MEDICAL EDUCATION RESOURCE

Free Radicals and Anti-Oxidants

? FREE RADICALS

? Definition

A **free radical** is any atom or molecule with **one or more unpaired electrons** in its outer orbit, making it highly reactive.

? Examples

- Superoxide (**O?•?**)
- Hydroxyl radical (**•OH**)
- Nitric oxide (**NO•**)
- Peroxyl radicals (ROO•)

? Sources

- Mitochondrial ETC leakage
- Cytochrome P450 reactions
- Inflammation (neutrophils/macrophages)
- Radiation (UV, X-ray)

- Pollution, cigarette smoke
- Drugs and toxins

? REACTIVE OXYGEN SPECIES (ROS)

? Definition

Highly reactive oxygen-containing molecules, including radicals and non-radicals.

? Major ROS

Free radicals:

- **Superoxide (O?•?)**
- **Hydroxyl radical (•OH)**
- **Peroxyl radicals (ROO•)**

Non-radicals that generate radicals:

- Hydrogen peroxide (**H?O?**)
- Hypochlorous acid (**HOCl**)
- Ozone (**O?**)

? GENERATION OF FREE RADICALS & ROS

? Physiological pathways

- **Mitochondrial ETC leakage** ? 1–3% of O? becomes superoxide.
- **Phagocytosis respiratory burst** (NADPH oxidase):
  O? ? O?•? ? H?O? ? HOCl
  (important for neutrophil killing)
- **Cytochrome P450** reactions
- **Prostaglandin/catecholamine metabolism**
- **Xanthine oxidase** during ischemia–reperfusion injury.

? Pathological generation

- Ionizing radiation (splits water ? **•OH radicals**)
- UV light
- Smoking, air pollution
- Ischemia–reperfusion injury
- Chronic inflammation
- Heavy metals ($Fe^{2?}$ via Fenton reaction)

? CELLULAR DAMAGE BY FREE RADICALS

ROS cause **oxidative stress**, damaging:

? 1. Lipids ? Lipid Peroxidation

ROS attack **polyunsaturated fatty acids** in membranes.

Effects:

- Loss of membrane integrity
- Increased permeability
- Cell swelling
- Mitochondrial damage

Highly exam-relevant for:

- Liver injury
- Atherosclerosis
- Radiation toxicity

? 2. Proteins ? Protein Oxidation

ROS cause:

- Cross-linking
- Fragmentation
- Enzyme inactivation

Seen in:

- Aging
- Cataract formation
- Neurodegenerative diseases

? 3. DNA ? DNA Damage

•OH causes:

- Base modification
- Strand breaks
- Mutations ? cancer risk

Seen in:

- UV radiation exposure
- Smoking
- Radiation therapy

? FREE RADICAL SCAVENGER SYSTEMS (ANTIOXIDANT DEFENSES)

Antioxidant mechanisms protect cells from ROS.

? A. ENZYMATIC ANTIOXIDANTS (VERY HIGH YIELD)

? 1. Superoxide Dismutase (SOD)

Converts:
O?•? ? H?O?

Types:

- Cytosolic (Cu/Zn-SOD)
- Mitochondrial (Mn-SOD)

? 2. Catalase

Present in **peroxisomes**.
Converts:
2H?O? ? 2H?O + O?

? 3. Glutathione Peroxidase (GPx)

Contains **selenium**.
Reduces:
H?O? ? H?O
Lipid peroxides ? alcohol

Uses reduced glutathione (GSH).

? 4. Glutathione Reductase

Regenerates GSH using **NADPH**.

? B. NON-ENZYMATIC ANTIOXIDANTS

? 1. Vitamin E (?-tocopherol)

- Most important lipid-phase antioxidant
- Prevents lipid peroxidation in membranes

? 2. Vitamin C (ascorbate)

- Regenerates vitamin E
- Scavenges hydroxyl radicals
- Important in smokers and chronic inflammation

? 3. Vitamin A & Carotenoids

- Quench singlet oxygen
- Protective in UV light exposure

? 4. Glutathione (GSH)

- Removes peroxides

- Maintains redox balance
- Reduced form necessary for GPx activity

? 5. Uric Acid

- Scavenges singlet oxygen & hydroxyl radicals

? 6. Bilirubin

- Powerful chain-breaking antioxidant in plasma
- Elevated in newborns as protective mechanism

? 7. Transferrin, Ferritin

Bind $Fe^{2?}$, prevent Fenton reaction.

? BODY SYSTEMS PROTECTING AGAINST ROS

- **NADPH**: Needed for glutathione regeneration
- **Thioredoxin system**
- **Ceruloplasmin**: Neutralizes free copper
- **Metallothioneins**: Bind heavy metals

- **Albumin**: Scavenges free radicals in plasma

? CLINICAL RELEVANCE

? High ROS found in:

- Atherosclerosis
- Diabetes mellitus
- Alcoholic liver disease
- Parkinson’s & Alzheimer’s diseases
- COPD
- Ischemia–reperfusion injury
- Cancer initiation (DNA damage)

? Antioxidant therapies:

- Vitamin E & C
- N-acetylcysteine (NAC)
- Selenium sources
- Polyphenols

? ULTRA-SHORT EXAM NOTES

- Free radicals have **unpaired electrons ? high reactivity**.
- ROS include **O?•?, H?O?, •OH, ROO•, HOCl**.
- Major sources: **ETC leakage, inflammation, radiation, P450, reperfusion**.
- Lipid peroxidation ? membrane damage (most common).
- Key enzymes: **SOD, catalase, GPx**.
- GSH + NADPH are essential for antioxidant defense.
- Vitamin E = membrane protector; Vitamin C = aqueous protector.

? INFLAMMATION & FREE RADICALS

? How ROS Are Generated in Inflammation

During acute and chronic inflammation, **neutrophils and macrophages** produce large amounts of ROS through:

1. Respiratory Burst (NADPH Oxidase System)

O? ? O?•? ? H?O? ? HOCl

- Superoxide produced by **NADPH oxidase**
- H?O? generated by **superoxide dismutase**
- HOCl generated by **myeloperoxidase (MPO)**

2. Nitric Oxide (NO•) Production

- Macrophages produce **NO•**
- NO• reacts with O?•? ? **Peroxynitrite (ONOO?)**, a strong oxidant

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? Effects of ROS in Inflammation

- Damage to invading microbes
- Also injures host tissues ? **oxidative stress**
- Vascular endothelial damage
- Increased permeability & edema
- Promotion of chronic inflammation (arthritis, IBD)

? RESPIRATORY DISEASES & ROS

Free radicals contribute to major lung diseases.

? Chronic Obstructive Pulmonary Disease (COPD)

Sources of ROS:

- Cigarette smoke (very rich in free radicals)
- Activated neutrophils in airways
- Damaged mitochondria

Effects:

- Destruction of alveolar walls
- Elastin fragmentation ? emphysema
- Persistent inflammation

? Asthma

- Eosinophils produce ROS
- Oxidative stress ? airway hyperresponsiveness
- Decreases activity of **antioxidants (SOD, catalase)**

? Interstitial Lung Disease

- Persistent inflammation ? ROS-mediated fibrosis
- Seen in pneumoconiosis, radiation lung injury

? Acute Respiratory Distress Syndrome (ARDS)

- Neutrophil burst ? HOCl, O?•?
- Endothelial damage ? capillary leakage

- Surfactant destruction ? respiratory failure

? Overall

Oxidative stress is one of the **central mechanisms** of chronic and acute respiratory diseases.

? RETROLENTAL FIBROPLASIA (RETINOPATHY OF PREMATURITY)

A classic exam favourite.

? Cause

Occurs in **premature infants** exposed to **high oxygen therapy**.

? Mechanism (Oxidative Pathway)

1. **High O?** ? retinal vessels constrict (vaso-occlusion).
2. Withdrawal of oxygen ? retina becomes relatively **hypoxic**.
3. Hypoxia triggers **VEGF** release ? excessive neovascularization.
4. Fragile new vessels bleed ?
    - Fibrous scarring
    - Retinal detachment
    - Blindness

? Free Radical Link

High oxygen environment increases ROS (especially in immature retina lacking antioxidant enzymes), contributing to capillary damage.

? Prevention

- Controlled oxygen therapy
- Pulse oximetry targeting **90–95% saturation**
- Screening of preterm infants

? REPERFUSION INJURY

? Definition

Tissue damage that occurs **after blood supply returns** to previously ischemic tissue.

? Why it happens

Reintroduction of oxygen leads to sudden burst of ROS:

? Major ROS Sources

1. **Mitochondrial respiration restart**
2. **Xanthine oxidase** converts accumulated hypoxanthine ? uric acid, producing O?•?
3. **Activated neutrophils** produce ROS

4. **Cytochrome P450 leakage**

? Consequences

- Lipid peroxidation of membranes
- Mitochondrial permeability transition ? cell death
- Calcium overload
- Endothelial swelling & thrombosis
- Worsened infarct size

? Clinical Conditions with Reperfusion Injury

- **Myocardial infarction** after thrombolysis
- **Stroke** after revascularization
- **Organ transplantation**
- **Tourniquet release in trauma**
- **Mesenteric ischemia**

? Antioxidant Protection

- SOD, catalase, GPx
- Vitamin C/E
- Allopurinol (prevents xanthine oxidase-mediated ROS)
- N-acetylcysteine

? ULTRA-SHORT REVISION BOX

- Inflammation generates ROS via **NADPH oxidase** & **MPO**.
- Respiratory diseases involve excessive oxidative stress from smoking & inflammation.
- Retrolental fibroplasia: **hyperoxia ? vasoconstriction ? hypoxia ? VEGF ? blindness**.
- Reperfusion injury: sudden **ROS overload** after restoring blood supply.

? ATHEROSCLEROSIS & FREE RADICALS

Free radicals and oxidative stress play a central role in the initiation and progression of atherosclerosis.

? How ROS contribute to atherosclerosis

1. Oxidation of LDL (Major Mechanism)

- ROS convert **LDL ? oxidized LDL (oxLDL)**.

- oxLDL is taken up by macrophages ? **foam cells**.
- Foam cells form **fatty streaks**, the earliest atherosclerotic lesions.

2. Endothelial Damage

- ROS injure endothelial cells ? reduced nitric oxide ? vasoconstriction.
- Damaged endothelium becomes **adhesive**, promoting leukocyte entry.

3. Smooth Muscle Proliferation

- ROS stimulate smooth muscle migration into intima ? plaque growth.

4. Inflammation Enhancement

- ROS activate NF-?B and inflammatory cytokines ? chronic vascular inflammation.

> **? Clinical relevance**

- Hyperlipidemia + ROS = accelerated plaque formation
- Smokers have extremely high oxidative LDL burden
- Antioxidants (Vitamin E, polyphenols) may reduce progression
- Diabetes increases ROS ? enhances atherosclerotic risk

? SKIN DISEASES & FREE RADICALS

Many skin pathologies are driven or worsened by oxidative stress.

? 1. Photoaging (UV-induced skin aging)

- UV light ? generates ROS in skin
- ROS damage collagen, elastin ? **wrinkles, laxity**
- Increases matrix metalloproteinases ? collagen breakdown

? 2. Melasma & Hyperpigmentation

- ROS stimulate melanocytes
- Increase melanin production ? dark patches
- Antioxidants used in cosmetic dermatology (vitamin C, niacinamide)

? 3. Acne

- Neutrophils in comedones generate ROS
- Increase inflammation & tissue damage
- Some anti-acne formulations include antioxidants

? 4. Psoriasis

- Hyperproliferation of keratinocytes produces ROS

- Oxidative stress amplifies inflammation

? 5. Vitiligo

- Excess hydrogen peroxide in skin damages melanocytes
- Antioxidants (calcium folinate, vitamin C/E, topical catalase mimetics) support treatment

? 6. Atopic Dermatitis

- Chronic inflammation ? ROS generation
- Barrier disruption increases oxidative injury

? AGE-RELATED DISEASES & FREE RADICALS

Aging is strongly connected with cumulative oxidative damage — the basis of the **Free Radical Theory of Aging**.

? 1. Neurodegenerative Disorders

? Alzheimer's Disease

- ?-amyloid generates ROS
- Lipid peroxidation + protein carbonylation
- Mitochondrial dysfunction

? Parkinson’s Disease

- Dopamine oxidation ? ROS
- Mitochondrial Complex I defect ? more ROS
- Damages substantia nigra neurons

? 2. Cataract

- Lens proteins oxidize ? clouding
- UV exposure accelerates oxidation
- Reduced glutathione (GSH) in older people worsens progression

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? 3. Aging Skin

- UV ? ROS ? collagen degradation
- Elastin damage ? wrinkles
- Reduced antioxidant enzymes with age

? 4. Sarcopenia (Age-related muscle loss)

- Mitochondrial ROS damage muscle fibers

- Decreased ATP ? reduced muscle strength
- Impaired repair mechanisms

? 5. Cardiovascular Aging

- Endothelial nitric oxide decreases due to ROS
- Increased arterial stiffness
- Higher risk of hypertension, thrombosis, and MI

? 6. Immune Senescence

- ROS damage lymphocytes and stem cells
- Reduced adaptive immunity
- Increased infections and cancer susceptibility

? 7. Diabetes & Aging

- Hyperglycemia ? advanced glycation ? ROS burst
- Mitochondrial oxidative stress ? insulin resistance
- Vascular complications (retinopathy, nephropathy)

? ULTRA-SHORT REVISION

- **Atherosclerosis:** Oxidized LDL ? foam cells ? plaques.
- **Skin diseases:** ROS central in UV-damage, melasma, vitiligo, psoriasis, acne.
- **Age-related diseases:** Alzheimer's, Parkinson's, cataract, skin aging, sarcopenia linked to cumulative ROS injury.
- Antioxidant enzymes (SOD, catalase, GPx) weaken with age ? more oxidative damage.

? LIPID PEROXIDATION

? Definition

Oxidative degradation of **polyunsaturated fatty acids (PUFAs)** in cell membranes by free radicals.

? Why it matters

- Major mechanism of **cell membrane damage**
- Leads to loss of membrane fluidity, integrity & function
- Produces toxic aldehydes (e.g., **malondialdehyde – MDA**), a marker of oxidative stress

? Where it occurs

- Biological membranes rich in PUFAs (liver, brain, skin)
- Lipoproteins (oxidized LDL ? atherosclerosis)

? MECHANISM OF LIPID PEROXIDATION

Lipid peroxidation follows **three classic phases**:

? 1. Initiation Phase

ROS + PUFA ? **Lipid radicals** (L•)

Key initiators:

- **Hydroxyl radical (•OH)** — most potent
- Peroxynitrite (ONOO?)
- UV radiation
- Ionizing radiation
- Heavy metals ($Fe^{2?}$ via Fenton reaction)

Reaction:
PUFA–H + •OH ? PUFA• + H?O
(The •OH removes H ? creates lipid radical)

? 2. Propagation Phase

Lipid radical reacts with oxygen ? **lipid peroxyl radical** (LOO•)

LOO• reacts with nearby PUFA ? new **lipid radical (L•)**
This forms a **chain reaction**.

Cycle:
L• + O? ? LOO•
LOO• + PUFA–H ? LOOH + L•

Products:

- Lipid hydroperoxide (**LOOH**)
- Malondialdehyde (**MDA**)
- 4-HNE (4-hydroxynonenal)

These molecules damage:

- Membrane proteins
- DNA
- Mitochondria
- Lipoproteins

? 3. Termination Phase

Occurs when two radicals combine ? **non-radical** stable product.

LOO• + LOO• ? non-radical
L• + LOO• ? stable complex

OR
Stopped by **chain-breaking antioxidants** (vitamin E, vitamin C).

? PREVENTIVE ANTIOXIDANTS (HIGH-YIELD)

These **prevent formation of free radicals** *before* they start damaging lipids.

? Examples

? 1. Metal chelators

Prevent Fenton reaction ($Fe^{2?}$? •OH).

- **Transferrin**
- **Lactoferrin**
- **Ferritin**
- **Ceruloplasmin**
- EDTA (lab)

? 2. Enzymatic antioxidants

- **Superoxide dismutase (SOD)** ? removes O?•?
- **Catalase** ? removes H?O?
- **Glutathione peroxidase** ? removes peroxides

? 3. Uric acid

Scavenges singlet oxygen.

? 4. Bilirubin

Protective chain-stopping antioxidant in plasma.

? 5. Albumin

Binds free copper/iron ? prevents radical formation.

Purpose: Stop ROS formation upstream, preventing initiation stage.

? CHAIN-BREAKING ANTIOXIDANTS

? Role

Interrupt the **propagation phase** by reacting with lipid peroxyl radicals (LOO•) and converting them into non-radical products.

? Key Chain-Breaking Antioxidants

? 1. Vitamin E (?-Tocopherol) — MOST IMPORTANT

- Lipid-soluble
- Present in membranes
- Neutralizes LOO• ? stops chain reaction
- First line of defense against lipid peroxidation

? 2. Vitamin C (Ascorbate)

- Water-soluble
- Regenerates **vitamin E**
- Scavenges •OH

? 3. Glutathione (GSH)

- Removes LOOH via glutathione peroxidase
- Restored by glutathione reductase + NADPH

? 4. Coenzyme Q (Ubiquinol)

- Membrane antioxidant
- Neutralizes lipid radicals

? 5. Carotenoids (?-carotene, lycopene)

- Quench singlet oxygen
- Protect lipids in membranes and skin

? 6. Polyphenols (tea, fruits)

- Donate hydrogen to radicals
- Stop propagation

? CLINICAL CONNECTIONS

? 1. Atherosclerosis

- LDL oxidation via lipid peroxidation ? foam cells ? plaque formation.

? 2. Skin Aging

- UV-induced lipid peroxidation damages collagen/elastin.

? 3. Neurodegeneration

- Brain is PUFA-rich ? vulnerable to ROS.

? 4. Liver damage

- Alcohol increases CYP2E1 ? ROS ? lipid peroxidation.

? 5. Cancer

- Lipid peroxidation byproducts like MDA are mutagenic.

? ULTRA-SHORT REVISION

- **Initiation:** ROS attacks PUFA ? lipid radical.
- **Propagation:** Lipid radical + O? ? peroxyl radical ? chain reaction.
- **Termination:** Radicals combine OR antioxidants stop chain.
- **Preventive antioxidants:** Stop free radicals from forming.
- **Chain-breaking antioxidants:** Stop ongoing lipid peroxidation.

? IMPORTANT POINTS TO REMEMBER

? Lipid Peroxidation

- Occurs mainly in **polyunsaturated fatty acids (PUFAs)** of membranes.
- One of the most important mechanisms of **cell membrane injury**.
- Produces toxic byproducts like **malondialdehyde (MDA)** and **4-HNE**, used as markers of oxidative stress.
- Particularly important in **liver**, **brain**, **skin**, and **LDL particles**.

? Initiation Phase

- Triggered by **hydroxyl radical (•OH)** ? most reactive species.
- Other initiators: UV, ionizing radiation, Fe²? (Fenton reaction), peroxynitrite.
- ROS abstracts hydrogen from PUFA ? **lipid radical (L•)**.

? Propagation Phase

- L• + O? ? **lipid peroxyl radical (LOO•)**.
- LOO• reacts with nearby PUFA ? **LOOH + new L•** ? chain reaction.
- Responsible for rapid spread of membrane damage.
- Generates **lipid hydroperoxides (LOOH)** and **MDA**.

? Termination Phase

- Occurs when **two radicals combine** ? stable product.

- Chain-breaking antioxidants (e.g., vitamin E) stop radical propagation.
- Marks the end of lipid peroxidation.

? Preventive Antioxidants (Stop ROS Formation)

? Key Concept: Prevent the *initiation* phase.

- **SOD** ? removes superoxide (O?•?).
- **Catalase** ? removes H?O?.
- **Glutathione Peroxidase (selenium-dependent)** ? removes peroxides (H?O?, LOOH).
- **Metal-chelating proteins**: transferrin, lactoferrin, ferritin, ceruloplasmin ? prevent Fenton reaction.
- **Albumin** ? binds free metals, prevents radical formation.
- **Uric acid** and **bilirubin** ? neutralize singlet oxygen.

? Chain-Breaking Antioxidants (Stop Propagation Stage)

? Key Concept: Break the radical chain by interacting with LOO•.

- **Vitamin E (?-tocopherol)** ? most important lipid-phase antioxidant; protects membranes.
- **Vitamin C (ascorbate)** ? regenerates vitamin E; scavenges aqueous radicals.
- **Glutathione (GSH)** ? detoxifies LOOH through GPx.
- **Coenzyme Q (ubiquinol)** ? membrane antioxidant.

- **Carotenoids (?-carotene, lycopene)** ? quench singlet oxygen.
- **Plant polyphenols** ? donate electrons to stop radical chains.

? High-Yield Clinical Pearls

- Oxidized LDL from lipid peroxidation ? **atherosclerosis**.
- UV-induced lipid peroxidation ? **photoaging**, melasma, skin inflammation.
- Alcohol metabolism (CYP2E1) increases ROS ? **fatty liver** and **hepatotoxicity**.
- High ROS in brain ? linked to **Alzheimer's and Parkinson's**.
- Newborn antioxidant systems are immature ? prone to **retinopathy of prematurity**.
- Reperfusion after ischemia produces ROS ? **further tissue injury**.

? Ultra-Short 10-Second Revision

- Lipid peroxidation = PUFA destruction by ROS.
- Steps: **Initiation ? Propagation ? Termination**.
- Preventive antioxidants stop radicals from forming.
- Chain-breaking antioxidants stop chain reactions already underway.
- Vitamin E = main membrane protector; GPx = removes peroxides.

? MCQs — Full Chapter: Free Radicals & Antioxidants

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1. A free radical is defined as a molecule that contains:

A. Excess electrons
B. Paired electrons
C. **Unpaired electrons**
D. No electrons

Answer: C

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2. Which of the following is the MOST reactive oxygen species?

A. Superoxide
B. Hydrogen peroxide
C. Singlet oxygen
D. **Hydroxyl radical (•OH)**

Answer: D

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3. Which enzyme produces superoxide during inflammation?

A. Xanthine oxidase
B. **NADPH oxidase**
C. Catalase
D. Nitric oxide synthase

Answer: B

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4. Hydrogen peroxide is converted to water and oxygen by:

A. GPx
B. SOD
C. **Catalase**
D. MPO

Answer: C

5. Which of the following is a non-radical ROS that can generate free radicals?

A. O?•?
B. •OH
C. NO•
D. **H?O?**

Answer: D

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6. The Fenton reaction requires which metal?

A. Sodium
B. Potassium
C. **Iron ($Fe^{2?}$)**
D. Zinc

Answer: C

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7. The primary site for mitochondrial ROS generation is:

A. Golgi apparatus
B. ER
C. **Electron Transport Chain (ETC)**
D. Peroxisome

Answer: C

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8. The toxic aldehyde formed during lipid peroxidation and measured clinically is:

A. Acetaldehyde
B. Formaldehyde
C. **Malondialdehyde (MDA)**
D. Uric acid

Answer: C

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9. Which phase of lipid peroxidation involves chain reaction amplification?

A. Initiation
B. **Propagation**
C. Termination
D. Stabilization

Answer: B

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10. Which antioxidant is present in lipid membranes and stops propagation phase?

A. Vitamin C
B. Glutathione
C. Uric acid
D. **Vitamin E**

Answer: D

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11. Which antioxidant regenerates Vitamin E?

A. Coenzyme Q
B. **Vitamin C**
C. Bilirubin
D. Selenium

Answer: B

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12. Selenium is required for which enzyme?

A. Catalase
B. SOD
C. **Glutathione peroxidase (GPx)**
D. Xanthine oxidase

Answer: C

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13. Preventive antioxidants primarily function by:

A. Breaking lipid radicals

B. Blocking LOO•

C. **Preventing formation of new ROS**

D. Stabilizing MDA

Answer: C

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14. Which of the following is a preventive antioxidant?

A. Vitamin E

B. Vitamin C

C. **Transferrin**

D. Coenzyme Q

Answer: C

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15. Lipid peroxidation is MOST harmful because it affects:

A. DNA only

B. Proteins only

C. **Biological membranes**

D. Cholesterol

Answer: C

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16. Free radical injury is central to which ocular disease in preterm infants?

A. Glaucoma

B. Cataract

C. **Retrolental fibroplasia (ROP)**

D. Strabismus

Answer: C

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17. Which free radical is produced during nitric oxide metabolism?

A. O?•?

B. •OH

C. **NO•**

D. H?O?

Answer: C

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18. In atherosclerosis, free radicals cause:

A. LDL hydrolysis

B. **LDL oxidation**

C. LDL polymerization

D. LDL glycation

Answer: B

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19. Which enzyme converts O?•? to H?O??

A. Catalase

B. GPx

C. **SOD**

D. MPO

Answer: C

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20. The final step (termination) of lipid peroxidation occurs by:

A. Creating more radicals

B. **Combining two radicals into a stable molecule**

C. Breaking lipids into aldehydes

D. Quenching hydroxyl radicals

Answer: B

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21. Which ROS is mainly responsible for DNA strand breaks?

A. O?•?

B. O?

C. H?O?

D. **•OH**

Answer: D

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22. Which condition shows highest oxidative damage due to smoking?

A. Hypothyroidism

B. **COPD**

C. Gallstone disease

D. Asthma

Answer: B

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23. Reperfusion injury occurs mainly due to:

A. ATP accumulation

B. Increased antioxidants

C. **Sudden ROS burst after restoring oxygen**

D. Excess nitric oxide removal

Answer: C

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24. A major plasma antioxidant that binds copper and prevents radical formation is:

A. Vitamin A

B. **Ceruloplasmin**

C. Myeloperoxidase

D. Albumin

Answer: B

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25. Which of the following is a chain-breaking antioxidant found in membranes?

A. Catalase

B. SOD

C. **Vitamin E**

D. Glutathione reductase

Answer: C

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26. Which antioxidant is strongest in aqueous (cytosolic) phase?

A. Vitamin E

B. Coenzyme Q

C. **Vitamin C**

D. Bilirubin

Answer: C

---

27. Which condition is MOST strongly linked with H?O? accumulation in skin?

A. Melasma

B. Acne

C. **Vitiligo**

D. Psoriasis

Answer: C

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28. Which enzyme deficiency increases oxidative stress in RBCs?

A. Lactate dehydrogenase

B. Myeloperoxidase

C. **G6PD deficiency**

D. Catalase deficiency

Answer: C

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29. Aging is accelerated by cumulative damage mainly to:

A. Cholesterol
B. **Mitochondrial DNA**
C. Lipoproteins
D. Lysosomes

Answer: B

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30. Which is the first-line antioxidant enzyme in mitochondria?

A. Catalase
B. GPx
C. **Mn-SOD**
D. NADPH oxidase

Answer: C

? CLINICAL CASE–BASED QUESTIONS (Whole Chapter)

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1. A 65-year-old smoker presents with progressive shortness of breath. CT chest shows emphysematous changes. Which mechanism contributes most to his lung damage?

- Cigarette smoke delivers **thousands of free radicals** per puff.
- ROS damage alveolar walls ? elastin breakdown ? emphysema.

Answer: Excess oxidative stress leading to lipid/protein oxidation in lungs.

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2. A premature infant on high oxygen therapy develops retinal detachment and blindness. What is the underlying mechanism?

- Excess O? ? ROS overload ? capillary damage ? hypoxia on withdrawal ? VEGF-mediated neovascularization.

Answer: ROS-mediated vascular injury ? retrolental fibroplasia (ROP).

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3. A 22-year-old G6PD-deficient male develops hemolysis after taking antimalarial drugs. Which mechanism is responsible?

- RBCs lack NADPH ? cannot regenerate **glutathione**.
- Peroxides accumulate ? membrane lipid peroxidation ? hemolysis.

Answer: Inability to detoxify ROS due to reduced glutathione.

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4. A patient with MI is treated with thrombolysis. 30 minutes later, chest pain worsens and biomarkers rise again. Mechanism?

- Reperfusion ? sudden supply of oxygen ? ROS burst.
- Xanthine oxidase, neutrophils contribute to ROS.

Answer: Reperfusion injury due to sudden ROS generation.

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5. A newborn has severe jaundice but mild oxidative stress. Which antioxidant explains this protection?

- Bilirubin acts as a natural antioxidant.

Answer: Elevated bilirubin functioning as an antioxidant.

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6. A 48-year-old diabetic has decreased distal sensation. His labs show increased MDA levels. What process is elevated?

- MDA = marker of **lipid peroxidation**.

Answer: Increased lipid peroxidation due to chronic oxidative stress.

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7. A patient presents with hyperpigmented patches worsened by sunlight. ROS involvement?

- UV generates ROS in skin ? stimulates melanocytes ? melasma.

Answer: UV-induced ROS activation of melanogenesis.

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8. A 75-year-old man has memory loss, cerebral atrophy, and oxidative markers elevated. Underlying mechanism?

- Mitochondrial ROS damage neuronal lipids/proteins in Alzheimer's disease.

Answer: Oxidative stress-mediated neurodegeneration.

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9. A smoker with coronary artery disease has high oxLDL levels. What caused this?

- ROS convert LDL ? oxidized LDL ? foam cells ? plaques.

Answer: Free radical–mediated oxidation of LDL in endothelium.

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10. A 45-year-old alcoholic has fatty liver with high CYP2E1 activity. What does this promote?

- CYP2E1 generates ROS ? lipid peroxidation ? liver injury.

Answer: Alcohol-induced ROS formation causing hepatic lipid peroxidation.

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11. A lab report shows high H?O? accumulation in melanocytes in a vitiligo patient. Which enzyme defect is likely?

- Catalase deficiency ? H?O? builds up ? melanocyte damage.

Answer: Reduced catalase activity causing H?O? accumulation.

12. An ischemic limb becomes swollen and painful after tourniquet release. Why?

- Sudden oxygen reentry ? ROS burst ? inflammation, endothelial injury.

Answer: Reperfusion injury from ROS excess.

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13. A 60-year-old man with chronic inflammation shows raised CRP and ROS markers. Neutrophils are responsible through which pathway?

- NADPH oxidase ? O?•? ? H?O? ? HOCl (myeloperoxidase).

Answer: Respiratory burst generating ROS in inflammation.

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14. A patient given excessive paracetamol develops liver failure. How does oxidative stress contribute?

- NAPQI depletes glutathione ? ROS accumulate ? hepatocyte necrosis.

Answer: GSH depletion ? inability to neutralize ROS.

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15. A patient has premature wrinkles and skin aging. What is central mechanism?

- UV-induced ROS ? collagen & elastin destruction.

Answer: ROS-mediated photoaging of skin.

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16. In COPD, what is the role of ROS from cigarette smoke?

- They destroy alveolar walls, activate neutrophils, damage surfactant.

Answer: Oxidative injury leading to emphysema development.

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17. A 30-year-old athlete consumes high oxygen during intense exercise. Why do antioxidant enzymes rise?

- ETC leakage generates more ROS ? increased SOD, catalase, GPx.

Answer: Upregulation of enzymatic antioxidants due to increased ROS.

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18. A term infant with respiratory distress is given high O?; later lung fibrosis develops. Which ROS is responsible?

- Oxygen toxicity ? •OH formation ? alveolar damage.

Answer: Hydroxyl radical–mediated pulmonary injury.

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19. Atherosclerotic plaque is examined and shows foam cells. What oxidized molecule is responsible?

- oxLDL due to lipid peroxidation.

Answer: Oxidized LDL formed by ROS.

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20. A patient with Parkinson's disease shows increased oxidative stress in substantia nigra. What caused it?

- Dopamine metabolism produces ROS ? mitochondrial dysfunction.

Answer: ROS generation from dopamine oxidation.

? VIVA VOCE — Free Radicals & Antioxidants (Whole Chapter)

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1. What is a free radical?

A molecule with **one or more unpaired electrons**, making it highly reactive.

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2. Give examples of free radicals.

Superoxide (O?•?), hydroxyl radical (•OH), nitric oxide (NO•).

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3. What is a reactive oxygen species (ROS)?

A reactive oxygen-containing molecule, radical or non-radical (e.g., H?O?, HOCl).

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4. Name the most dangerous ROS.

Hydroxyl radical (•OH).

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5. What is the primary source of ROS in the body?

Mitochondrial electron transport chain leakage.

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6. What is respiratory burst?

Rapid ROS generation by neutrophils via **NADPH oxidase**.

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7. Which enzyme converts superoxide into hydrogen peroxide?

Superoxide dismutase (SOD).

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8. Which enzyme breaks down hydrogen peroxide?

Catalase or **glutathione peroxidase (GPx).**

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9. Which antioxidant enzyme requires selenium?

Glutathione peroxidase.

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10. What is the role of glutathione?

Neutralizes peroxides and maintains cellular redox balance.

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11. What is lipid peroxidation?

ROS-mediated oxidation of **PUFAs** in membranes.

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12. Name the three phases of lipid peroxidation.

Initiation, **propagation**, **termination**.

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13. What starts the initiation phase?

Attack by **hydroxyl radical** on membrane lipids.

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14. What is formed in propagation?

Lipid peroxyl radicals (LOO•) and **lipid hydroperoxides (LOOH).**

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15. How does the termination phase occur?

Two radicals combine to form a **stable non-radical**.

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16. What is malondialdehyde (MDA)?

A toxic product of lipid peroxidation; marker of oxidative stress.

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17. Give examples of preventive antioxidants.

SOD, catalase, GPx, transferrin, ferritin, ceruloplasmin.

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18. Function of preventive antioxidants?

Prevent **formation** of ROS (act before initiation phase).

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19. What are chain-breaking antioxidants?

Antioxidants that **stop propagation** by neutralizing LOO•.

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20. Example of a chain-breaking antioxidant.

Vitamin E (?-tocopherol).

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21. How does Vitamin C act in antioxidant defense?

Regenerates **vitamin E** and scavenges aqueous radicals.

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22. What antioxidant is abundant in plasma and binds copper?

Ceruloplasmin.

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23. What is the physiological uncoupler in brown fat?

Thermogenin (UCP-1).

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24. Which condition is strongly linked to LDL oxidation?

Atherosclerosis.

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25. How does smoking increase oxidative stress?

Introduces large numbers of free radicals into lungs ? COPD.

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26. How do ROS contribute to skin aging?

UV-generated ROS damage collagen and elastin.

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27. Why is the brain highly susceptible to oxidative injury?

High PUFA content + high oxygen use + low antioxidants.

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28. What causes reperfusion injury?

Sudden ROS burst when oxygen returns to ischemic tissue.

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29. How do ROS participate in inflammation?

Neutrophils generate ROS (respiratory burst) for microbial killing.

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30. What leads to retinopathy of prematurity?

Hyperoxia ? ROS ? retinal vessel damage ? neovascularization.

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31. Which radical is responsible for DNA strand breaks?

Hydroxyl radical (•OH).

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32. How does glutathione peroxidase act on lipid peroxides?

Converts **LOOH ? alcohol**, preventing propagation.

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33. Examples of non-enzymatic antioxidants.

Vitamin E, Vitamin C, glutathione, carotenoids, uric acid, bilirubin.

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34. Which antioxidant is most important in membranes?

Vitamin E.

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35. Why is catalase highly active in peroxisomes?

Peroxisomes generate large amounts of H?O?.

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36. What antioxidant protects newborns naturally?

Bilirubin.

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37. Why does G6PD deficiency cause hemolysis?

Low NADPH ? low GSH ? peroxide accumulation in RBCs.

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38. What is ONOO??

Peroxynitrite ? formed from NO• + O?•? ? potent oxidant.

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39. Which vitamins work together in antioxidant cycles?

Vitamin E and Vitamin C.

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40. What is the main antioxidant in mitochondria?

Mn-SOD (manganese SOD).