THE PENTOSE PHOSPHATE PATHWAY / THE HEXOSE MONOPHOSPHATE SHUNT PATHWAY / THE PHOSPHOGLUCONATE PATHWAY

- A specialized pathway - geared towards production of NADPH and Ribose 5-phosphate (R5P).

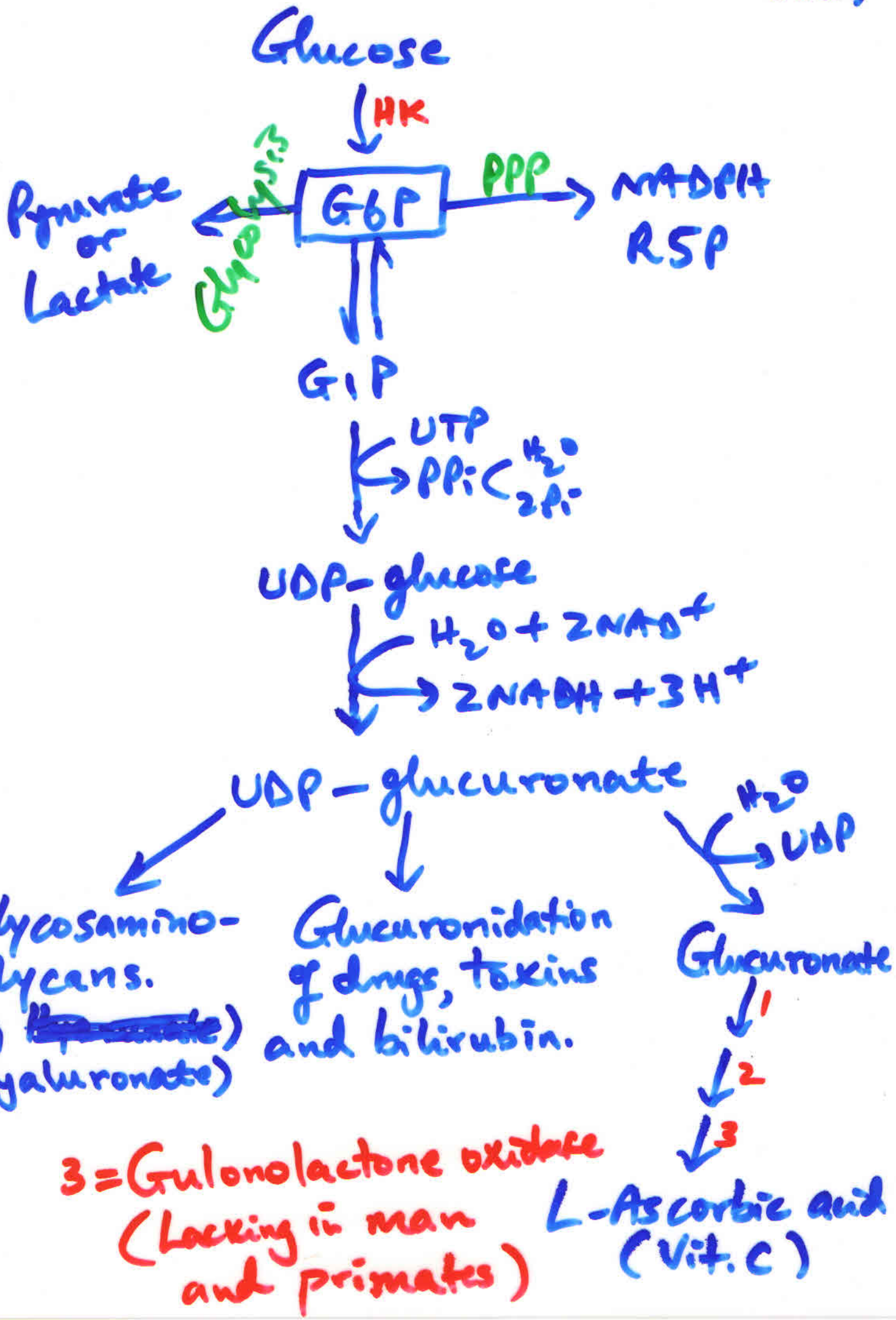
i.e a) NADPH — Chemical energy in form of reducing power.

b) R5P — For synthesis of nucleotides → Nucleic acids (DNA RNA

c) Interconversion of 3, 4, 5, 6 & 7 Carbon sugars. It is linked to the Glycolytic pathway by its non-oxidative reactions i.e. this interconversion serves as a link between the two pathways.

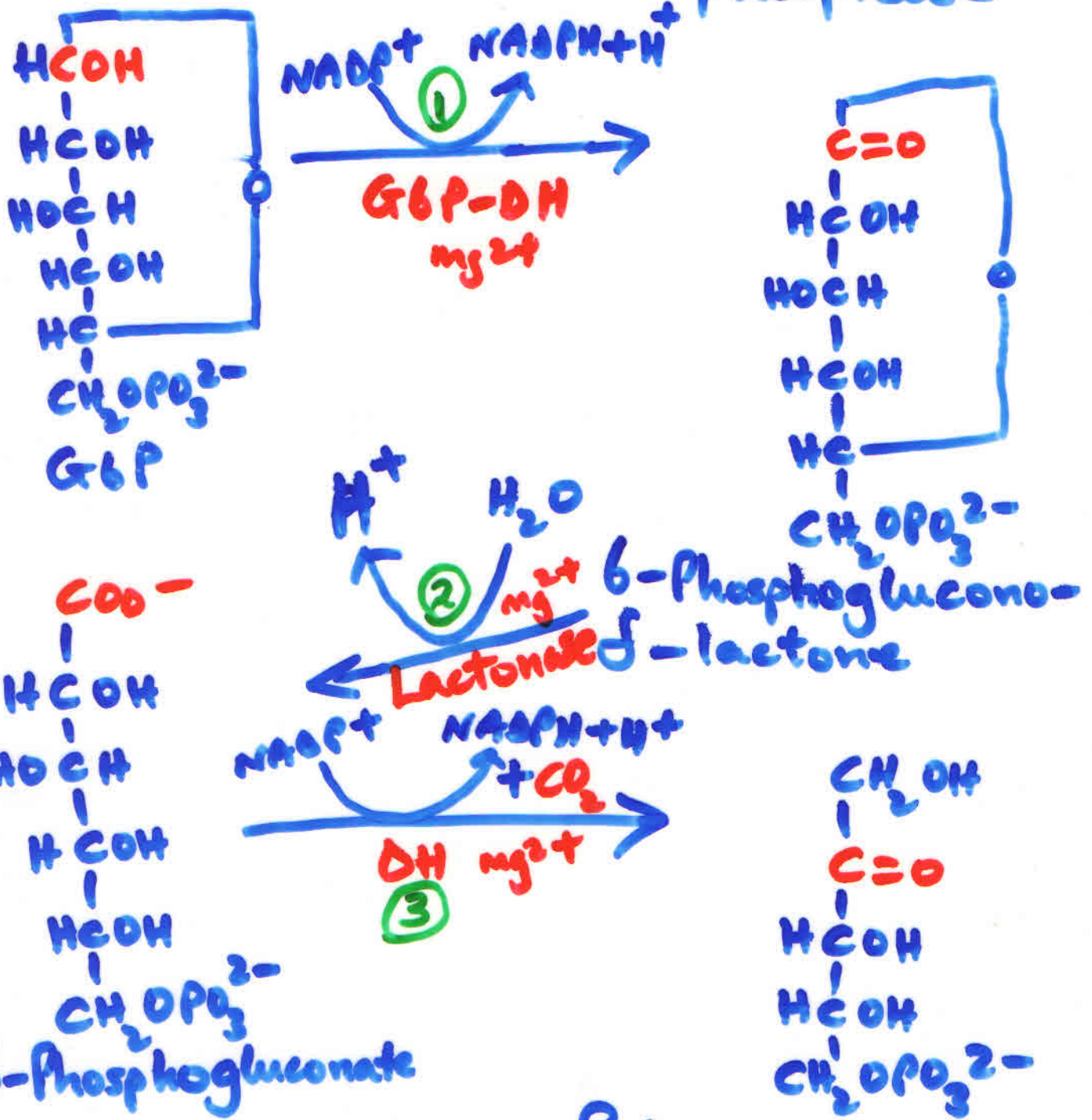
Active in Liver, Adipose tissue, Mammary gland, RBC, adrenal Cortex. It is a Cytosolic pathway.

- It consists of an OXIDATIVE PHASE and a NON-OXIDATIVE PHASE


Glucose
HK
Pyruvate or Lactate
Glycolysis
G6P
PPP
NADPH
R5P
G1P
UTP
PPi
2Pi
UDP-glucose
H2O + 2NAD+
2NADH + 3H+
UDP-glucuronate
H2O
UDP
Glycosamino-glycans.
(e.g [redacted])
(Hyaluronate)
Glucuronidation of drugs, toxins and bilirubin.
Glucuronate
1
2
3
3=Gulonolactone oxidase
(Lacking in man and primates)
L-Ascorbic acid
(Vit. C)

OXIDATIVE PHASE (3 STEPs)

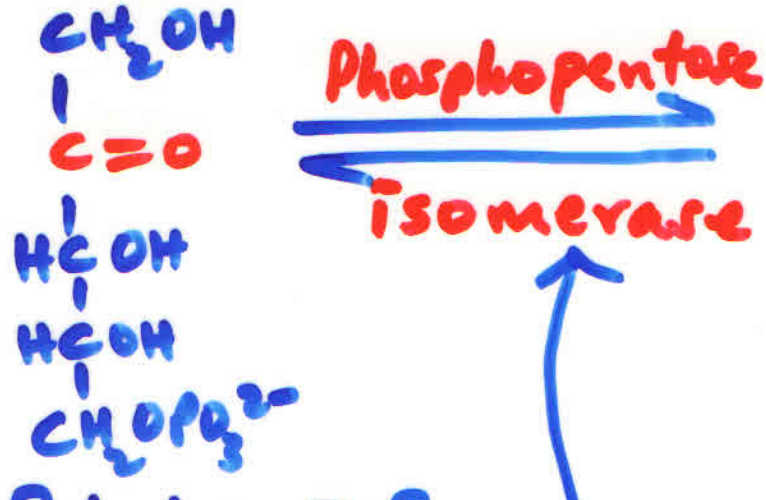
Glucose → (3 steps) → Ribulose 5-Phosphate



* Dehydrogenation
Hydrolysis
Decarboxylation & dehydrogenation

$G6P + 2NADP^+ + H_2O \longrightarrow Rib.5\text{-}P + 2NADPH + 2H^+ + CO_2$

NON-OXIDATIVE



Ribulose 5-P

Ribose 5-P

Similar to - G6P → F6P
- DHAP → G3P

1) Make ATP, CoA-SH, $NADH^+$, FADH, DNA, RNA etc.

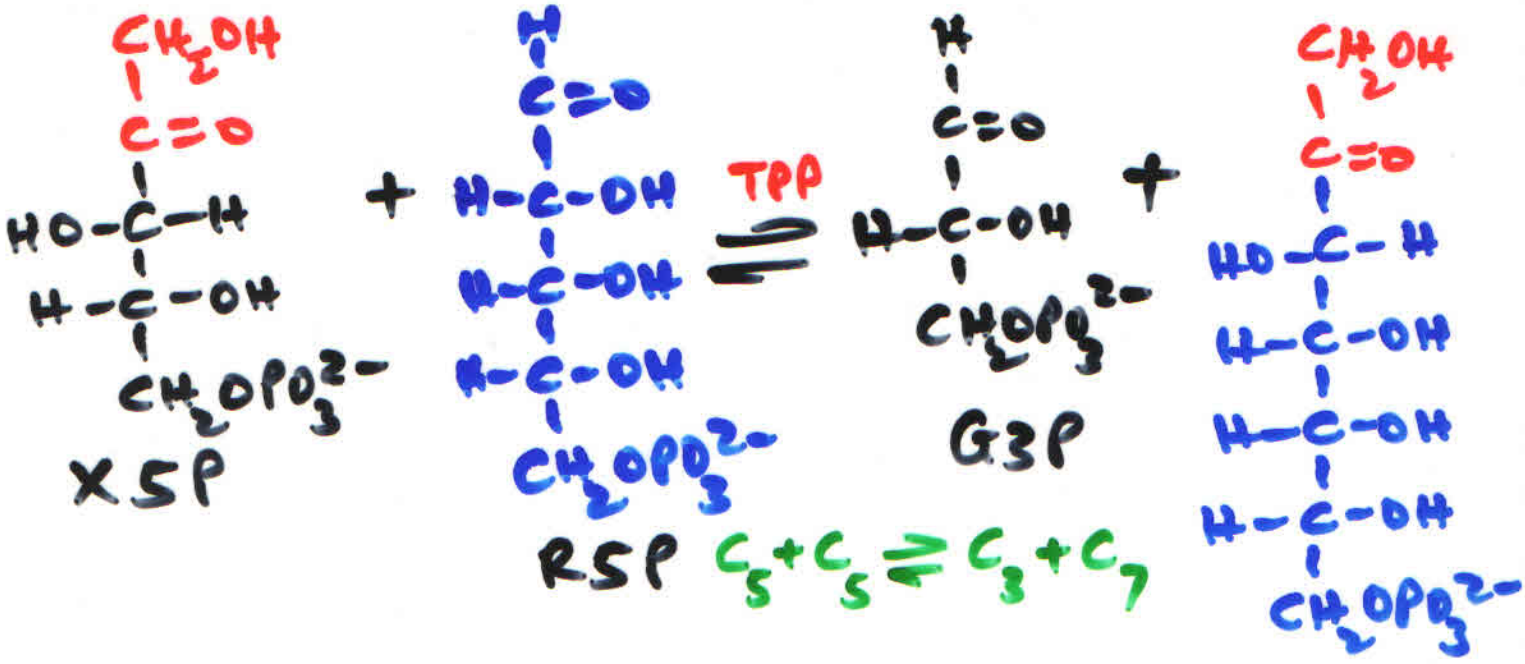
2) Can be converted to G3P and F6P to provide for glycolytic intermediates. This is catalysed by 2 enzymes.
- Transketolase
- Transaldolase

The two enzymes promote the link between PPP and glycolysis.

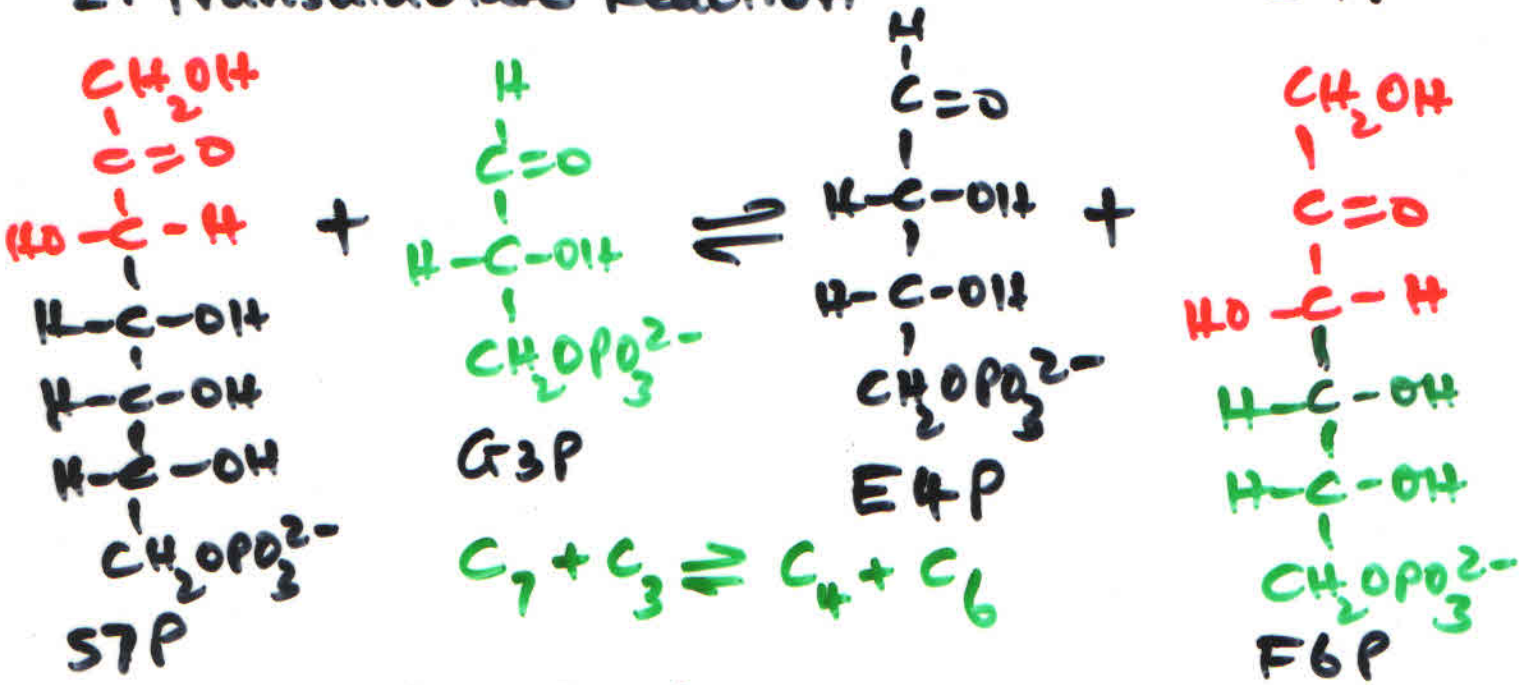
3-Epimerase

Xylulose 5-P

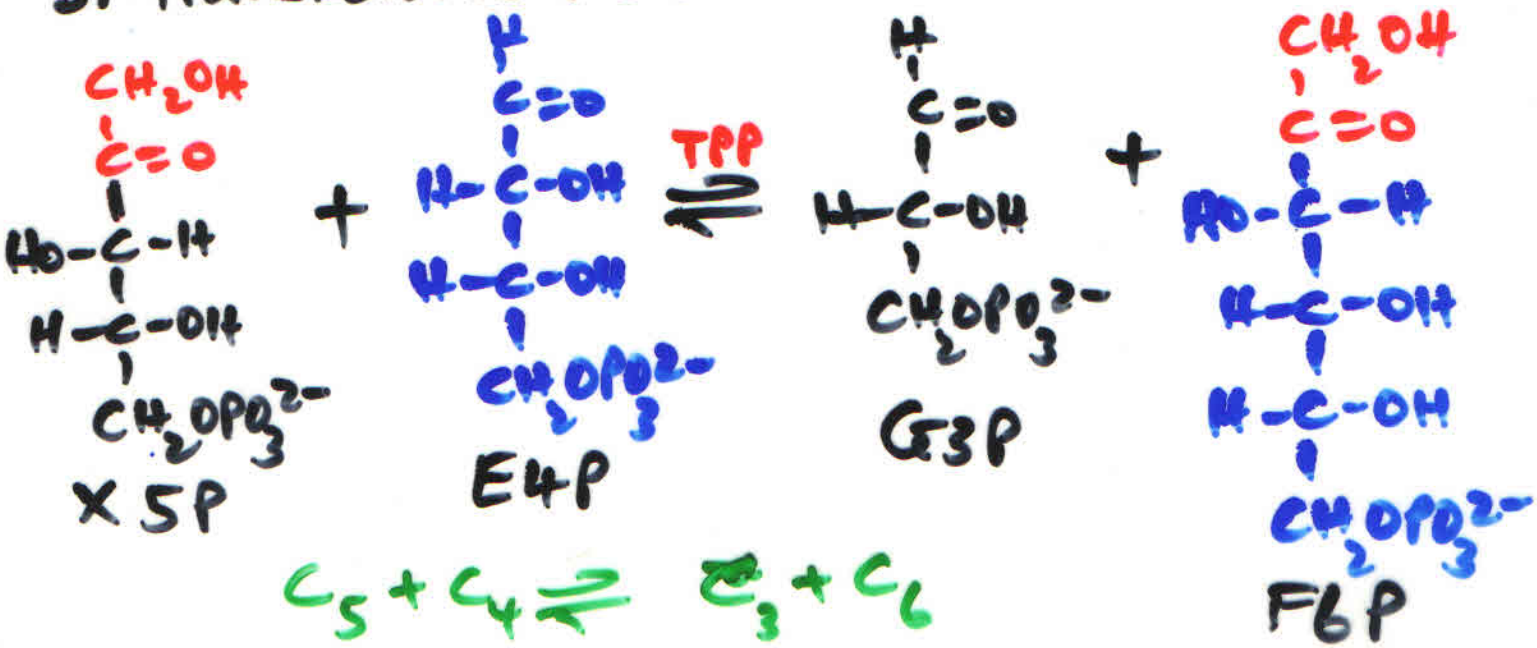
1. Transketolase Reaction



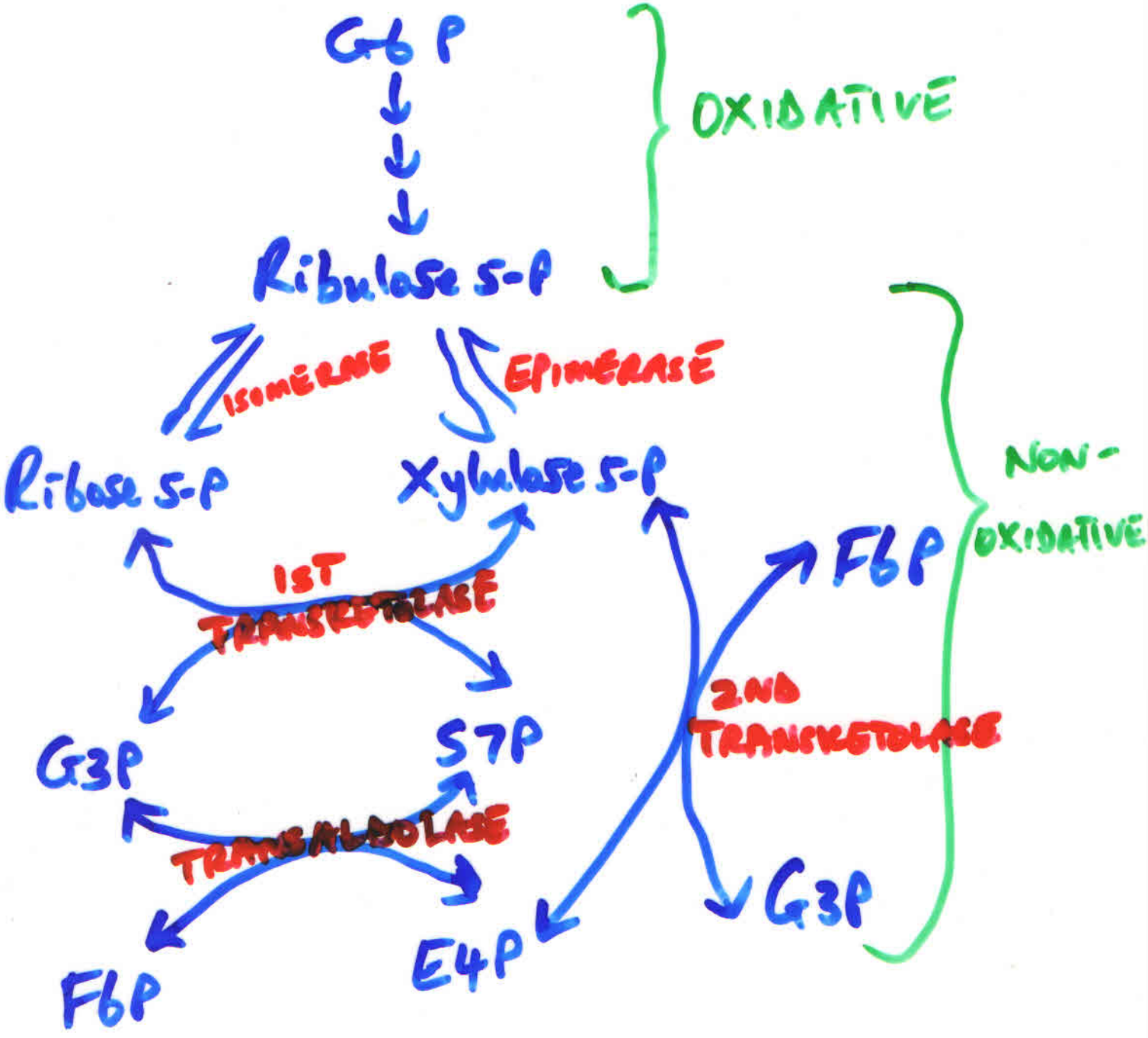
2. Transaldolase Reaction



3. Transketolase Reaction



PPP = SUMMARY



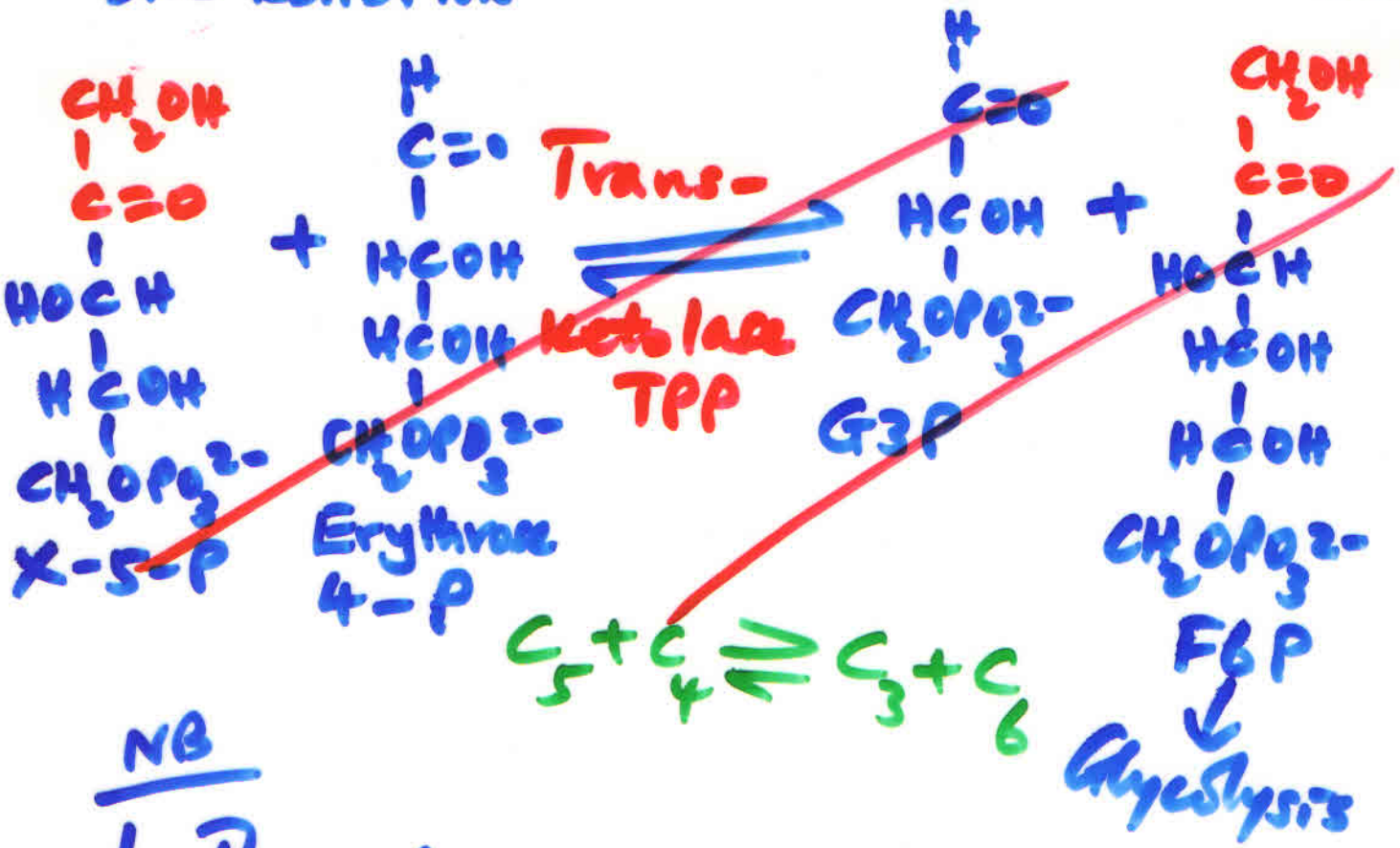
NET

3 Ribulose 5-P ⟶ 1 R5P + 2 X5P ⟶

2 F6P + 1 G3P

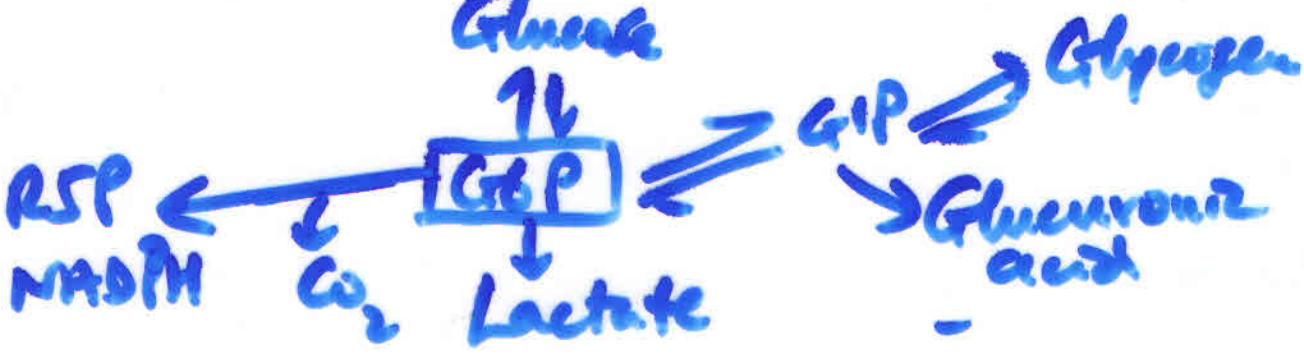
Glycolytic intermediates

3RD REACTION



NB

1. The rate of the oxidative phase is controlled by the level of NADPH. The [NADP+]/[NADPH] is low.
2. The rate of the non-oxidative phase is controlled by the availability of substrates and the need for NADPH, R5P and ATP.



The 2 enzymes create a reversible link.

Transketolase – transfers 2 carbon unit

Transaldolase – 3 carbon unit

3 R5P ⇌ 2 F6P + G3P → Glycolysis

Ribulose 5-P ⇌ Ribose 5-P

Xylulose 5-P.

= 3 R5P.

3 reversible steps;
2 by Transketolase
1 by Transaldolase

Transketolase

- Has TPP as the prosthetic group.
It is a transient carrier of aldehyde group.

- The aldehyde group is transferred from a ketose to an aldose (acceptor).
- The enzyme may be defective in its binding ability to TPP causing a neuropsychiatric disorder known as Wernicke-Korsakoff Syndrome. Genetical or lack of Thiamine (B_1). Alcoholics tend to display such a syndrome.

Human RBC

PPP is very active. The NADPH yielded stops unsaturated FAs in the cell membrane from undergoing abnormal reactions with O_2 and to keep Iron atoms of Hb in their normal Fe^{2+} valence state.

Genetic disease – G6P-DH defective.
- RBC tend to undergo hemolysis - loss of Hb → anemia.

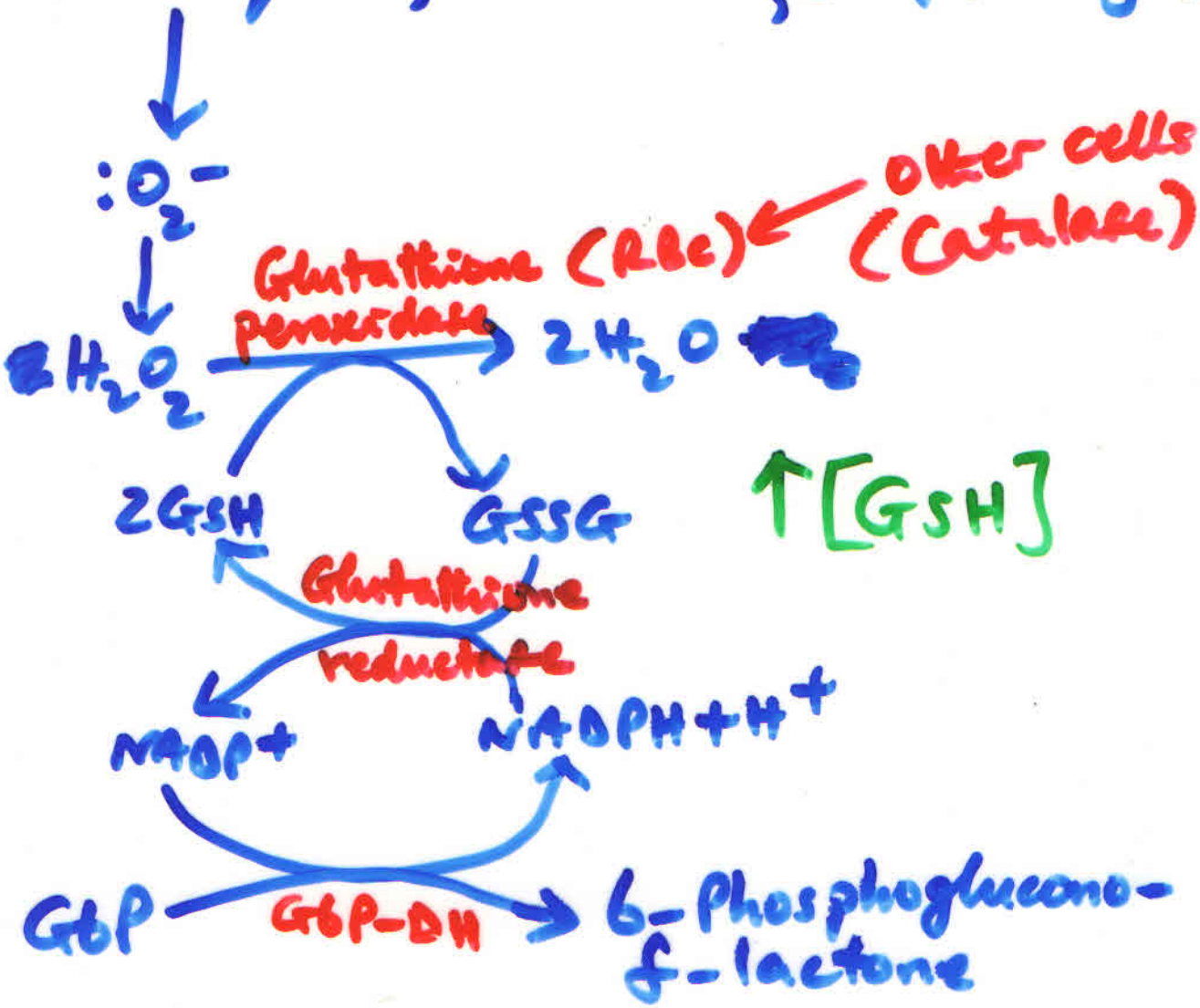
* – Give some of the antimalarials – anemia worsened.
eg. Primaquine

Black urine
Jaundice ⟹ Death
Hb content drop

↓[NADPH]

1. Detoxification of H_2O_2 is inhibited.
2. Cellular damage – lipid peroxidation.
3. Erythrocyte breakdown.
4. Protein and DNA oxidation.

Primaquine, Herbicides, Sulfa drugs:



Incomplete reduction of O_2 causes cell injury;

$4H^+ + 4e^- + O_2 \longrightarrow 2H_2O$

$2H^+ + 2e^- + O_2 \longrightarrow H_2O_2$

$H^+ + e^- + O_2 \longrightarrow :O_2^-$

They attack unsaturated fatty acid components of membrane lipids.

Toxic derivatives of O_2 are scavanged by protective enzymes.

$O_2 \longrightarrow :O_2^- \xrightarrow{H^+} HO_2^\cdot \xrightarrow{HO_2^\cdot,\ O_2} H_2O_2$

Superoxide anion (radical)

Hydroxyl radical

Hydrogen peroxide

$:O_2^- + :O_2^- \xrightarrow[\text{Superoxide dismutase}]{2H^+} H_2O_2 + O_2$

$2H_2O_2 \xrightarrow[\text{Catalase}]{} 2H_2O + O_2$

$H_2O_2 + AH_2 \xrightarrow[\text{Peroxidase}]{} 2H_2O + A$

reductant e.g. GSH

e.g. GSSG

Role of NADPH ?

$GSSG + NADPH + H^+ \xrightarrow{GR} 2GSH + NADP^+$

The free sulfhydryl (-SH) group of GSH maintain the cysteine residues of Hb and other red-cell proteins in the reduced state.

- GSH also used in detoxification.

Occurrence.

11% of Blacks have G6P-DH deficiency. Majority have Sickle-cell trait and have reduced GSH.

Advantage - Malaria parasites are unable to survive - so they do not suffer malaria = NYANZA.

GLUCONEOGENESIS

= "formation of new sugar"

It is the synthesis of glucose from non-CHO precursors. An important pathway particularly in BRAIN and RED BLOOD CELL.

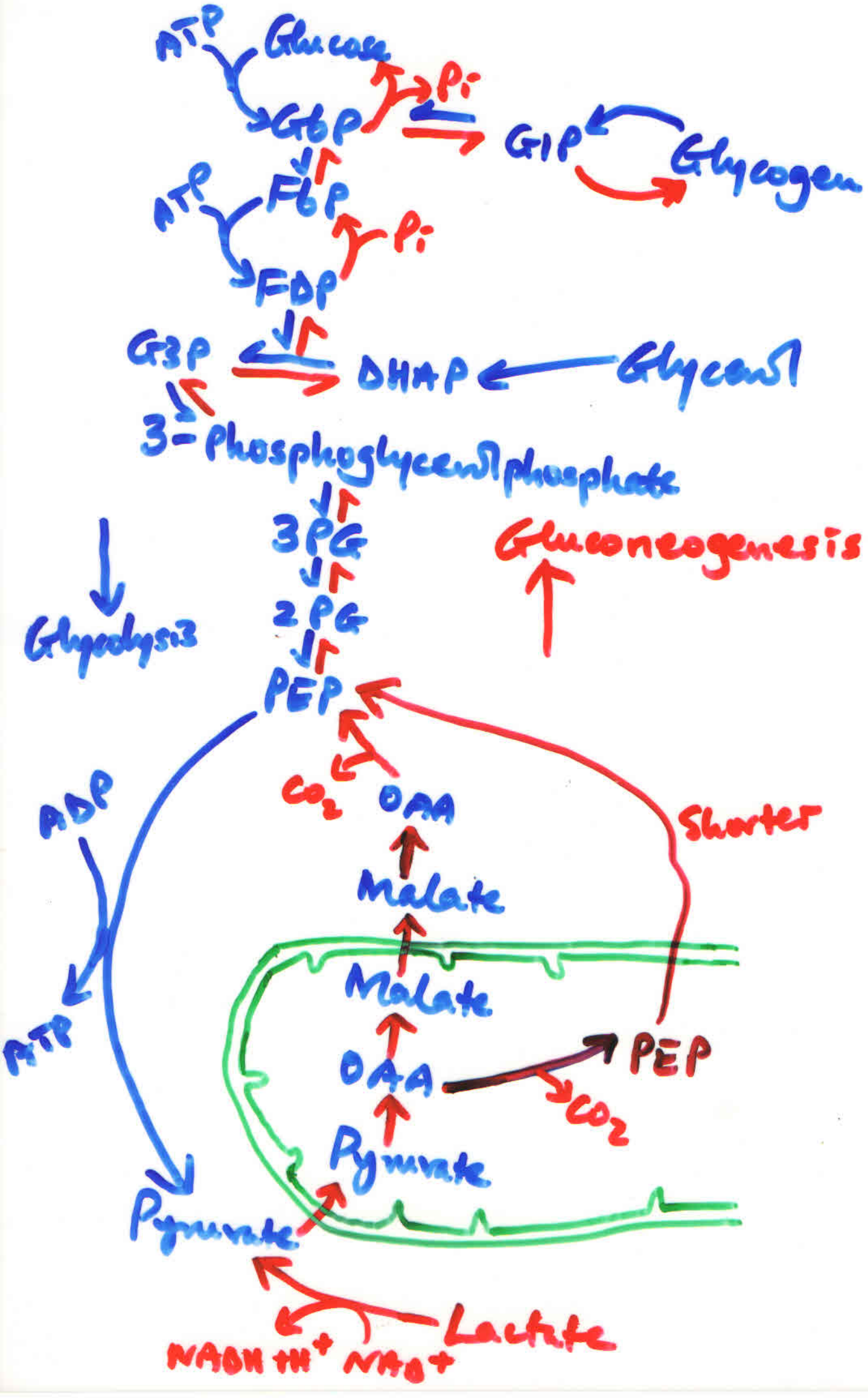
It takes place during 1) Starvation
2) Fasting
3) After intense muscle activity

SITE

1) Liver
2) Kidney cortex
* 3) Very little in brain, skeletal muscle and heart muscle.

THE LIVER AND KIDNEY HELP TO MAINTAIN THE GLUCOSE LEVEL IN BLOOD SO THAT BRAIN AND MUSCLE CAN USE IT.

- Occurs mainly in cytosol and few reactions in matrix (mit.)


ATP
Glucose
Pi
G6P
G1P
Glycogen
ATP
F6P
Pi
FDP
G3P
DHAP
Glycerol
3-Phosphoglycerol phosphate
3PG
Gluconeogenesis
Glycolysis
2PG
PEP
CO2
OAA
Shuttle
ADP
Malate
Malate
ATP
OAA
PEP
CO2
Pyruvate
Pyruvate
Lactate
NADH H+
NH4+

Enzymatic differences between glycolysis and gluconeogenesis

Glycolysis

1. Hexokinase
2. PFK
3. PK

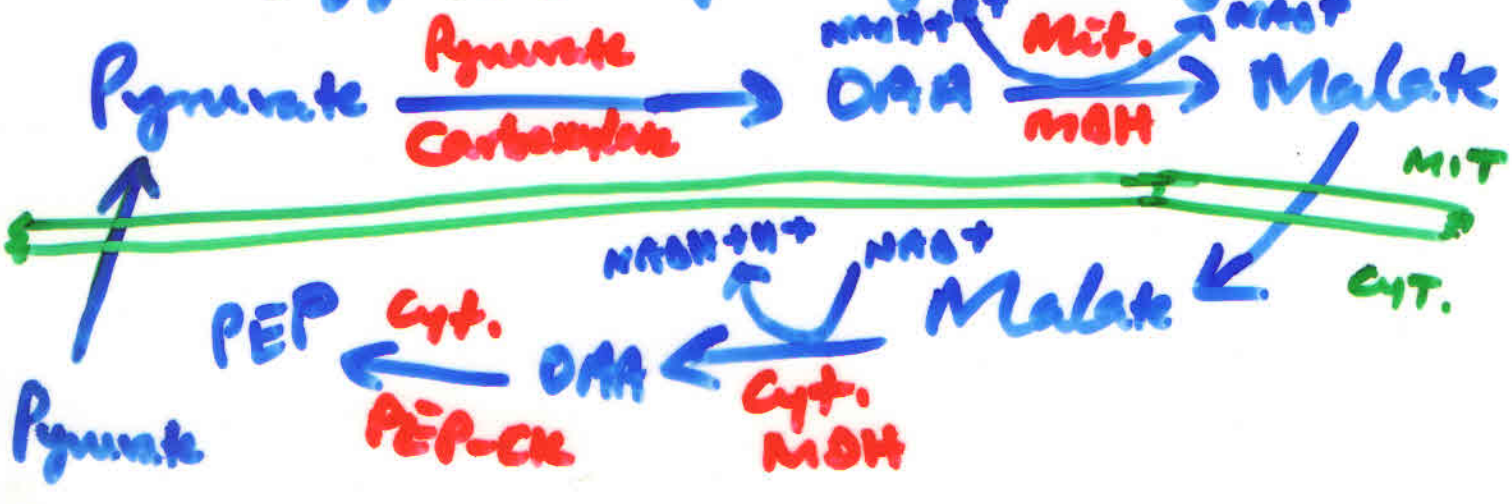
Gluconeogenesis

1. Glucose 6-phosphatase (G6Pase)
2. FDPase
3. Pyruvate carboxylase
   MDH (x2)
   PEP-CK

∴ Gluconeogenesis is not a reversal of glycolysis.

Glycolysis has 3 irreversible reactions which must be bypassed in gluconeogenesis

1) The PK reaction is bypassed by 4 enzymatic steps in gluconeogenesis.



2) The PFK reaction is bypassed by the FDPase reaction;

$$F6P + H_2O \xrightarrow{FDPase} F6P + P_i$$

3) The Hexokinase reaction is bypassed by the G6Pase reaction;

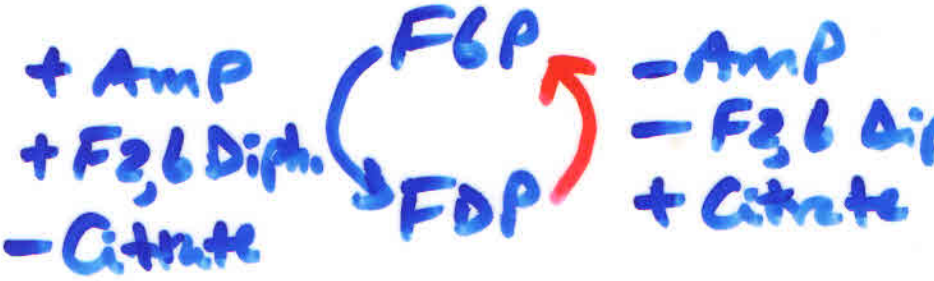
$$G6P + H_2O \xrightarrow{G6Pase} Glucose + P_i$$

G6P ↑ transported into lumen,

G6Pase – located in the lumen of the SER.

Glucose and P_i leave lumen into cytosol.

* Gluconeogenesis and glycolysis are reciprocally regulated;
e.g. PFK Vs FDPase



Gluconeogenesis is a costly process;

Glucose ↑ Pyruvate

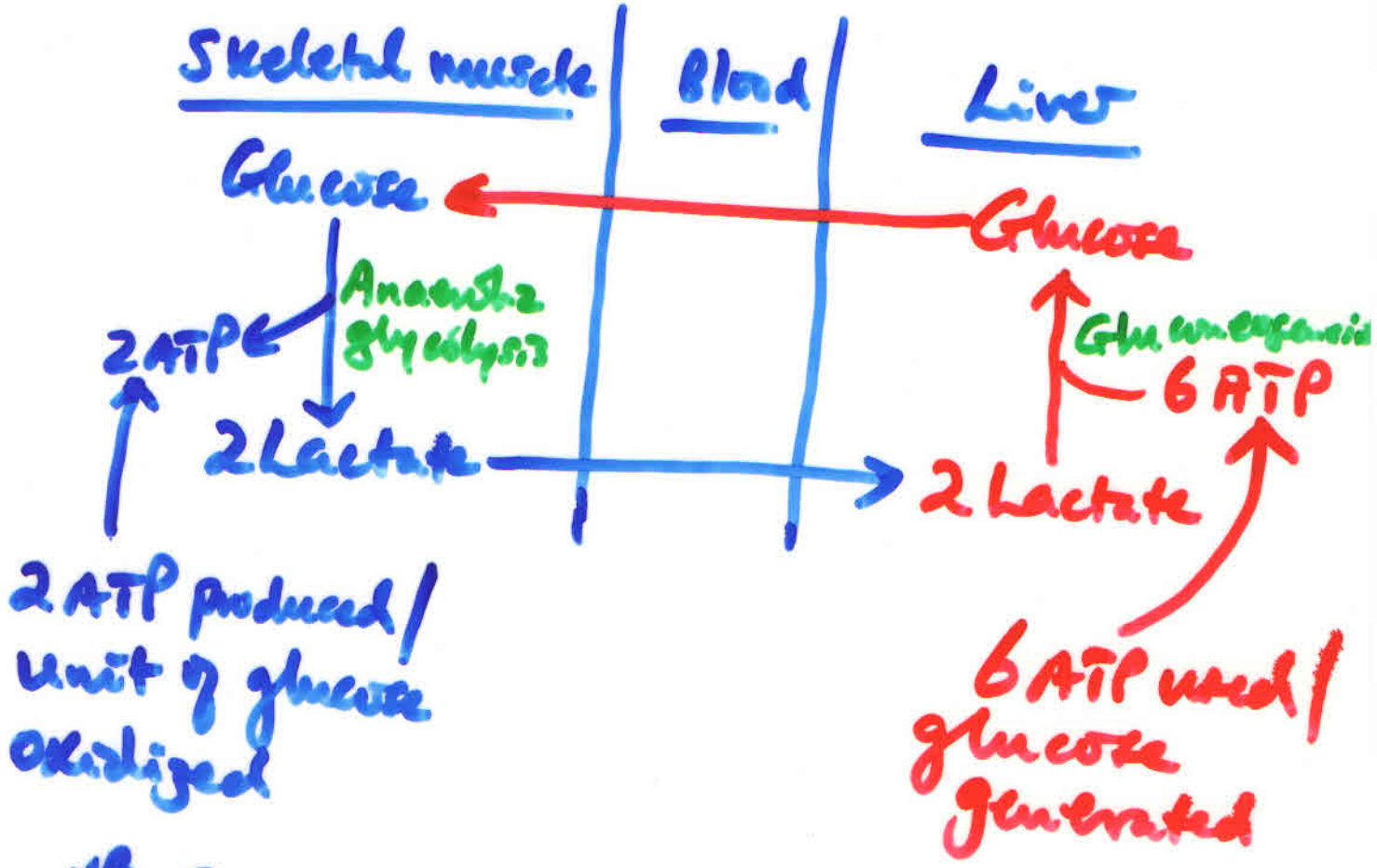
4 ATP < 2 from PC
2 from Phosphoglycerate kinase

6 ATP

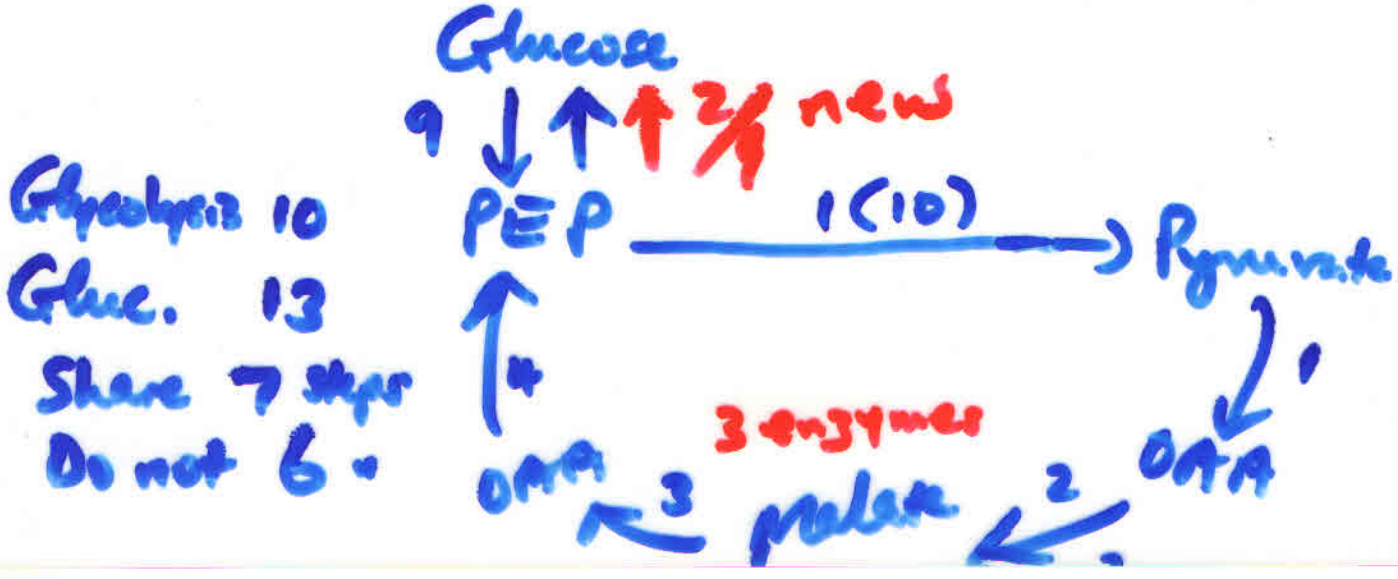
2 GTP – from PEP-CK reaction

$2\,GTP + 2\,ATP \rightleftharpoons 2\,GDP + 2\,ATP$

THE CORI CYCLE



NB = The pyruvate is reduced to Lactate to regenerate NAD^+ for glycolysis. Formation of lactate buys time so that the metabolic burden is shifted from muscle to liver.



Gluconeogenesis - active in ruminants eg Cow

Cellulose (β1-4) —Cellulase→ Glucose —Fermentation by bacteria→ Lactate, Acetate, Propionate, Butyrate (90%)

Glucose → 10% - Brain
- Milk - lactating Cow

Effect of alcohol;
Inhibits gluconeogenesis
Causing hypoglycemia.

Gluconeogenesis is active in germinating seeds - Converts fats and proteins to Glucose.

Fats → Acetylcoa → → Succinate → Glucose ← Gluconeogenesis

Metformin

* Recall : Glyoxylate cycle

* Active (x3) in Diabetes Type II.
↓ PEP-CK / G6Pase ↑ Glucose uptake ↑ FA oxidation