Oxygen Toxicity & free Radical

Biradical $O_2^{\uparrow\uparrow}$

$\downarrow$

$\downarrow$

radical O_2^-

non-radical H_2O_2

radical $OH^{\bullet}$

$\rightarrow$ ROS

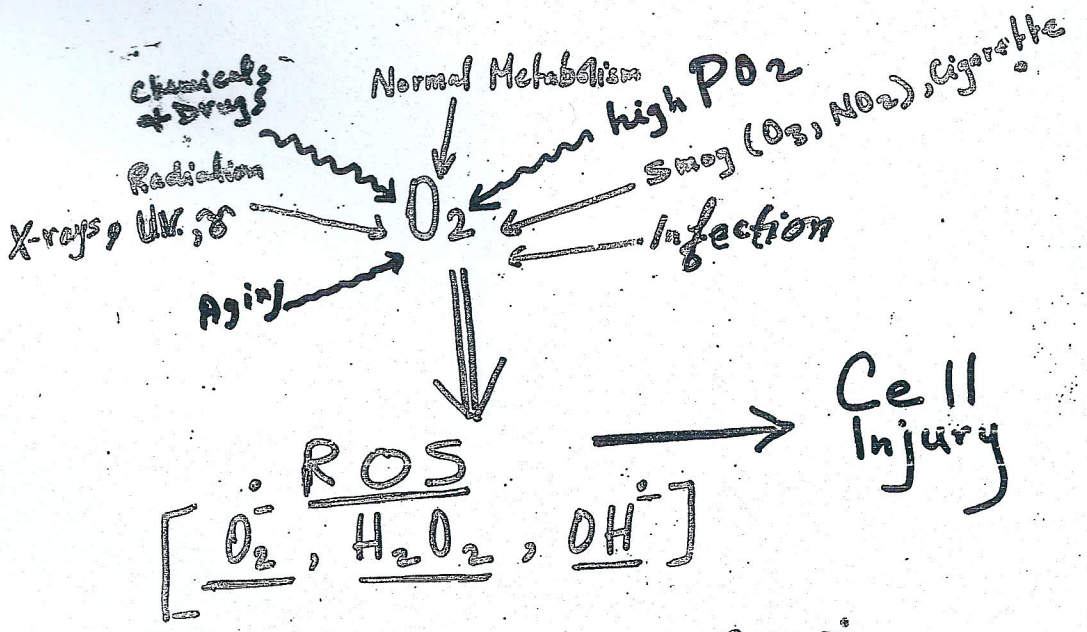
O_2 Metabolism and Toxicity

- O_2 Consumption
  - $\geq 90\%$ —R.C.→ ATP
  - Oxidases (transfer $\bar{e}$ to O_2 + reduced to H_2O & H_2O_2)
  - Oxygenases (Incorporate Oxygen)
    - → Mono -
    - → Di -

3-5% of consumed O_2 → ROS

Reactive Oxygen Spiecies (ROS) :-

Generated by
- normal Metabolism
- Environmental factors



Others → .organic peroxides RCOO˙
.hypochlorous acid HOCl
.RNOS

- Some of the Diseases associated with ROS injury

- Atherosclerosis
- Respiratory Disease (Emphysema / Bronchitis)
- Parkinson's Disease
- Cancer
- Diabetes
- Liver Damage
- motor neuron disease
- Aging

- ROS and Cellular Damage
  - Causes of Diseases
  - contribute to complication of many chronic Diseases

- Proteins, lipids, Nucleic acids & Carbohydrates are affected

- Most susceptible amino acids
  Pro, his, arg, Cys, Met.

  Oxid of a.a. → fragmentation of protein
  → aggregation → Proteolytic digestion

- Membrane lipids

- DNA damage
  e.g. strands break

The Main Biological Targets of ROS

- PUFA : Polyunsaturated fatty acids.
- Proteins
- DNA

PUFA attack

$$\underset{\text{PUFA}}{\underline{LH}} + OH^{\bullet} \longrightarrow \boxed{L^{\bullet}} + H_2O$$

lipid free radical

$$L^{\bullet} + O_2 \longrightarrow \underline{LOO^{\bullet}}$$

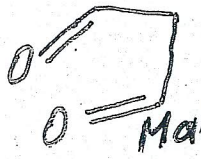
peroxyl radical

$$\underset{\text{PUFA}}{\underline{LH}} + LOO^{\bullet} \longrightarrow \underbrace{LOOH}_{\text{lipidhydro-peroxide}} + \boxed{L^{\bullet}}$$

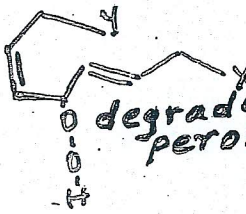
another lipid free radical

→ chain reaction is set via lipid radicals in producing lipidhydroperoxides

→ Degradation of peroxidized lipids → generating harmful products

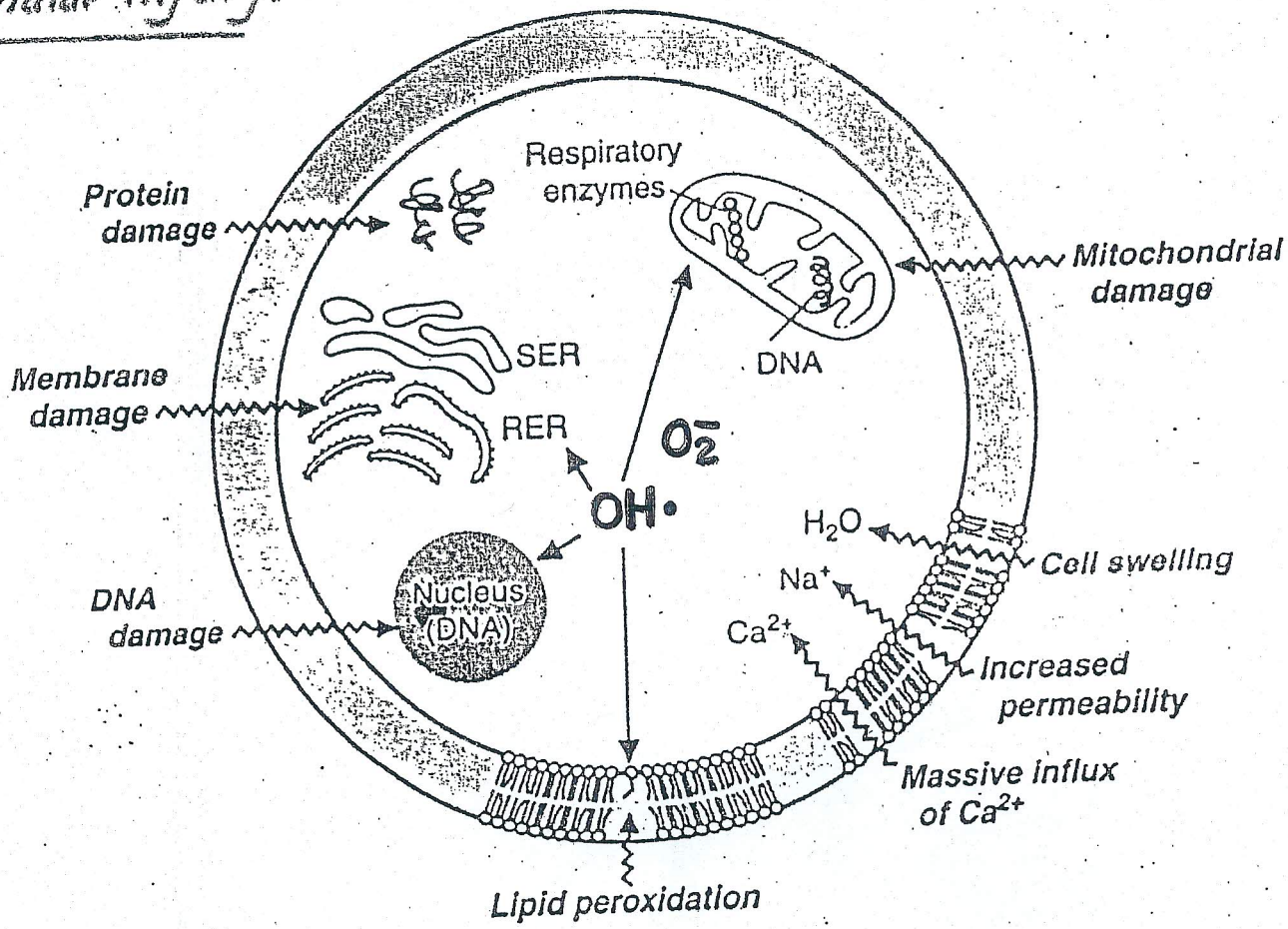


Malondialdehyde "MDA"



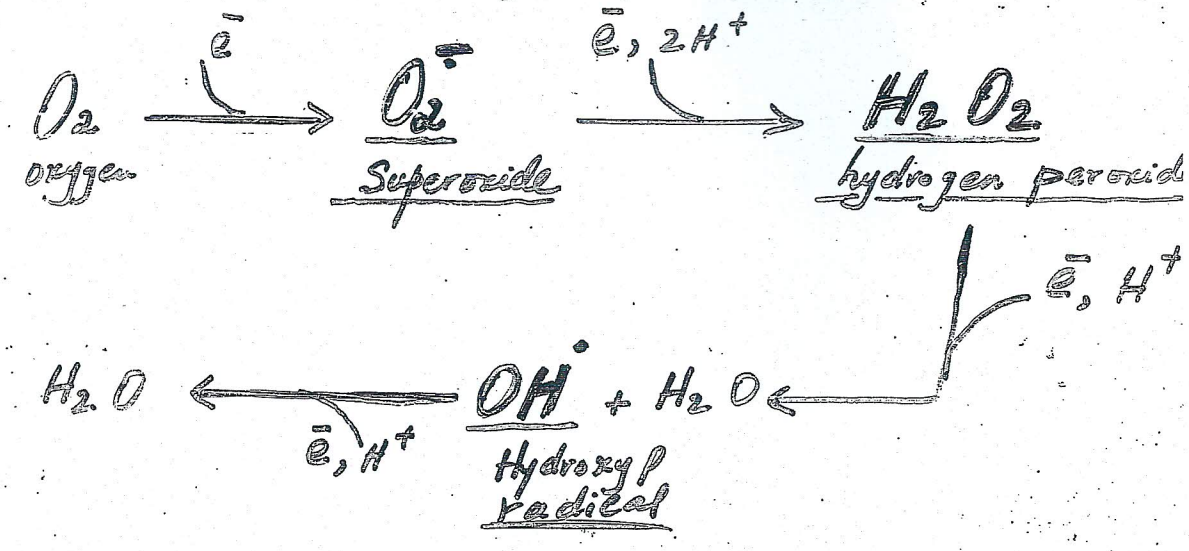
degraded lipid peroxide

Free Radical- Mediated Cellular Injury.



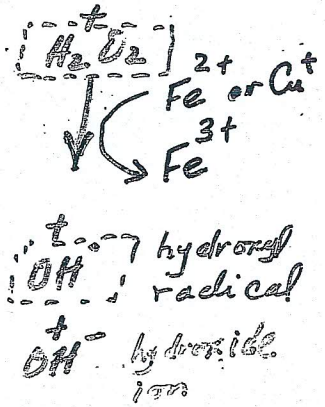
ROS

One-Electron Reduction Steps of Oxygen
(Generation of ROS)

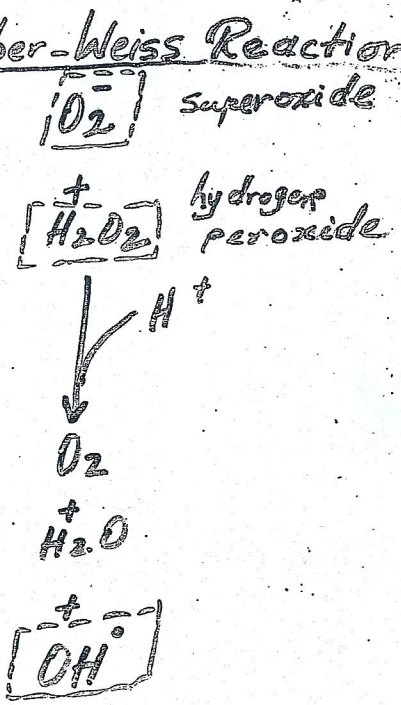


Generation of the hydroxyl radical $OH^{\cdot}$

The Fenton Reaction



The Haber-Weiss Reaction



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SOURCES of ROS in the cell :-

- Oxidases

$\bar{e} + O_2 \rightarrow H_2O$ or H_2O_2

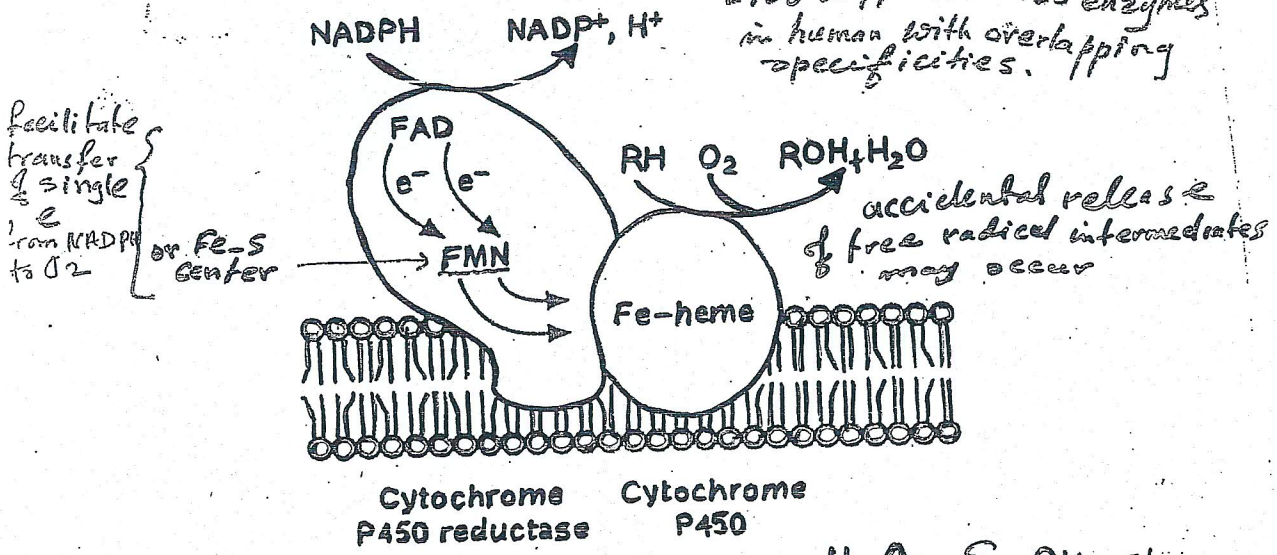
most oxidases (peroxidase) $\rightarrow H_2O_2$ $\xrightarrow{\text{Fenton reaction}}$ $OH^{\cdot}$

Oxidases are confined to sites equiped with protective enzymes

- Oxygenases
  - monooxygenases (hydroxylases)
  - Dioxygenases
    - $\rightarrow$ Thromboxanes
    - $\rightarrow$ PG
    - $\rightarrow$ Leukotrienes
- Coenzyme Q in R.C.
- Respiratory Burst during phagocytosis $\rightarrow O_2^{\cdot}, H_2O_2, OH^{\cdot}, NO, HOCl$
- Ionizing Radiation $\rightarrow OH^{\cdot}$

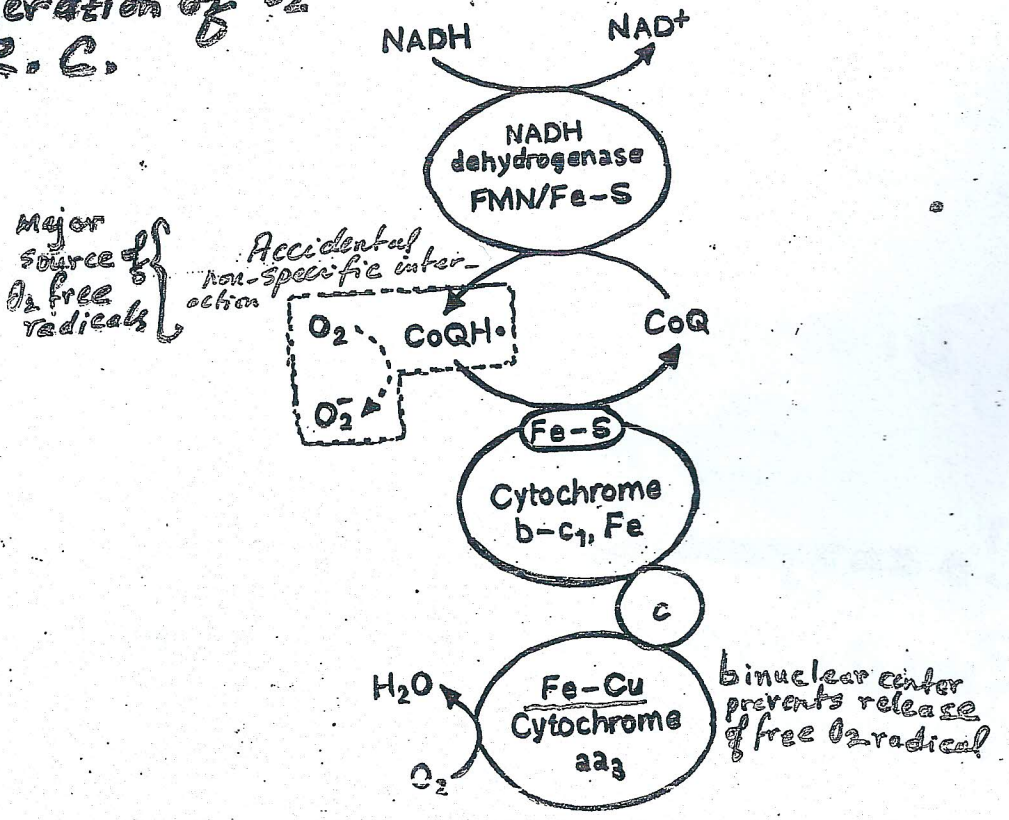
Cytochrome P 450 enzymes :-

Superfamily of structurally related monooxygenases
- 100 different iso enzymes in human with overlapping specificities.



$$O_2 + S + \text{Electron donor} - XH_2 \longrightarrow H_2O + S\text{-}OH + \text{Electron donor} - X$$

Generation of O_2^- by R. C.



:- Cytochrome P450 Monooxygenase
(Mixed Function oxygenase)

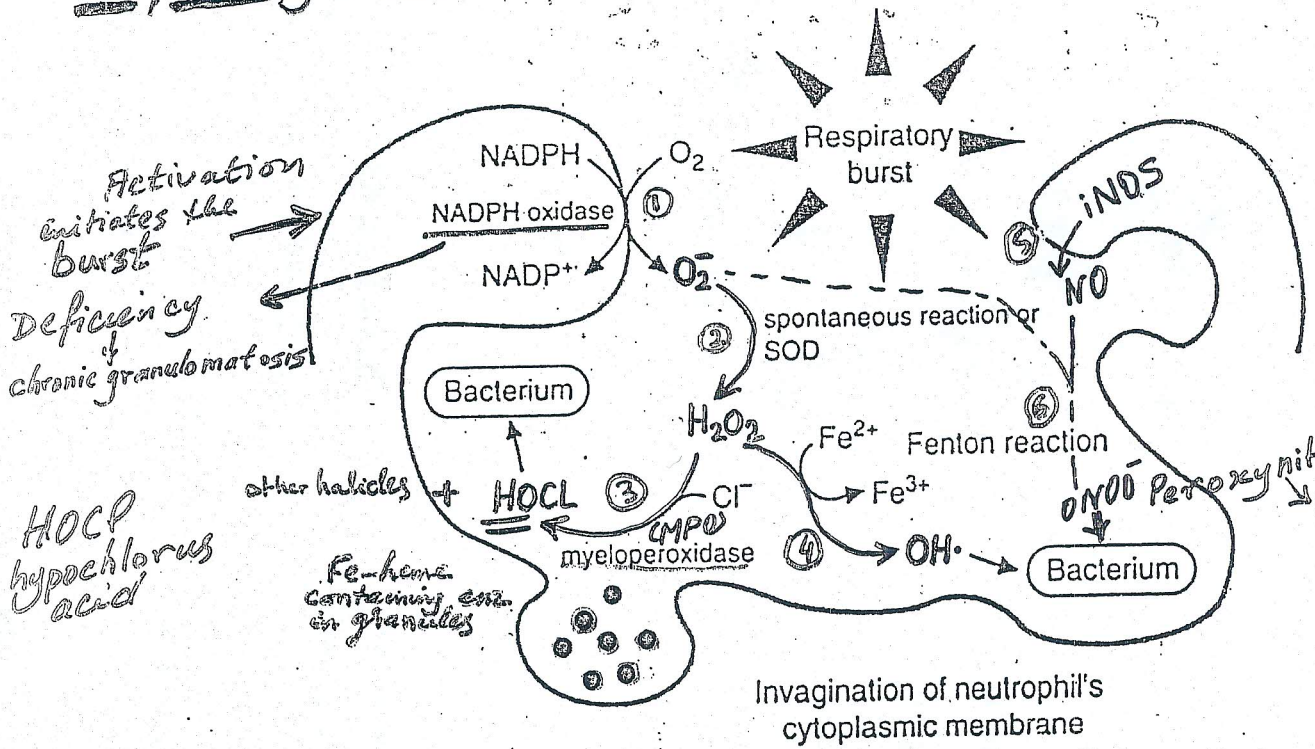
$$R\text{-}H + O_2 + NADPH + H^+ \longrightarrow R\text{-}OH + H_2O + NADP^+$$

R → steroid
→ drug
→ other chemical

1- Mitochondrial System
Hydroxylation of steroids in steroid hormone-producing tissues
synthesis of bile acids
synthesis of biologically active Vit D

2- Microsomal System
Detoxification of foreign compounds (xenobiotics)
Activation or inactivation of Drugs
solubilization

Production of reactive Oxygen species during the phagocytic Respiratory burst by activated macrophages, neutrophils & eosinophils.



HOCl - hypochlorous acid

powerful toxin - halogenation and ox^n.

e.g. Fe-- & SH - centers, ox. decarboxylation, ox. deamination breaking peptide bonds

OH· & HOCl attacks bacterial cells → lysis

30 - 60 min

Consumption of O_2 } ← Respiratory Burst

$ONOO^-$ Peroxynitrite

H^+ physiologic pH

Peroxynitrous acid

$HONO_2$

$NO_2^\cdot$

NO_3^- safe

NO_2^+ nitronium ion (nitration agent)

OH· free radical

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