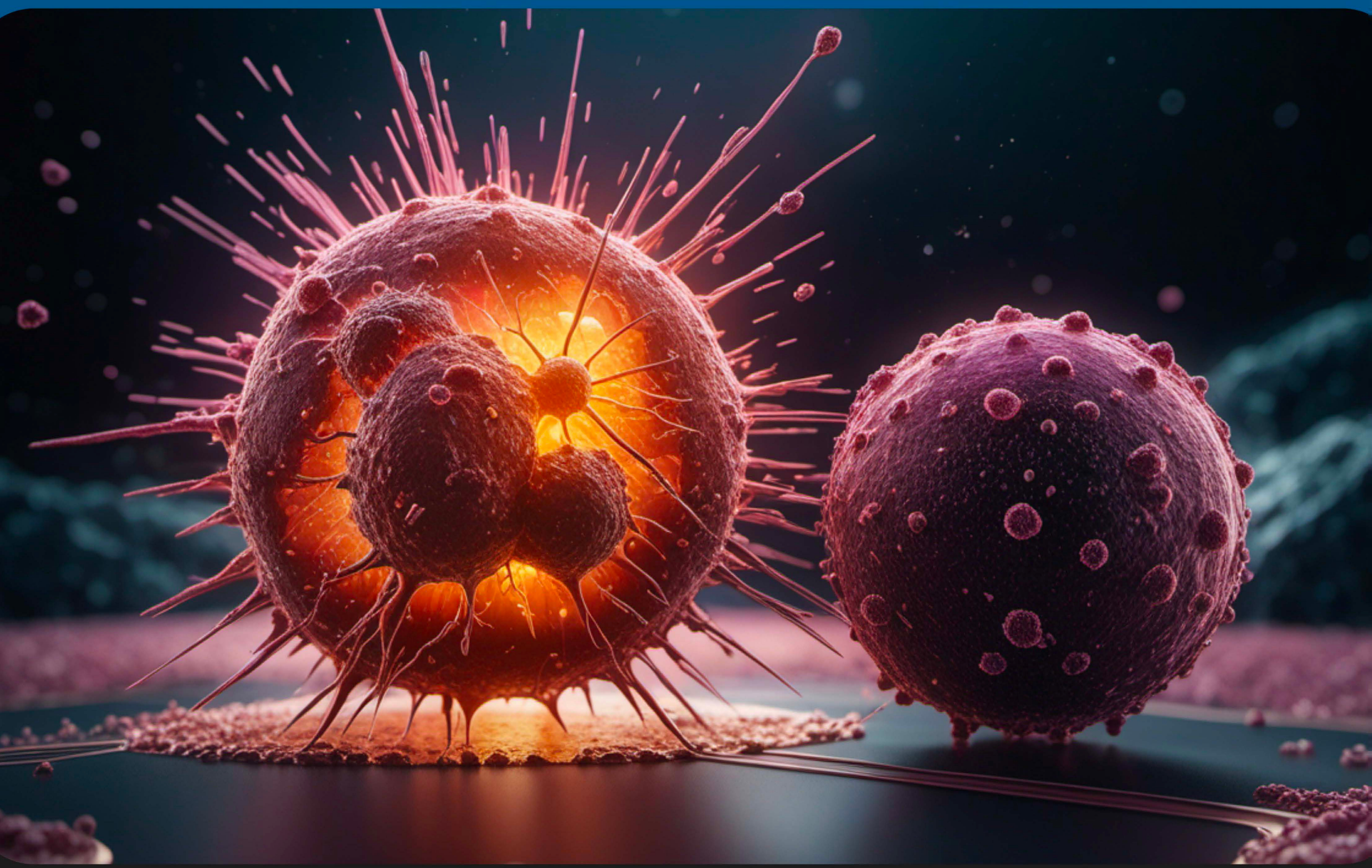
CELL BIOLOGY & BIOCHEMISTRY

TAILORED FOR MEDICAL STUDENTS, USMLE, PLAB, PA & NURSING



4th EDITION

MedicalNote.in

PDF

150 PAGES

MEMBRANE POTENTIAL & EXCITABLE TISSUES

MEMBRANE POTENTIAL & EXCITABLE TISSUES

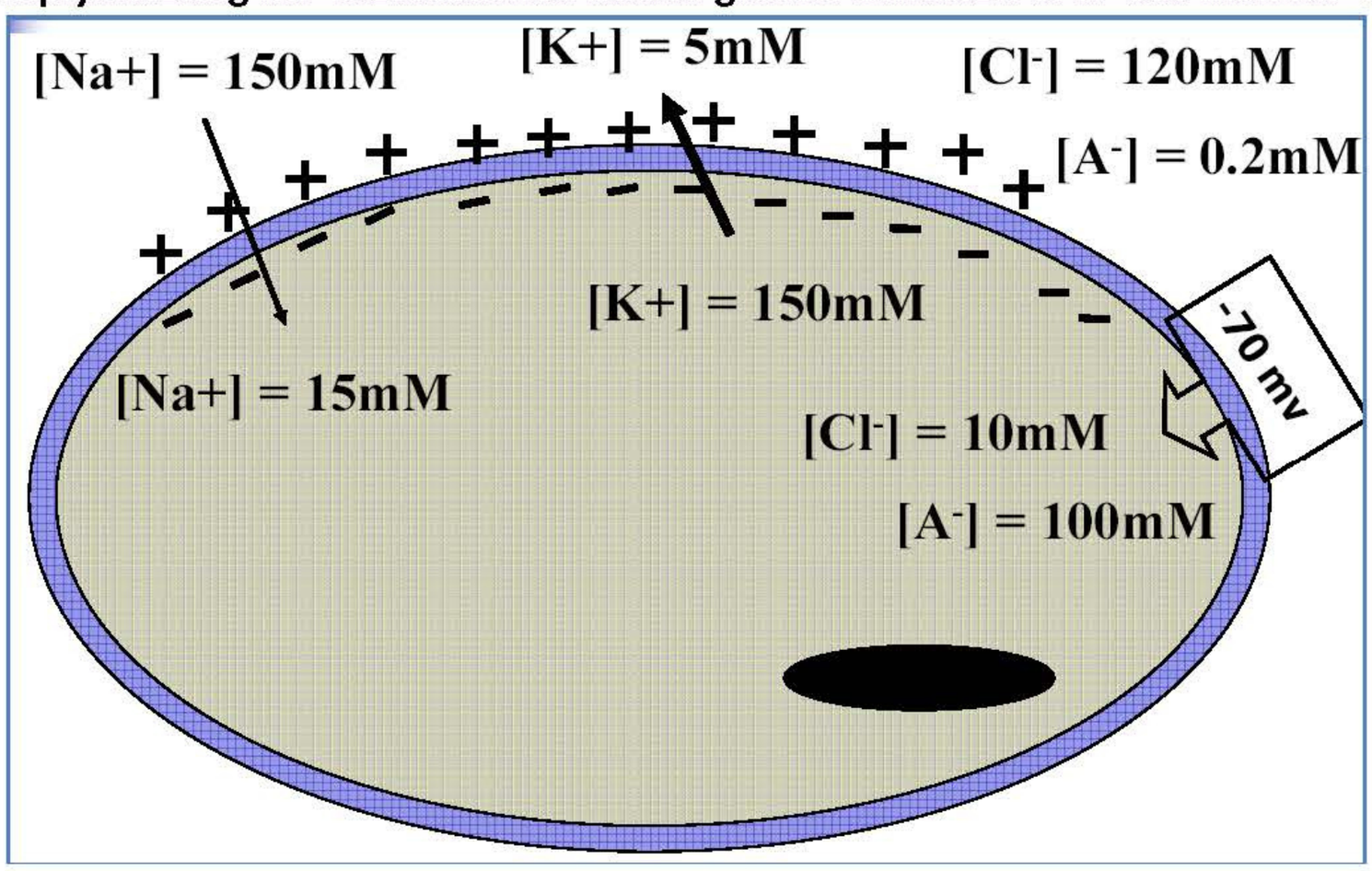
Membrane Potential:

- **= Voltage across membrane**
- **Cause**: unequal distribution of ions (K^+ & Na^+)
- Result of selective/differential permeability of specific plasma membrane proteins (mainly ion channels)
- Evident in all living cells (ranges between -20 & -200mV)
- **In excitable tissues – stimulation causes change in Membrane Potential**
  - Results in activation of the cell
  - Nervous & Muscle Tissues = Excitable Tissues
- **Membrane Potential Depends on:**
  - **Relative permeability** of PM to ions
  - Each ion's **concentration gradient**
  - **Electrochemical gradient**
- **Resting Membrane Potential:**
  - Stable membrane potential of cells when unstimulated
  - **For Nerve Cells** – approx -70mV

Ion Distribution Across Plasma Membrane

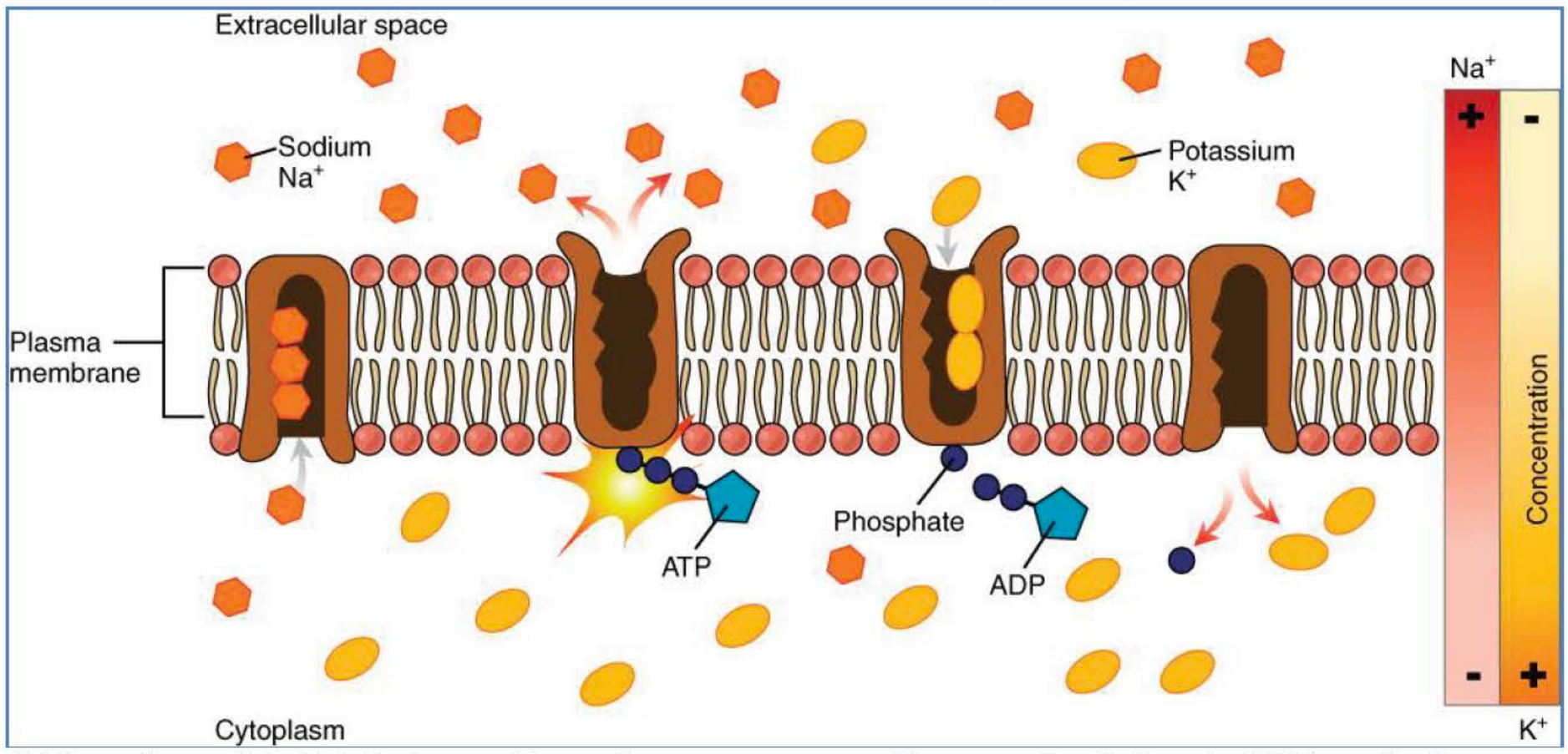
- **K^+: [greater inside cell]**
  - At rest, membrane is **much** more permeable to K^+ than to Na^+
  - Ie: K^+ diffuses out of the cell through **leakage channels** down its concentration gradient
    - Therefore, loss of positive charge from cell makes:
      - Inside the cell negative
      - Outside the cell positive
    - Eventually the negativity of the inner membrane face attracts K^+ back into the cell
      - Therefore, concentration gradient drives K^+ out and is equally opposed by electrical gradient **(equilibrium potential has been reached)**
- **Na^+: [greater outside cell]**
  - Membrane has much lower permeability to Na^+
  - Negative inner membrane-face attracts Na^+ into cell, but is opposed by low permeability
  - Therefore low diffusion of Na^+ into cell

****Simply: Resting MP is established due to greater diffusion of K^+ out than Na^+ in****



The Na/K ATPase: Maintaining the Resting Membrane Potential

- Na passively diffuses into cell and K passively diffuses out
- So Why doesn't the chemical & electrochemical gradients dissipate?
- The **Concentration Gradients** for both Na & K are **maintained** by the **Na/K ATPase**



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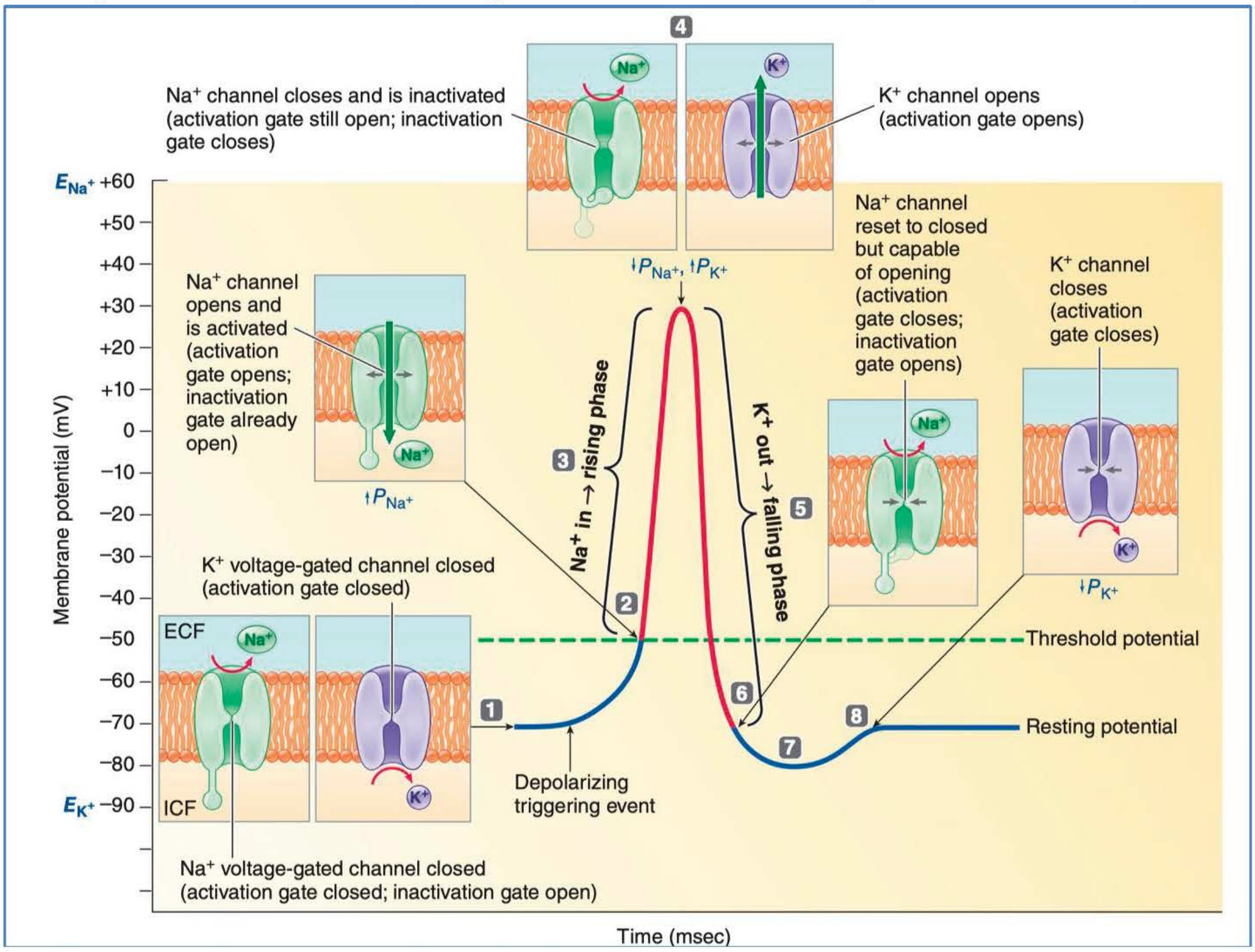
Excitable Tissues (Nerves/Muscle)

- In excitable cells, **stimuli** can **alter the permeability** of the membrane **to K^+ and/or Na^+**
  - Via opening/closing **gated ion channels** (**ligand/chemically gated**, **voltage gated,** mechanically gated, vibration gated, temperature gated)
- This changes the membrane potential
- If the membrane potential is sufficiently altered, an action potential is initiated
- **Action potential:** an **electrical impulse** generated and conducted along a **nerve's** axon in response to stimuli



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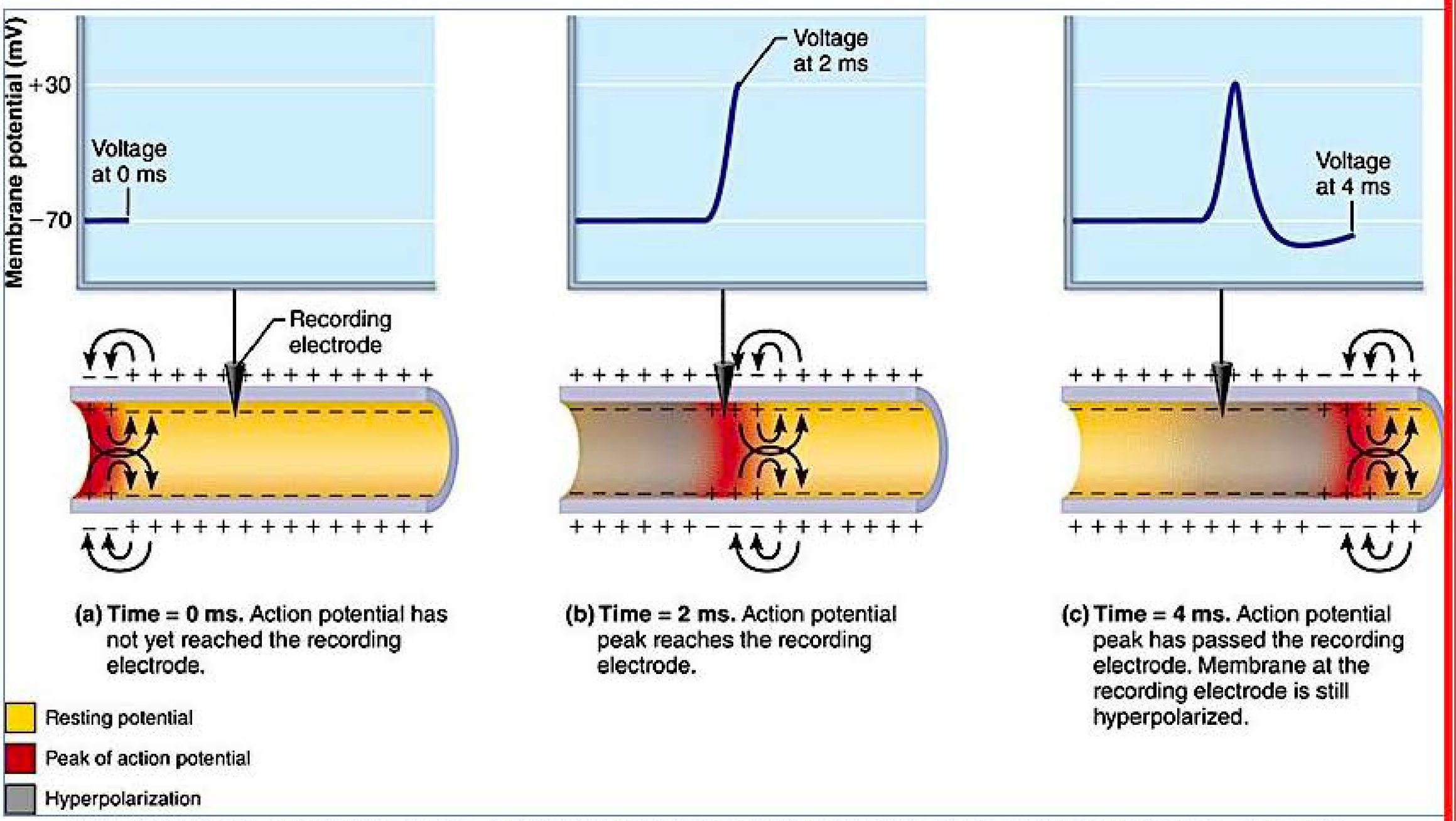
Impulses: are conducted along the length of the axon

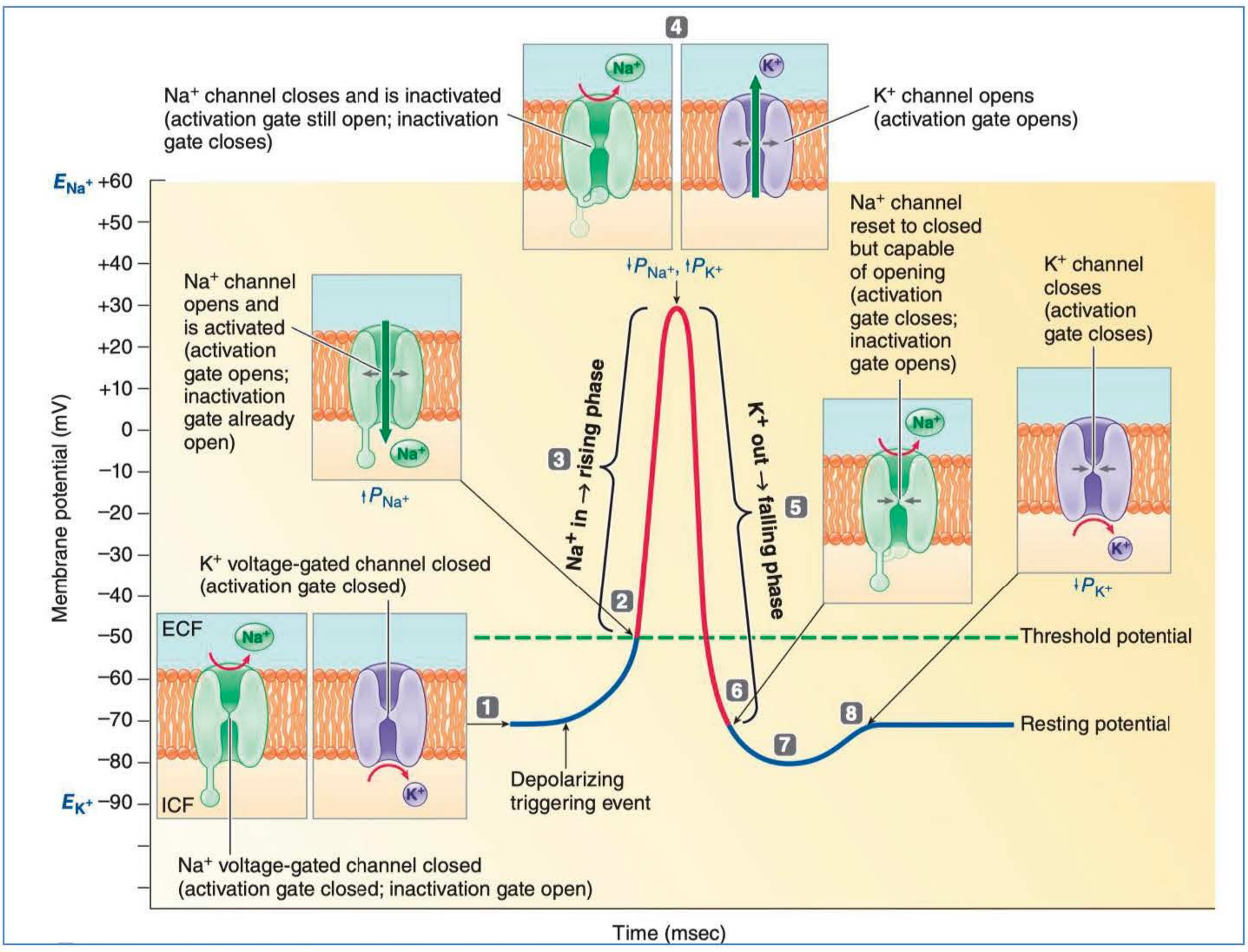
- A wave of action potentials – opening and closing of voltage gated ion channels
- **Action potential:** an impulse frozen in time
- Depolarisation, repolarisation and hyperpolarisation of membrane



Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Action-potential-propagation-along-an-axon-12_fig5_308369018 [accessed 21 Feb, 2022]

Neuronal Action Potentials:

- **Phase 1 – Resting Phase:**
  - Membrane is **much** more permeable to K^+ than to Na^+
  - Greater diffusion of K out than Na in
  - Therefore inside is negative/Outside is positive
  - **Both Na & K voltage gated channels are CLOSED**
- **Phase 2 – Depolarisation Phase:**
  - Mechanical/chemical/vibratory/other stimulus opens some Na^+ channels
  - → Na^+ flows into the cell
  - Therefore membrane potential becomes less negative (Ie: It depolarises)
  - If the MP reaches approximately **-55mV (threshold)**, the **voltage gated Na^+ channels open**
  - → Na^+ influx increases dramatically – until MP reaches approximately **+30mV** where the voltage-gated Na^+ channels close
- **Phase 3 – Repolarisation Phase:**
  - @ approximately +30mV K^+ voltage gated channels open (permeability of K increases & Na decreases)
  - Large outflow of K^+ → membrane potential becomes more negative (repolarises) and returns to -70mV
- **Phase 4 – Hyperpolarisation (undershoot) Phase:**
  - K^+ channels remain open past -70mV and MP becomes more negative than at rest
  - K^+ channels close and Na/K ATPase returns the MP to normal (-70mV)



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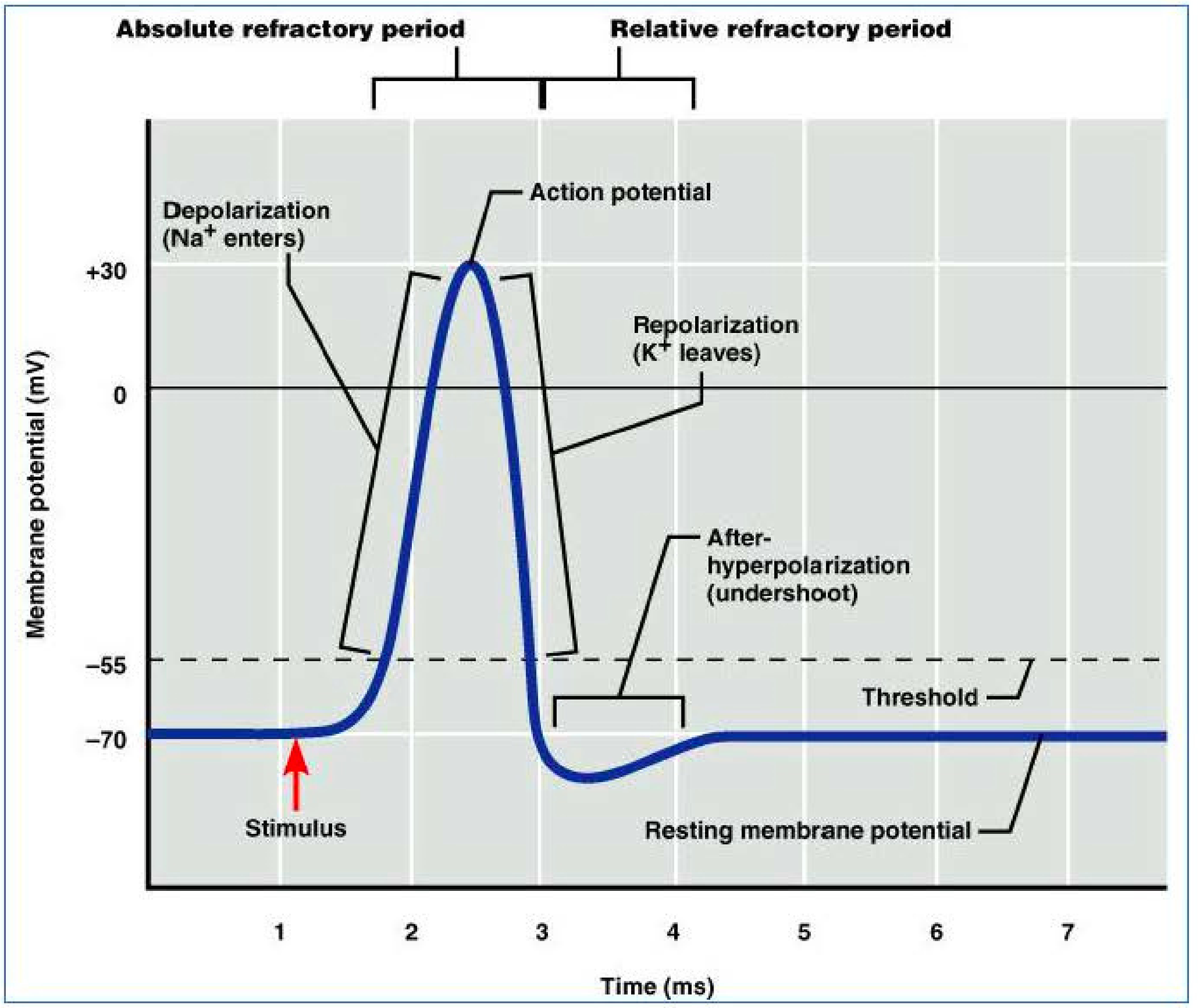
Refractory Periods During the Action Potential:

- **Basically the total time between a stimulus creating an action potential and the MP returning to rest**
  - Usually 3-4ms
  - Determines how soon a neuron can respond to another stimulus
- **Divided into 2 sub-periods:**
  - **Absolute Refractory Period –** no additional stimulus (no matter how large) can initiate a further action potential
    - Stimulus →Depolarisation
    - Repolarisation
  - **Relative Refractory Period –** If an additional stimulus is to initiate another action potential during this time, it must be larger in order to reach threshold
    - Hyperpolarisation → Rest



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TISSUE INJURY & CELLULAR ADAPTATIONS

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Cellular Responses to Stress & Noxious Stimuli:

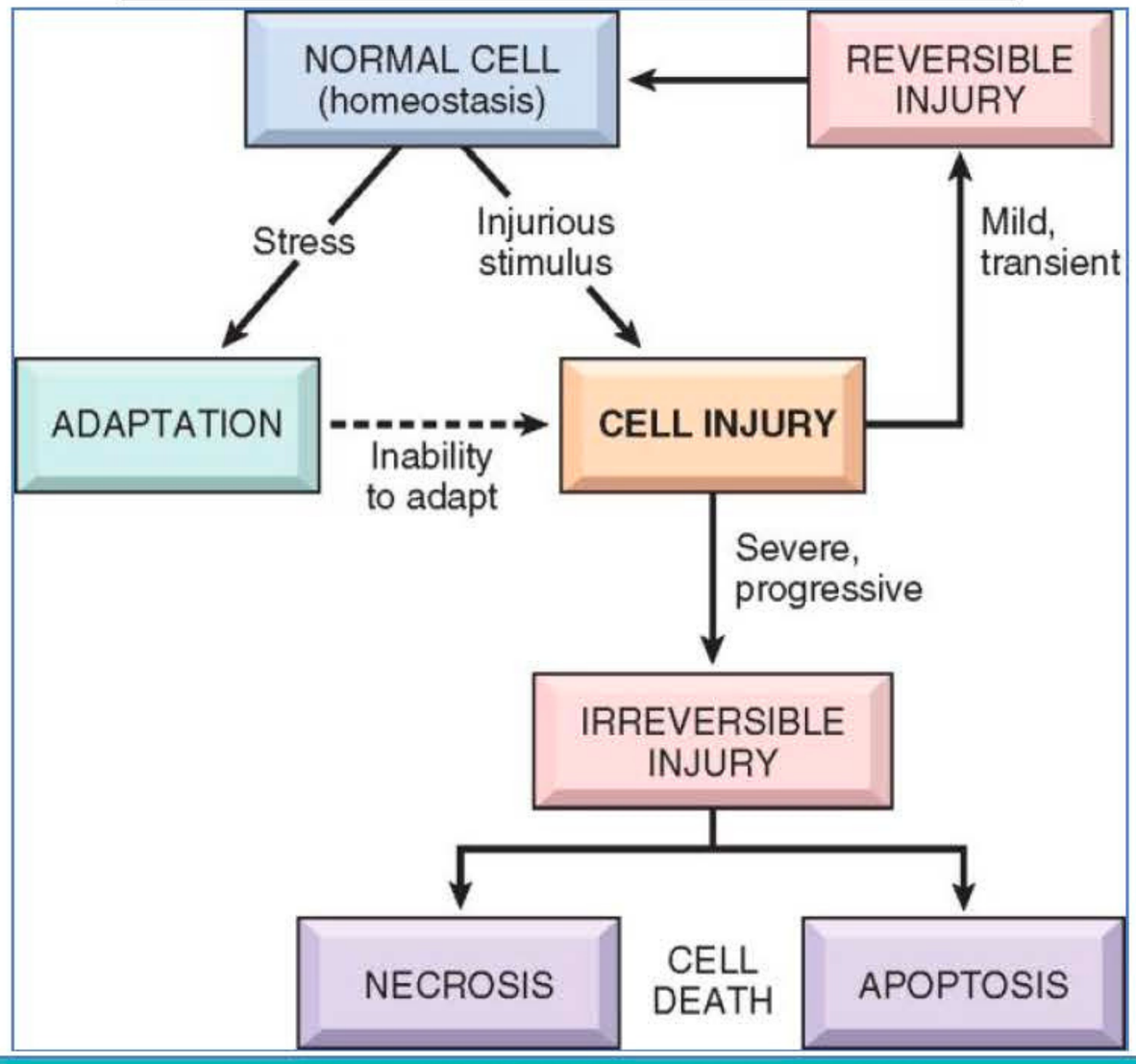


TABLE 1–1 Cellular Responses to Injury

Nature of Injurious Stimulus	Cellular Response
ALTERED PHYSIOLOGICAL STIMULI; SOME NONLETHAL INJURIOUS STIMULI	**CELLULAR ADAPTATIONS**
• Increased demand, increased stimulation (e.g., by growth factors, hormones) • Decreased nutrients, decreased stimulation • Chronic irritation (physical or chemical)	• Hyperplasia, hypertrophy • Atrophy • Metaplasia
REDUCED OXYGEN SUPPLY; CHEMICAL INJURY; MICROBIAL INFECTION	**CELL INJURY**
• Acute and transient • Progressive and severe (including DNA damage)	• Acute reversible injury Cellular swelling fatty change • Irreversible injury → cell death Necrosis Apoptosis
METABOLIC ALTERATIONS, GENETIC OR ACQUIRED; CHRONIC INJURY	**INTRACELLULAR ACCUMULATIONS; CALCIFICATION**
CUMULATIVE SUBLETHAL INJURY OVER LONG LIFE SPAN	**CELLULAR AGING**

1 Cellular Responses to Stress and Toxic Insults: Adaptation , Injury , and Death.
https://www.semanticscholar.org/paper/1-Cellular-Responses-to-Stress-and-Toxic-Insults-%3A/fbffc46199b0539126b45c3f23933708f7dc3948

Cellular Adaptations - in Response to Stress:

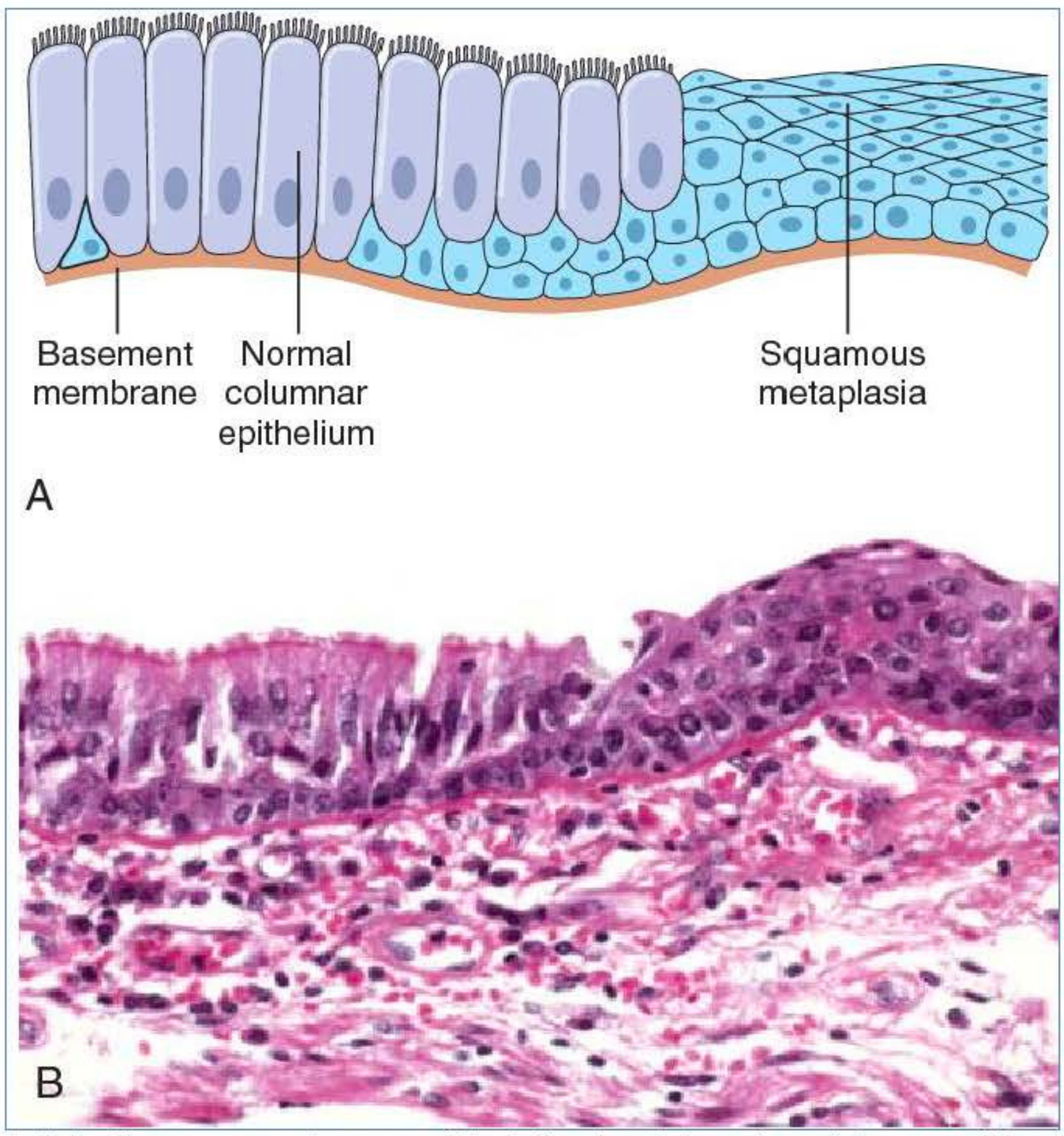
- (Cells may *Adapt* & *Change Their Size/Number/Structure/Function* in response to Changing Demands/↑Physiological Stress/Pathological Stimuli)

- **Hypertrophy:** (↑Size of Cells)
  - Hypertrophied organs have NO *New* Cells, just *Larger* Cells
  - Often a response in cells that are unable to divide – Eg: Muscles Cells
  - The Most Common Stimulus = ↑Workload
  - **Physiological Hypertrophy:**
    - Eg: Growth of Myometrium (Uterine Muscle) during Pregnancy
    - Eg: ↑Muscle Mass following Exercise (Both Cardiac & Skeletal)
  - **Pathological Hypertrophy:**
    - Eg: Cardiac Hypertrophy as a compensatory mechanism for Heart Failure
  - **Mechanisms of Hypertrophy:**
    - ↑ Workload → Triggers Mechanical Sensors/Growth Factors/Vasoactive Agents → ↑Synthesis of Cellular Proteins
    - Hypertrophy is the result of ***Increased Production of Cellular Proteins***

- **<u>Hyperplasia:</u>** (↑Number of Cells)
    - Same stimulus as Hypertrophy (↑Workload), however cells are capable of dividing → ↑in Number
    - **Physiologic Hyperplasia:**
        - **'Hormonal':**
            - Increases the Functional Capacity of a Tissue *When Needed*
            - Eg: Mammary Gland Hyperplasia during Pregnancy
        - **'Compensatory':**
            - Increases Tissue Mass after Damage or Partial Resection
            - Eg: Hyperplasia after removing part of the Liver
    - **Pathologic Hyperplasia:**
        - Mostly caused by *Excesses of Hormones/Growth-Factors* acting on target cells
        - Distinct from 'Cancer' in 2 ways:
            - **1)** There are NO MUTATIONS in genes regulating cell division, &
            - **2)** The Hyperplasia regresses if the Hormonal Stimuli is removed
        - Eg: 'Endometrial Hyperplasia' – an example of *Abnormal* hormone-induced hyperplasia
        - Eg: 'Benign Prostatic Hyperplasia' – induced by Androgens
        - Eg: Skin warts due to Papillomavirus
    - **Mechanisms of Hyperplasia:**
        - Hyperplasia is the result of *Growth-Factor-Driven Proliferation* of *Mature Cells* & sometimes *Stem Cells*

- **<u>Atrophy:</u>** (↓Size & ↓Cell Number)
    - Can be Due to:
        - ↓Workload
        - Loss of Innervation
        - Diminished Blood Supply
        - Loss of Endocrine Stimulation (Eg: Ovaries during menopause)
        - Inadequate Nutrition
    - **Physiologic Atrophy:**
        - Eg: Common during normal foetal development
        - Eg: Atrophy of Uterus following Parturition
    - **Pathologic Atrophy:**
        - Depends on the underlying cause; Can be general or localized:
            - Disuse Atrophy – (↓Workload)
            - Denervation Atrophy – (Loss of innervations)
            - Diminished Blood Supply – (Ischaemic)
            - Inadequate Nutrition
            - Loss of Endocrine Stimulation:
            - Tissue Compression
    - **Mechanisms of Atrophy:**
        - Initial Response – Cell decreases in size & organelles → ↓Metabolic Demands
        - This results from ↓Protein Synthesis & ↑Protein Degradation in cells
        - Cells may also resort to ***Autophagy*** ("Self-Eating"), eating its own components for nutrients

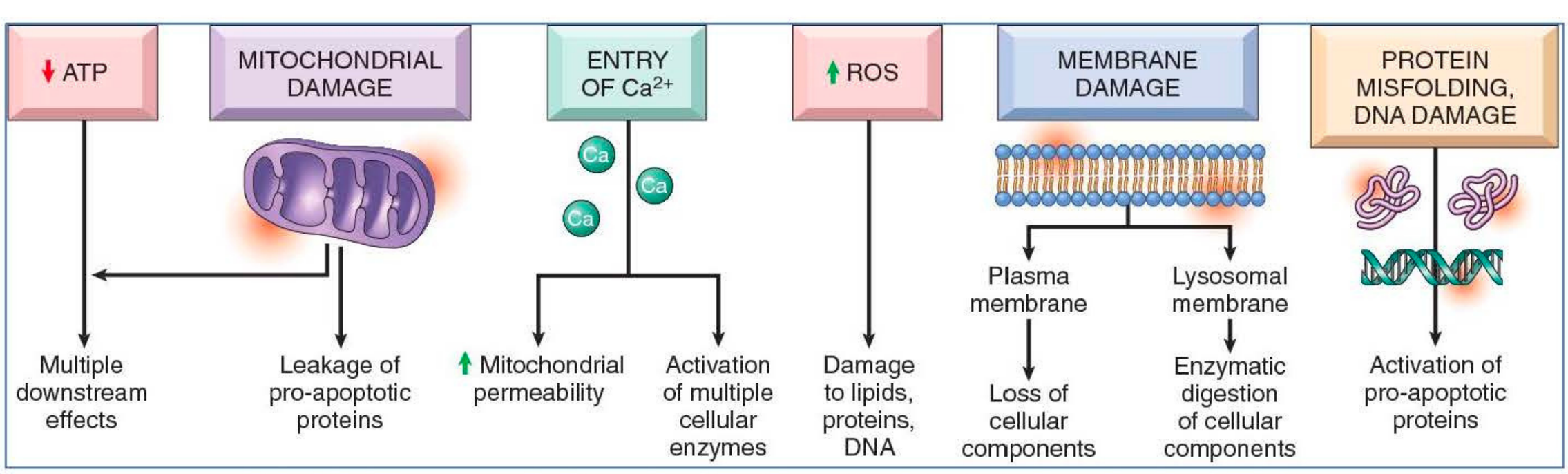
- **Metaplasia:** (Reversible Change in Phenotype of Cells)
    - A reversible change in which one differentiated cell type is replaced by another cell type
    - It is an adaptive substitution of vulnerable cells for cells types better able to withstand the adverse environment
    - **Pathologic Metaplasia:**
        - Eg: Gastro-Oesophageal Reflux Disease → Oesophagus changes from *Squamous* to *Columnar* Epithelium in lower Oesophagus (Gives better protection against acid)
        - Eg: Chronically Irritated Mucous Membranes of Respiratory Tract change from *Columnar* to *Squamous* from Smoking (This affects the Mucociliary Escalator since there are no cilia)
        - Eg: Connective Tissue Metaplasia – The formation of cartilage/bone/adipose tissue in tissues that normally don't contain these elements (Eg: Bone formation in muscle)
    - **Mechanisms of Metaplasia:**
        - It is the result of a *Reprogramming of Stem Cells* beneath the stressed cells, which change their potential phenotype
        - This is due to Cytokines/Growth Factors/Extracellular Matrix-interactions with environment



1 Cellular Responses to Stress and Toxic Insults: Adaptation , Injury , and Death. https://www.semanticscholar.org/paper/1-Cellular-Responses-to-Stress-and-Toxic-Insults-%3A/fbffc46199b0539126b45c3f23933708f7dc3948

Cell Injury & Cell Death – in Response to Noxious Stimuli:

- When cells are stressed so severely that they can no longer adapt
- Injury may progress through a reversible stage and may culminate in cell death
- **Note:** Cell injury is Reversible up to a point, but if the stimulus persists, or is severe enough, it becomes irreversible → Cell Death
- **Causes of Cell Injury:**
  - **#1 Oxygen Deprivation → Ischaemic/Hypoxic Injury:**
    - Deficiency of oxygen (Hypoxia)→ ↓Aerobic Oxidative Respiration
    - The most common form of injury in clinical practice
    - **Causes include:**
      - Reduced Blood Flow (Ischaemia)
      - Inadequate oxygenation of the blood (Systemic Hypoxia)
      - Decreased O_2 carrying capacity of blood (eg: Anaemia/CO-Poisoning)
  - **Physical Agents:**
    - Eg: Mechanical Trauma
    - Eg: Extreme Temperatures (Hot & Cold)
    - Eg: Sudden changes in pressure
    - Eg: Radiation
    - Eg: Electric Shock
  - **Chemicals & Drugs (Acid/Basic/Toxic/etc)**
  - **Infectious Agents (Directly or by Toxins)**
  - **Immunological Reactions:**
    - Eg: Immune reactions to self-antigens → Autoimmune Diseases
  - **Genetic Derangements (Mutations affect essential cellular constituents)**
  - **Nutritional Imbalances:**
    - Eg: Vitamin Deficiencies
    - Eg: Excess cholesterol → Atherosclerosis



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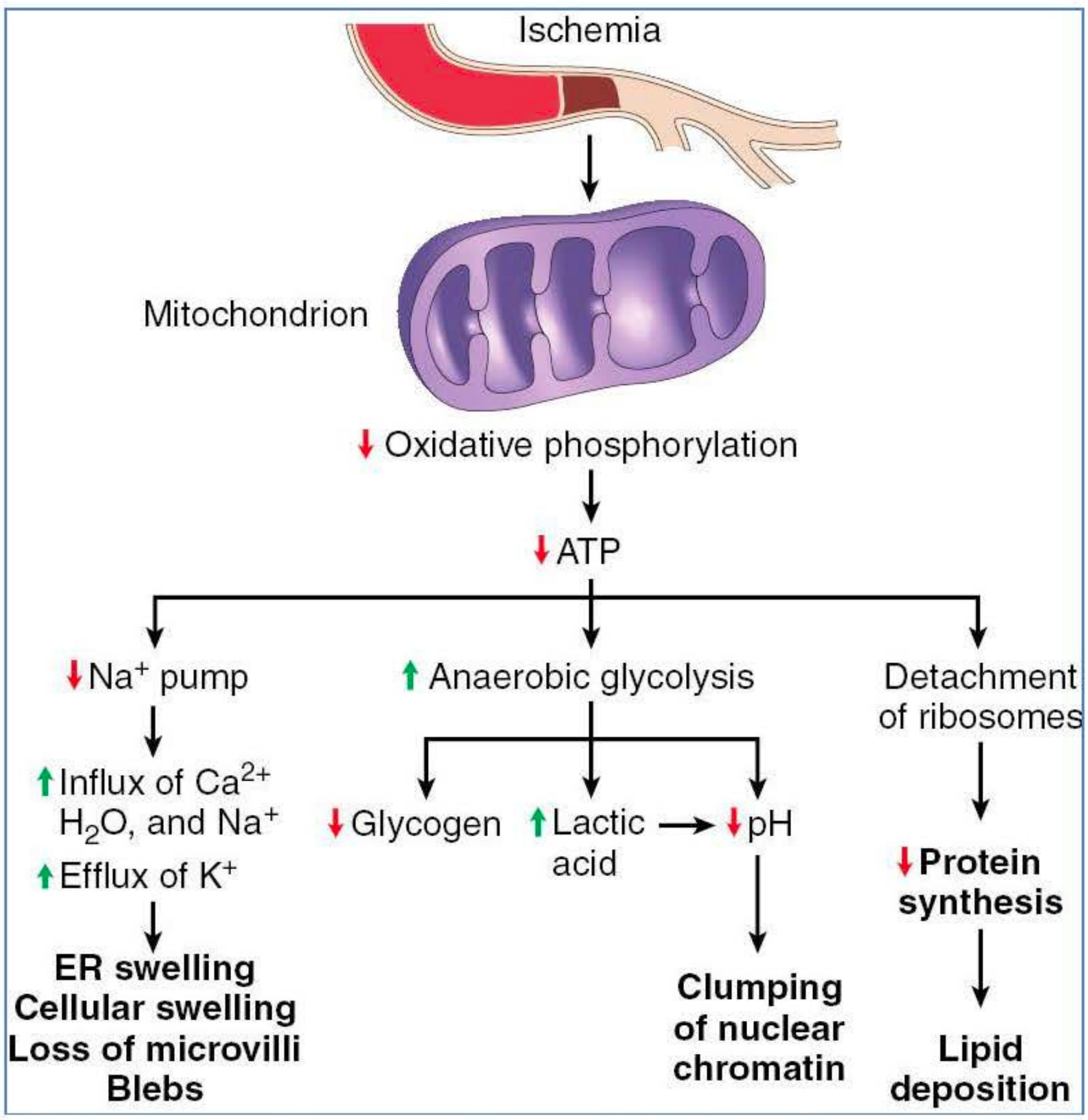
- **Q – Why do the *Centro-Lobular* Hepatocytes always seem to be worse off during Toxic/Ischaemic Injury?**
  - **A – 2 Reasons:**
    - Centro-lobular areas receive second-hand blood from the outer-lobular areas, which is:
      - a) Low in Oxygen,
      - b) Low in Nutrients
      - & c) Full of cell-waste
    - Blood tends to pool in the centro-lobular region due to the slow-draining single central vein → The cells are exposed to the toxins for slightly longer

Biochemical Mechanisms of Cell Injury:

- **Depletion of ATP:**
  - **Major Causes:**
    - **Ischaemia** → ↓O_2 & ↓Nutrients
      - Hypoxia → ↓Oxidative Phosphorylation
      - Nutrient Depletion → ↓Metabolism (including Glycolytic pathway)
      - Note: Tissues with greater glycolytic capacity (eg: Liver) last longer than those without (eg: Brain)
    - **Certain Toxins** – Affecting Electron Transport Chain - (Eg: Cyanide, Oligomycin, Rotenone, Antimycin, Carbon-Monoxide) → Prevents Oxidative Phosphorylation
    - **Mitochondrial Damage**→ Leakage of Pro-Apoptotic Proteins (Eg: Cytochrome-C)
  - **Major Metabolic Pathways that are Vulnerable:**
    - *Glycolytic Pathway (Some anaerobic capacity)
    - *Oxidative Phosphorylation of ADP→ATP (Electron Transport Chain - Mitochondria)
  - **Consequences** → ATP is required for all processes within the cell. Hence, deficiency →
    - ↑Anaerobic Glycolysis:
      - →Glycogen Depletion
      - →Lactic Acid Buildup → ↓pH → ↓Activity of essential Enzymes
    - ↓Active Membrane Transport:
      - Failure of Na/K-ATPase → Intracellular Na^+ Accumulation →Cell Swelling
      - Failure of Ca pump → Ca Influx → widespread damage (see diagram)
    - ↓Protein Synthesis
    - ↓Lipogenesis
    - Ultimately leads to Irreversible Mitochondrial/Lysosomal Membrane Damage → Cell Death.



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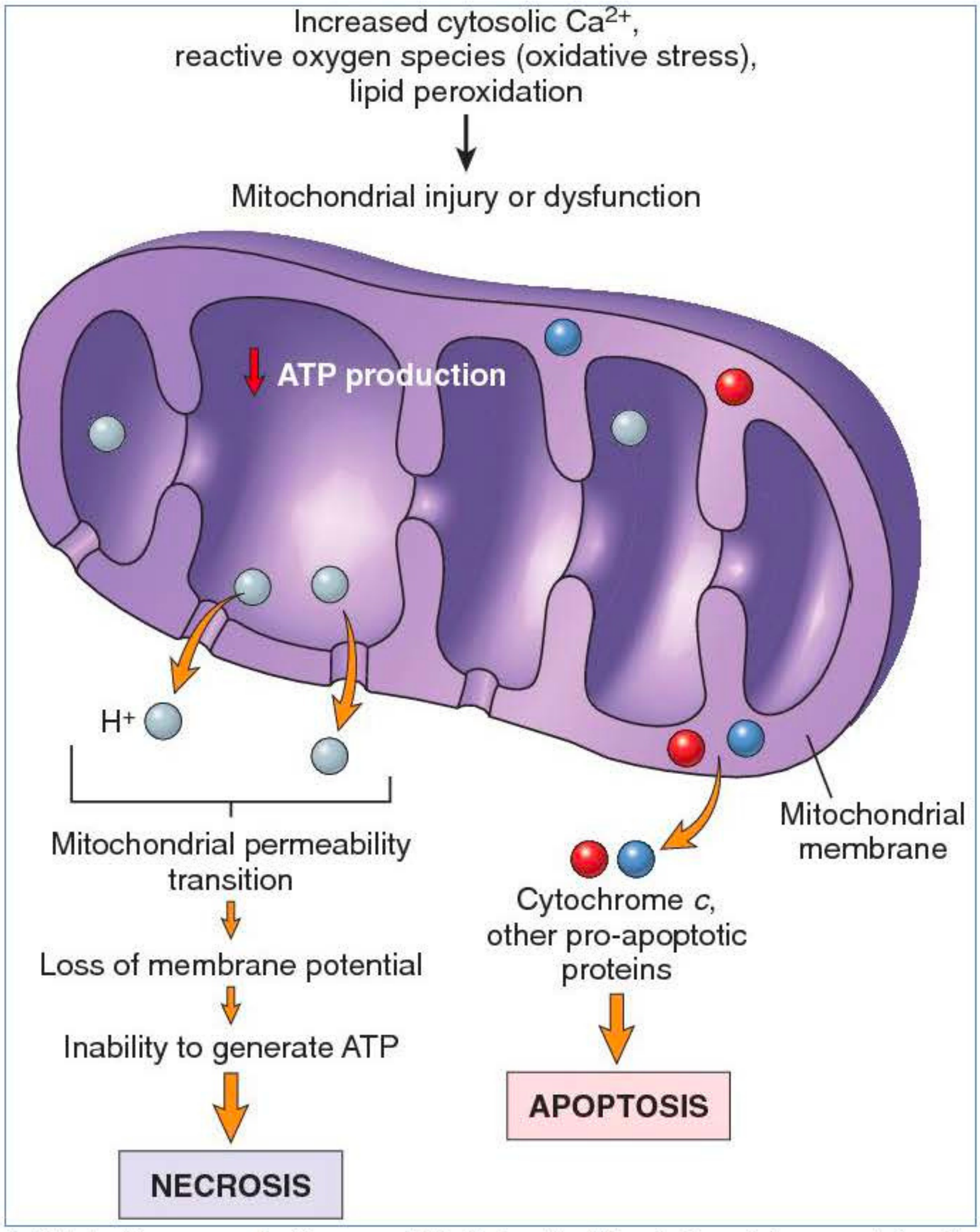
- **Mitochondrial Damage:**
  - **Note:** Irreparable mitochondrial damage *kills cells* – due to reliance on oxidative metabolism
  - **Major Causes:**
    - **Hypoxia**
    - **Free Radicals**
    - **High Cytosolic Ca^+**

    } → ↑Mitochondrial Permeability
  - **Consequences →**
    - High-Conductance channels, called ***Mitochondrial Permeability Transition Pores***, form in mitochondrial membrane → Loss of Mitochondrial Membrane Potential → Failure to Oxidative Phosphorylation → ATP Depletion → Necrosis of cell
    - Leakage of Inter-mitochondrial-membrane substances (Eg: Cytochrome-C) can activate Apoptotic Pathways (Ie: The Caspase Cascade)



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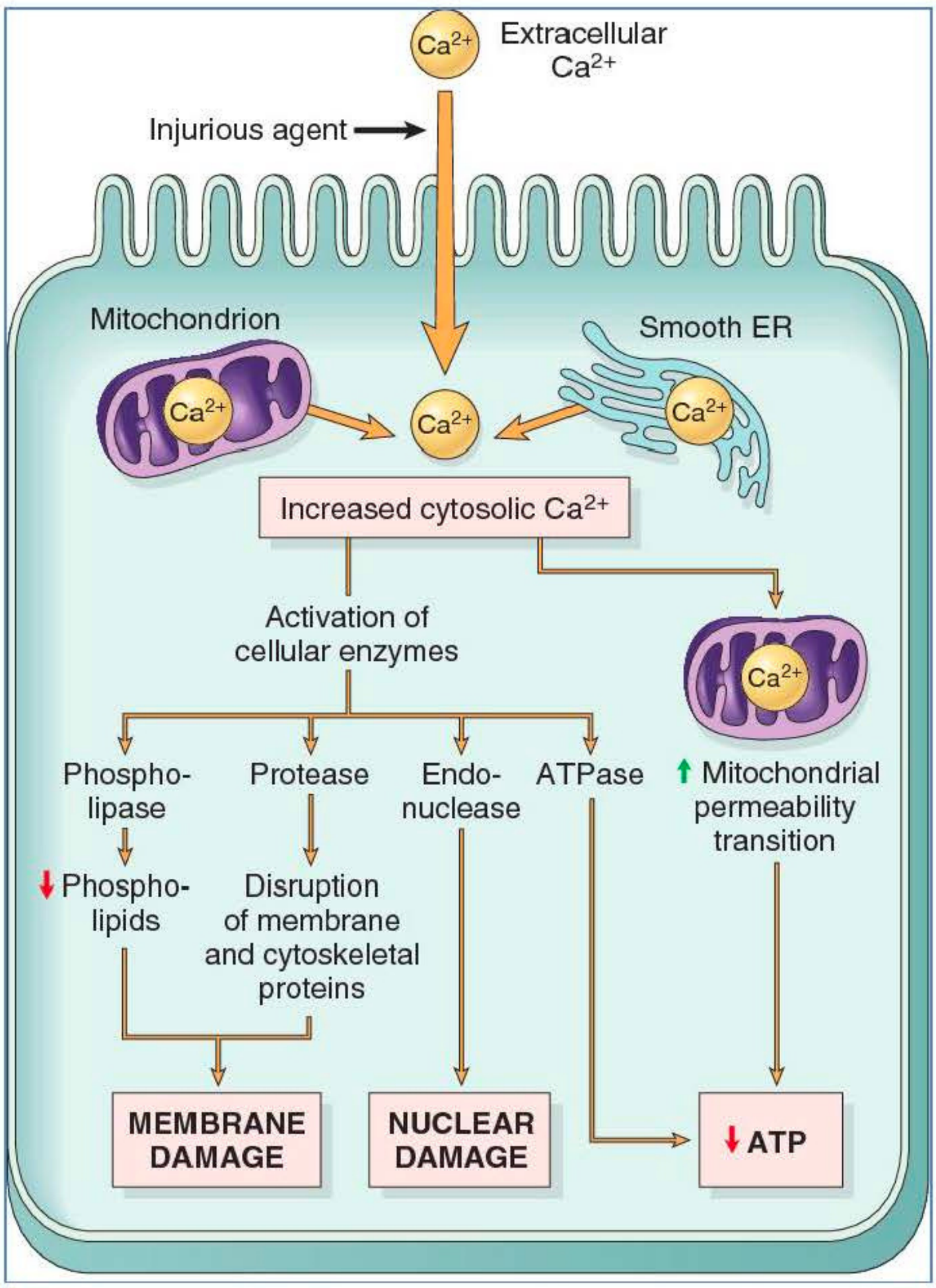
- **Loss of Calcium Homeostasis & Ca^+ Influx:**
  - Ca^+ is normally maintained at very low concentrations in the Cytosol by *Energy-Dependent* Systems
  - **Major Causes:**
    - **Toxins** → Causing Ca^+ release from intracellular stores (Mitochondria & Endoplasmic Reticulum)
    - **Hypoxia** → ATP Depletion → Can't feed Active Ca^+ Export Systems → Net Ca^+ influx across the Plasma Membrane
  - **Consequences** →
    - ↑Ca^+ → Opens *Mitochondrial Permeability Transition Pores* in mitochondrial membrane → Loss of Mitochondrial Membrane Potential → Failure to Oxidative Phosphorylation → ATP Depletion → Necrosis of Cell
    - ↑Ca^+ → Activates destructive enzymes (ATPases, Phospholipases, Proteases & Endonucleases) – See Diagram
    - ↑Ca^+ → Direct Activation of Caspases & Leakage of Cytochrome-C → Induces Apoptosis by Direct Activation of Caspases & release of pro-apoptotic substances (Including Cytocrhome-C)



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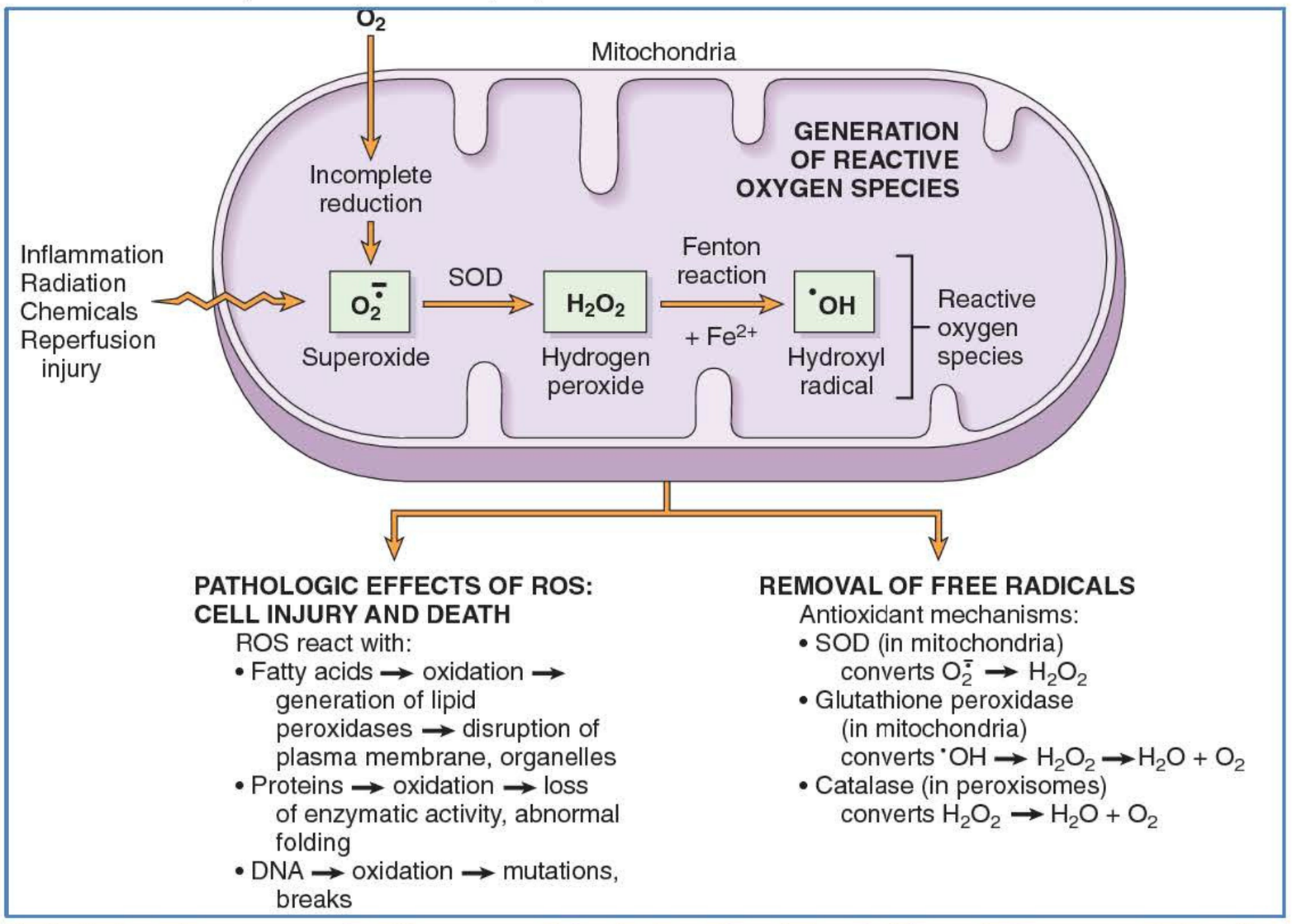
- **<u>Oxygen-Derived Free-Radicals (Oxidative Stress):</u>**
  - **What are Free Radicals?**
    - AKA: Reactive Oxygen Species
    - Are normal by-products of mitochondrial respiration
    - Are chemicals with a ***Single Un-Paired Valent Electron*** → Oxidising Potential
  - **Major Causes: (Generation of ROS):**
    - **Normal Metabolism** - Normal Redox reactions during normal metabolic processes
    - **Radiation** - Absorption of radiant energy (Eg: UV/Xray/Microwave)
    - **Inflammation** - Produced by Phagocytes during Inflammation
    - **Chemicals** - Metabolism of some exogenous Chemicals (eg: some Drugs)
    - **Re-Perfusion Injury –** Exacerbation of Injury due to Restoration of blood flow to Ischaemic Tissues
  - **Removal of ROS:**
    - **Spontaneous Decay** - in the presence of H_2O
    - **Radical-Scavenging Systems** - Enzymatic mechanisms that remove Free Radicals
    - **Antioxidants** - (eg: Vits A/E/C) Remove/Mop Up/Prevent/Inactivate Free Radicals
    - **Proteins** - Reactive metals are bound to storage/transport proteins in blood
  - **What is "Oxidative Stress"?:**
    - Imbalance occurs between Free-Radical production & Radical-Scavenging-Systems
    - Ie: ↑↑Free-Radicals
  - **Consequences of ↑ROS→**
    - **Membrane-Lipid Peroxidation:**
      - Oxidative damage of Lipids within Plasma/organelle Membranes
      - → Damages membranes
    - **Oxidative Modification of Proteins:**
      - → Damage Active Sites on Enzymes
      - → Disrupt Conformation of Structural Proteins
      - Enhance action of Proteases → Continued Protein Degradation
    - **DNA Damage:**
      - Oxidative damage → breaks in the DNA strands/Mutations/Cross-Linking/etc – Ie: Stuff that isn't supposed to happen
      - → Cellular Ageing
      - → Cancer
    - **Cell Death:**
      - By Necrosis OR Apoptosis



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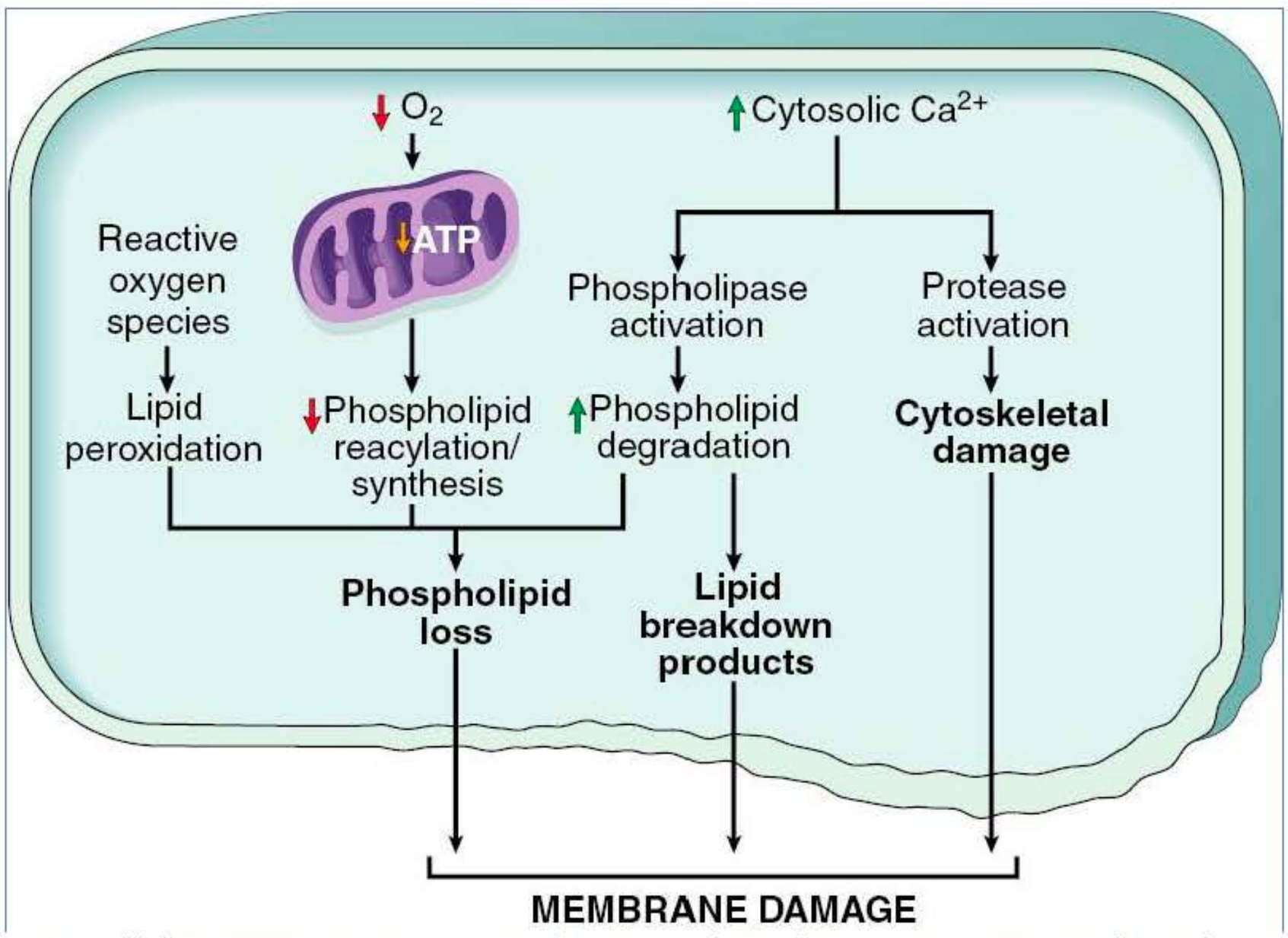
- **<u>Defects in Membrane Permeability:</u>**
  - **Causes: Occurs in all forms of Cell Injury – (EXCEPT Apoptosis):**
    - **Eg: Ischaemia →**
      - ATP Depletion → ↓Phospholipid Synthesis
    - **Eg: Free-Radicals →**
      - Membrane-Lipid Peroxidation
      - Oxidative Modification of Proteins (structural/enzymes/Cytoskeleton)
    - **Eg: Ca^{+} - Mediated activation of Phospholipases →**
      - ↑Phospholipid Degradation
    - **Eg: Bacterial Toxins (Endotoxins)**
    - **Eg: Viral Proteins**
    - **Eg: Lytic Complement Components (Eg: The "Membrane Attack Complex")**
    - **Eg: Perforins – from cytolytic lymphocytes (Cytotoxic-T & NK cells)**
    - **Eg: Physical Trauma**
    - **Eg: Chemical Agents**
  - **Consequences →**
    - **Mitochondrial Membrane Damage (↑Permeability) →**
      - ↓ATP Production &
      - Release of Pro-Apoptotic proteins (Cytochrome-C)
    - **Plasma Membrane Damage →**
      - Loss of Osmotic balance
      - Influx of Ions
      - Influx of fluids
      - Loss of Cellular Contents & Essential Metabolic Substrates
    - **Lysosomal Membrane Damage →**
      - Leakage of Destructive Enzymes into Cytoplasm:
        - RNAses
        - DNAses
        - Proteases
        - Phosphatases
        - Glucosidases
        - Cathepsins

        } → Cells Die by Necrosis



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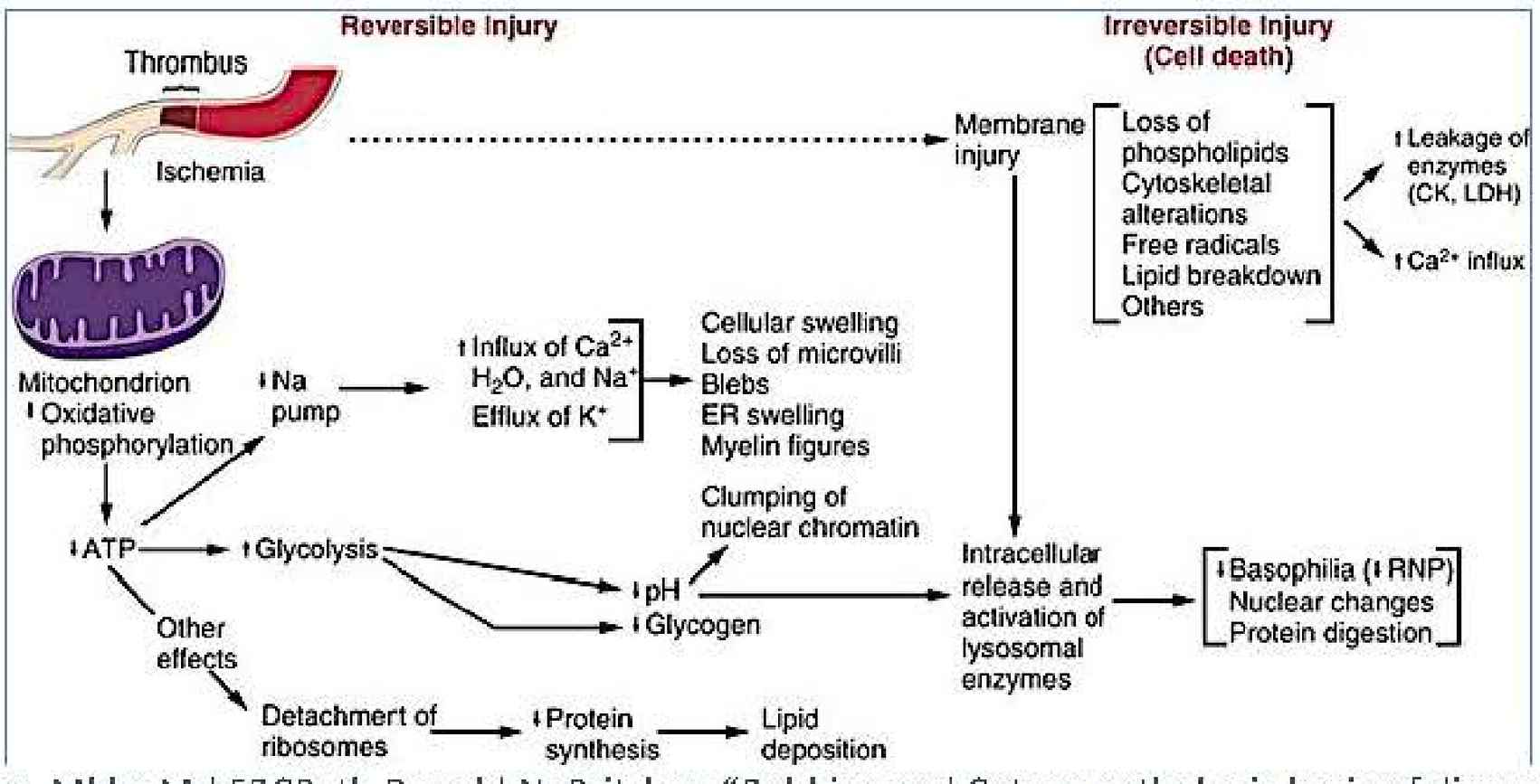
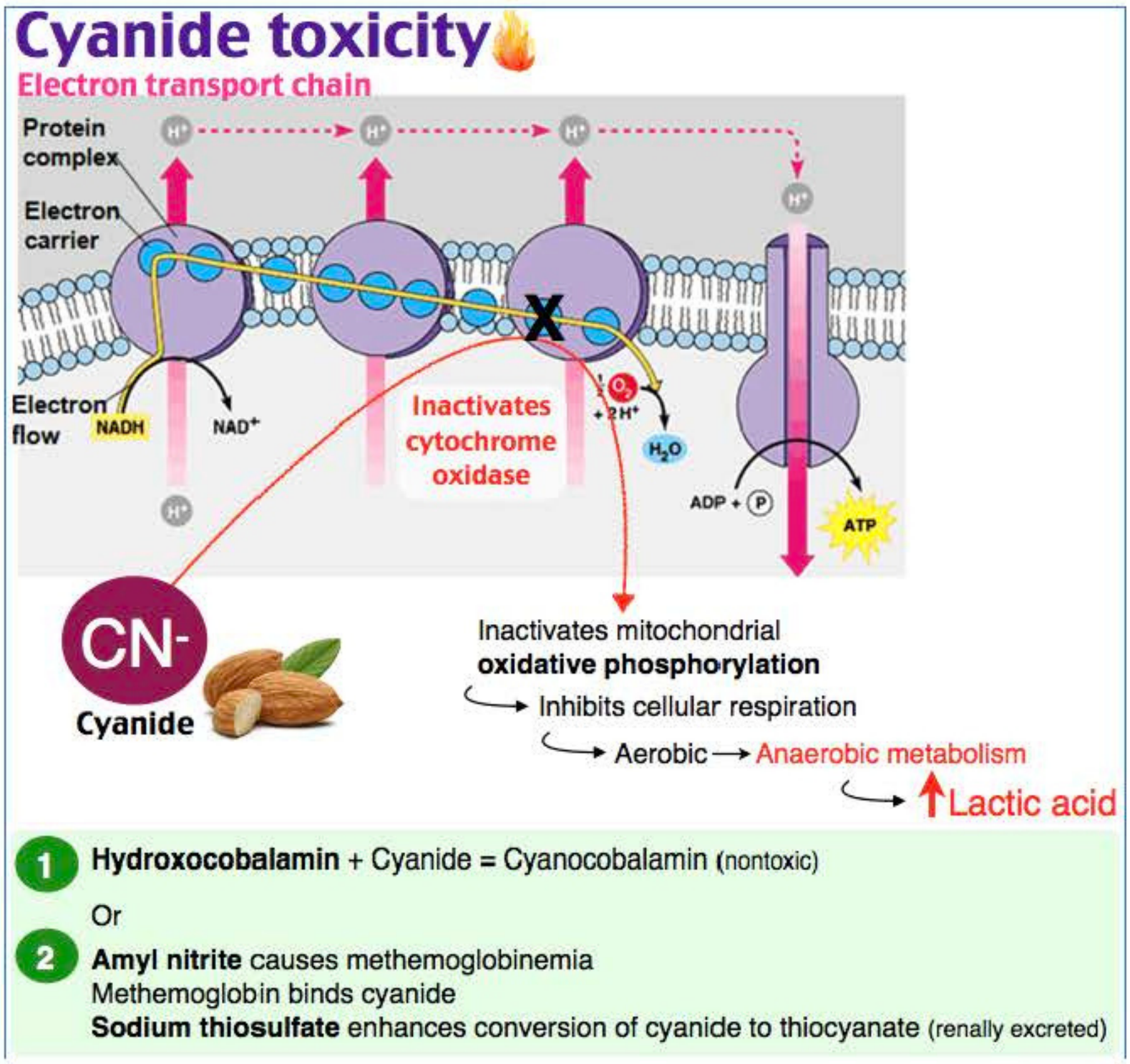
- **Ischaemic & Hypoxic Injury:**
  - Most common type of cell injury
  - **Ischaemia Vs Hypoxia:**
    - **Ischaemia =** ↓Supply of O_2 & Nutrients due to ↓Blood Flow
      - Note: Anaerobic Glycolysis stops after glycolytic substrates are exhausted
    - **Hypoxia =** ↓Supply of O_2
      - Note: Anaerobic Glycolysis can still continue
  - **Consequences** →
    - **Reversible Consequences:**
      - ↓Oxidative Phosphorylation → ↓ATP
      - Failure of Na/K-ATPase → Na Influx → Fluid Influx → Cell Swelling
      - Anaerobic Metabolism →↓Glycogen, ↑Lactic Acid, ↓pH
      - ↓Protein Synthesis
      - Ca^{-} Influx
      - Cytoskeleton Disperses → Loss of Ultrastructural Features → Formation of "Blebs" on cell surface
      - Membrane Damage
      - Mitochondrial Damage
      - **Note: If O_2 is restored, all of the above are reversible**
    - **Irreversible Consequences:**
      - MASSIVE Ca^{-} Influx (Particularly if the ischaemic zone is re-perfused)
        - →Leakage & Activation of Self-Digestive Enzymes
      - Severe Swelling of Mitochondria
      - Extensive Plasma-Membrane Damage:
        - → Continued Loss of: Proteins/Enzymes/Coenzmes/RNA
      - Swelling of Lysosomes
      - **Note: Even If O_2 is restored, the above are Irreversible**
      - **Death by Necrosis →**
        - Cell Components degraded
        - Leakage of cellular enzymes (Eg: Troponin I & Creatinine Kinase)
        - Entry of Extracellular molecules into dying cell
        - Dead cells become *'Myelin Figures'* (composed of phospholipids) →
          - →Phagocytosed
          - →Degraded further to FFA's
          - →Calcified
  - **What is Ischaemia-Reperfusion Injury?:**
    - Phenomenon where Restoration of blood flow to **Irreversibly-Injured** Ischaemic Tissues →Exacerbation & Acceleration of Injury AS WELL AS Further Injury
    - **Theories as to Why:**
      - Re-oxygenation → ↑Generation of Free Radicals
      - Activation of The *Complement-System* (Don't know why)



Vinay Kumar, Mbbs Md FRCPath Donald N. Pritzker. "Robbins and Cotran pathologic basis of disease." (2015).

- **Chemical Injury:**
  - **Major Causes:**
    - Direct damage
  - **→ Direct injury by combining with critical molecular components:**
    - Eg: Mercury - binds to cell-membrane proteins → ↑Permeability & ↓Ion Transport
    - Eg: Cyanide – binds with Cytochrome-Oxidase → Inhibits Oxidative Phosphorylation

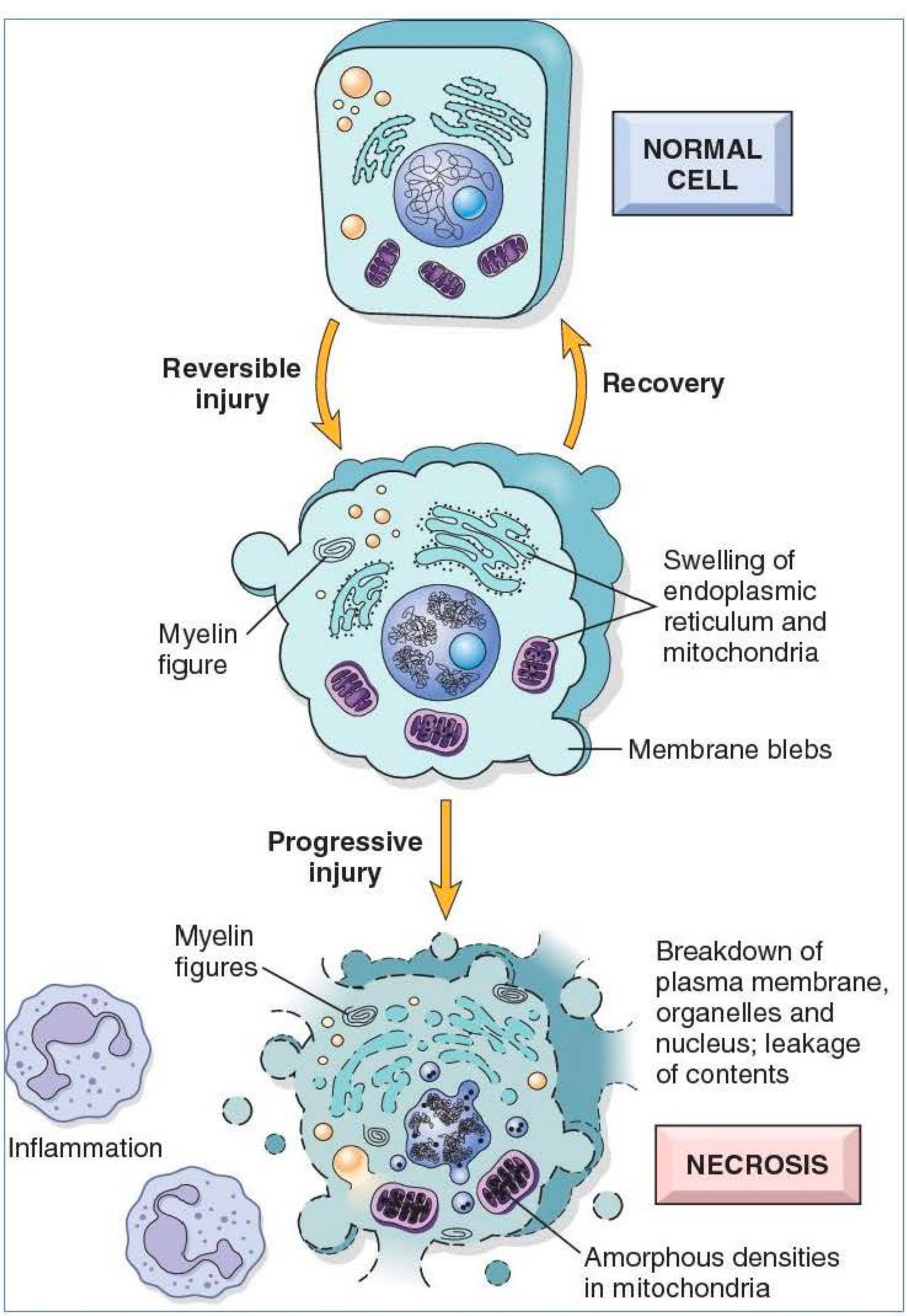


https://richkosh.blogspot.com/2019/05/zyklon-b-hydrogen-cyanide.html?m=1

Morphological Alterations in Cell Injury:

- **Reversible:**
  - Early stages where the functional/morphological changes are reversible if damaging stimulus is removed
  - **2 Common Histological Features:**
    - **1: Cellular Swelling (Hydropic Change)**
      - **Mechanism:**
        - Failure of energy-dependent ion pumps in the PM → Cells are incapable of maintaining Ionic & Fluid Homeostasis
    - **2: Fatty Change**
      - Frequently seen in injured Hepatocytes (Toxic injury) & Myocardial Cells (Hypoxic Injury)
      - Typically seen in Toxic or Hypoxic Injury
      - **Mechanism:**
        - Interferes with the enzymes that package fat into Lipoproteins & allow fat export from the liver. Decreased function of these enzymes leads to lipid accumulation in Hepatocytes
  - **Other Features:**
    - **Blebbing of the Plasma Membrane**
    - **Detachment of Ribosomes from the ER**
    - **Clumping of Nuclear Chromatin**

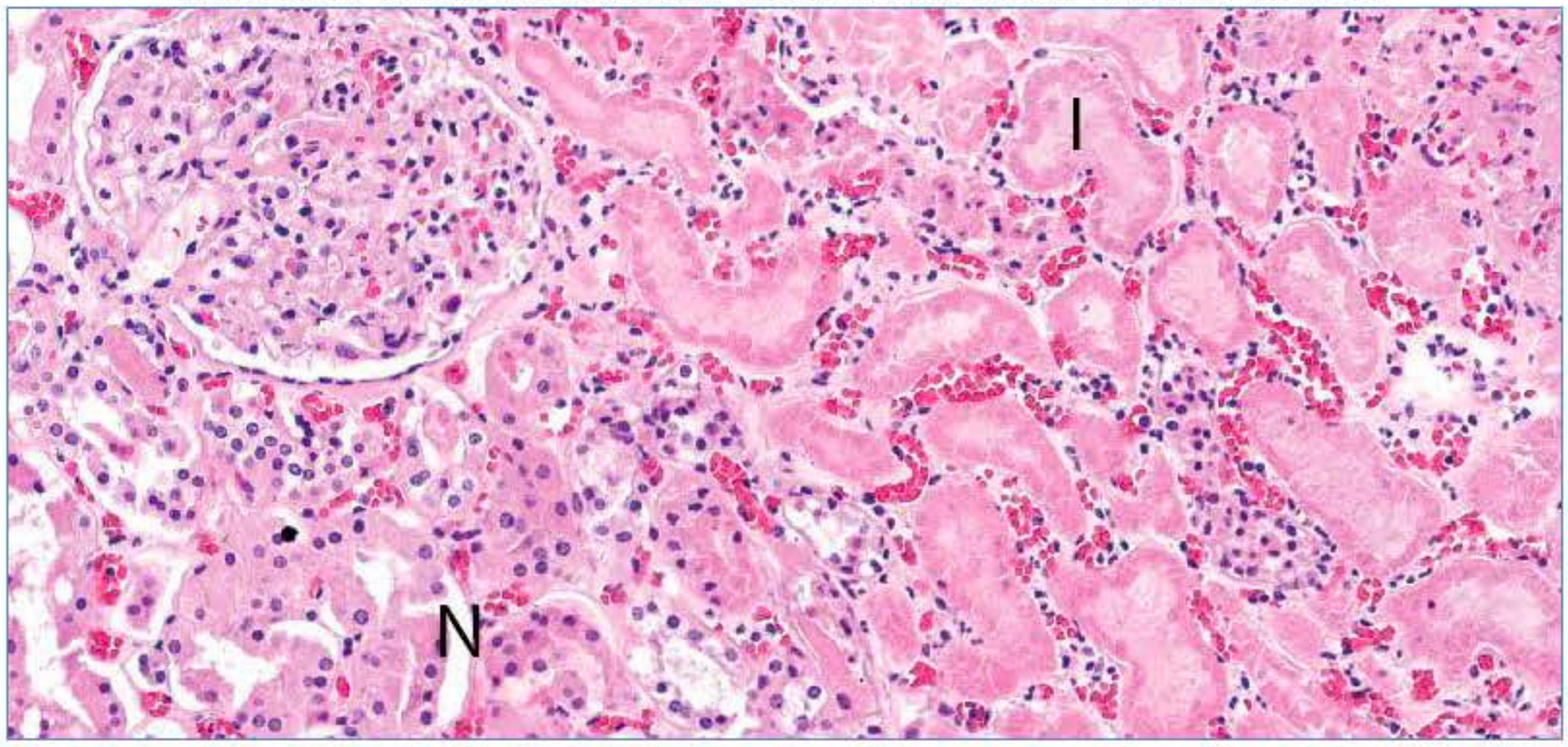
- **<u>Irreversible → Necrosis:</u>**
    - Result of Denaturation of Intracellular Proteins & Enzymatic Self-Digestion
    - Cells Lose Membrane-Integrity → Spill their contents → Local Inflammation
    - **Morphological Features of Nuclear Degeneration:**
        - **Pyknosis** – Nuclear Shrinkage, chromatin condenses into a solid, shrunken basophilic mass → ↑Basophilia (Staining with basic dyes)
        - **Karyorrhexis** – The Pyknotic Nucleus fragments → within 1-2 days, the Nucleus totally disappears
        - **Karyolysis** – Basophilia of the chromatin fades due to loss of DNA through enzymatic degradation



1 Cellular Responses to Stress and Toxic Insults: Adaptation , Injury , and Death. https://www.semanticscholar.org/paper/1-Cellular-Responses-to-Stress-and-Toxic-Insults-%3A/fbffc46199b0539126b45c3f23933708f7dc3948

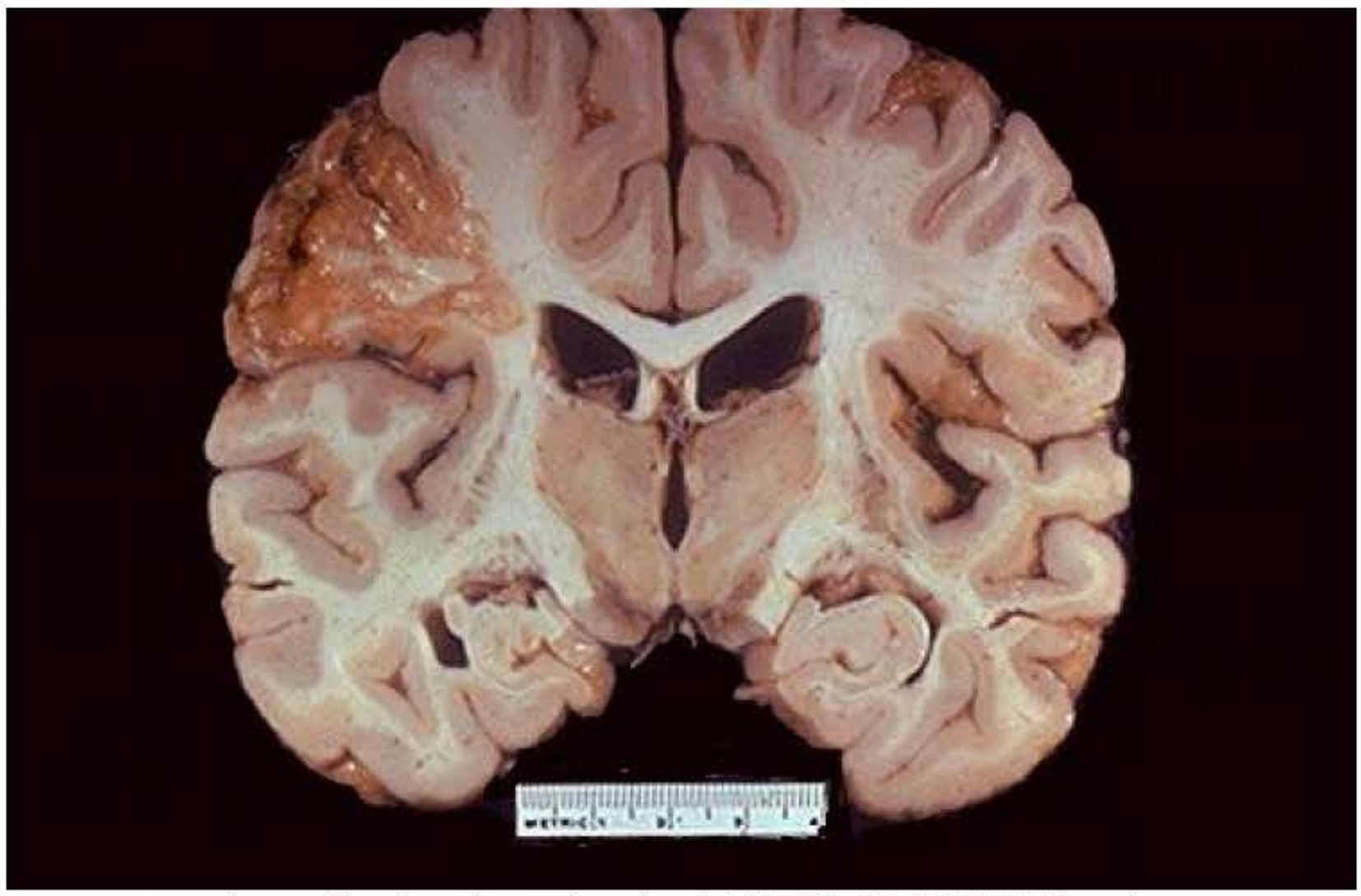
Patterns of Tissue Necrosis:

- **#1 - Coagulative Necrosis:**
  - **Caused by Hypoxia/Ischaemia/Infarction** → Denaturation of cell Proteins (similar to cooking an egg); also blocks the proteolysis of the dead cells → Cell outline remains for days/weeks
    - **Eg:** Myocardial Infarction
    - **Eg:** Gangrene – Usually Appendages that have lost blood-supply
  - **The basic cell-outline remains** for several days. This is because the Lysosomal Enzymes usually responsible for structural breakdown are denatured. Hence, affected tissues have a firm texture
  - **Mechanism of Cell Death:**
    - ***Ischaemia*** (except in the brain) leads to Coagulative Necrosis (Infarct)



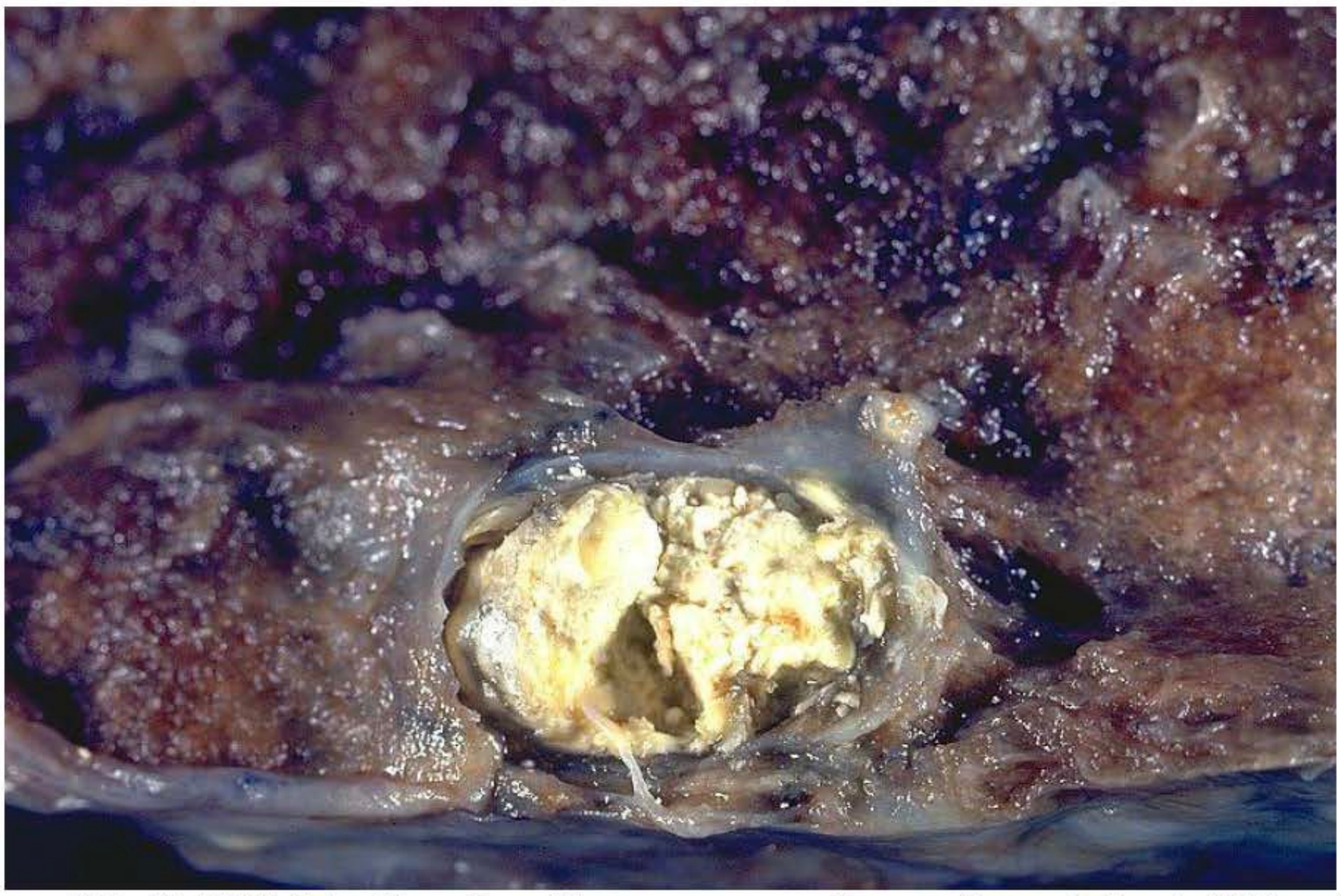
Above: Kidney Infarct (Macro & Micro) "N" = Normal Tissue; "I" = Infarct

- **Liquefactive Necrosis:**
  - **Caused by Bacterial (sometimes fungal) Infections & Subsequent Inflammation** → Dead bacteria & dead Neutrophils form ***Pus***, the liquid viscous mass → Abscess
    - **Note: Exception** – *Hypoxic Death* of CNS Neurons leads to Liquefactive Necrosis
  - **Eg:** Abscess in Lymph Node



https://webpath.med.utah.edu/CINJHTML/CINJ024.html

- **<u>Caseous ("Cheese-Like") Necrosis:</u>**
  - **Caused by Tuberculosis, Syphilis & Certain Fungi;** It can be considered a combination of Coagulative & Liquefactive Necrosis
  - **Microscopically – A "*Granuloma*"** - The necrotic area is a collection of lysed cells & amorphous granular debris, enclosed within a distinctive Inflammatory Border



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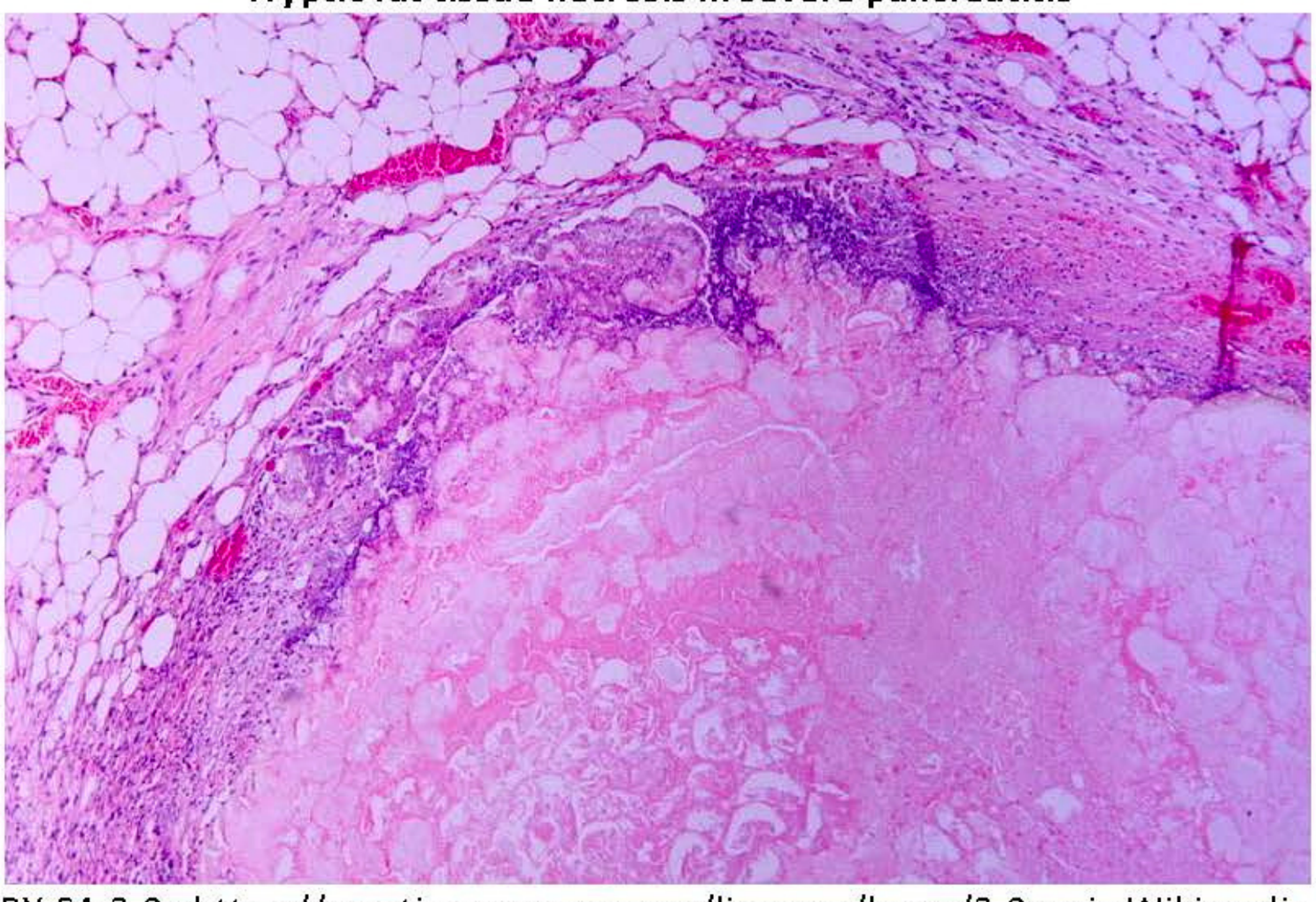
- **<u>Fat Necrosis:</u>**
  - **Local areas of Fat Destruction, Typically Caused by release of Activated Pancreatic Lipases on Adipose Tissues** → (Acute Pancreatitis)
    - **Eg: Acute Pancreatitis** → Release of activated pancreatic lipases from damaged pancreas into peritoneal cavity → acts on fat on mesenteries
    - **Eg: Breast-Tissue Necrosis**
  - Looks like – Chalky-white areas surrounded by an Inflammatory Reaction

Tryptic fat tissue necrosis in severe pancreatitis



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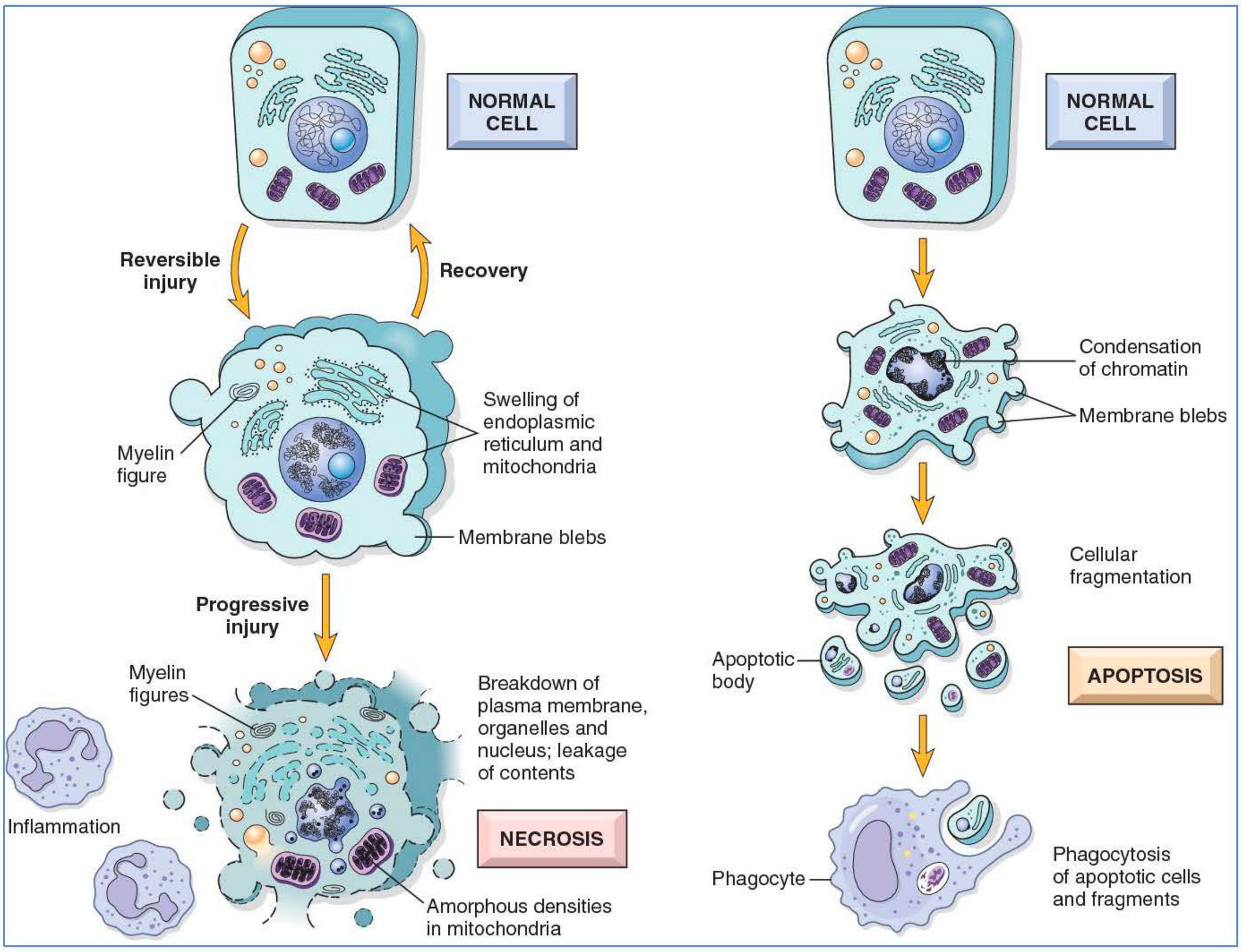
Apoptosis (NOT Necrosis):

- **What is it?**
  - A pathway of cell death induced by tightly-regulated 'Suicide' program → Activate enzymes that degrade the cell's own Nuclear DNA & Cytoplasmic Proteins
  - The Cell then breaks up into fragments (***Apoptotic Bodies***), which are phagocytosed
  - By not spilling cell contents, Apoptosis doesn't elicit inflammation (Unlike Necrosis)
- **Causes of Apoptosis:**
  - **Apoptosis in Physiologic Situations:**
    - **Elimination of Unwanted/Aged/Harmful cells**
    - **Eg:** Embryogenesis
    - **Eg:** B/T-Cell Negative-Selection
    - **Eg:** Endometrial Breakdown during menstrual cycle
  - **Apoptosis in Pathologic Conditions:**
    - **Elimination of Cells that are Irreversibly Injured, without Collateral Damage**
    - **Eg:** DNA damage (Radiation/Chemotherapy/Hypoxia)
    - **Eg:** Accumulation of Misfolded Proteins → Endoplasmic-Reticular Stress (or ER-Stress)
    - **Eg:** T-Cell Mediated Apoptosis of Virally-Infected Cell



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