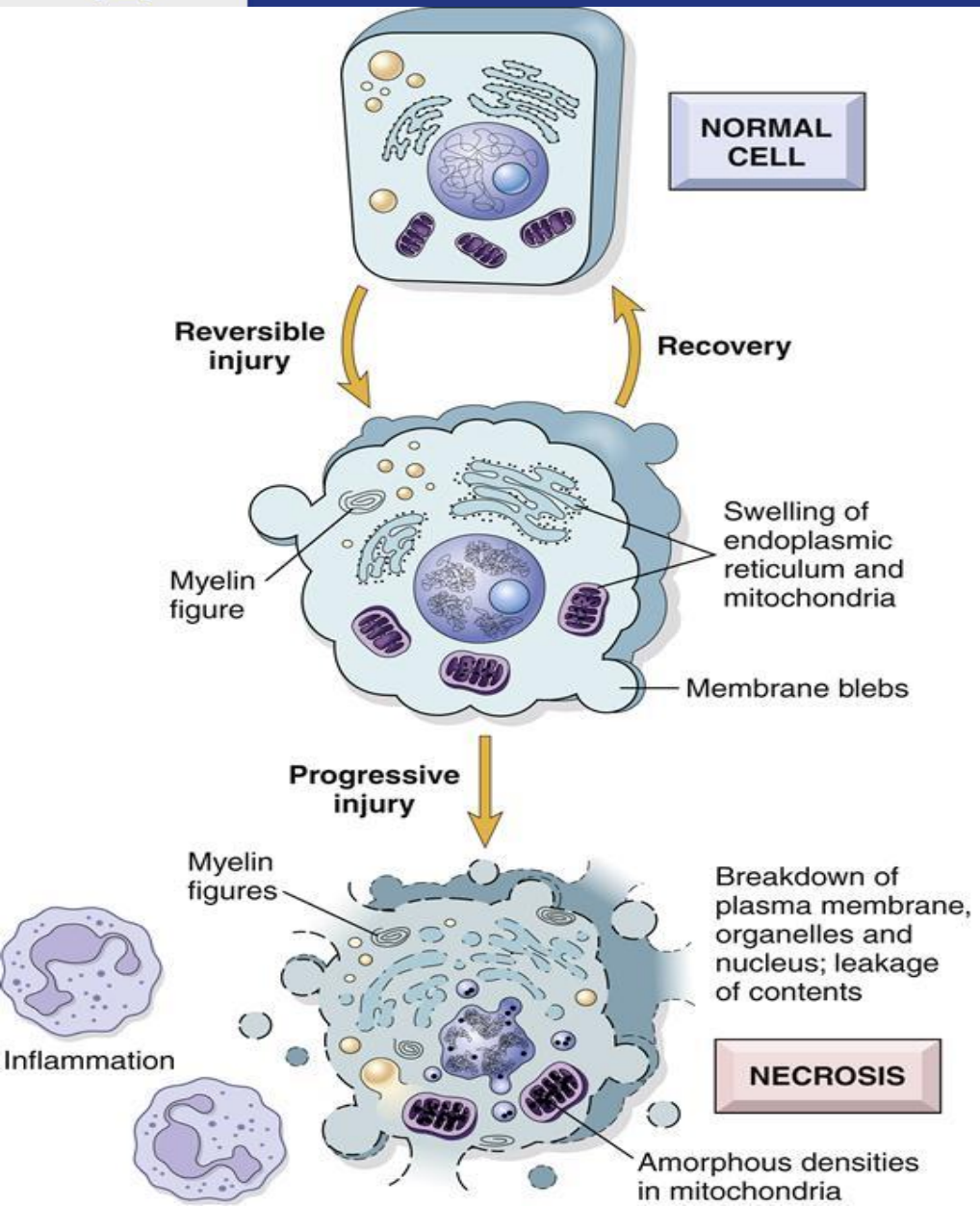


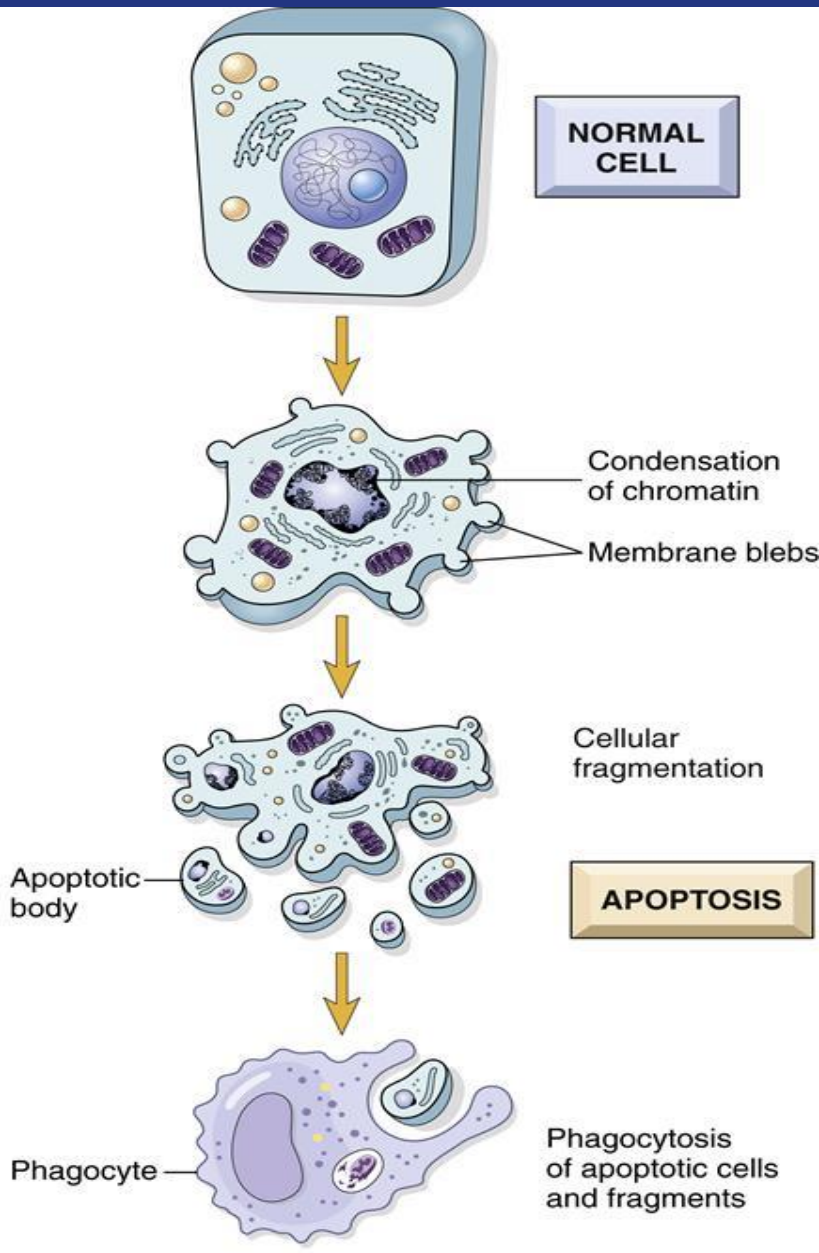
Necrosis



- ***Necrosis** represents the irreversible stop of cell activity, death of the cell or one part of the tissue or entire organ in still living body*.
- **Necrosis may be defined as *accidental death or violent death* occurring in the result of action of harmful factors – endogenous or exogenous.**
- **Necrosis is followed by *necrobiosis* – the process of cell, tissue, organ death, that represents the transition stage of the structure from life to death ("*cellular agony*").**

Necrosis vs Apoptosis





Necrosis vs Apoptosis

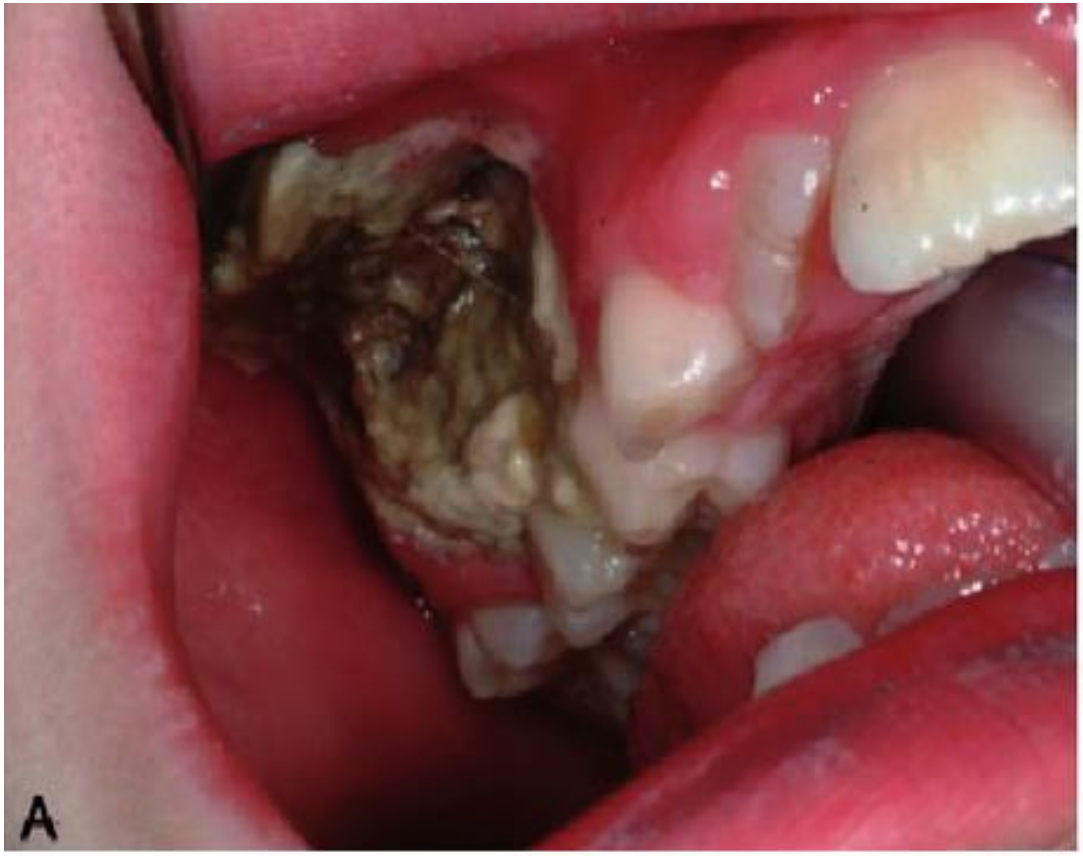
Necrosis

- Cellular swelling
- Membranes are broken
- Cell lyses, eliciting an inflammatory reaction
- DNA fragmentation is random, pyknosis, karyorrehxis, karyolysis.
- Mechanism – ATP depletion, membrane injury, free radical damage.
- In vivo, whole areas of the tissue are affected

Apoptosis

- Cell shrinkage
- Membranes remain intact
- Cell is phagocytosed, no tissue reaction
- DNA fragmentation in to nucleosome size fragments.
- Mechanism – caspase activation, endonuclease and proteases.
- In vivo, individual cells appear affected

Ulcero-necrotic stomatitis



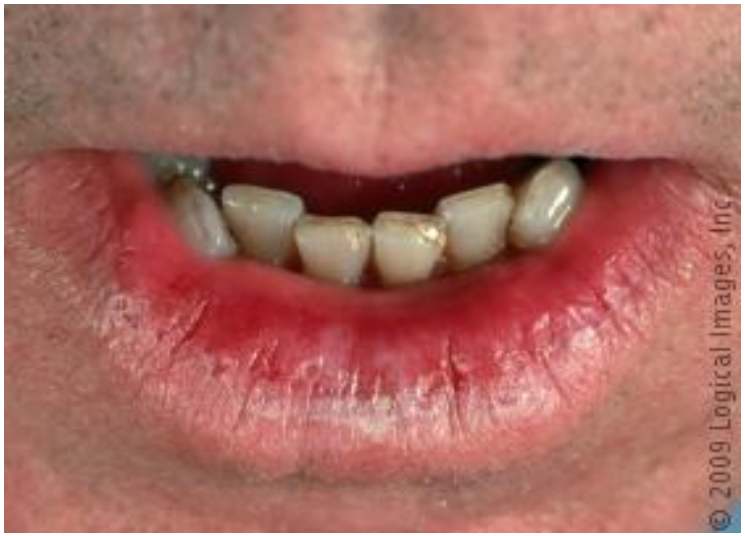
A necrotic ulcer in the gingival mucosa spread from the alveolar process into the buccal mucosa.

Etiological factors: mechanical, chemical (destruction of *adamantine and dentin*)

- **Viral infections**
- **Agranulocytosis**
- **Allergic stomatitis**
- **Heavy metal intoxication**

Multiple necrosis of the mouth mucosa

Multiple necrosis of the mouth mucosa occurs in actinic disease. In this disorder initially there is bucal and labial mucosal tumefaction with hyperemia, petechia, the mucosa being dry and pale, a sensation of burning is characteristic.



THANK YOU
for your
ATTENTION!