Biomolecular Mechanism of Antioxidant Activity in Aging Process

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Revolution in human biology

↓

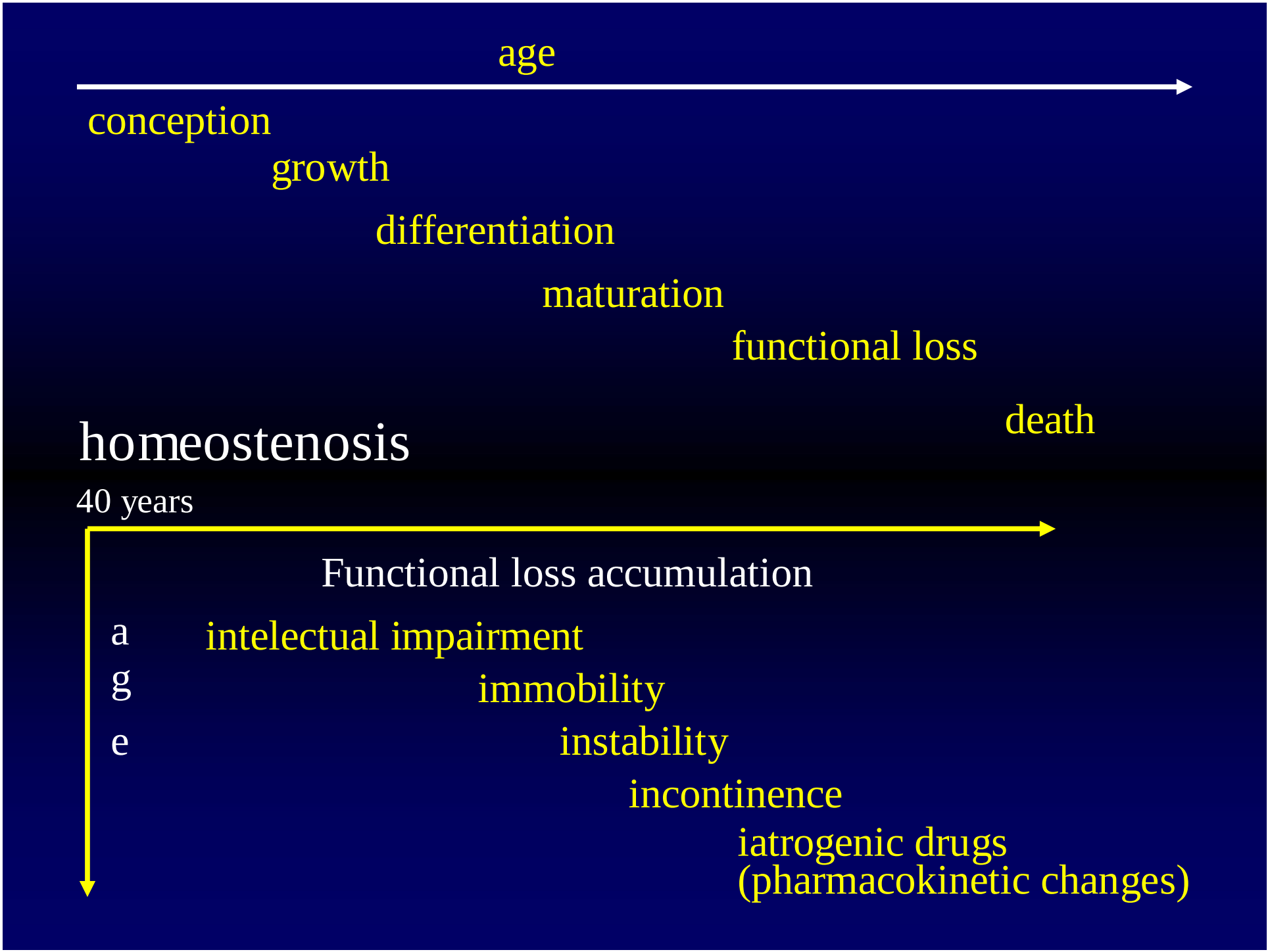
Increased life-span

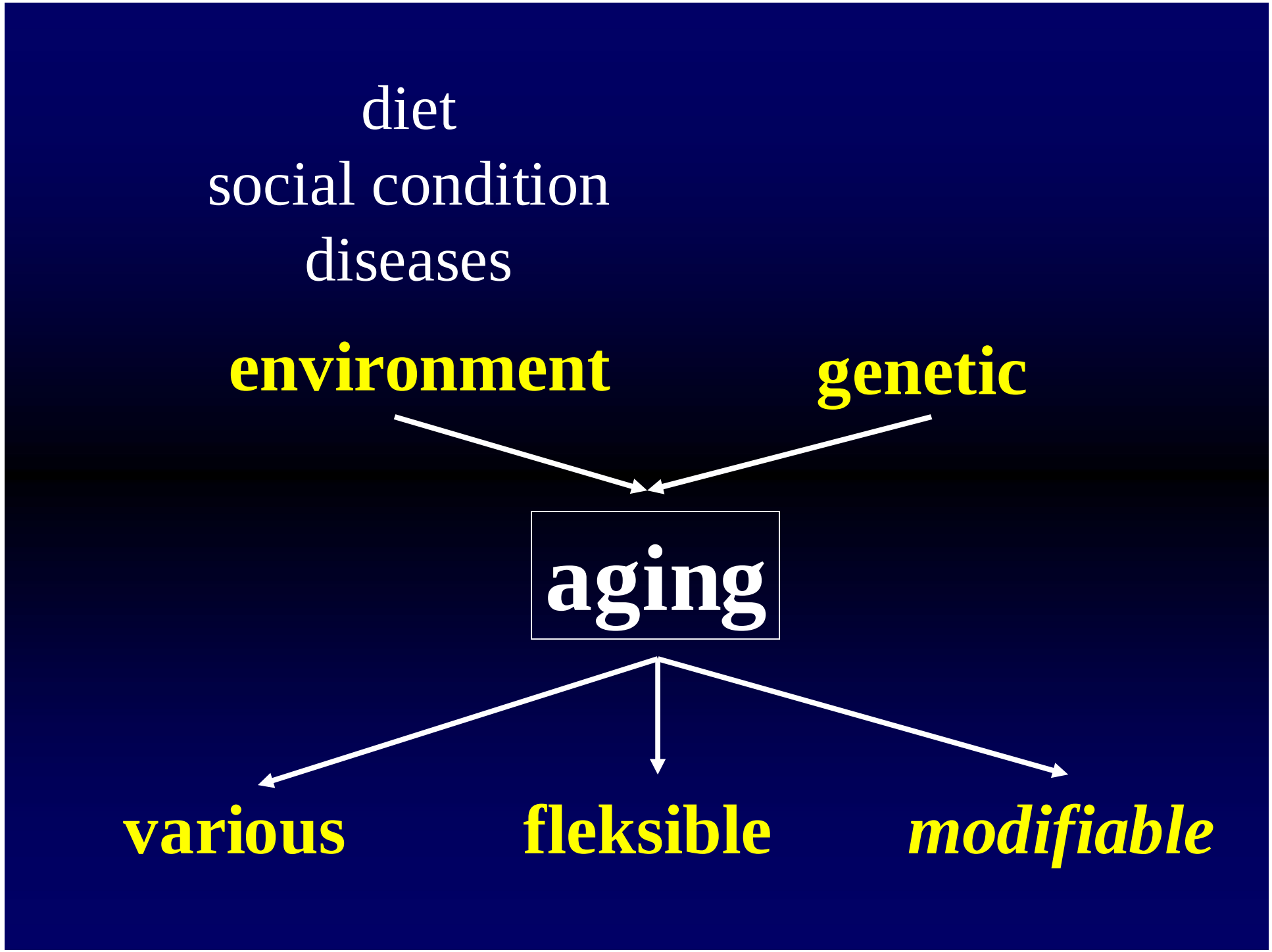
↓

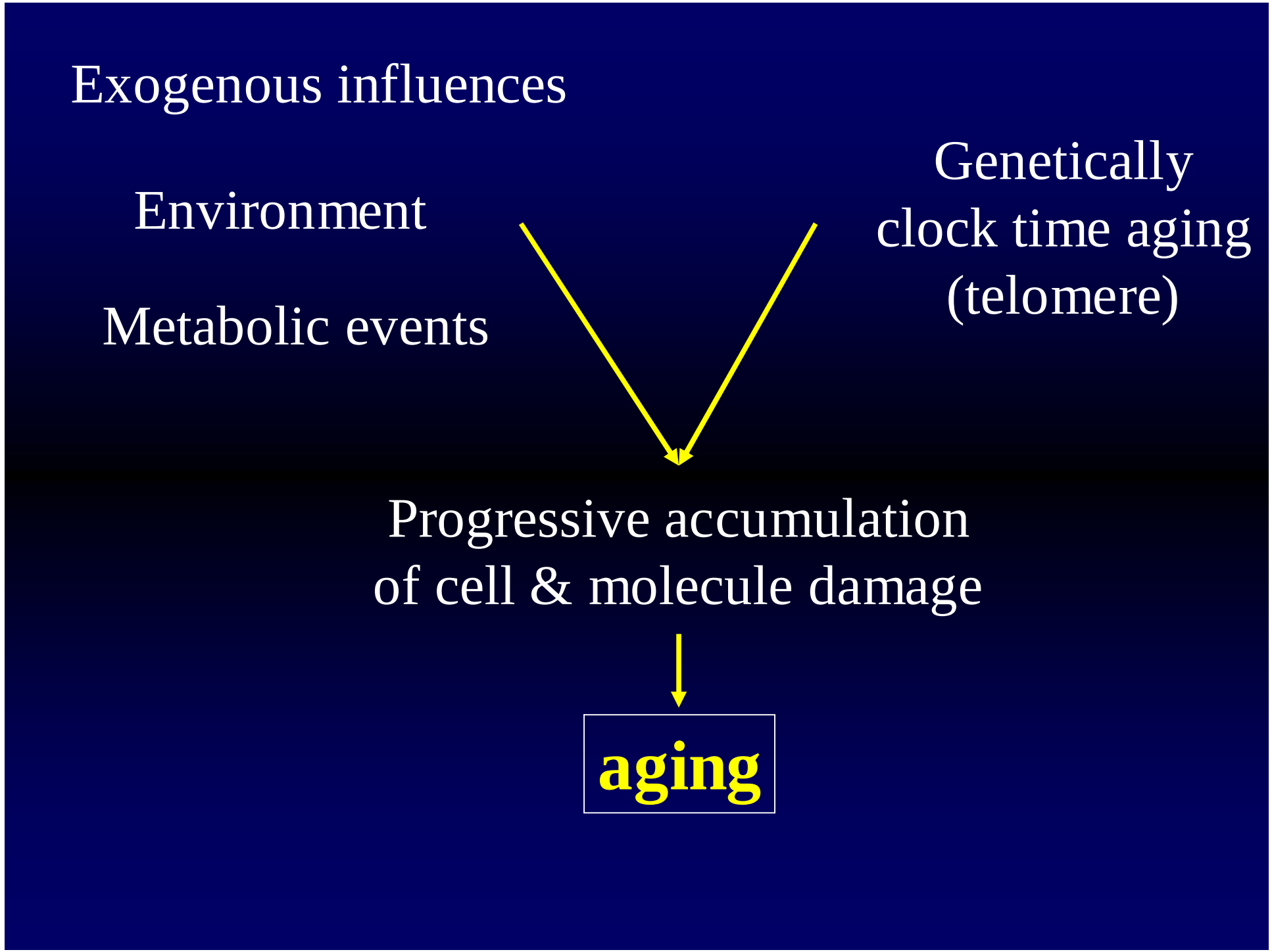
Increased age group in population

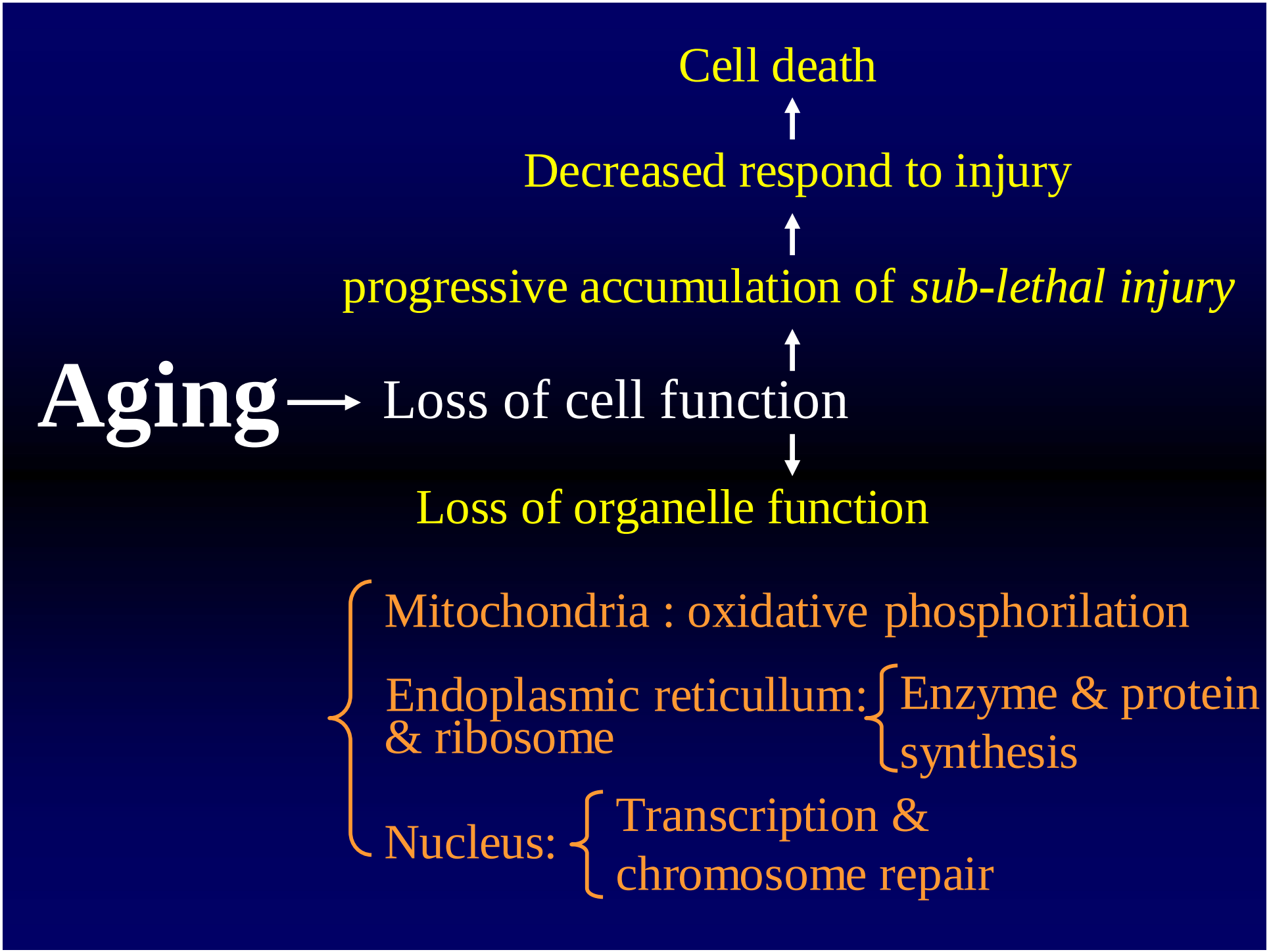
↓

World-wide health issue


age
conception
growth
differentiation
maturation
functional loss
death
homeostenosis
40 years
Functional loss accumulation
a
g
e
intelectual impairment
immobility
instability
incontinence
iatrogenic drugs
(pharmacokinetic changes)


diet
social condition
diseases
environment
genetic
aging
various
fleksible
modifiable


Exogenous influences
Environment
Metabolic events
Genetically
clock time aging
(telomere)
Progressive accumulation
of cell & molecule damage
aging


Cell death
Decreased respond to injury
progressive accumulation of *sub-lethal injury*
Aging → Loss of cell function
Loss of organelle function
Mitochondria : oxidative phosphorilation
Endoplasmic reticullum: & ribosome
Enzyme & protein synthesis
Nucleus:
Transcription & chromosome repair

Theory of aging

somatic mutation

free radical

apoptosis

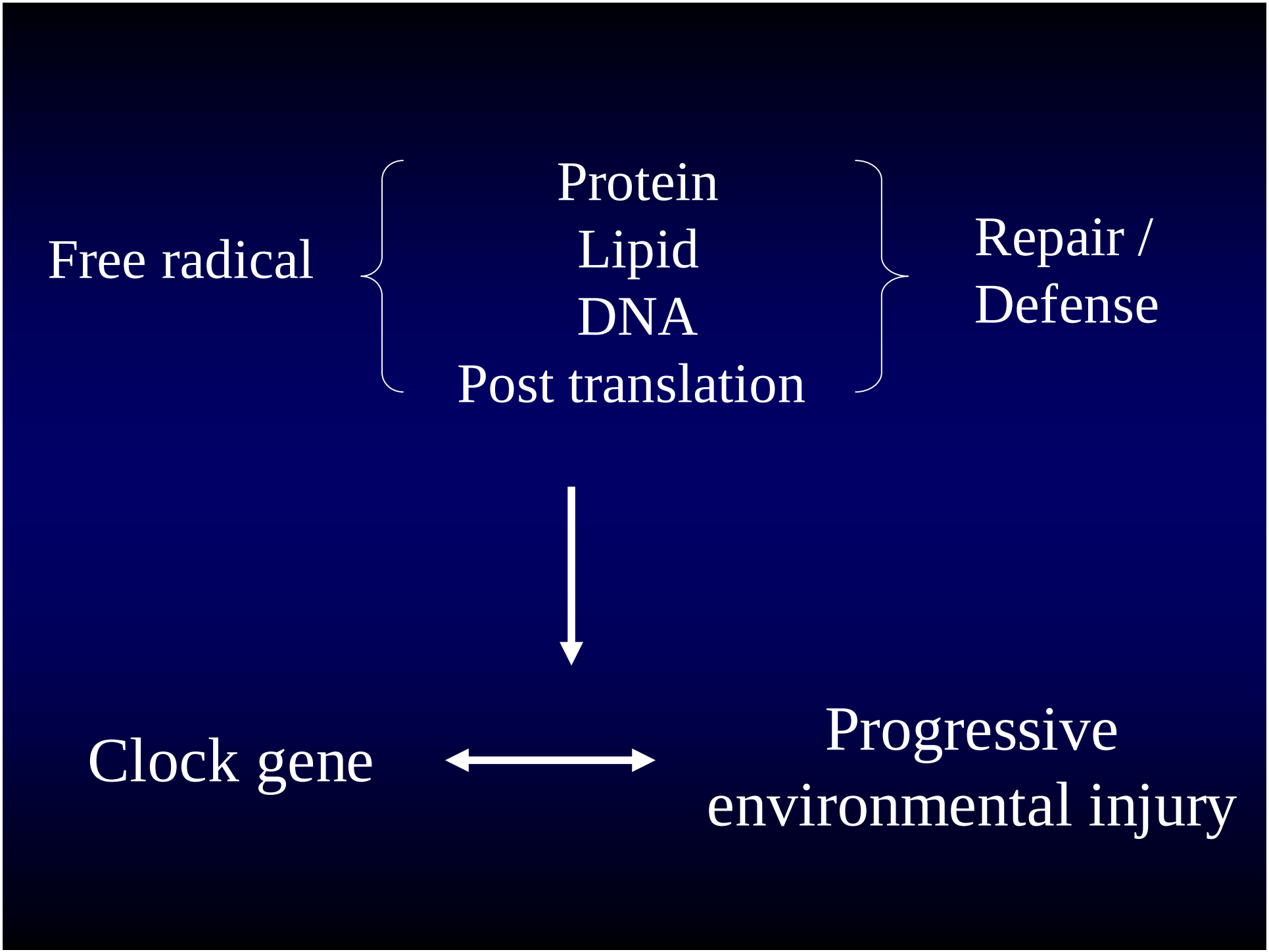
immunology

neuroendocrine

Excessive physiological change

Clear biological change

Mechanism ?


Free radical
Protein
Lipid
DNA
Post translation
Repair /
Defense
Clock gene
Progressive
environmental injury

Free radical

- chemical species which have unpaired electron(s)
- seek other electron(s) to become paired
- reactive and attack other molecules

Active oxygen and related species

O_2^{*-}	superoxide	LO^*	lipid alkoxyl radical
HO^*	hydroxyl radical	LO_2^*	lipid peroxyl radical
L^*	lipid radical	HO_2^*	hydroperoxyl radical
NO_2^*	nitrogen dioxide	RS^*	thiyl radical
NO^*	nitric oxide	P^*	protein radical

Free radical reactions

Hydrogen atom transfer

$X^* + RH \rightarrow XH + R^*$

β-Scission reaction

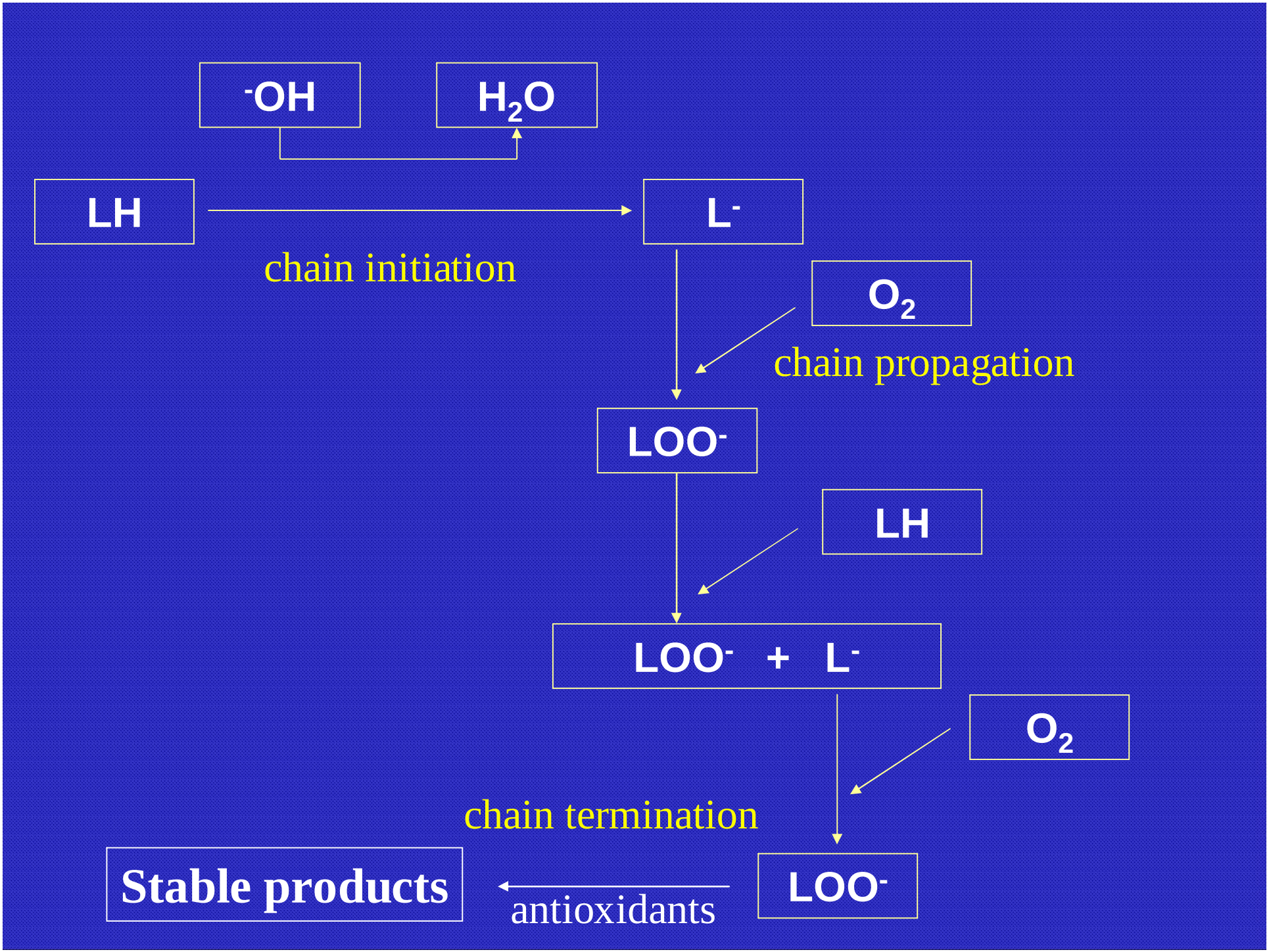
$X^* \longrightarrow Y^* + \text{products}$

Aromatic substitution reaction

Coupling reaction

$R^* + R^* \longrightarrow R\text{-}R$

Addition reaction


·OH
H2O
LH
L·
chain initiation
O2
chain propagation
LOO·
LH
LOO· + L·
O2
chain termination
Stable products
antioxidants
LOO·

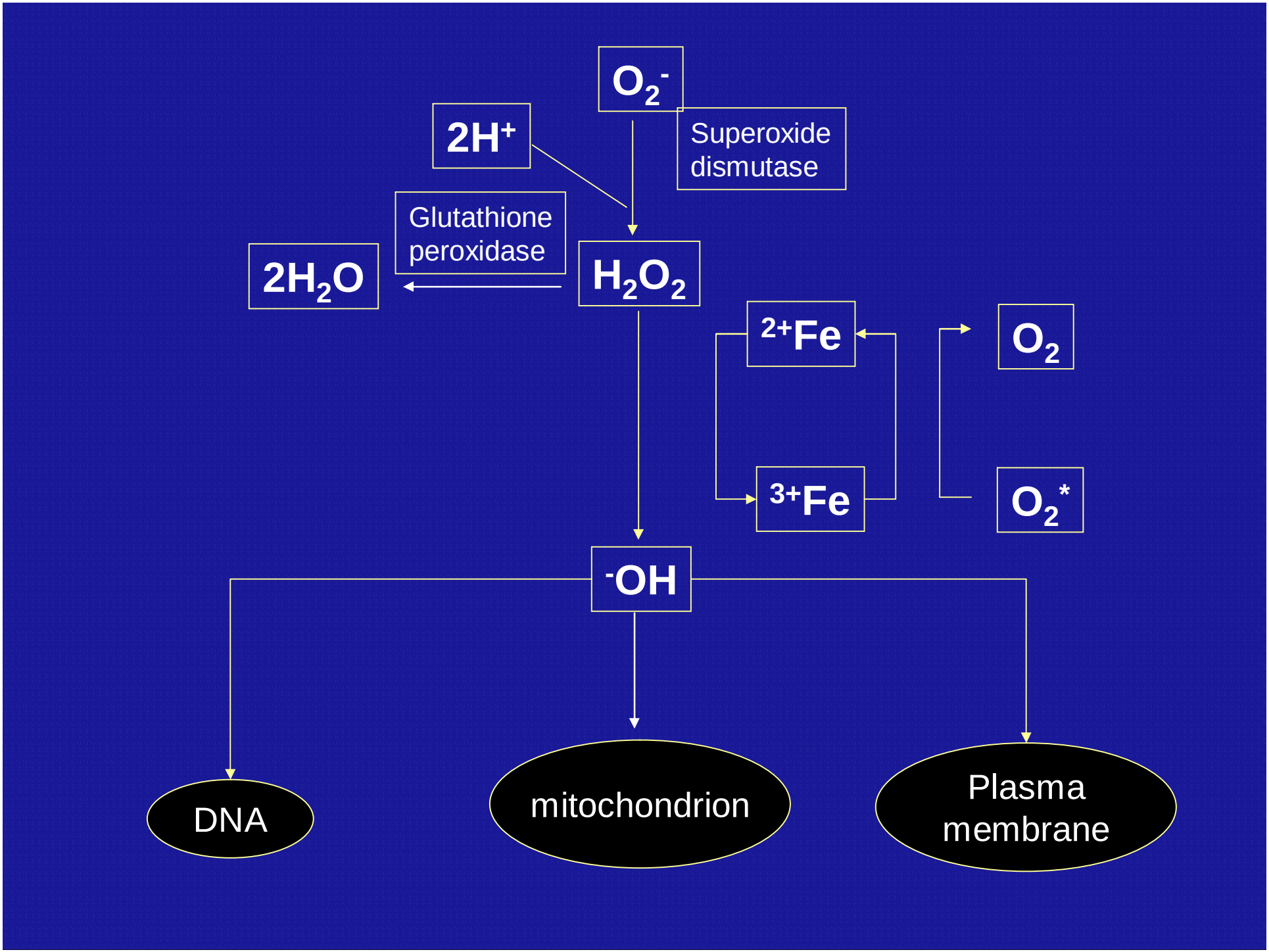
Free radical

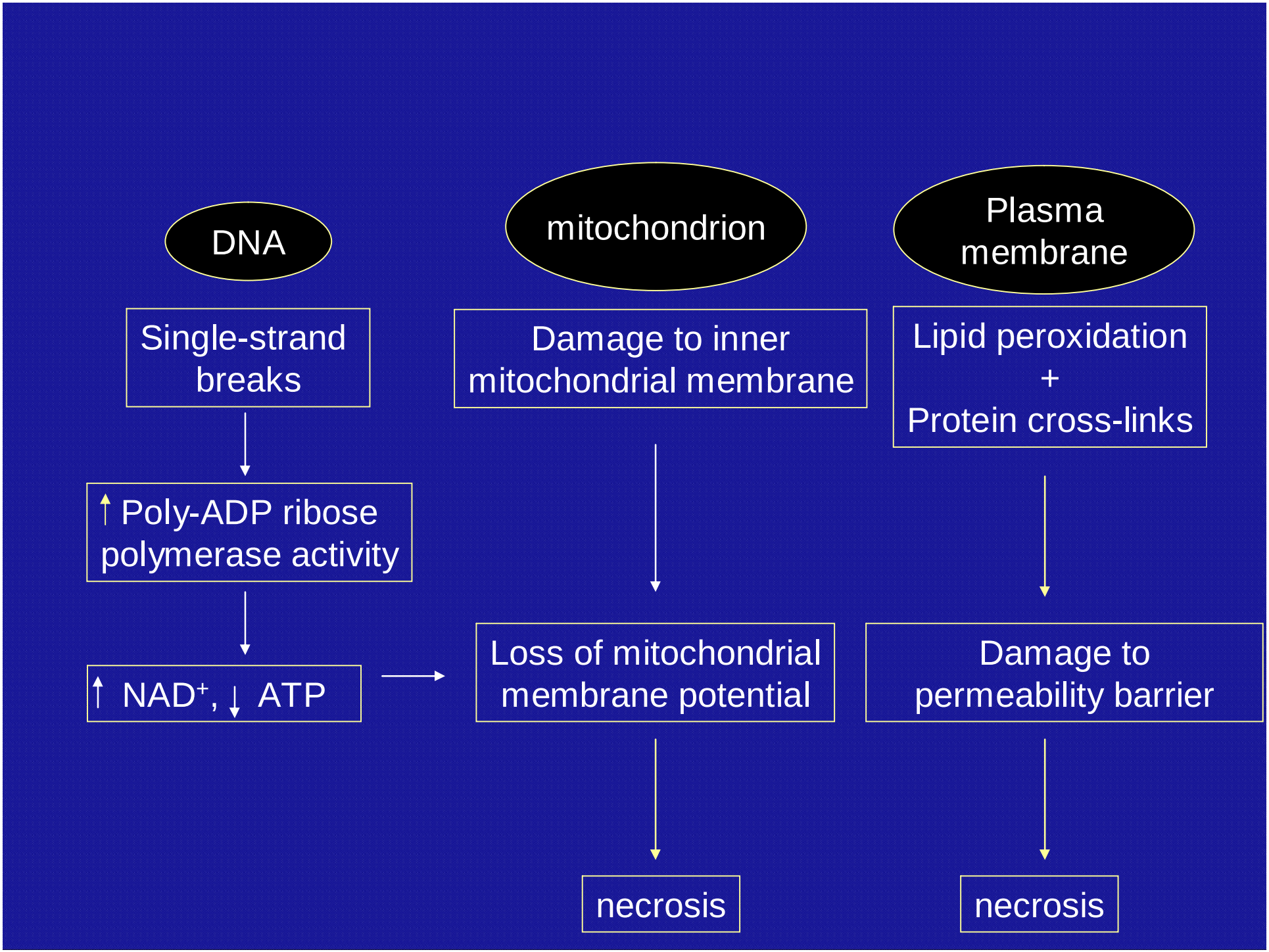
- has important physiological role
  - energy production
  - synthesis biological compounds
  - phagocytosis
  - signal transduction
- may exert toxic effect (cell injury)
- causative role in a variety of disease
  - * heart diseases
  - * cancer
  - * toxic hepatitis

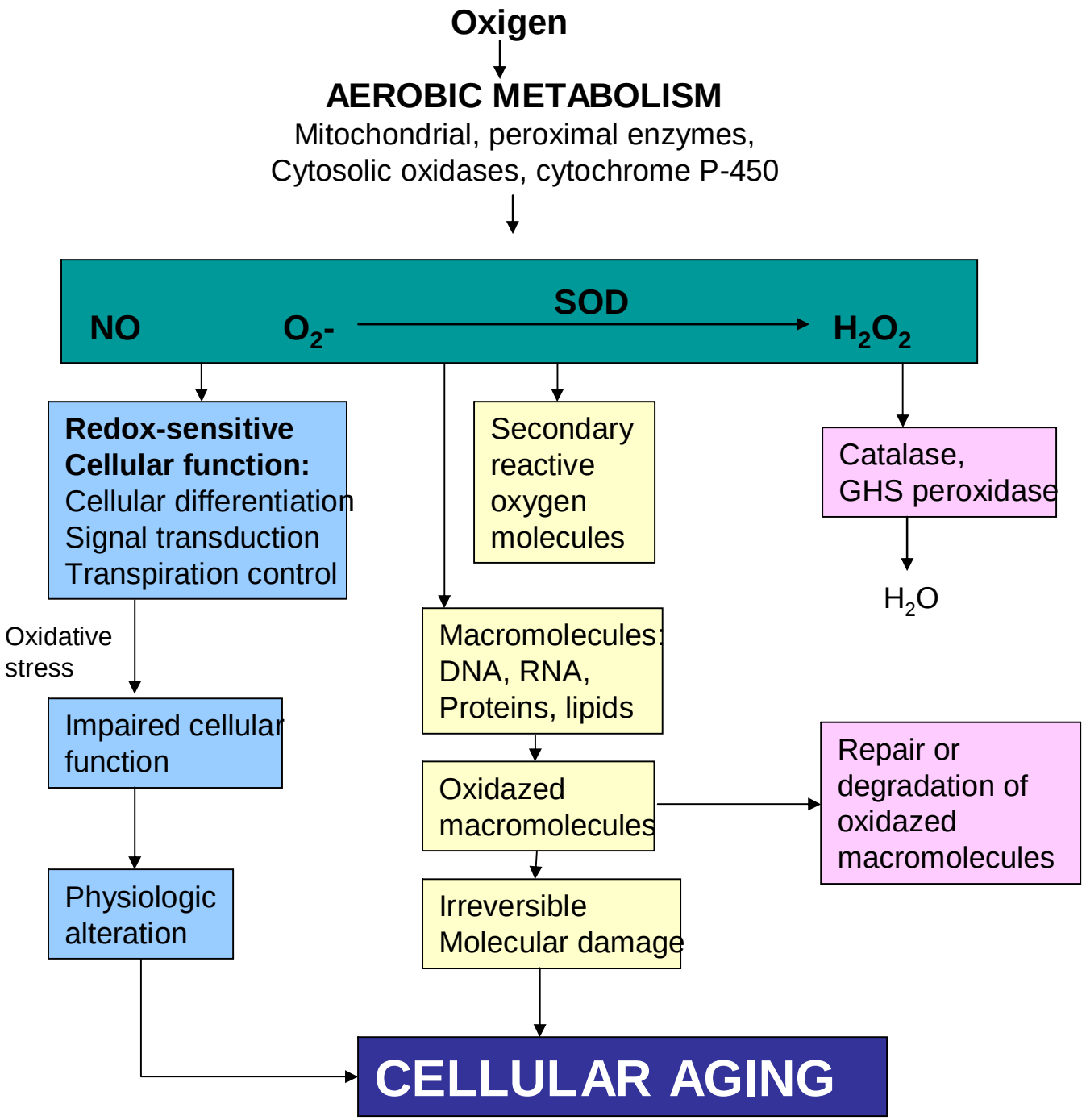
} aging

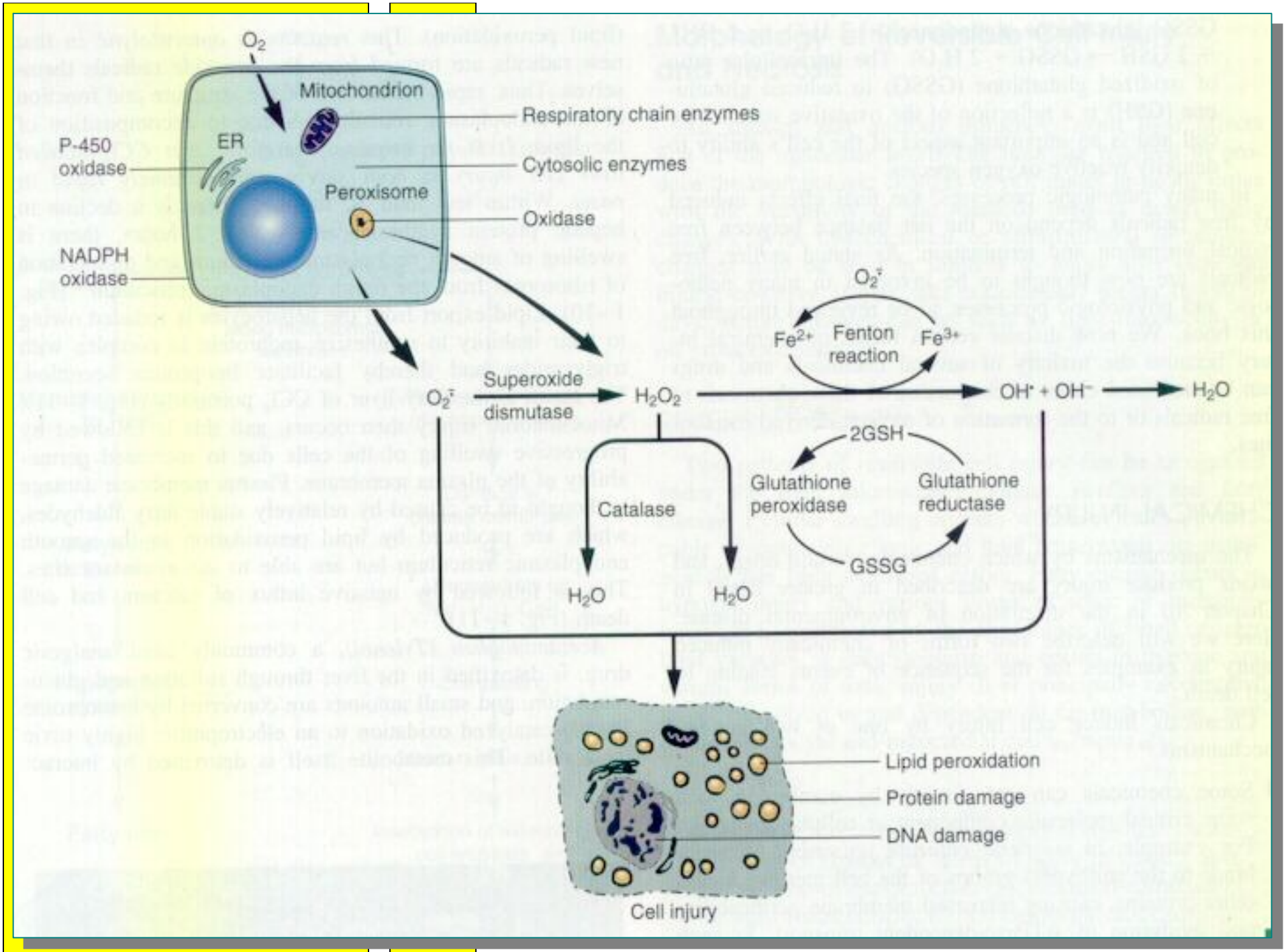
Free radical

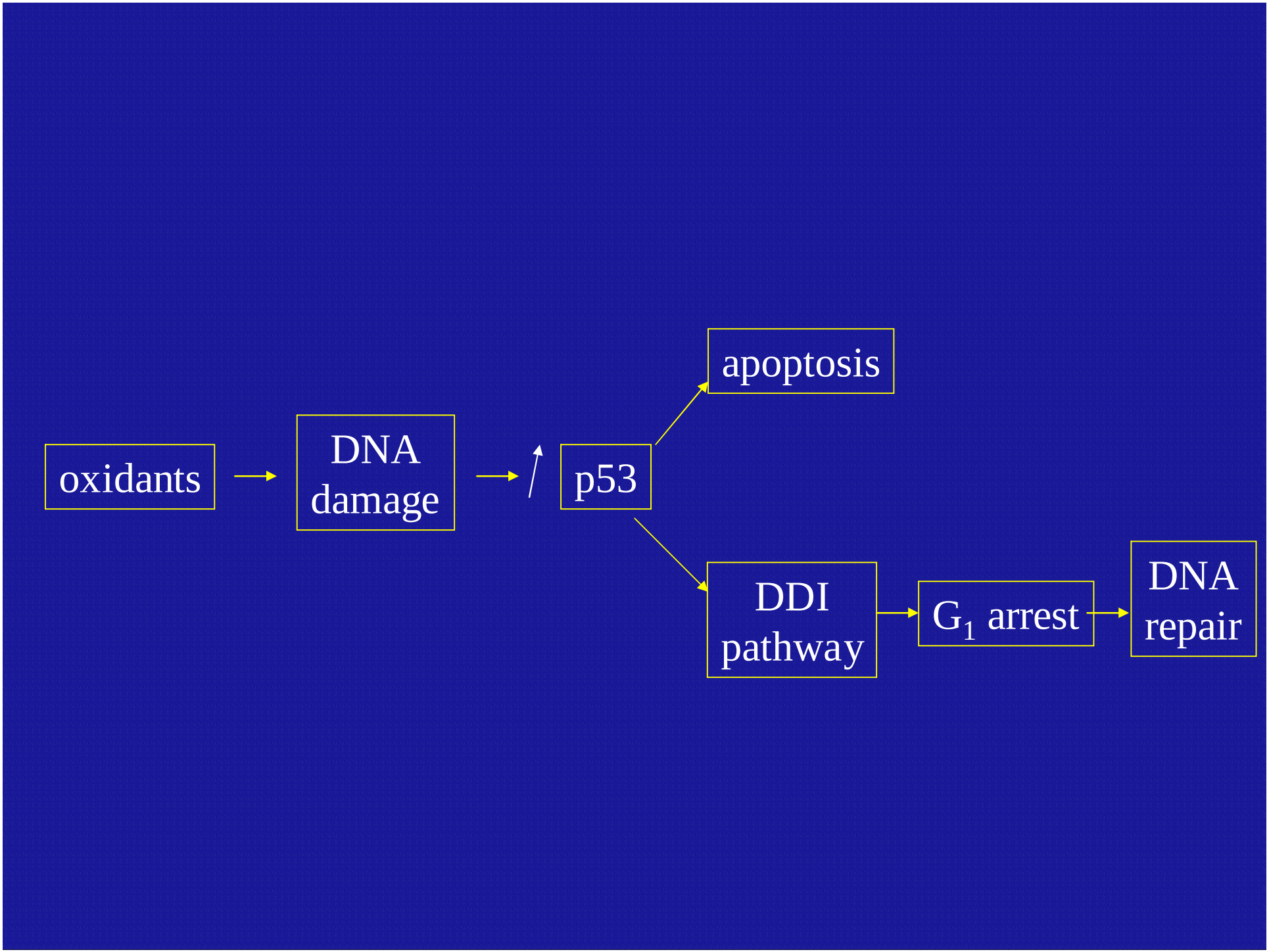
- attacks all biological materials
  - lipids
  - sugars
  - proteins
  - DNA
- induce oxidation
- caused oxidative damages
  - * membrane dysfunction
  - * protein modification
  - * enzyme inactivation
  - * breaks DNA strand


O_2^-
$2H^+$
Superoxide dismutase
Glutathione peroxidase
$2H_2O$
H_2O_2
^{2+}Fe
^{3+}Fe
O_2
O_2^*
^-OH
DNA
mitochondrion
Plasma membrane


DNA
mitochondrion
Plasma membrane
Single-strand breaks
Damage to inner mitochondrial membrane
Lipid peroxidation + Protein cross-links
↑ Poly-ADP ribose polymerase activity
↑ NAD+, ↓ ATP
Loss of mitochondrial membrane potential
Damage to permeability barrier
necrosis
necrosis


Oxigen
AEROBIC METABOLISM
Mitochondrial, peroximal enzymes,
Cytosolic oxidases, cytochrome P-450
NO
O2-
SOD
H2O2
Redox-sensitive
Cellular function:
Cellular differentiation
Signal transduction
Transpiration control
Secondary
reactive
oxygen
molecules
Catalase,
GHS peroxidase
H2O
Oxidative
stress
Macromolecules:
DNA, RNA,
Proteins, lipids
Impaired cellular
function
Oxidazed
macromolecules
Repair or
degradation of
oxidazed
macromolecules
Physiologic
alteration
Irreversible
Molecular damage
CELLULAR AGING


O_2
Mitochondrion
Respiratory chain enzymes
P-450 oxidase
ER
Cytosolic enzymes
Peroxisome
Oxidase
NADPH oxidase
O_2^-
Fe^{2+}
Fenton reaction
Fe^{3+}
O_2^-
Superoxide dismutase
H_2O_2
$OH^\bullet + OH^-$
H_2O
2GSH
Glutathione peroxidase
Glutathione reductase
Catalase
GSSG
H_2O
H_2O
Lipid peroxidation
Protein damage
DNA damage
Cell injury


oxidants
DNA damage
p53
apoptosis
DDI pathway
G_1 arrest
DNA repair

Defense system *in vivo* against oxidative damage

1. Preventive antioxidants : suppress free radicals formation

a. Non-radical decomposition

- catalase
- glutathione peroxidase (cellular and plasma)
- phospholipid hydroperoxide
- glutathione S-trasferase

b. Sequestration of metal by chelation

- transferin
- hemopexin
- albumin
- haptoglobin
- ceruloplasmin

c. Quenching of active oxygen species

- superoxide dismutase (SOD)
- carotenoids, vitamin E

Defense system *in vivo* against oxidative damage

2. Radical-scavenging antioxidants :

- scavenge radicals
- inhibit chain initiation
- break chain propagation

hydrophilic : vitamin C, uric acid, bilirubin, albumin
lipophilic : vitamin E, ubiquinol, carotenoids, flavonoids

3. Repair and de novo enzymes

- repair the damage
- reconstitutes membranes

lipase, protease, transferase
DNA repair enzymes

4. Adaptation : generate appropriate antioxidant enzyme
transfer to the right site, time and concentration

Defense system *in vivo* against oxidative damage

1. Endogenous
    - GSH
    - Fe-catalase
    - NADPH
    - ubiquinol-10 (reduced coenzyme Q_{10})
    - MN, Cu, Zn-superoxide dismutase (SOD)
    - uric acid
    - lipoic acid
    - hormones w/ antioxidants activity (melatonin, DHEA, etc)
    - metal binding protein
        albumin, ceruloplasmin, transferin
        heptoglobin, hemopexin

Defense system *in vivo* against oxidative damage

2. Exogenous

   - tocopherols & tocotrienols (vitamin E)
   - ascorbate (vitamin C)
   - vitamin A and carotenoids
   - Se (selenium)
   - phytochemicals w/ antioxidant activity
   - dietary CoQ_{10}, glutathione, lipoic acid, etc
   - food antioxidants

Free radical formation in aging
(primary or secondary)

Metabolic events/excess
DNA cross link
Membrane lipid oxidation
Cell injury
Respiratory chain burst

Defense system against oxidative damage in aging

Decrease NADH/NADPH
Decrease antioxidant enzyme activity
Increase demand on defense system
cell injury

Free radicals and antioxidants

are double-edge swords

The balance of beneficial and toxic effects

is determined by relative importance

of many competing biological reactions

Free radical action :

clear mechanism

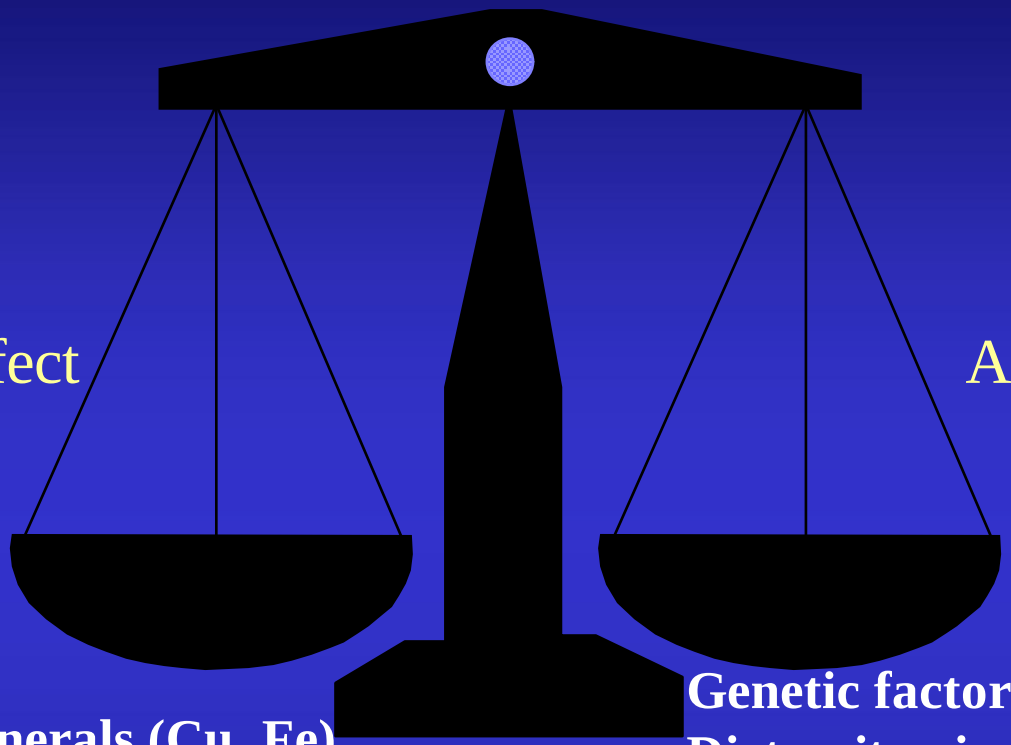
unclear biological impact

Oxidative status

Free radical

Anti oxidant

Determinants of oxidative status in humans



Prooxidants effect

Antioxidant effect

Genetic factors
Diet : PUFA
Divalent minerals (Cu, Fe)
Prooxidant nutrients
Environment : pollutants, tobacco, UV
Alcohol
Injury, diseases, medications
Physiological states : prematurity,
aging, strenuous exercise
Stress (physiological & emotional)

Genetic factor
Diet : vitamins (A, C, E)
minerals (Se, Zn, Cu, Mn, Fe)
antioxidant food component
Alcoholic drinks
Exercise program

Imbalance oxidative status (oxidative stress)

Increase
free radicals production

Decrease
antioxidant production

Continuing cycle of metabolic stress

Free radicals : physiological role

exert toxic effect

essential for : energy production,

synthesis biological compounds

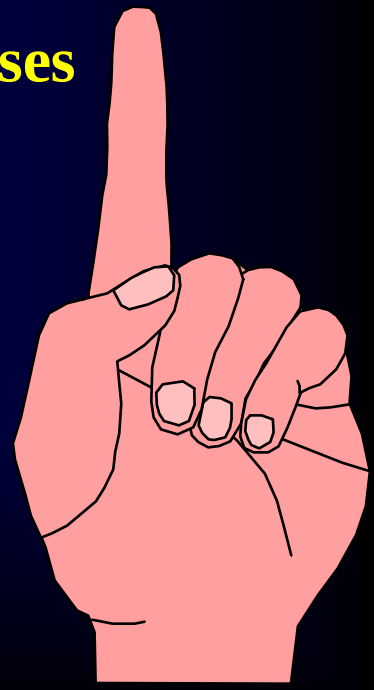
phagocytosis

signal transduction

play causative role in a variety of diseases and aging

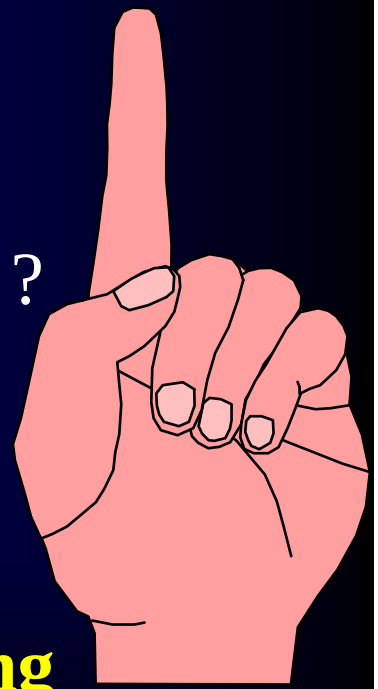
Antioxidants : suppress oxidative damage

important in aerobic organisms



- Antioxidant status is dynamic,
  affected by many factors
- Antioxidant defense includes a variety of
  antioxidants systems, evolved over a very long time
- Individual antioxidants is components of systems
  with major interdependence and interactions

Aging : clear biological impact, mechanism ?
Free radical : clear mechanism, biological impact ?



Antioxidants increase the healthy & delayed aging


Request for materilas : tachmad@fk.unpad.ac.id
Thank you