Three thermodynamic quantities that describe the energy changes occurring in a chemical reaction

1. Gibbs free energy, G, expresses the amount of energy capable of doing work during a reaction at constant temperature and pressure

I. Exergonic reaction: When a reaction proceeds with the release of free energy, the free-energy change, ΔG, has a negative value

II. Endergonic reaction: The system gains free energy and ΔG is positive

2. Enthalpy, *H*, is the heat content of the reacting system. It reflects the number and kinds of chemical bonds in the reactants and products

III. When a chemical reaction releases heat, it is said to be exothermic; the heat content of the products is less than that of the reactants and ΔH has, by convention, a negative value

IV. Reacting systems that take up heat from their surroundings are endothermic and have positive values of ΔH

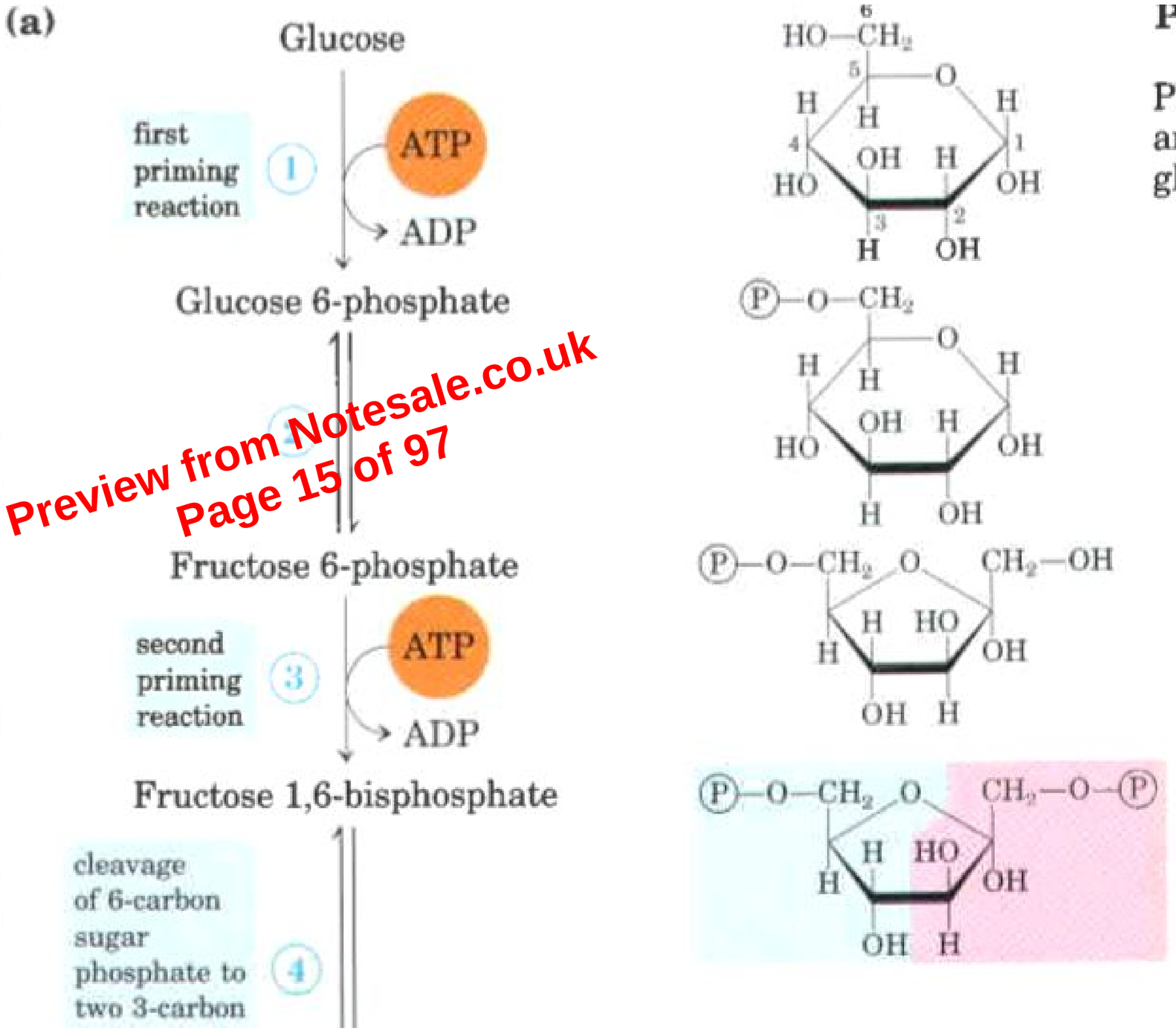
Introduction to metabolism

- Metabolism is the process through living systems acquire and utilize free energy they need to carryout their various function
- They do so by coupling the exergonic reaction of nutrient oxidation to the endergonic process require to maintain the living state such as mechanical work, the active transport of molecules against concentration gradient and biosynthesis of complex molecules
- Phototrophs acquire free energy from sun through photosynthesis, light energy powers the endergonic reaction of Co2 and Water to form carbohydrates and oxygen
- Chemotrophs obtain their free energy by oxidizing organic compounds (Pro, CHO, Lipids), obtained from phototrophs

- This free energy is most often coupled to endergonic reaction through the intermediate synthesis of high energy phosphate compound, ATP
- In addition to being completely oxidized, nutrients are broken down in a series of metabolic reaction to common intermediates that are used as precursor in the synthesis of other biological molecules
- A remarkable property of living system….we maintain this steady state by a sophisticated set of metabolic regulatory system
- Metabolic Pathways
- A series of consecutive enzymatic reactions that produce specific products, their reactants, intermediates and products are referred to as metabolites
- The reaction pathways that comprise metabolism often divided into two categories

Metabolism of Carbohydrates

- carbohydrates are a major source of energy for the living cells. First cellular constituent synthesized by green plants during photosynthesis from carbon dioxide and water, on absorption of light. Thus, light is the ultimate source of energy for all biological process. Glucose is utilized as a source of energy, it is synthesized from non-carbohydrate precursors and stored as glycogen to release glucose as and when the need arises. The other monosaccharides important in carbohydrate metabolism are fructose, galactose and mannose
- Glycolysis: The oxidation of glucose to pyruvate and lactate
- Citric acid cycle: The oxidation of acetyl CoA to CO2. Krebs cycle is the final common oxidative pathway for carbohydrates, fats aminoacids, through acetyl CoA.
- Glycogenolysis: Break down of Glycogen to Glucose
- Glycogenesis:
- Gluconeogenesis:
- Hexose monophosphate shunt: Alternative pathway to glycolysis and TCA cycle or the oxidation of glucose
- Uronic acid pathway: Glucose is converted to glucuronicacid, pentoses in some animals, to ascorbic acid
- Galactose metabolism: Concerned with the conversion of galactose to glucose and the synthesis of lactose
- Fructose metabolism *:* The oxidation of fructose to pyruvate
- Amino sugar and mucopolysaccharide metabolism:



Preparatory phase

Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate

1. Hexokinase
2. Phosphohexose isomerase
3. Phospho-fructokinase-1
4. Aldolase
5. Triose phosphate isomerase

- Phosphofructokinase and fructose 1,6-bisphosphatase are also reciprocally controlled by fructose 2,6-bisphosphate in the liver. The level of F-2,6-BP is low during starvation and high in the fed state, because of the antagonistic effects of glucagon and insulin on the production and degradation of this signal molecule. Fructose 2,6-bisphosphate strongly stimulates phosphofructokinase and inhibits fructose 1,6-bisphosphatase. Hence, glycolysis is accelerated and gluconeogenesis is diminished in the fed state. During starvation, gluconeogenesis predominates because the level of F-2,6-BP is very low. Glucose formed by the liver under these conditions is essential for the viability of brain and muscle

Gluconeogenesis is Energetically Expensive, but Essential

The sum of the biosynthetic reactions leading from pyruvate to free blood glucose is

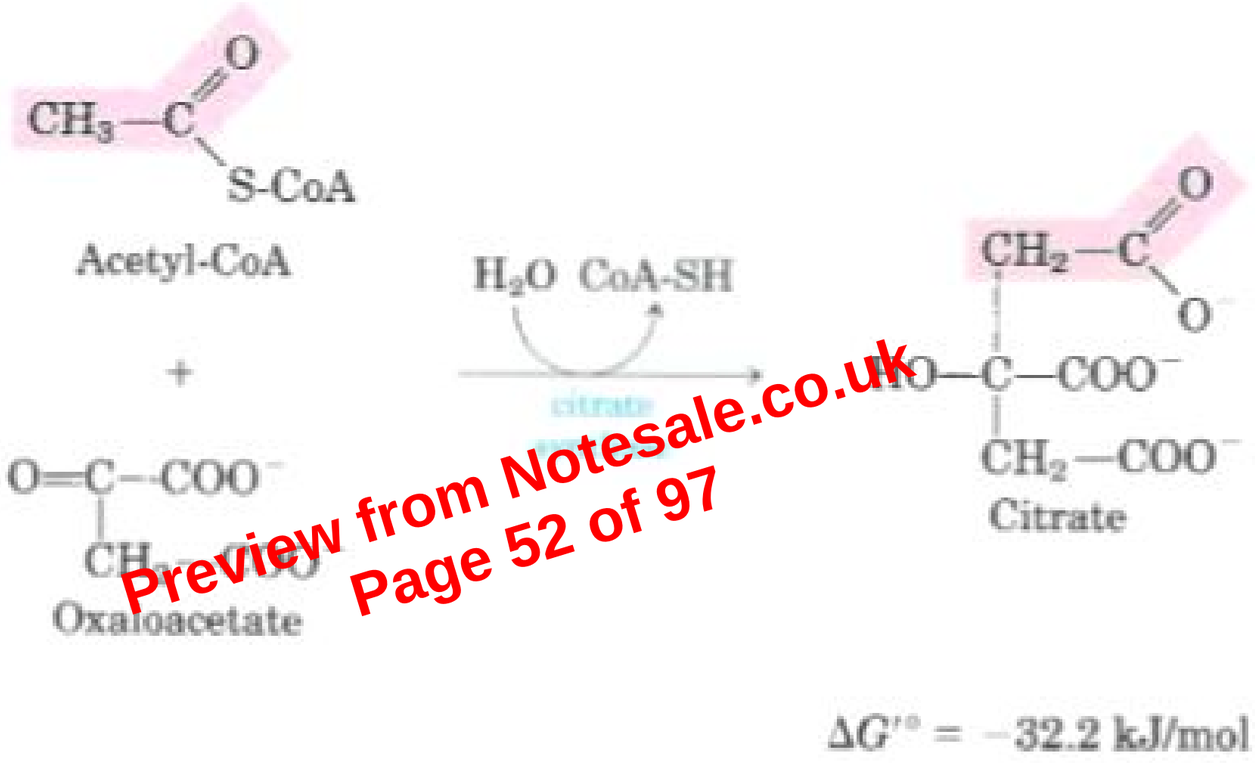
2 Pyruvate + 4ATP + 2GTP+ 2NADH+ 2H+ + 4H2O → glucose + 4ADP+ 2GDP+ 6Pi + 2NAD+

For each molecule of glucose formed from pyruvate, six high-energy phosphate groups are required, four from ATP and two from GTP. In addition. two molecules of NADH are required for the reduction of two molecules of 1,3-bisphosphoglycerate. Clearly, this equation is not simply the reverse of the equation for conversion of glucose to pyruvate by glycolysis, which would require only two molecules of ATP:

Glucose + 2ADP + 2Pi + NAD+ ---> 2 pyruvate + 2ATP+ 2NADH + 2H+ + 2H2O

The synthesis of glucose from pyruvate is a relatively expensive process. Much of this high energy cost is necessary to ensure the irreversibility of gluconeogenesis. Under intracellular conditions, the overall free-energy change of glycolysis is at least -63 kJ/mol. Under the same conditions the overall free energy change of gluconeogenesis is -16 kJ/mol. Thus both glycolysis and gluconeogenesis are essentially irreversible processes in cells

- The PDH complex is composed of multiple copies of three enzymes: pyruvate dehydrogenase, E1 (with its bound cofactor TPP); dihydrolipoyl transacetylase, E2 (with its covalently bound lipoyl group); and dihydrolipoyl dehydrogenase, E3 (with its cofactors FAD and NAD
- The combined dehydrogenation and decarboxylation of pyruvate to the acetyl group of acetyl-CoA, requires the sequential action of three different enzymes and five different coenzymes or prosthetic groups-thiamine pyrophosphate (TPP), flavin adenine dinucleotide (FAD), coenzyme A (CoA, sometimes denoted CoA-SH, to emphasize the role of the -SH group), nicotinamide adenine dinucleotide (NAD), and lipoate. Four different vitamins required in humann utrition are vital components of this system: thiamine (in TPP), riboflavin (in FAD), niacin (in NAD), and pantothenate (in CoA).



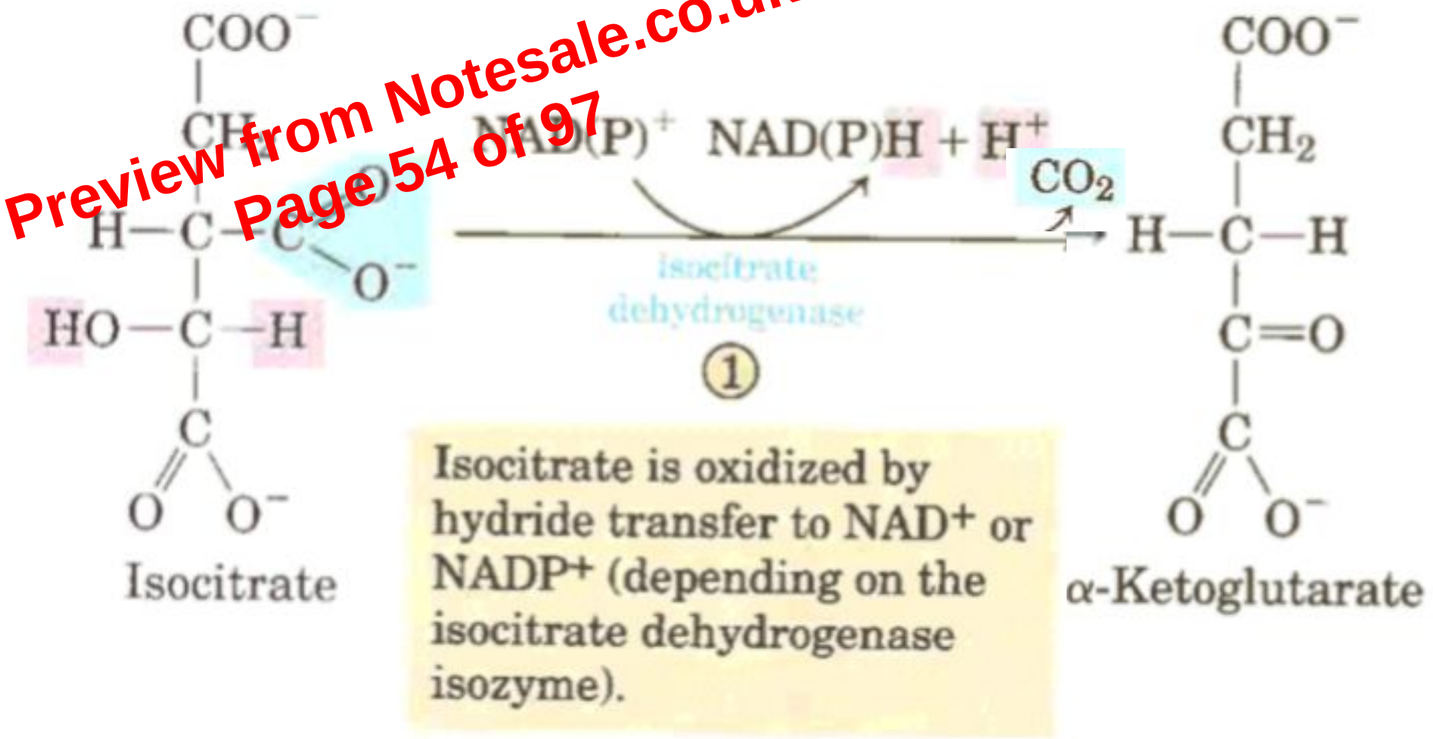
(1)

- The first reaction of the cycle is the condensation of acetyl-CoA with oxaloacetate to form citrate, catalyzed by citrate synthase

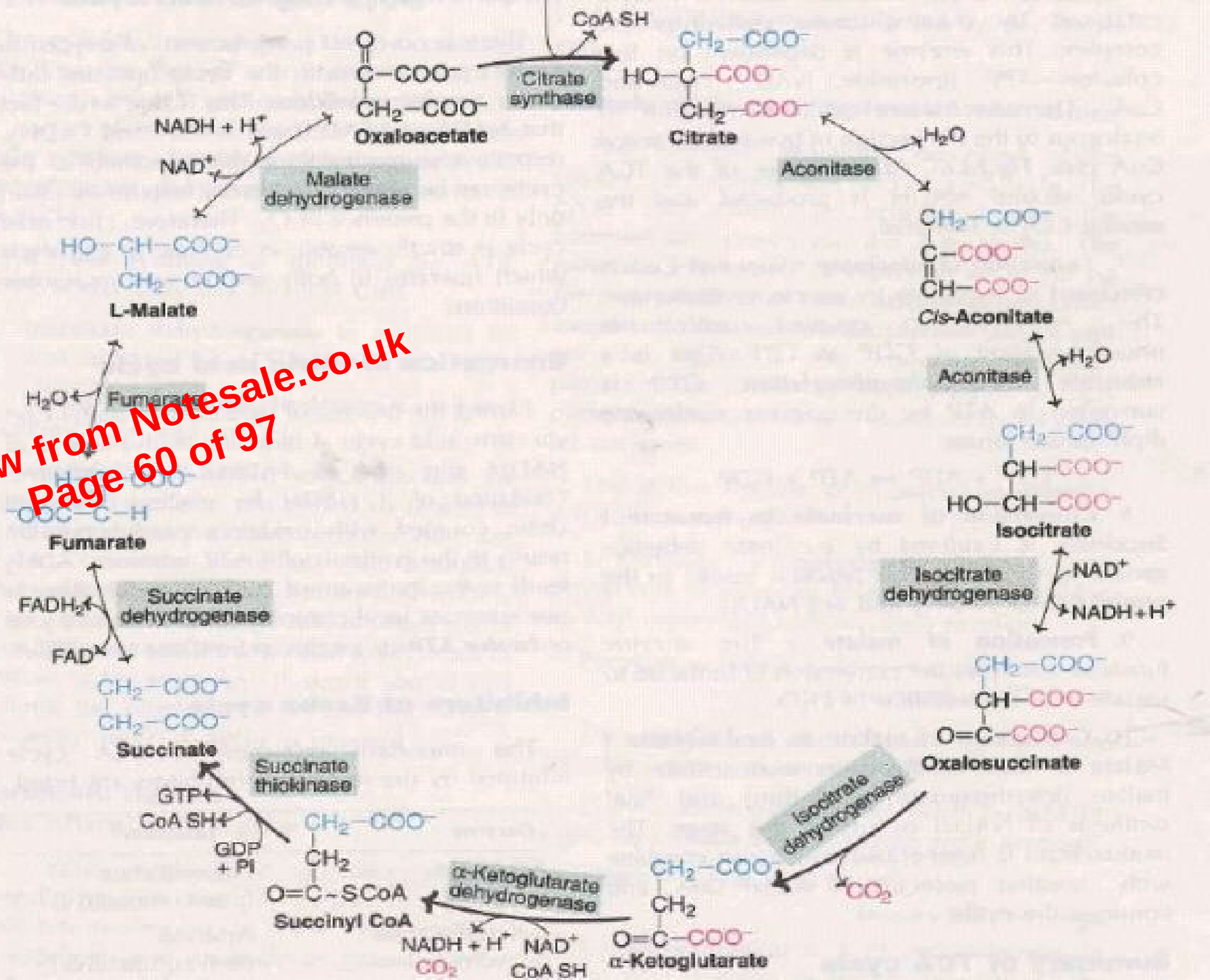
- In this reaction the methyl carbon of the acetyl group is joined to the carbonyl group (C-2) of oxaloacetate. CitroylCoA is a transient intermediate formed on the active site of the enzyme. It rapidly undergoes hydrolysis to free CoA and citrate, which are released from the active site. The hydrolysis of this high-energ/ thioester intermediate makes the forward reaction highly exergonic. The large, negative standard free-energy change of the citrate synthase reaction is essential to the operation of the cycle because, as noted earlier, the concentration of oxaloacetate is normally very low, the CoA liberated in this reaction is recycled to participate in the oxidative decarboxylation of another molecule of pyruvate by the PDH complex.

(3) Oxiation of Isocitrate to α-Ketoglutarate

- In the next step, isocitrate dehydrogenase catalyzes oxidation of isocitrate to form α-ketoglutarate. Mn2+ in the active site interacts with the carbonyl group of the intermediate oxalosuccinate, which is formed transiently but does not leave the binding site until decarboxylation converts it to a-ketoglutarate



Isocitrate is oxidized by hydride transfer to NAD^+ or $NADP^+$ (depending on the isocitrate dehydrogenase isozyme).

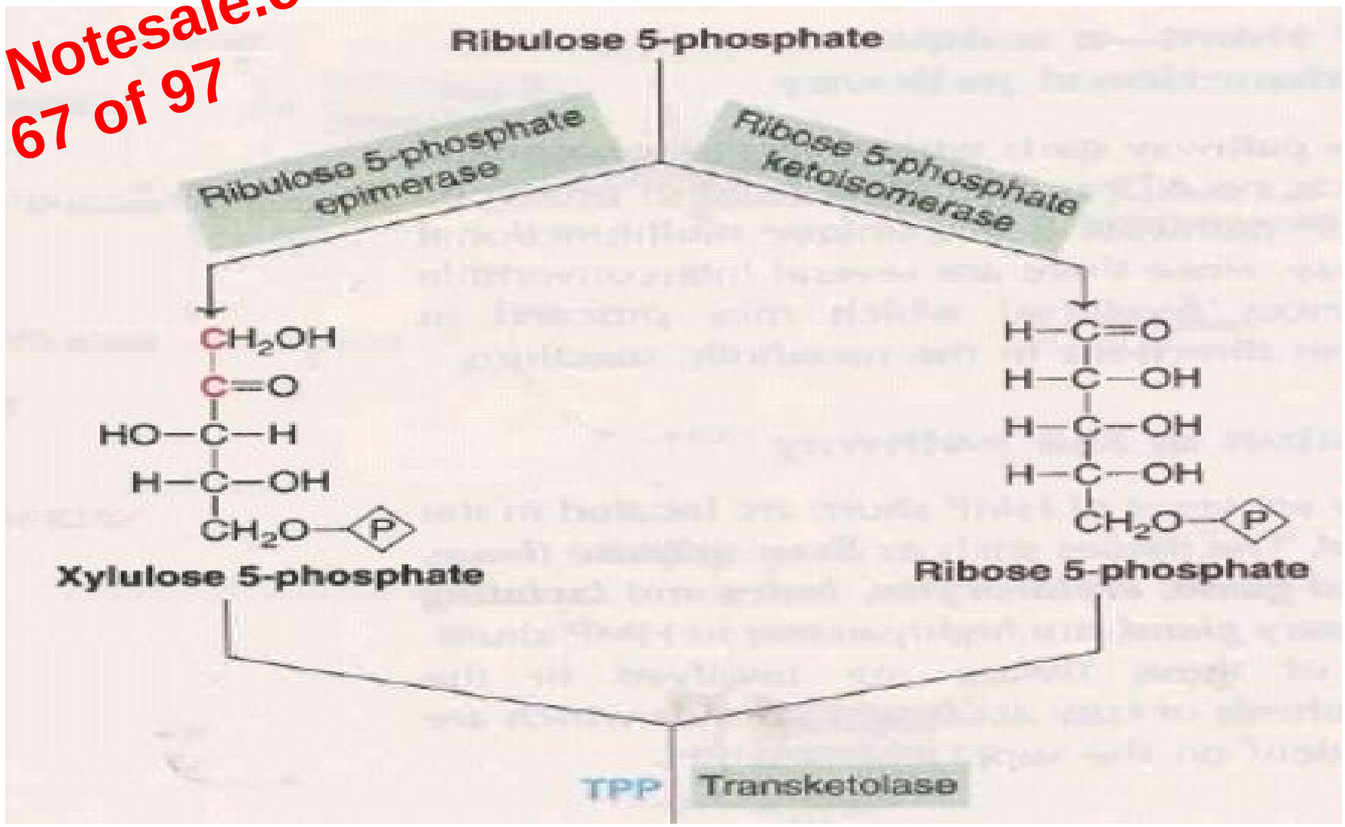


G6PD regulates HMP shunt

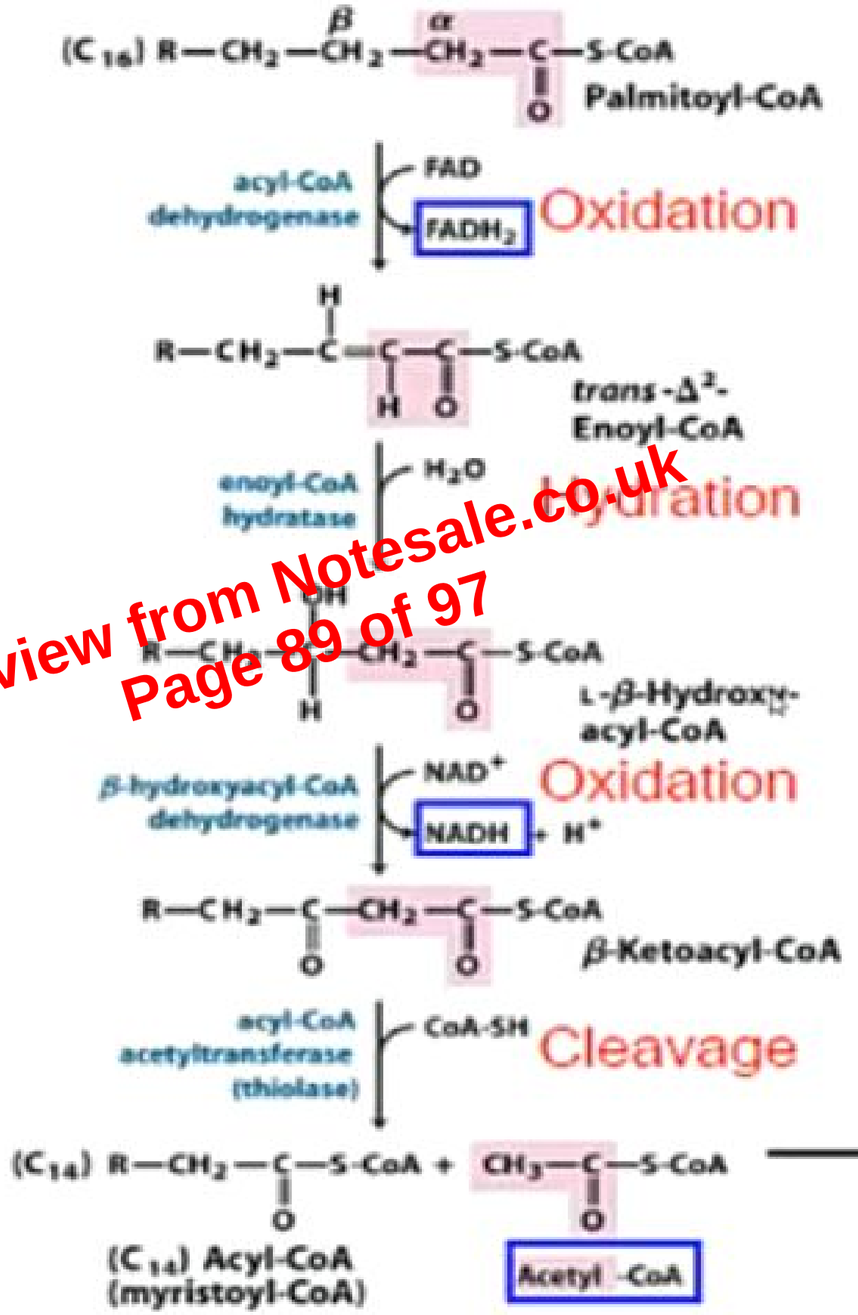
- The first reaction catalysed by G6PD is most regulatory in HMP shunt. This enzyme catalyzes an irreversible reaction. NADPH competitively inhibits G6PD. It is the ratio of NADPH/NAD+ that ultimately determines the flux of this cycle

Non oxidative phase

- The non-oxidative reactions are concerned with the interconversion of three, four, five and seven carbon monosaccharides. Ribulose 5-phosphates acted upon by an epimerase to produce xylulose-5-phosphate while ribose-5-phosphate keto isomerase converts ribulose 5-phosphate to ribose 5-phosphate

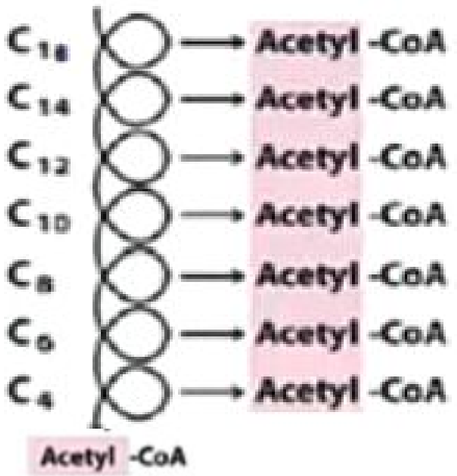


β-Oxidation



1. β carbon is focal point of four repeated reactions:
   - Oxidation
   - Hydration
   - Oxidation
   - Cleavage

2. Four steps → remove 2C unit, to produce Acetyl-CoA, $FADH_2$ and NADH.



How Much?

7 rounds of β-ox

7 $FADH_2$

7 NADH

8 Acetyl-CoA

β- oxidation

Oxidation : Acyl CoA undergoes dehydrogenation by an FAD-dependent flavor enzyme, acyl CoA dehydrogenase. A double bond is formed between two and three carbons

Hydration: Enoyl CoA hydratase brings about the hydration of the double bond to form β-hydroxyacyl Co

Oxidation : β –Hydroxy acyl CoA dehydrogenase catalyses the second oxidation and generates NADH. The product formed is β –ketoacyl CoA

Cleavage : The final reaction in β –oxidation is the liberation of a 2 carbon fragment, acetyl CoA from acyl CoA. This occurs by a thiolytic cleavage catalysed by β –ketoacyl CoA thiolase

- Propionyl CoA is carboxylated in the presence of ATP, CO2 and vitamin biotin to D-methyl malonyl CoA.
- Methyl malonyl CoA racemase converts the methyl malonyl CoA to L-form. This reaction (D to L) s essential or the entry of this compound into the metabolic reactions of the body.
- The next enzyme, methyl malonylCoA mutase, is dependent on vitamin B12 (deoxy adenosyl cobalamin). it catalyzes the conversion of methyl malonyl CoA (a branched compound) to succinyl CoA (a straight chain compound), which can enter citric acid cycle