G6PD Deficiency

- Common disease
- characterized by hemolytic anemia
- 200 – 400 millions individuals worldwide
- Highest prevalence in Middle East, S.E. Asia, Mediterranean
- X-linked inheritance
- > 400 different mutations
- Deficiency provides resistance to falciparum malaria

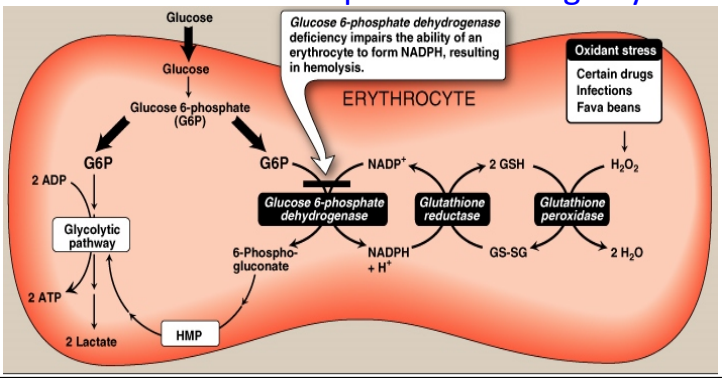
Role of G6PD in red blood cells

Peroxides + GSH ⟶ G-S-S-G + $2H_2O$

G-S-S-G + NADPH ⟶ 2GSH + NADP+

GSH helps maintain the SH groups in proteins in the reduced state

Oxidation ➔ denaturation of proteins and rigidity of the cells



Precipitating Factors inG6PD Deficiency

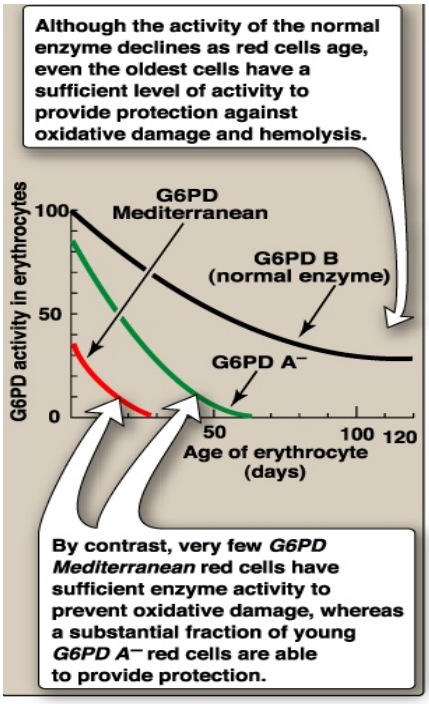
- Oxidant drugs
  - Antibiotics e.g. Sulfomethxazole
  - Antimalaria Primaquine
  - Antipyretics Acetanalid
- Favism
- Infection
- Neonatal Jaundice

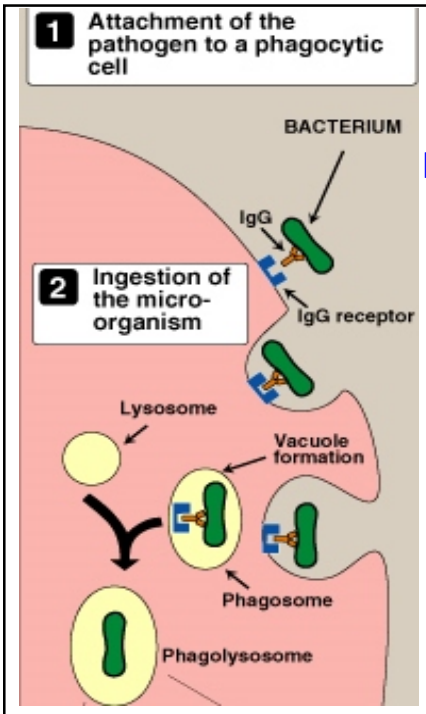
G6PD Deficiency Variants

- Wild type B
- Mediterranean Variant B^- (Class II) : 563C → T
- African Variant A^- (Class III); two point mutation
- African Variant A; Normal activity 80%
- Very severe deficiency (Class I)
- Majority missense mutation point mutation
- Large deletions or frame shift; Not Observed

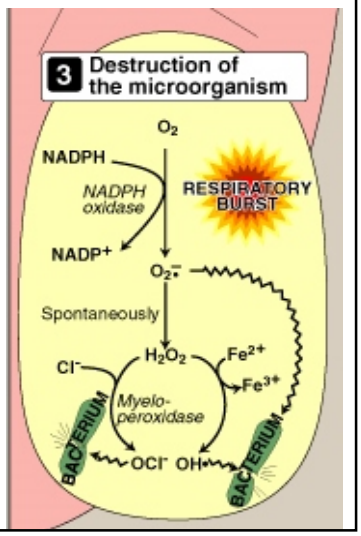
Classification of G6PD Deficiency Variants

Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	60–150%



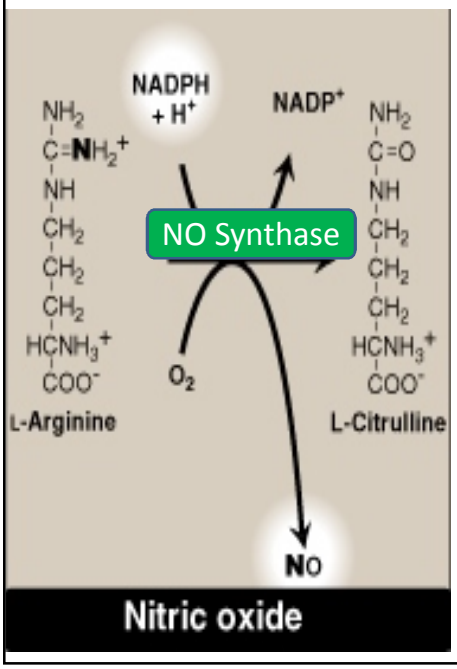


Phagocytosis; the oxygen dependant pathway of microbial killing by White Blood Cells (WBC)



NO and Reactive Nitrogen Oxygen Spciese (RNOS)

- Free radical diffuses readily
- Essential for life and toxic
- Neurotransmitter , vasodilator
- ↓Platelet aggregation
- At high concentration combines with O_2 or O_2 to form **RNOS**
- **RNOS** are involved in neurodegenerative diseases and inflammatory diseases



NO Synthesis

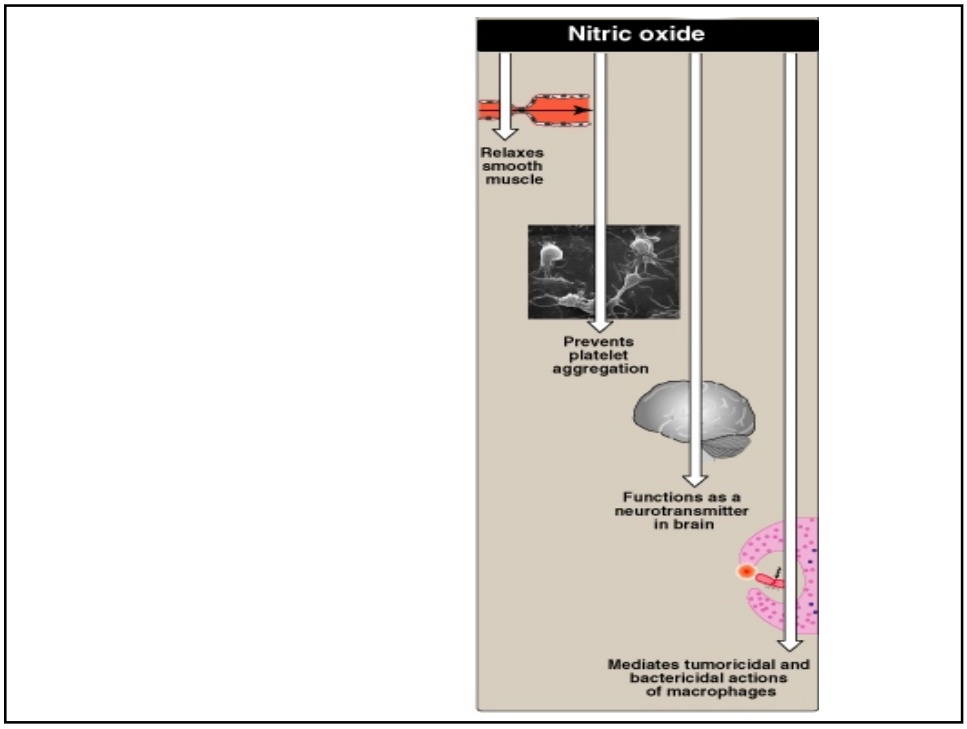
NO Synthase
Three isoforms
nNOS neural
eNOS endothelial
Both are constitutive

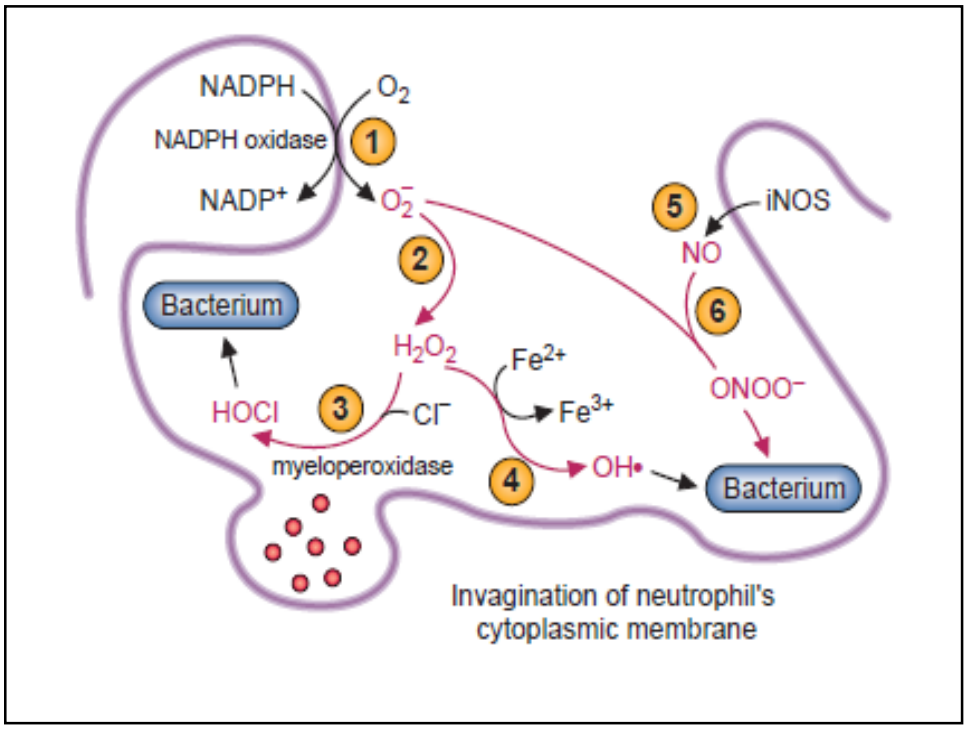
iNOS inducible
Induction of transcription in many cells of immune system ➔ ↑↑ NO ➔ RNOS to kill invading bacteria

Action of NO on vascular endothelium

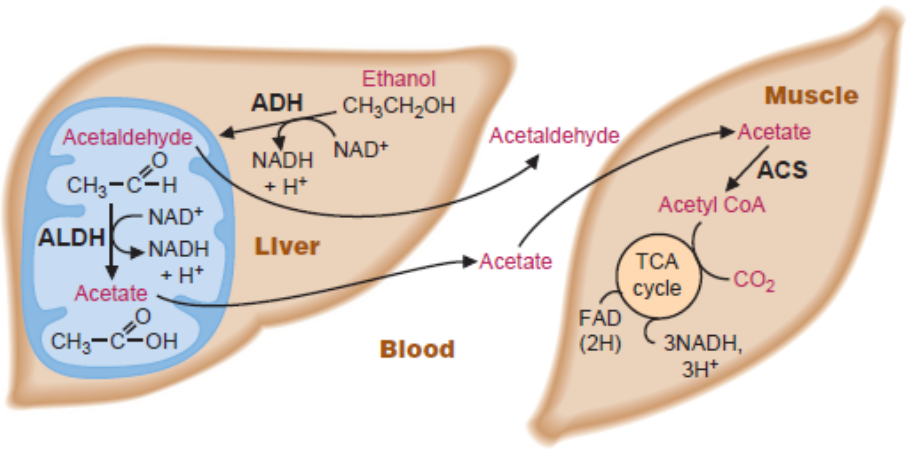
Synthesis by endothelia cells → smooth muscle

NO (+)
GTP → cGMP
cGMP (+) → Protein Kinase G
Protein Kinase G → Phosphorylation of Ca^{2+} channels
Phosphorylation of Ca^{2+} channels → ↓↓Ca^{2+} muscle relaxation

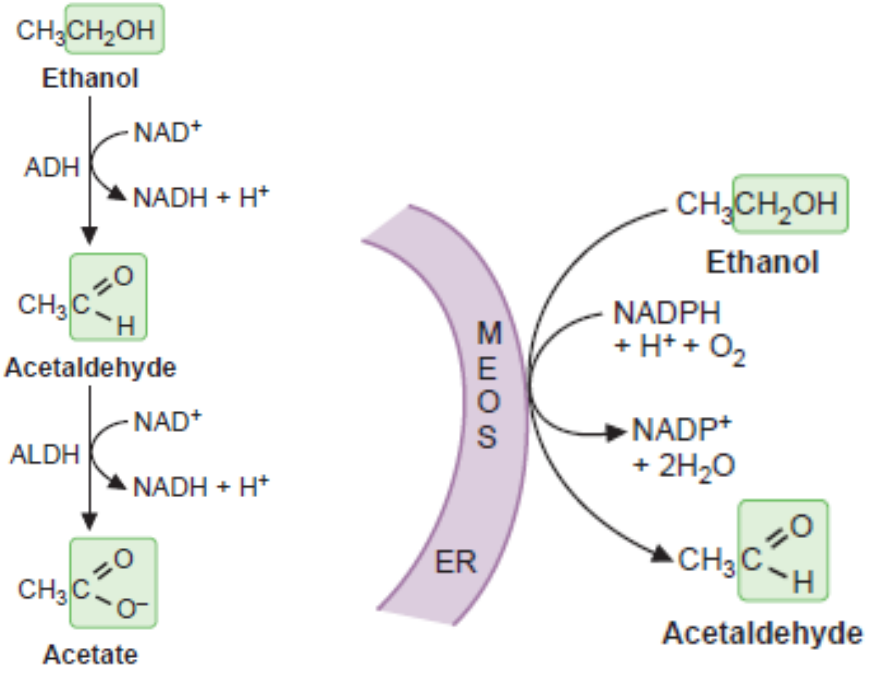

Nitric oxide
Relaxes smooth muscle
Prevents platelet aggregation
Functions as a neurotransmitter in brain
Mediates tumoricidal and bactericidal actions of macrophages

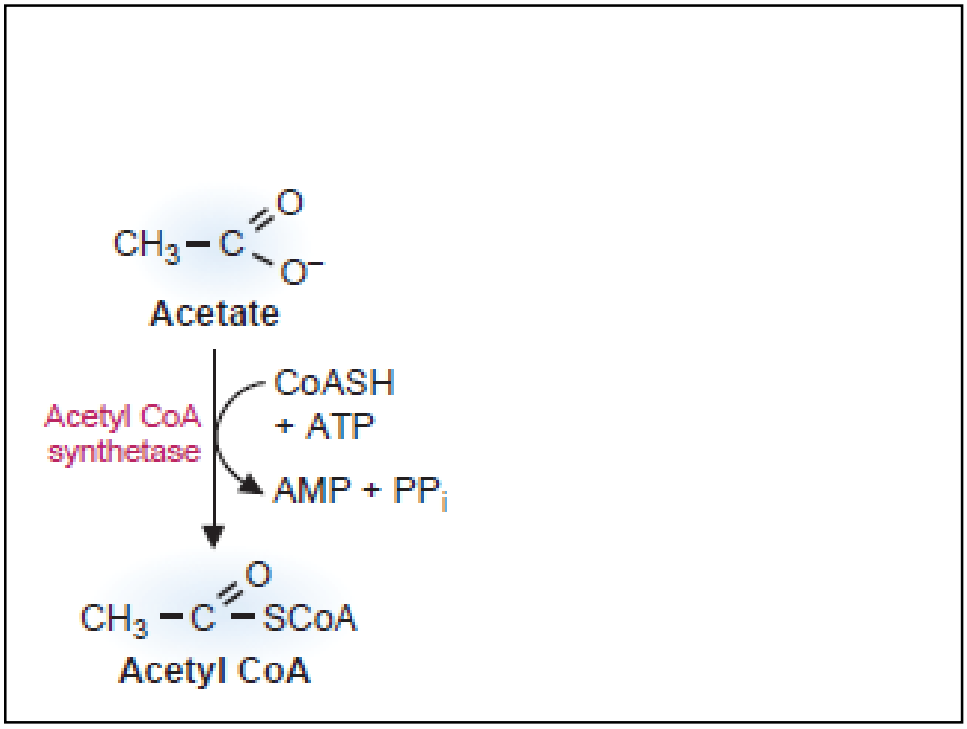

NADPH
O_2
NADPH oxidase
1
$NADP^+$
O_2^-
5
iNOS
NO
2
Bacterium
6
H_2O_2
Fe^{2+}
ONOO⁻
HOCl
3
Cl^-
Fe^{3+}
myeloperoxidase
4
OH•
Bacterium
Invagination of neutrophil's cytoplasmic membrane

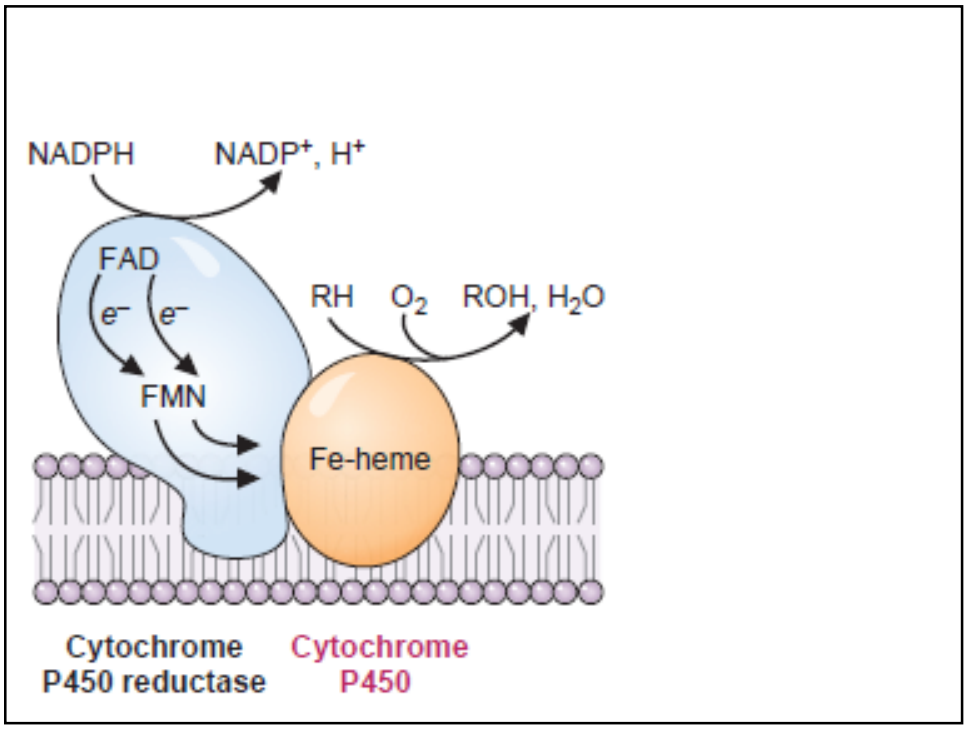
Metabolism of Alcohol



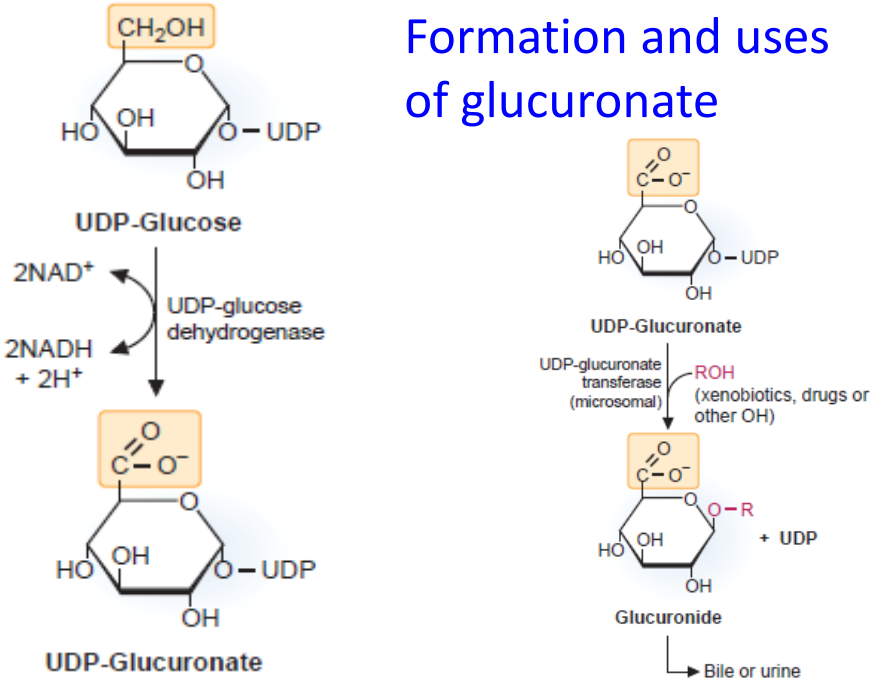
ADH: Alcohol Dehydrogenase
ALDH: Acetaldehyde Dehydrogenase
ACS: Acetyl CoA Synthetase

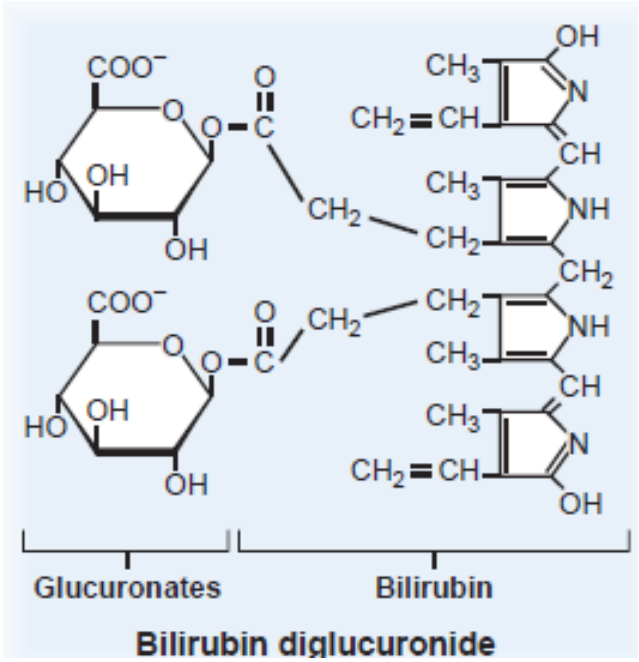



CH3 – C
O
O–
Acetate
Acetyl CoA synthetase
CoASH
+ ATP
AMP + PPi
CH3 – C – SCoA
O
Acetyl CoA


NADPH
NADP+, H+
FAD
e–
e–
FMN
RH
O2
ROH, H2O
Fe-heme
Cytochrome P450 reductase
Cytochrome P450

Formation and uses of glucuronate





UDP-Glucose Metabolism