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Carbohydrate Metabolism

Synopsis

- **Introduction to Metabolism**
- **Ingestion** of Carbohydrates
- **Digestion** and **Absorption** Of Carbohydrates.
- **Transportation** and **Uptake** of Glucose by cells.
- **Utilization/Assimilation** of Carbohydrates.
- **Fate of Glucose ,Galactose** and **Fructose**
  (Associated Anabolic and Catabolic Pathways)
- **Excretion** Of Metabolic end products of Carbohydrates
- **Applied aspects**/Associated **Metabolic Disorder/Inborn Errors** of Carbohydrate Metabolism.

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- Various Fates of Glucose/Metabolic Pathways Associated to Glucose.
- Complete Oxidation Of Glucose
  1. Glycolysis and Rapaport Leubering Cycle
  2. PDH Complex Reaction
  3. TCA cycle

- **Glycogen Metabolism**
  1. **Glycogenesis**
  2. **Glycogenolysis**
- HMP shunt/Pentose Phosphate Pathway
- Gluconeogenesis
- Cori's Cycle/Glucose Alanine Cycle.
- Blood Glucose Regulation
- Glucose Tolerance Test (GTT)

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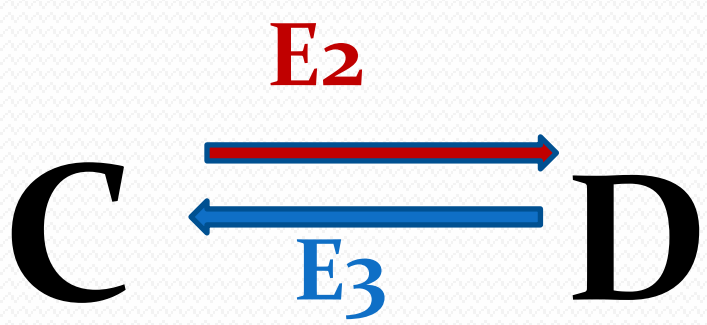
- Glycosuria
- Diabetes Mellitus.
- Galactose metabolism
- Galactosaemia
- Fructose Metabolism
- Essential Fructosuria

- **Irreversible Reactions-**
  - Different set of Enzyme required.
  - Non equilibrium Reactions.
  - **Regulatory steps.**



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Types Of Biochemical Reactions

- Oxidation/Dehydrogenation /Hydroxylation
- Reduction
- Hydrolytic
- Carboxylation
- Decarboxylation

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- **Phosphorylation**
- **Dephosphorylation**
- **Amination**
- **Deamination**
- **Isomerization**
- **Hydration**
- **Dehydration**

Metabolic Pathway

- Metabolic pathway is a **series of well defined and significant biochemical reactions** followed one after another giving **intermediate products** and finally **end product** of the pathway.

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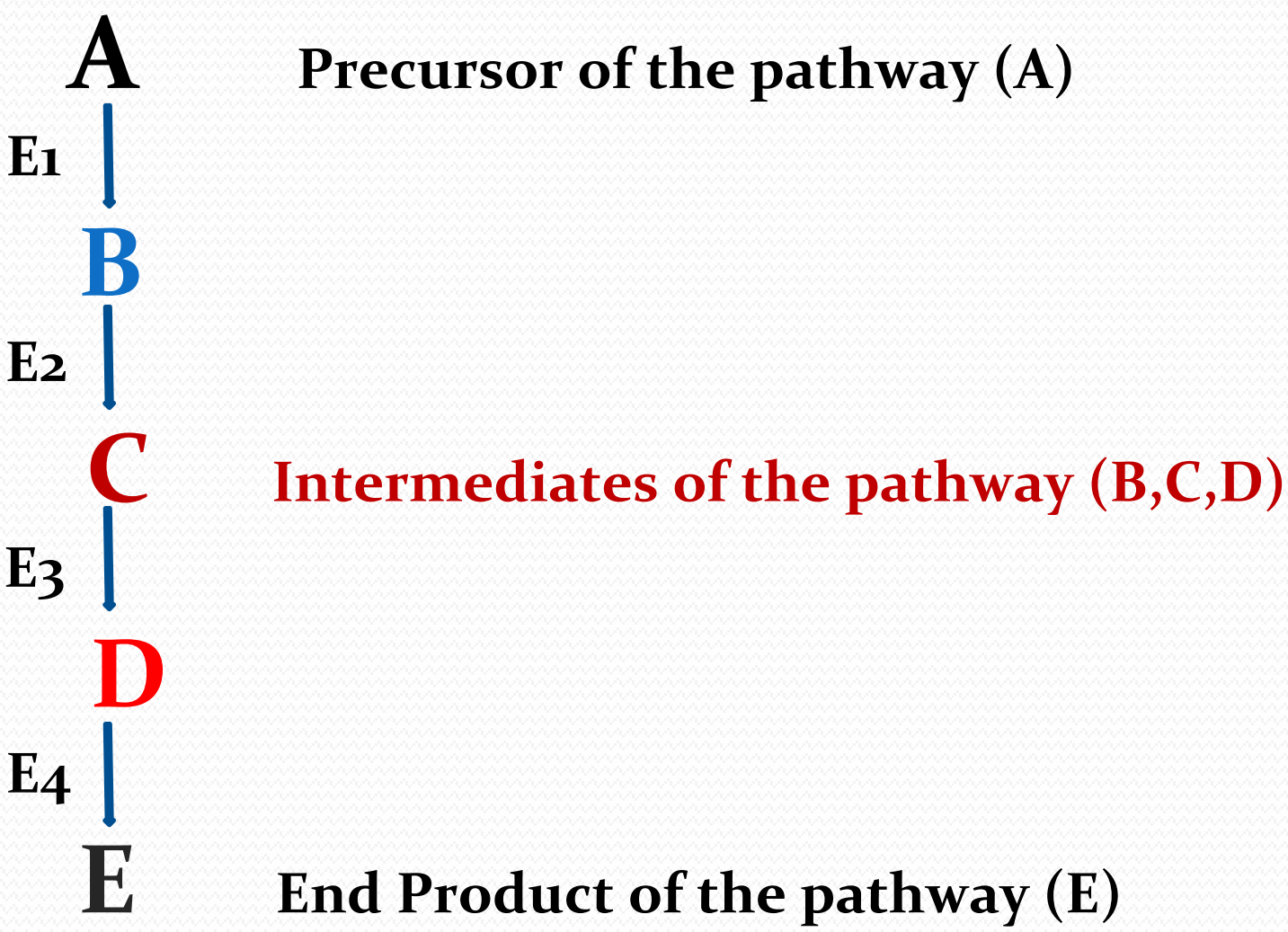

Organization of Pathways

- Pathways consist of sequential steps.
- The enzymes may be **separate.**
- May form a **multienzyme complex.**
- May be a **membrane-bound system.**
- New research indicates that **multienzyme complexes are more common** than once thought.

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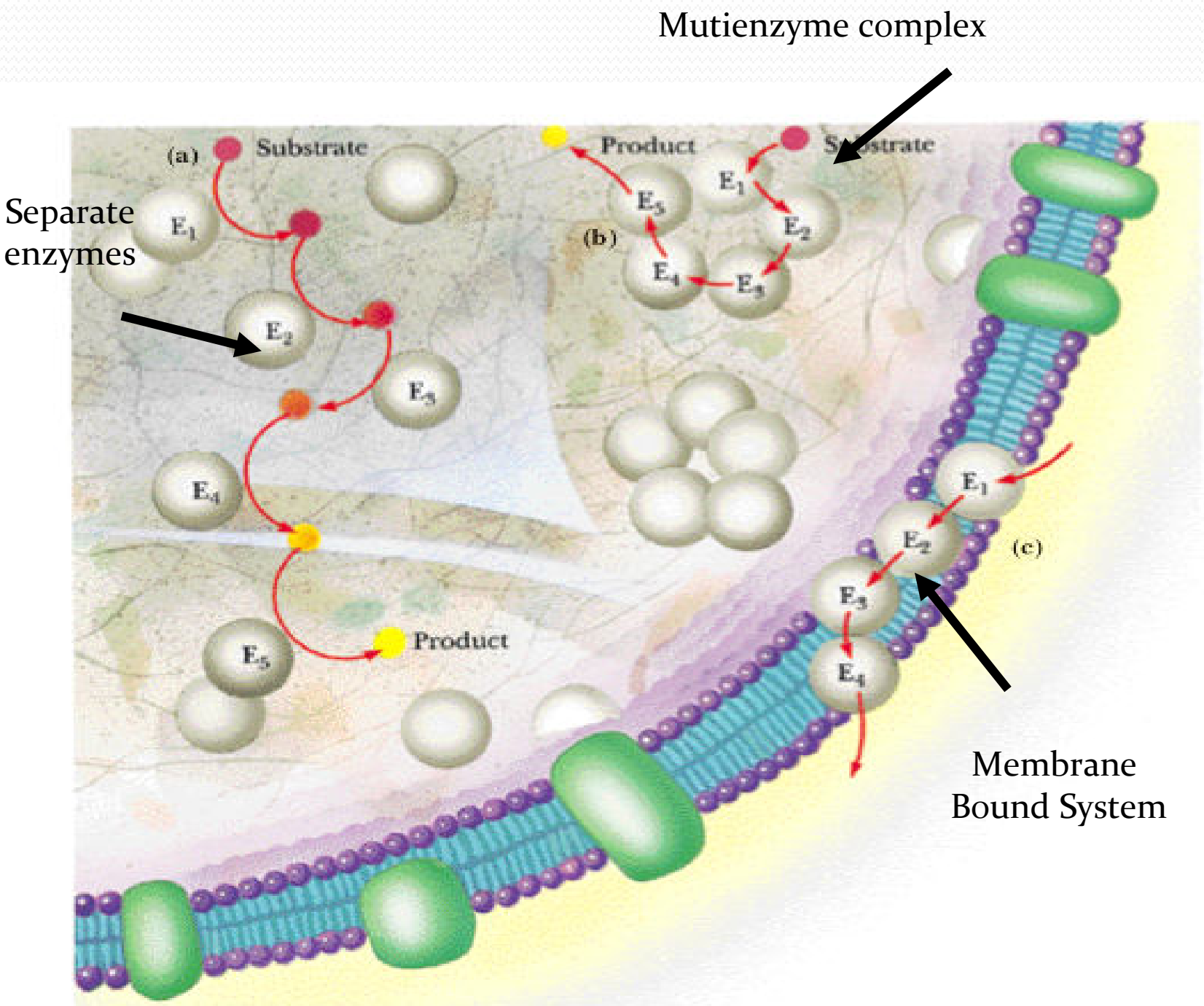

Organization of Pathways

Closed Loop
(intermediates recycled)

Linear
(product of rxns are substrates for subsequent rxns)

Spiral
(same set of enzymes used repeatedly)

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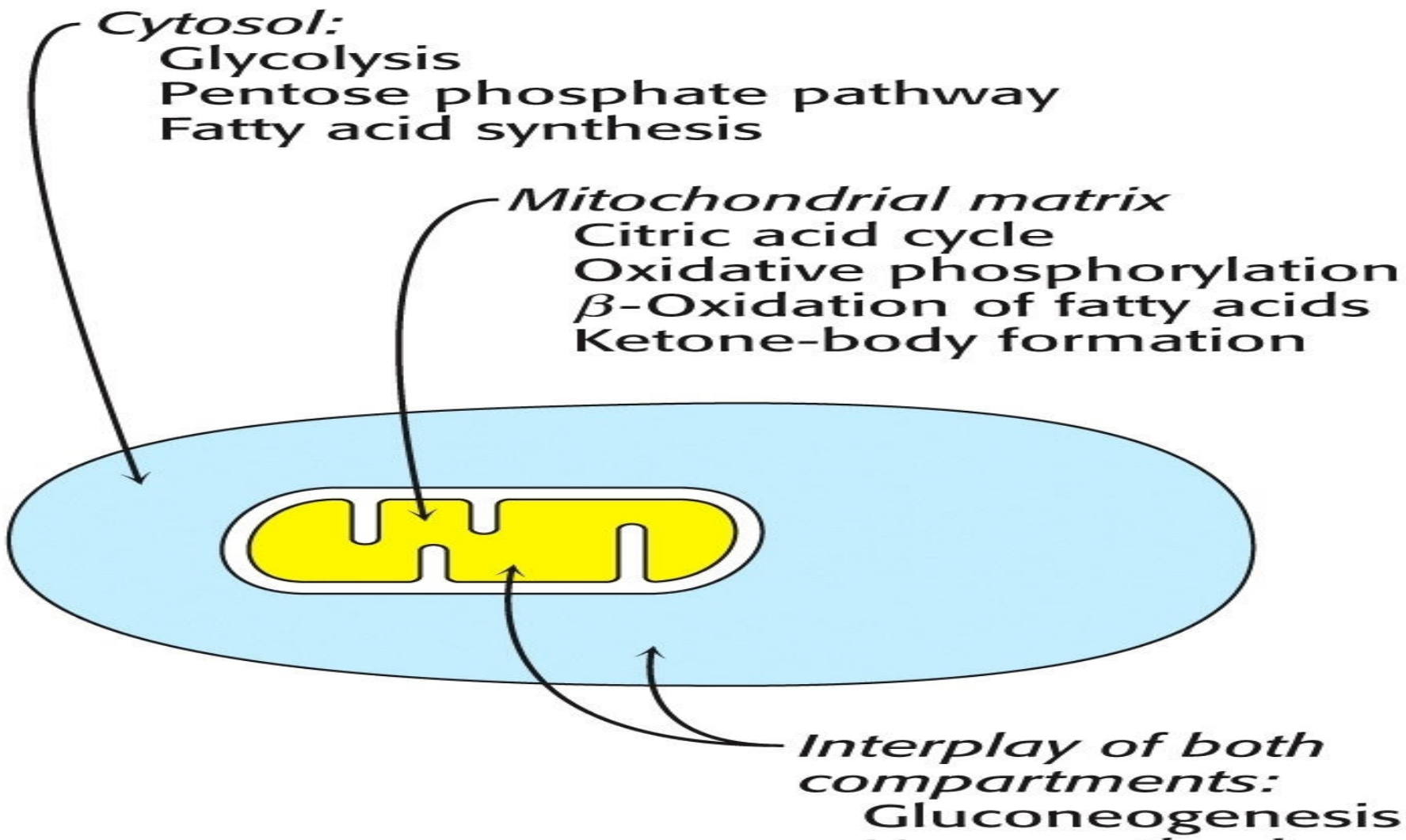
Compartmentalization Of Metabolic Pathways



- Compartmentalization of pathways permits integration and regulation of metabolism.

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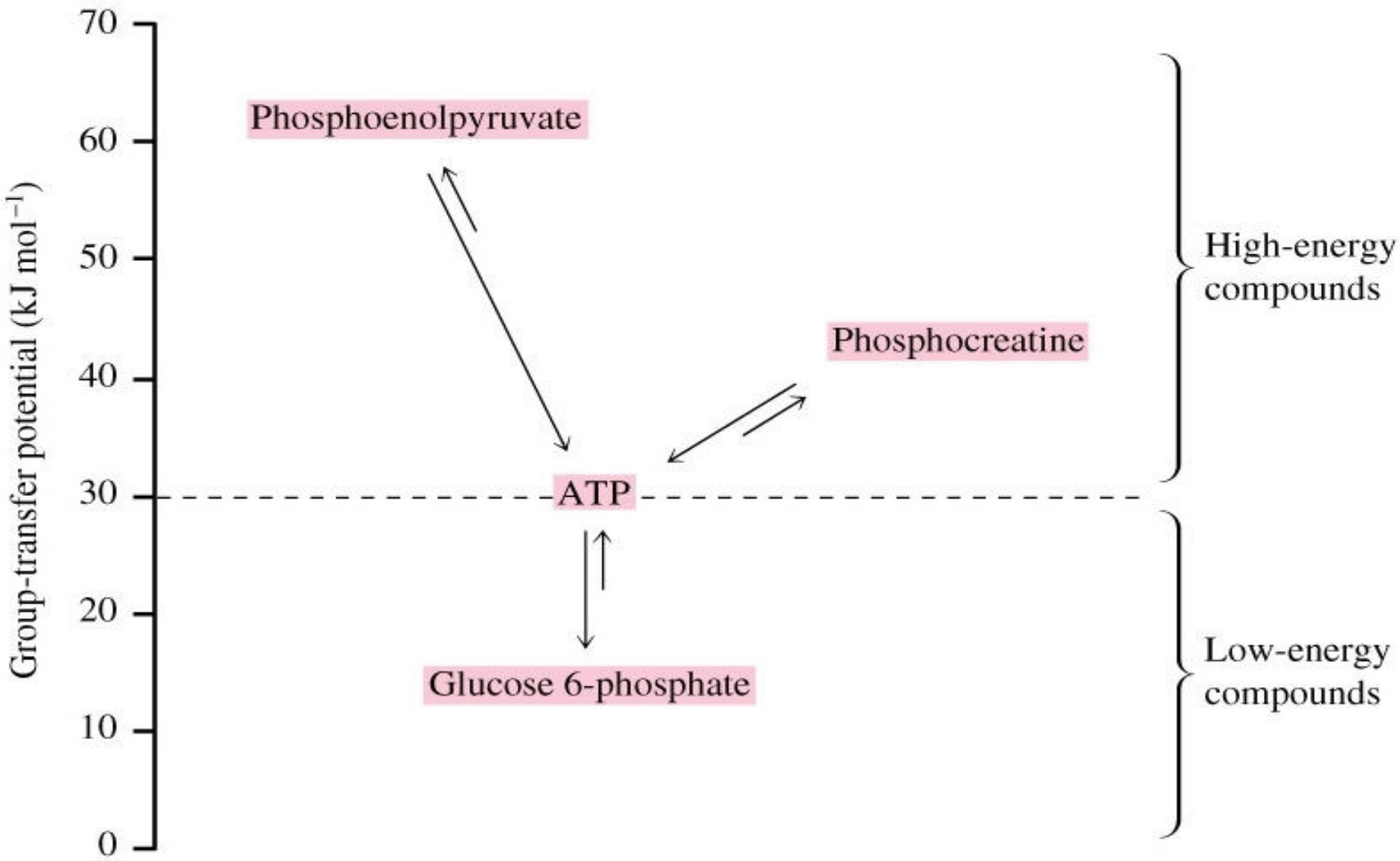
Phosphoryl-group Transfer



Types Of Metabolic Pathway

- **Catabolic**/Degradative /Energy Generating/ATP producing Pathways/Exothermic.

- **Anabolic**/Synthetic/Energy Utilizing/ ATP Using Pathways/Endothermic.

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- Catabolic pathways involve oxidative reactions producing reducing equivalents- **$NADH+H^+$ and $FADH_2$.**

- Catabolic pathways converge to few end products.

- Anabolic **pathways diverge to synthesize many biomolecules.**

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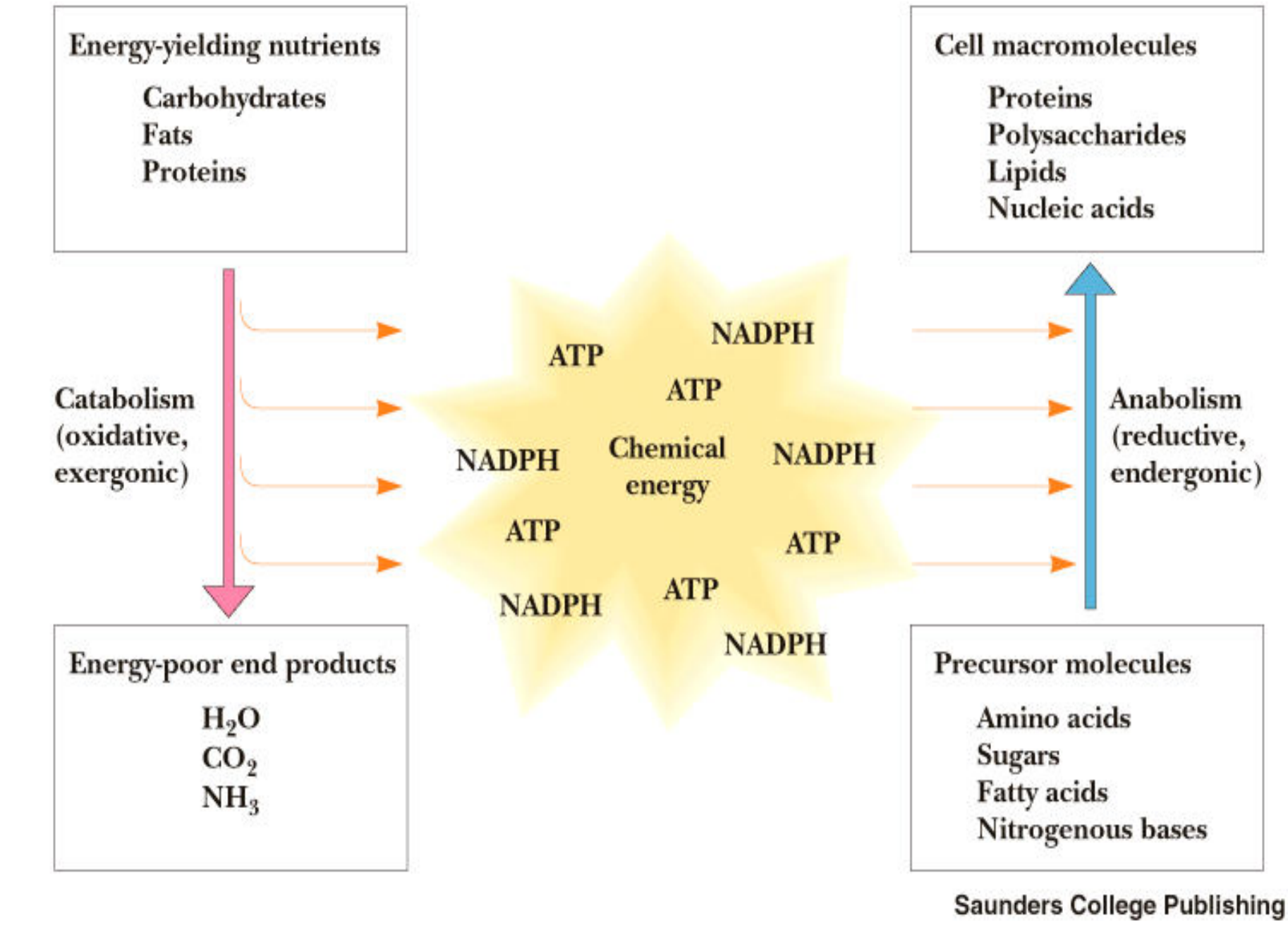
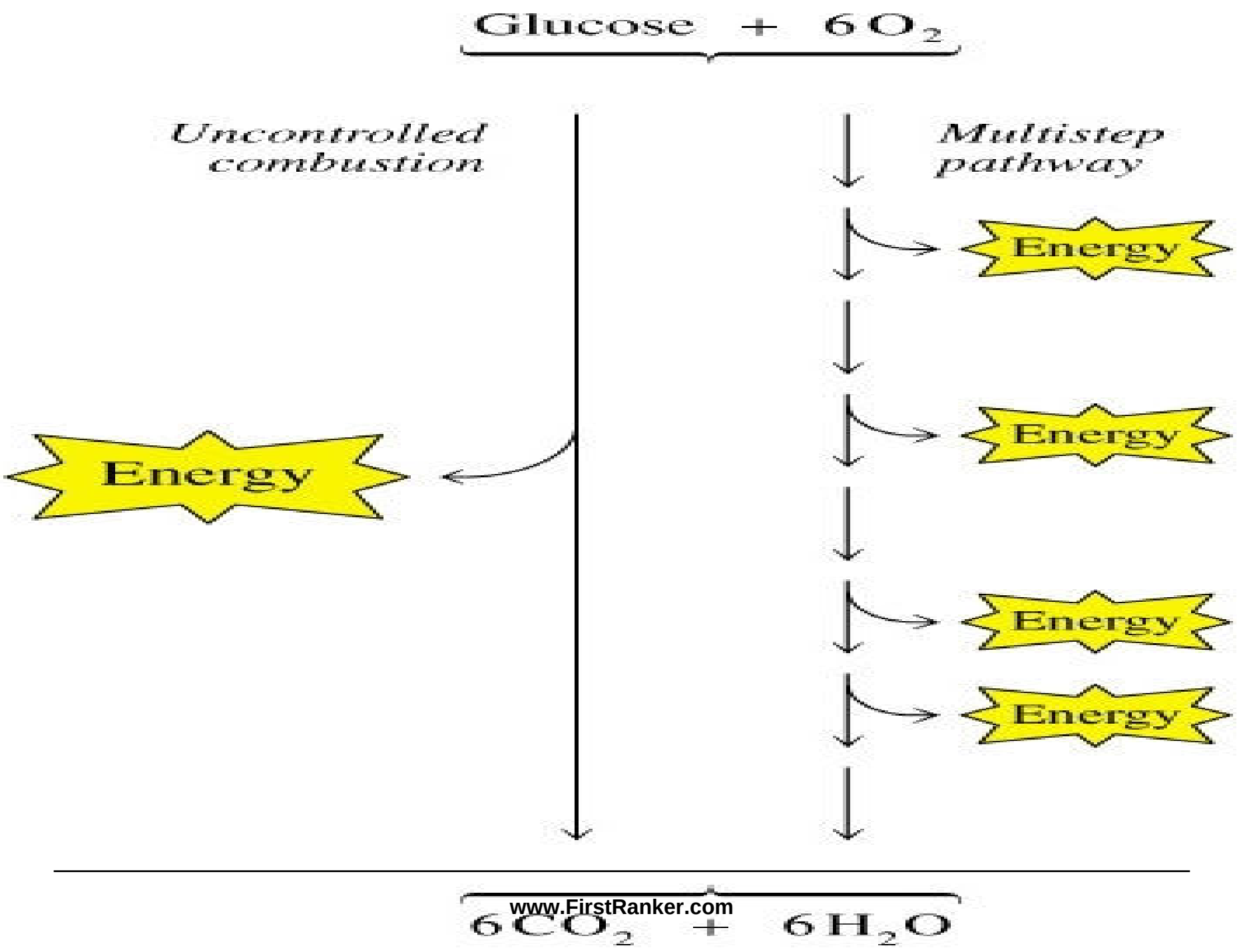
Figure 18.4





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- Some pathways serve both in catabolism and anabolism ,those are **Amphibolic pathways.**

- **Amphibolic Pathways** occur at the **crossroads of metabolism.**

- **Amphibolic pathways links** between **Anabolic and Catabolic pathways.**

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Regulation of Metabolic Pathways

- Regulation means **stimulation and inhibition of pathways** as per cellular need.
- **Hormones regulate** the metabolic pathways.
- Metabolic pathways are regulated to allow the organism to **respond to changing conditions.**

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- Every **metabolic pathway** has its **specific regulatory enzymes/key enzymes.**

- **Hormones regulate** by either stimulating /inhibiting the **regulatory/key enzymes** of the pathway.

Modes Of Metabolic Regulation

- **Allosteric regulation**
- **Covalent modification**
- **Control of enzyme levels**
- **Compartmentalization**
- ~~**Metabolic specialization of organs**~~

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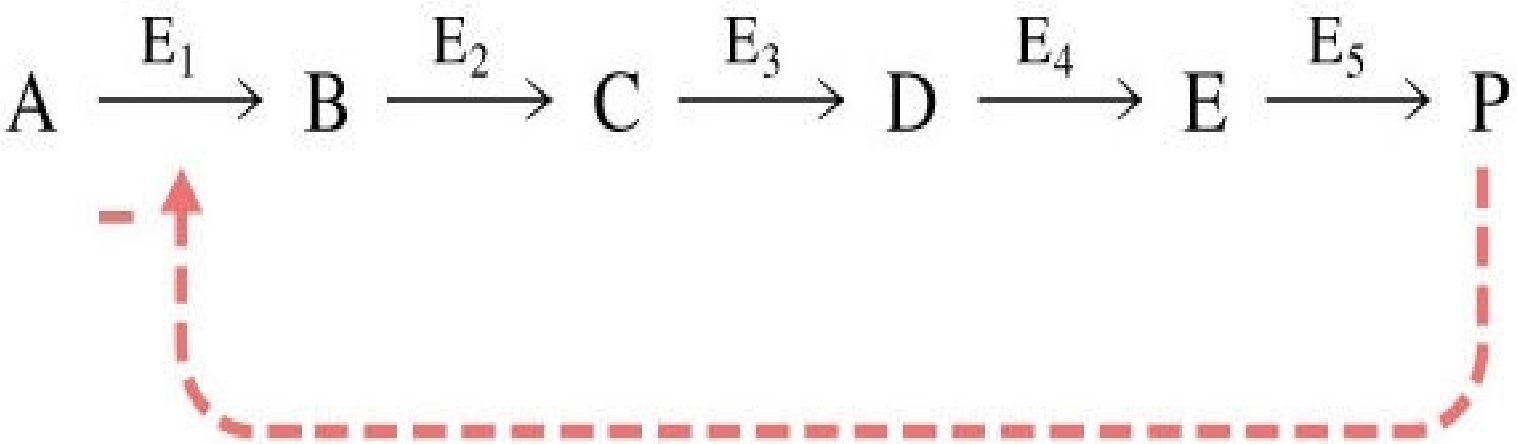
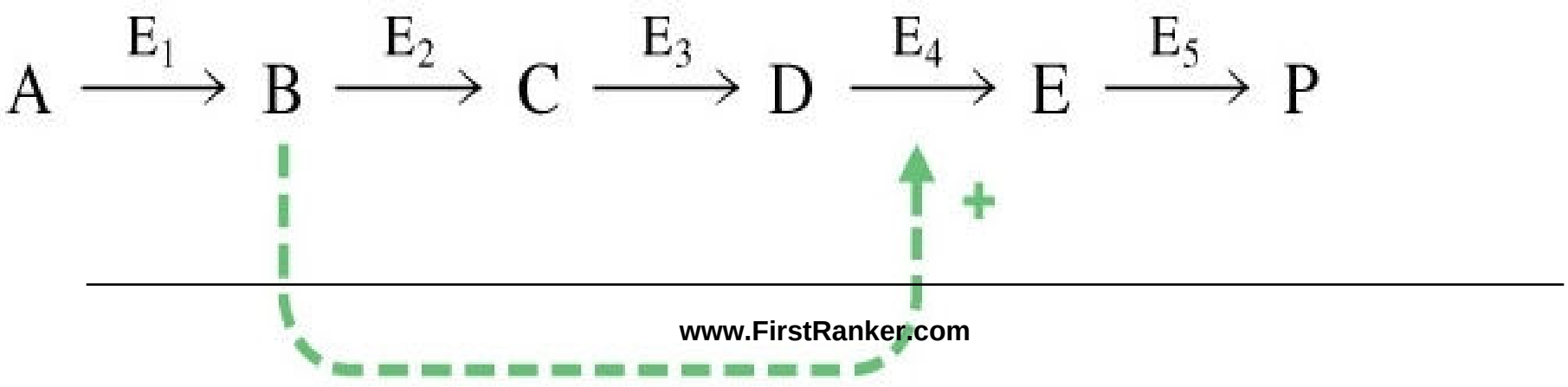
- **Feedback inhibition** – product of pathway down regulates activity of early step in pathway



- **Feedforward activation** – metabolite produced early in pathway activates down stream enzyme



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Regulating Related Catabolic and Anabolic Pathways

- **Anabolic & catabolic pathways** involving the **same compounds** are **not the same**.
- **Some steps** may be **common to both**
- **Others** must be **different** - to ensure that each pathway is spontaneous.
- This also **allows regulation** mechanisms to turn **one pathway onn and the other off.**

Modes Of Enzymes Regulation

- Alteration in membrane permeability.
- Conversion of Inactive to Active form.
- Stimulation of mRNA translation.
- Induction of new mRNA formation.
- Repression of mRNA formation.

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- **Knowledge of normal metabolism is essential for :**
- Understanding adaptations of
  - **Starvation**
  - **Exercise**
  - **Pregnancy and lactation.**
- Understanding of metabolic disorders.

Abnormal Metabolism Is Due To

- Nutritional Deficiencies
- Enzyme Defects
- Hormonal Defects
- Drug and Toxin Interactions

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- **Normal Enzyme** and **Hormonal** activities gives **normal metabolism** and health to human body.
- **Defect in Enzymes** and **Hormones derange the normal metabolism**.

Derangement in Metabolism

- Any defect or derangement in normal pattern of metabolism leads to **metabolic disorders.**
- **Mutation in Genes** of Enzymes, forms defective Enzymes.
- Congenital defect of Enzyme leads to **Inborn Error Of Metabolism.**

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Inborn Error Of Metabolism

- **Congenital deficiency** of any single **Enzyme** of a metabolic pathway leads to **Inborn Errors of Metabolism.**

Enzyme Deficiency of a Metabolic Pathway

- **Blocks** the **metabolic reaction.**
- **Blocks** the **metabolic pathway.**
- **Accumulates** and **excrete intermediate product** of the pathway.
- **No formation** of **end product** of the pathway.
- **Affects** other **interrelated** metabolic **pathways.**

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Methods Used to Study Metabolism

- **Metabolic Reactions/Metabolic Pathways were studied :**
  - **Using whole organism/Cellular fractions**
  - **Using Metabolic Probes.**
  - **Using Radioisotopes.**

Ingestion Of Dietary Carbohydrates

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Why To Eat Dietary Carbohydrates?

- Carbohydrates **predominantly not biosynthesized** by human body.
- Carbohydrates are **required for metabolic and structural role to human body.**

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- **Precursors for biosynthesis** of nutritionally **non essential amino acids.**

- To get the **role of dietary fiber .** (Cellulose , Hemicellulose ,Pectin Lignin, Agar)

- **Carbohydrate** is a **primary source of energy** and a **preferred fuel of the body.**
- 60-80% of energy intake comes from Carbohydrates.
- **Carbohydrate foods are cheap, readily available and palatable.**

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- **“ Fat Burns Under The Flame Of Carbohydrates”**

- For the complete oxidation of Fat there needs Carbohydrates.

How much Carbohydrates To Eat?
OR
Amount Of Carbohydrates To Be Eaten

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- **R.D.A for dietary Carbohydrates = 400- 600 gm/day**
  (Depends upon the human activities)

- 1 gram of Carbohydrate when completely oxidized in the body generates 4 kcal of energy.

- **Calorific value for dietary Carbohydrates is 4 kcal.**

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Dietary forms Of Carbohydrates and their Rich Sources

What Forms Of Dietary Carbohydrates Eaten?

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Dietary Forms Of Carbohydrates	Rich sources of Food
Monosaccharides Glucose Fructose	Fruits Honey and Fruits
Disaccharides Sucrose Lactose Maltose	Common table sugar, Sweets recipes, Juices, Tea Milk and Milk Products Malt grain ,Germinating seeds
Polysaccharides Starch (**Predominant**) Glycogen (NonVeg Eater) Cellulose	Grains, Pulses, Potatoes, Tubers ,Tapioca Meat, Chicken, Liver Whole grains ,Dates, Green leafy

- Cellulose is rich in unrefined whole grain (Husk).
- Cellulose is poor in refined grains (Kernel).

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Significance Of Cooking and Mastication of Food

- During **cooking** there is **hydrolysis of many bonds** of food constituents.
  - **Cooking makes the food:**
    - **Tasty**
    - **Soft**
    - **Chewable**
    - **Eatable**
    - **Easily Digestible**

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- **Mastication** of food takes place in **mouth**.

- Mastication is **biting and chewing** of **food** with **teeth** to break **large morsals** of food into **small particles** mixed with saliva to form **bolus**.

- **Proper mastication** of food in mouth **facilitates** for **good digestion** and **absorption** of food constituents.

Digestion of Dietary Carbohydrates by Specific Glycosidases

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- **Digestion of carbohydrate** involves **cleavage of Glycosidic bonds** present in Polysaccharides and Disaccharides to **form free Monosaccharides.**
- **Glycosidases** are **Carbohydrate Digesting Enzymes** which **cleaves specific glycosidic bonds.**
- There are **specific Glycosidases** for each Carbohydrate form.

Digestion of Monosaccharides

- **Dietary Monosaccharides / Simple Sugars** (Free Glucose /Free Fructose)
- **Requires no digestion** and are **ready for absorption.**

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- Monosaccharides are **readily absorbable forms** from GIT lumen.
- Simple sugars **require very less time** to reach blood and cells.
- Drinking **Glucon–D** give **instant energy** in very few

Digestion Of Disaccharides

- **Digestion of Disaccharides** takes place in **small intestine.**
- Disaccharides are digested by **specific Disaccharidases.**
- **Lactase, Maltase, Sucrase** (Invertase) and Isomaltase are specific Disaccharidases.

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- **Lactase** cleaves **β (1-4)** glycosidic bond of **Lactose**
- **Maltase** cleaves **α (1-4)** glycosidic bond of **Maltose**
- **Sucrase** cleaves **α1 β2** glycosidic bond of **Sucrose**

Lactose —Lactase→ Glucose + Galactose

Maltose —Maltase→ Glucose + Glucose

Sucrose —Sucrase→ Glucose + Fructose

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Digestion Of Polysaccharides

- **Starch and Glycogen** are **digested** by enzyme **α Amylase.**

- **α Amylase** is a **Starch and Glycogen digesting enzyme.**

Types of Amylases

- **Salivary Amylase**
  (Mouth-Salivary Juice)
- **Pancreatic Amylase**
  (Small Intestine-Pancreatic Juice)

- **α Amylase cleaves** -α(1-4) glycosidic bonds of Starch , Dextrin and Glycogen.

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- Chloride ion is an inorganic cofactor for α-Amylase activity.

- Digestion of Starch and Glycogen **begins in mouth** by the action of salivary α Amylase (pH- 6.6)

- Digestion of Starch is **incomplete in mouth.**
- **Dextrin is an intermediate of Starch digestion.**

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- Significant and **complete digestion** of Starch occurs **in intestine** by Pancreatic Amylase(pH 7.1).
- **Maltose and Isomaltose** are **end products** of Starch digestion by **Amylase activity**.

- Maltose and Isomaltose are then hydrolyzed by Maltase and Isomaltase to liberate free Glucose units.
- **Thus end product of Starch digestion is many Glucose units.**

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No Digestion of Dietary Cellulose

- Dietary **Cellulose is not digested** in human GIT due to **absence of Cellulase** digesting enzyme Cellulose.
- Cellulase in ruminants **cleaves β (1-4)** glycosidic bonds of Cellulose to **form Cellobiose.**

- **Dietary Oligosaccharides** are not digested by GIT enzymes.
- Bacterial enzymes act upon it to **produce gas.**
- **Thus Oligosaccharides of diet apt to cause flatulence.**

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No Digestion Of Carbohydrates in Stomach

- Gastric juice of stomach has:
  - **No specific Glycosidase** for Carbohydrate digestion.
  - **No optimal pH** for enzyme action.

- Salivary Amylase of mouth carried to stomach along with food bolus is inhibited by vey low pH of gastric juice.

Monosaccharides is an End Product Of Carbohydrate Digestion.

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- **End products of Carbohydrate digestion are :**

Monosaccharides- **Glucose (80%)**
Galactose
Fructose

Absorption Of Monosaccharides

- Monosaccharides an end product of Carbohydrate digestion are absorbable forms.
- **Site of Absorption :**
  - **Small Intestine**
    - ❖ **Duodenum**
    - ❖ **Upper part of Jejunum**

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Relative Rates of Absorption

- Coefficient /Relative rates of absorption of different Monosaccharides in intestine:
  - Glucose= 100
  - Galactose = 110
  - Fructose = 43
  - Mannose = 20
  - Xylose = 15
  - Arabinose = 09

Modes of Absorption

- **Glucose and Galactose – (Complete)**

  Active Transport mechanism
- **Fructose –**

  Facilitated Diffusion
- **Pentose-**

  Simple Passive Diffusion.

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Absorption Of Glucose

- Glucose absorption by active transport mechanism.
- **Sodium dependent Symport Co-Transport** type.

(Secondary Active Transport)

- **Glucose Transportation Requires:**
  - Protein carrier molecule
  - Na^+ ions
  - Sodium-Potassium ATPase.
  - ATP

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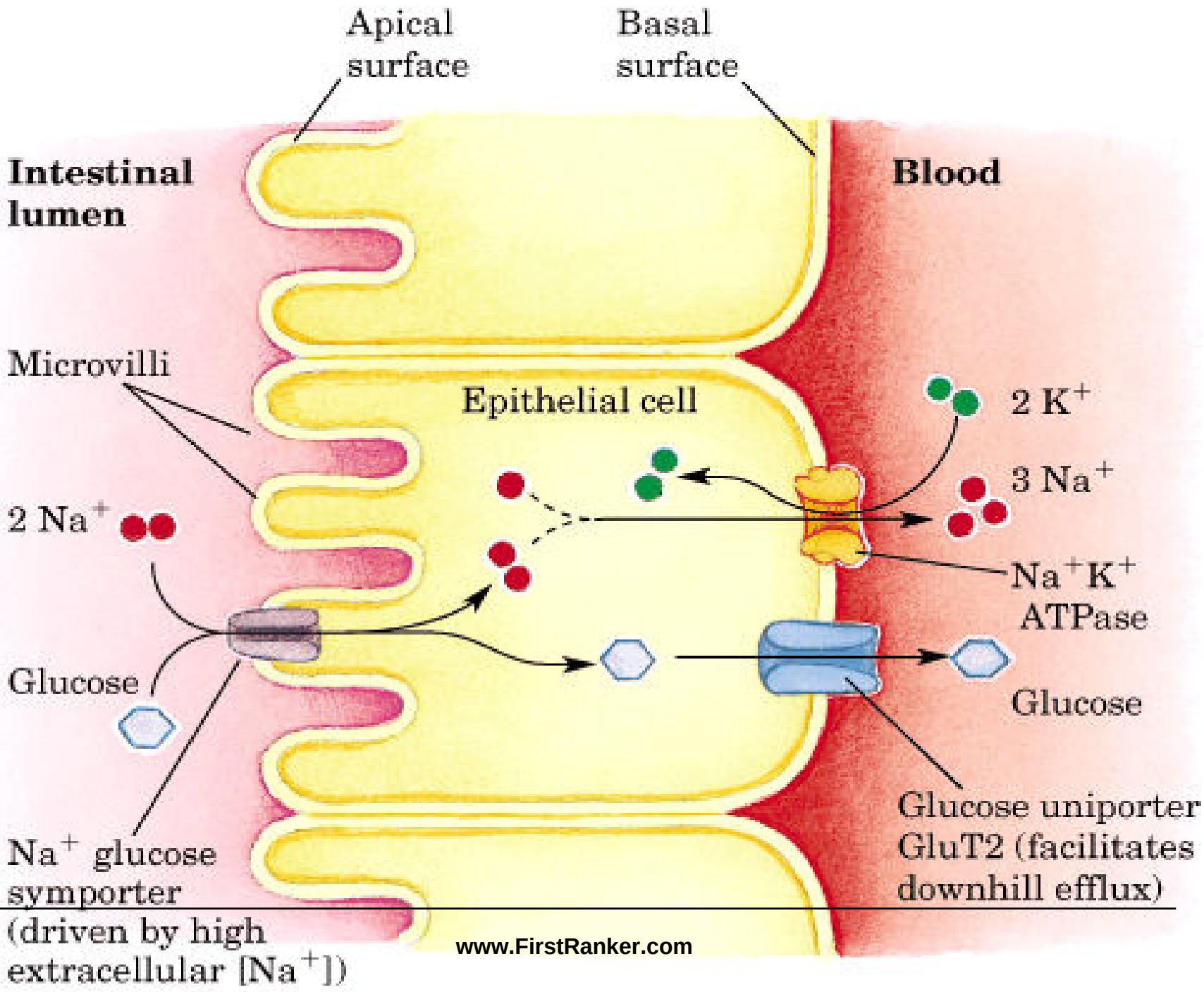
- Glucose and Galactose are absorbed by same Glucose transporter.
- Absorption of Glucose and Galactose is complete since it is by active transport mechanism.



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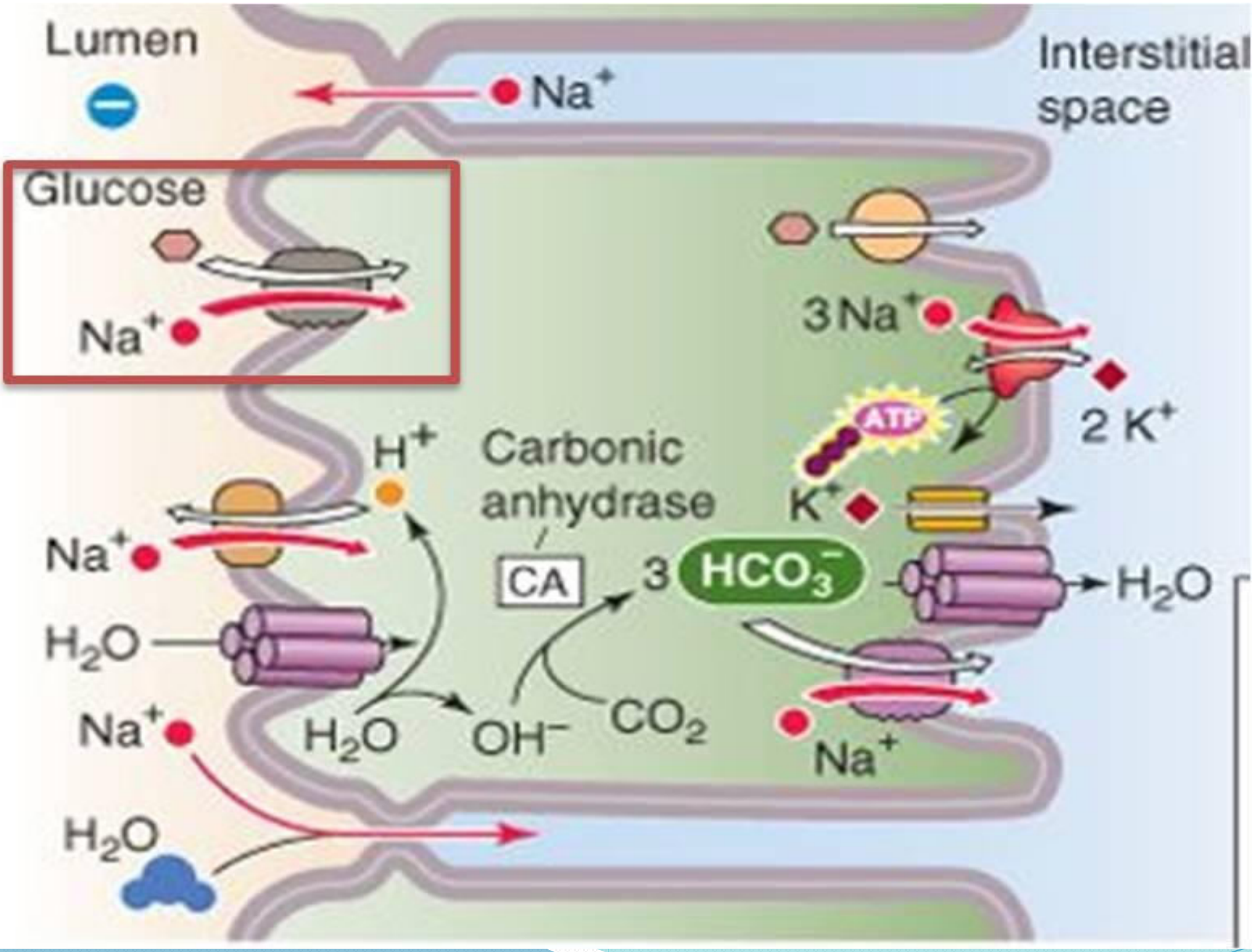

- Absorbed Glucose ,Galactose and Fructose simply diffuse in blood capillaries and carried from intestine to Liver by **Hepato Portal Circulation.**
- Thus **Liver** is the **first station** to receive dietary Carbohydrates.

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- From **Liver** Carbohydrates are then distributed **to remaining all tissues** and cells of human body through **systemic circulation of blood.**

Disorders Of Carbohydrate Digestion and Absorption.

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Lactose Intolerance

Lactose Intolerance

- Dietary Lactose not tolerated.
- No digestion and absorption of dietary (Milk) Lactose.

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Causes

- Congenital / Acquired
- **Deficiency** of Lactose digesting enzyme ‘**Lactase**’

Biochemical Alterations

- Dietary Lactose not digested due to **deficient Lactase**.
- Lactose remains in GIT and is acted upon by bacterial enzymes to Lactic acid and Gas (H_2,CO_2, Methane).

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- Lactic acid and Lactose are washed out through fecal excretion.
- Loss of body water and electrolytes through feces.
- Water and Electrolyte imbalance/Dehydration (Mixed Type Dehydration)

Clinical Manifestations

- Lactic acid excretion causes **irritant osmotic diarrhea.**
- Gas excretion **causes flatulence.**
- Abdominal cramps.
- Increased motility of intestine.
- Weakness.
- Confusion.

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Diagnosis

- Benedicts Test on stool specimen .
- Positive result of Benedicts test confirms diagnosis.

Management

- Lactose intolerance is managed by avoiding dietary intake of foods (Milk and Milk Products) containing Lactose.
- Intake of Curds which contains Lactobacillus.

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Incidence and Prevalence

- More than half of world population is suffering from Lactose Intolerance.
- 90 % Asians
  (More in South India)
- 10 % Africans.

Glycaemic Index (GI) Of Carbohydrate Foods.

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- **Glycemic index (GI)** measures an increase in post prandial(PP) blood Glucose after ingestion of dietary Carbohydrates.

- GI of a food is calculated **in comparison** with an equivalent amount of Glucose liberated by food such as bread/boiled rice.

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Glycaemic Index Of Common Foods

Foods	Glycaemic Index
Potatoes, Corn Flakes	80-90
Whole Wheat Bread, White Rice	70-79
Brown Rice, Bananas	60-69
Buck Wheat, Frozen Peas.	50-59
Peas, Beans	40-49
Legumes, Milk, Ice cream, Peanuts.	< 40

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Factors Affecting GI

- **Degree and pattern of rise in post prandial Glycaemia depends on:**
  - **Amount** of **dietary Carbohydrate** ingested.
  - **Type** of **dietary Carbohydrate** ingested.
  - **Extent of dietary Carbohydrate** digested and absorbed in GIT.

- **Steep rise** of post prandial Glucose is noted on **ingestion of refined sugars.**
- **Refined free sugars** enter the blood and body **pleasantly, imperceptibly and effortlessly within very less time.**

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- **Less steep rise** of post prandial Glucose is noted on **ingestion** of dietary complex carbohydrates like **Starch/Cellulose.**
- **Starchy food** takes **more time as it takes effort to chew and less palatable** than refined and simple sugar.

Factors Reducing Post Prandial Glycaemia

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- Eating complex Carbohydrates (Starch/ Glycogen).
- Inadequate cooking of Starch.
- Inadequate chewing and mastication of eaten food.

- Eating non digestible Carbohydrate Cellulose.
- Eating large particle size of food.
- Presence of Enzyme inhibitors in food.
- Presence of Protein or fat in association with Carbohydrates.

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- Calorific value of sugar and starch is same 4 Kcal/gm.
- One who consumes sweets and refined sugars get more calories and prone to grow over weight.

Importance to know GI of Foods

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- Foods with high Glycaemic Index (GI) increases the post prandial glycaemia.

- Foods with low GI decreases the post prandial glycaemia.

- **Knowing the GI value of food helps:**
  - In **planning a rational diet** for patients of **Diabetes mellitus.**
  - In planning diet for persons to **gain and loose weight.**

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Uptake Of Glucose Within The Cells

- Absorbed Glucose is carried from intestine through **Hepato portal circulation** and reaches the Liver.

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- Glucose is transported into the cells with the help of specific membrane bound Proteins termed **Glucose Transporters.**

Glucose Transporters

- Glucose Transporters (GluT) are **Transmembrane proteins** present in cell membranes
- They help in uptake of Glucose from blood into cells.

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- Glucose Transporters may be Insulin dependent/Insulin independent.

Types Of Glucose Transporters

- **GLUT-1 to GLUT-14** (Glucose Transporter Isoforms) exist in the membranes of various body cells.
- These **Glucose transporters** involved in **Glucose uptake** from blood **into specific tissues.**

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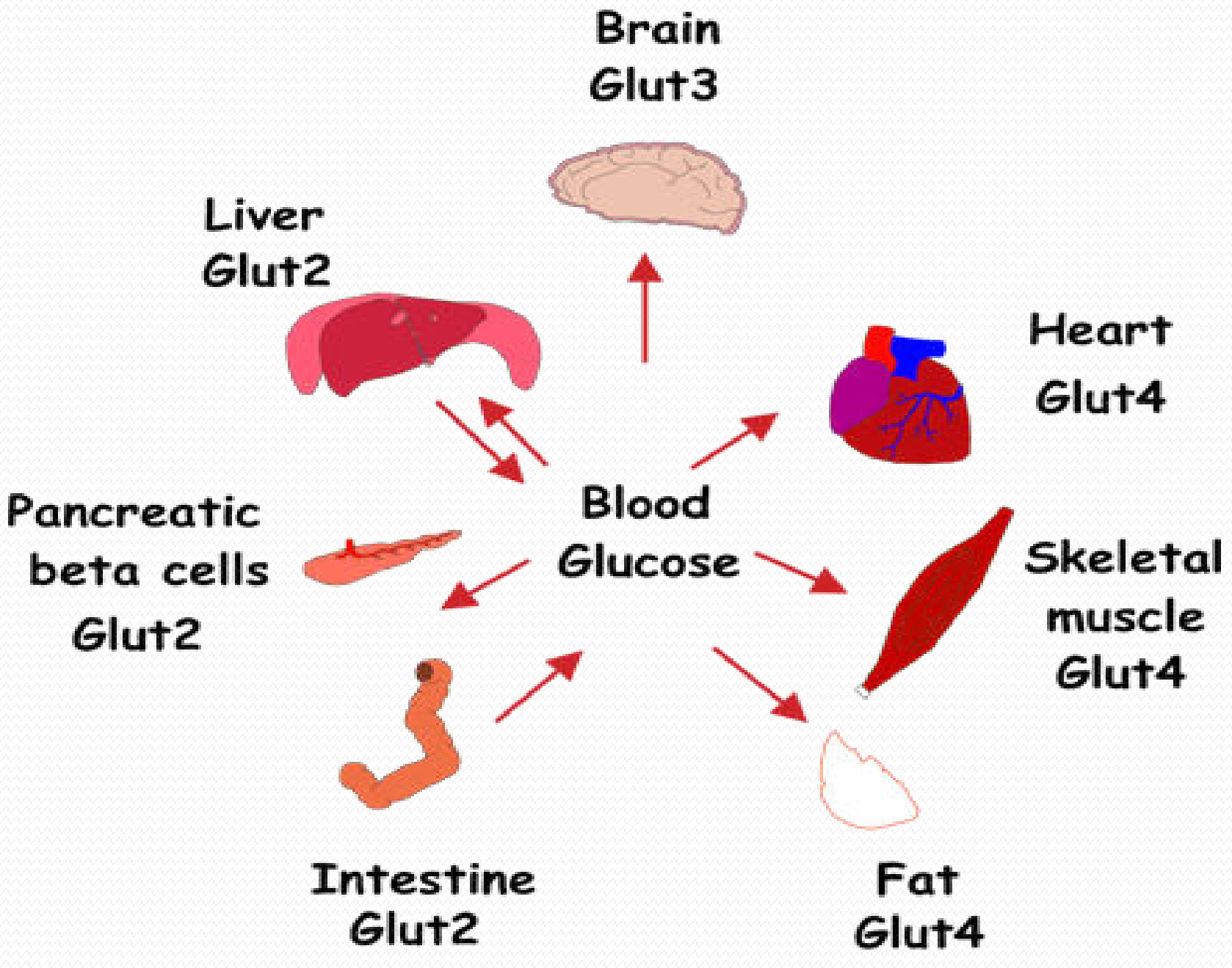

Type of GluT	Present on Organs	Property
Glu T1	RBC 's, Brain, Retina, Placenta	Insulin Independent
GluT2	Liver, Intestinal cells	Insulin Independent
GluT3	Neuron, Brain	Insulin Independent
GluT4	Skeletal Muscles, Heart, Adiposecytes	**Insulin Dependent**
GluT5	Testis, Kidney, Sperms	Poor ability for Glucose and has good uptake property for Fructose.
GluT7	Liver Endoplasmic reticulum	Glucose transported from E.R to cytosol.

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- **Sodium Dependent Glucose Transporter -1 (SGluT-1)**
- Present in **membranes of intestinal mucosal cells.**
- Helps in uptake of Glucose from intestinal lumen to intestinal mucosal cells.
- Defect in SGluT-1 leads to Glucose malabsorption.

- Sodium Dependent Glucose Transporter -2 (SGluT-2)
- Present in kidney tubules
- Defect in SGluT-2 leads to Renal Glycosuria.

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Inhibitors Of Glucose Transport

- **Glycosides :**
  - **Phlorizin**
    (Inhibitor of Glucose Transporter-SGluT-1 of Intestine)
  - **Ovabain**
    (Inhibitor of Na-K ATPase)
- They reduces blood Glucose.
- Therapeutically used to control blood Glucose in Diabetes mellitus.

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Locking Of Glucose Within The Cells

- **Free Glucose is permeable to cell membrane.**
- Glucose entered in cells is phosphorylated to **Glucose-6-Phosphate** (Impermeable) and **locked within the cells.**

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Glucokinase in Liver

- Glucokinase in presence of ATP and Mg^{++} ions Phosphorylates the Glucose to Glucose-6-Phosphate when first enters the hepatocytes.

- The Glucokinase is specific for Glucose
- It has **high Km value** i.e low affinity for Glucose for phosphorylation reaction.

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- As Glucokinase is slow in action **not all Glucose** molecules entered in hepatocytes **are phosphorylated and locked.**
- The remained free form of Glucose come out of Liver and carried through Systemic circulation.

- Thus Glucose from systemic circulation diffuses into extra hepatic tissues.

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Hexokinase In Extrahepatocytes

- The Glucose entered in extra hepatocytes is phosphorylated to Glucose-6-PO_4 by an action of Hexokinase in presence of ATP and Mg^{++} ions.

- Hexokinase has **low Km value** i.e very high affinity for Glucose for phosphorylation reaction.
- Glucose is readily locked by Hexokinase in extra hepatocytes at a very low Glucose concentration.

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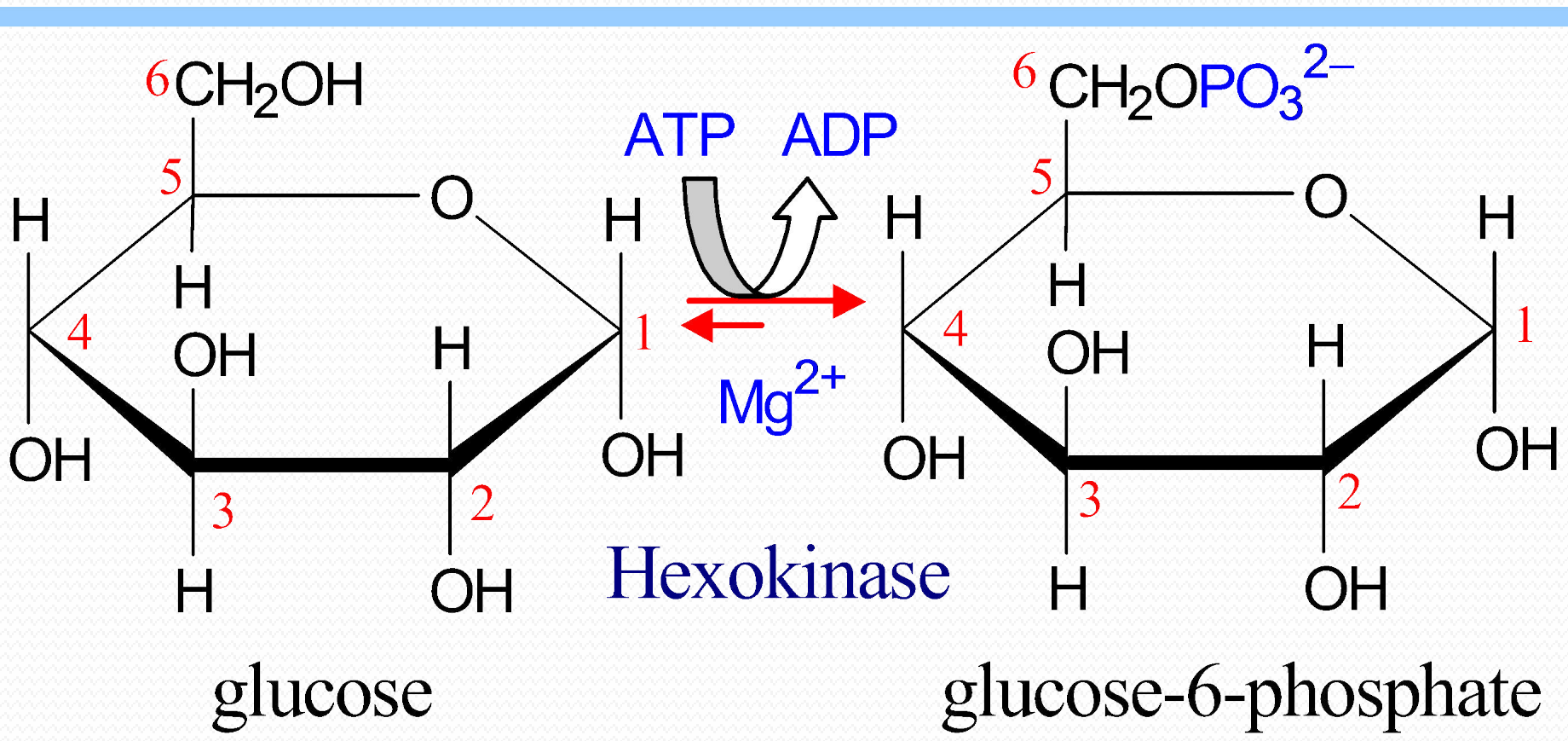
Glucokinase	Hexokinase
Phosphorylates Glucose to Glu-6-Po4 in hepatocytes.	Phosphorylates Glucose to Glu-6-Po4 in extra hepatocytes.
Glucokinase has high Km value	Glucokinase has low Km value
Glucokinase acts when Glucose concentration is high(> 100 mg%)	Hexokinase acts when Glucose concentration is low.(< 100 mg%)
Glucokinase is very specific acts only on Glucose.	Hexokinase is not so specific acts on Glucose ,Fructose and Mannose.
Glucokinase is dependent on Insulin.	Hexokinase is not under influence of Insulin.
Glucokinase is not inhibited by Glucose-6-PO4.	Hexokinase is inhibited by Glucose -6-PO4.



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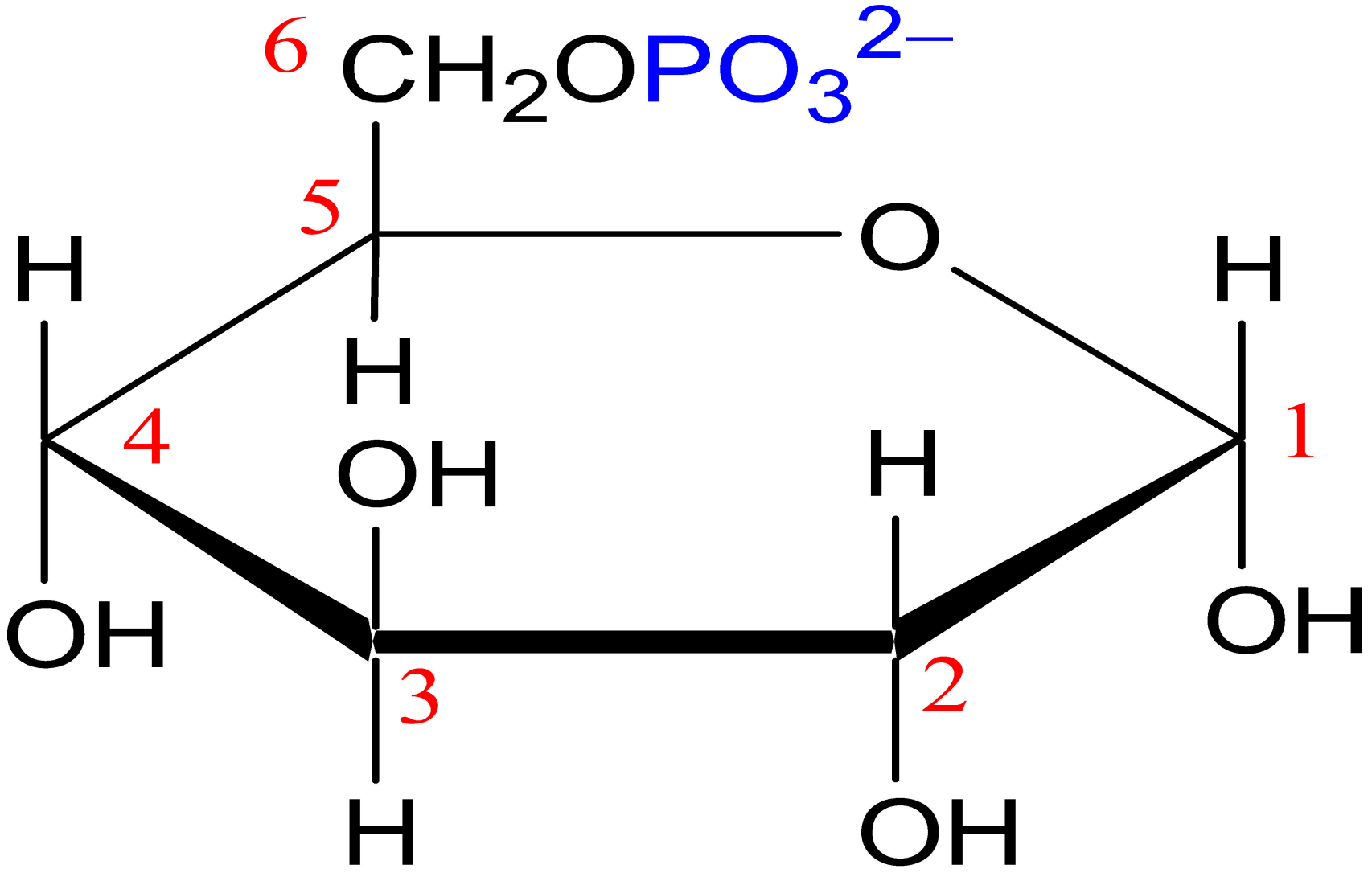
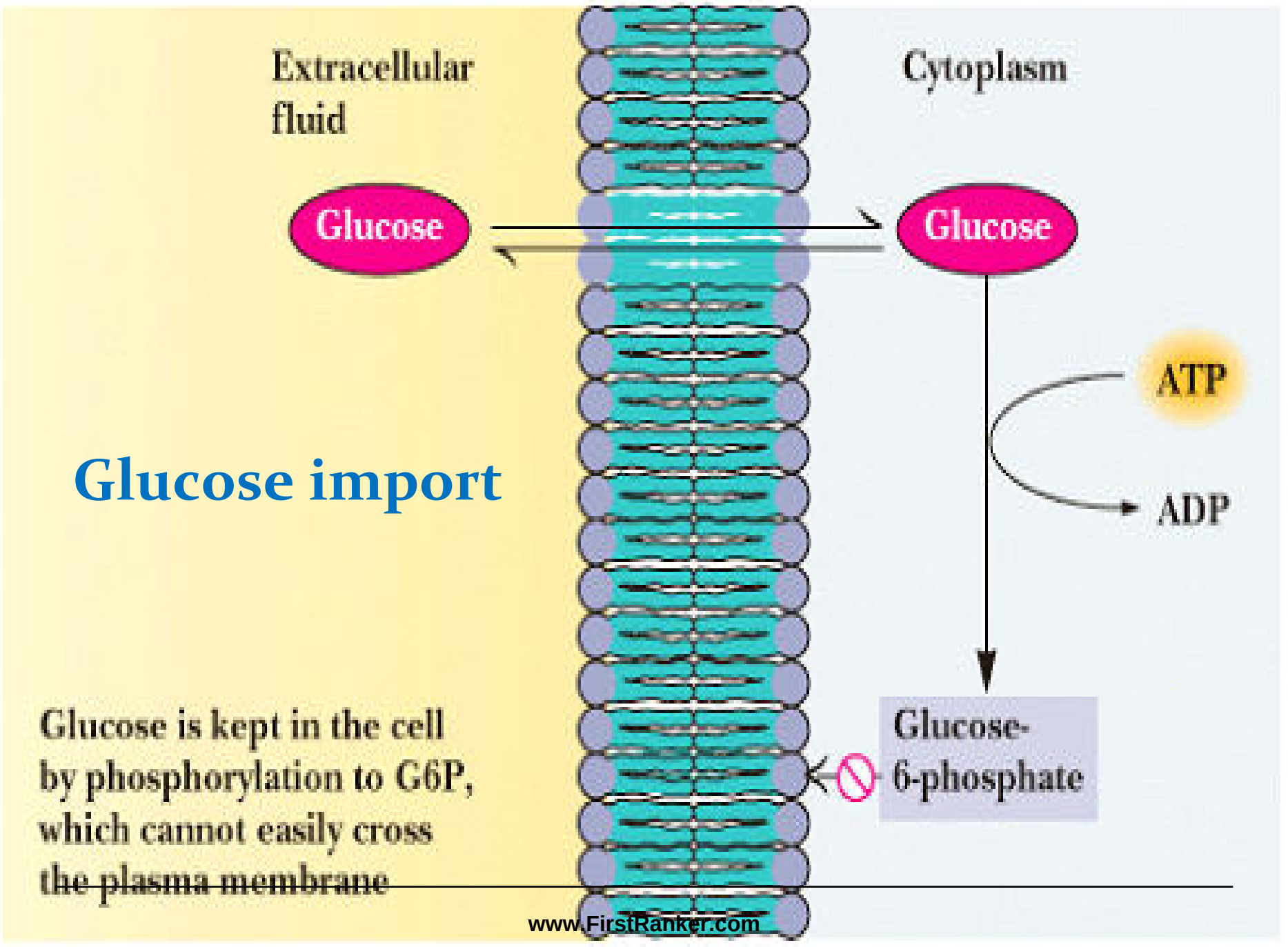


glucose-6-phosphate



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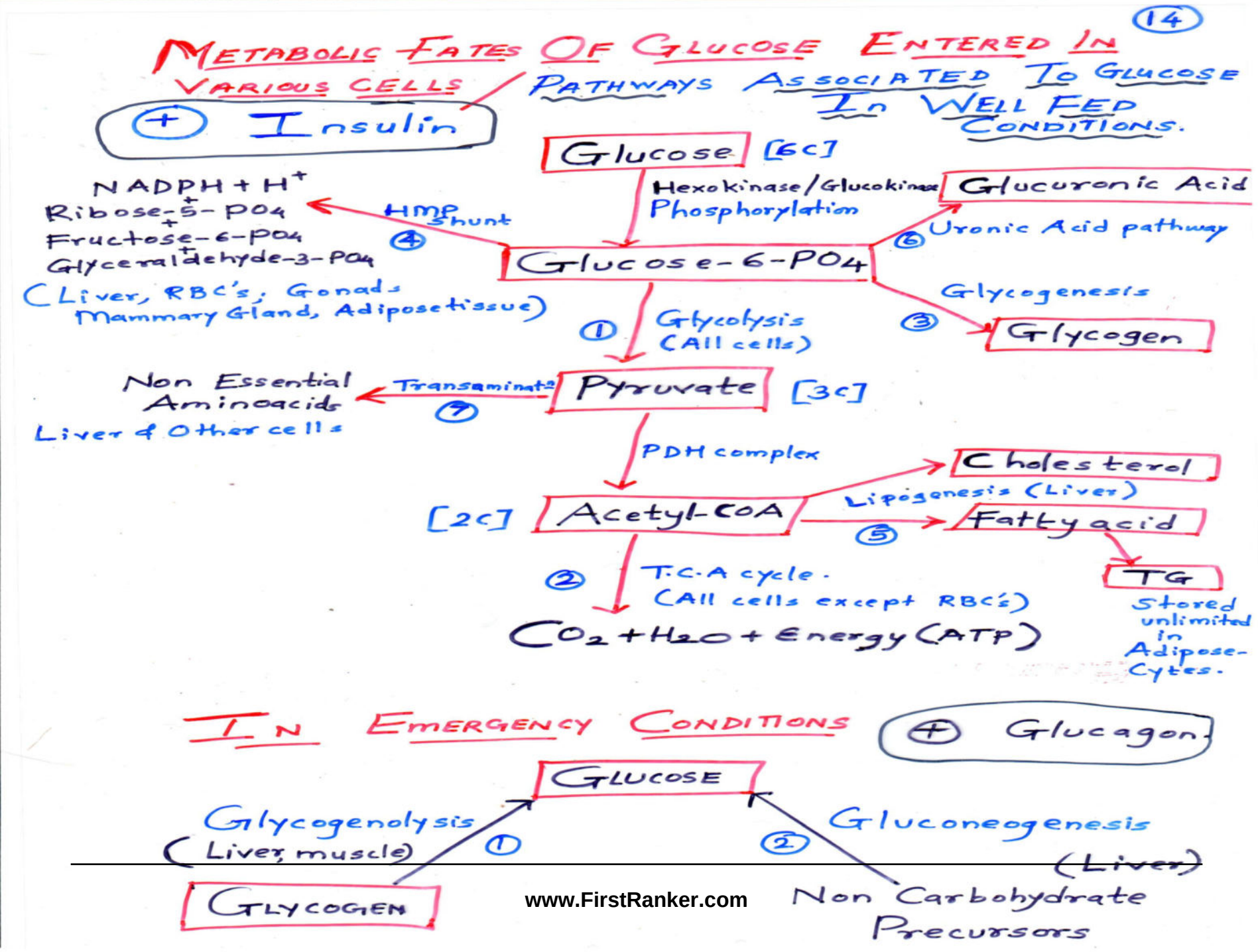
Metabolic Fates Of Glucose

Overview of Glucose Metabolism



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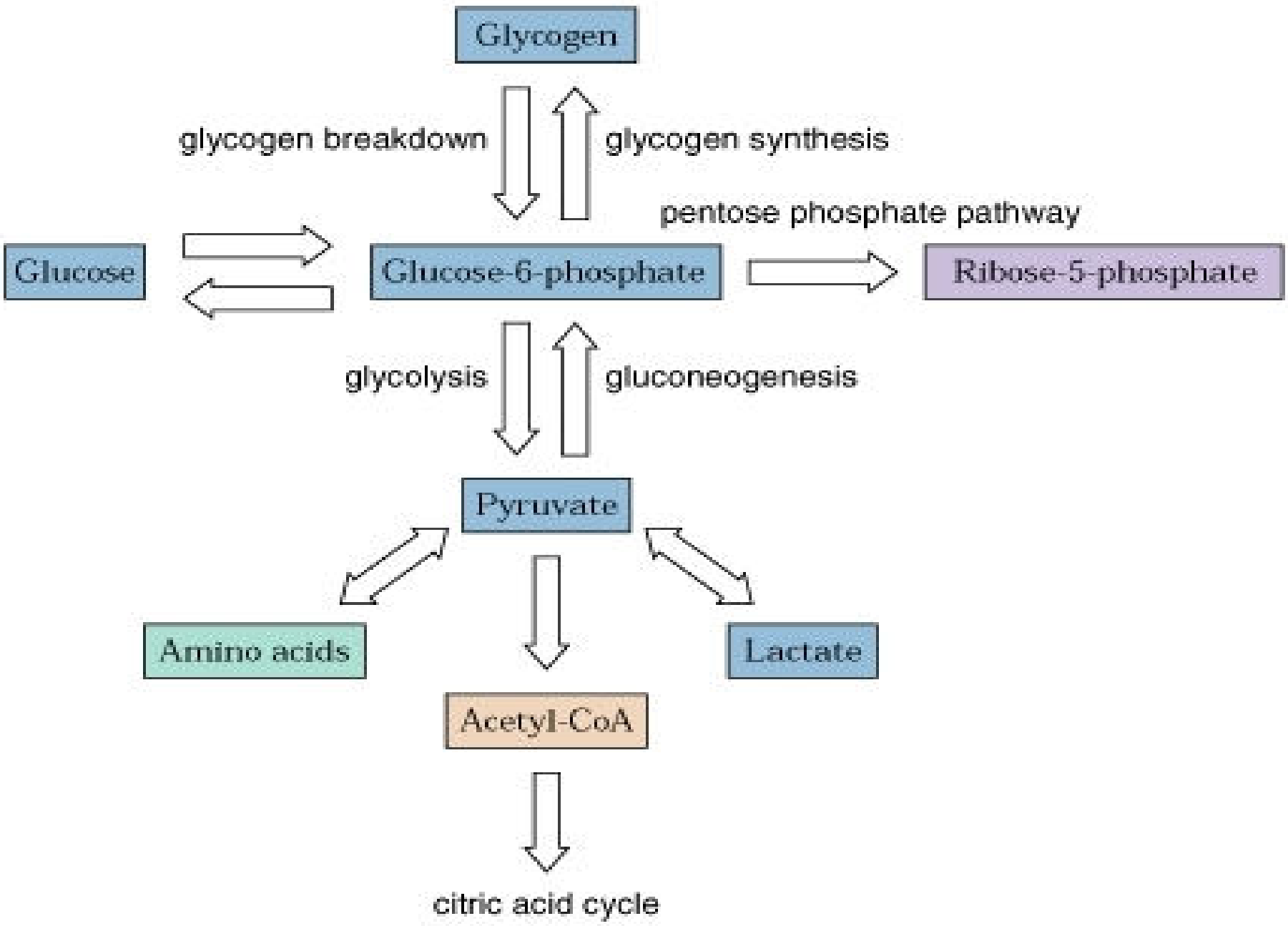

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Metabolic Pathways of Glucose In Well Fed Condition

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- In well fed condition Under the influence of Insulin.
- Glucose-6-PO_4 is metabolized as follows:
  - For Oxidation to produce chemical form of energy ATP.
  - For Storing Glucose.(Glycogen and TAG)
  - For production of Glucose derivatives for metabolic use.

- **Complete Oxidation Of Glucose via (In all Cells)**
  - **Glycolysis/EMP pathway**
  - **PDH complex reaction**
  - **TCA Cycle/Krebs Cycle**

- **Formation and Storage of Glycogen by**
  - **Glycogenesis (Liver and Muscles).**

- **Alternative Glucose Oxidation**
  - **HMP Shunt (NADPH+ H^+ and Ribose)**
  - **Uronic Acid Pathway (Glucoronic acid)**

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- **Glucose is transformed to :**
- **Lipids(Lipogenesis)**
  - Fatty acids
  - TAG
  - Cholesterol
- **Proteins building blocks.**
  - **Non essential Amino acids.**
- **Precursor for Lipogenesis is Acetyl –CoA.**
- **Precursor for Amino acids is Pyruvate, OAA**

Metabolic Pathways of Glucose In Emergency Condition

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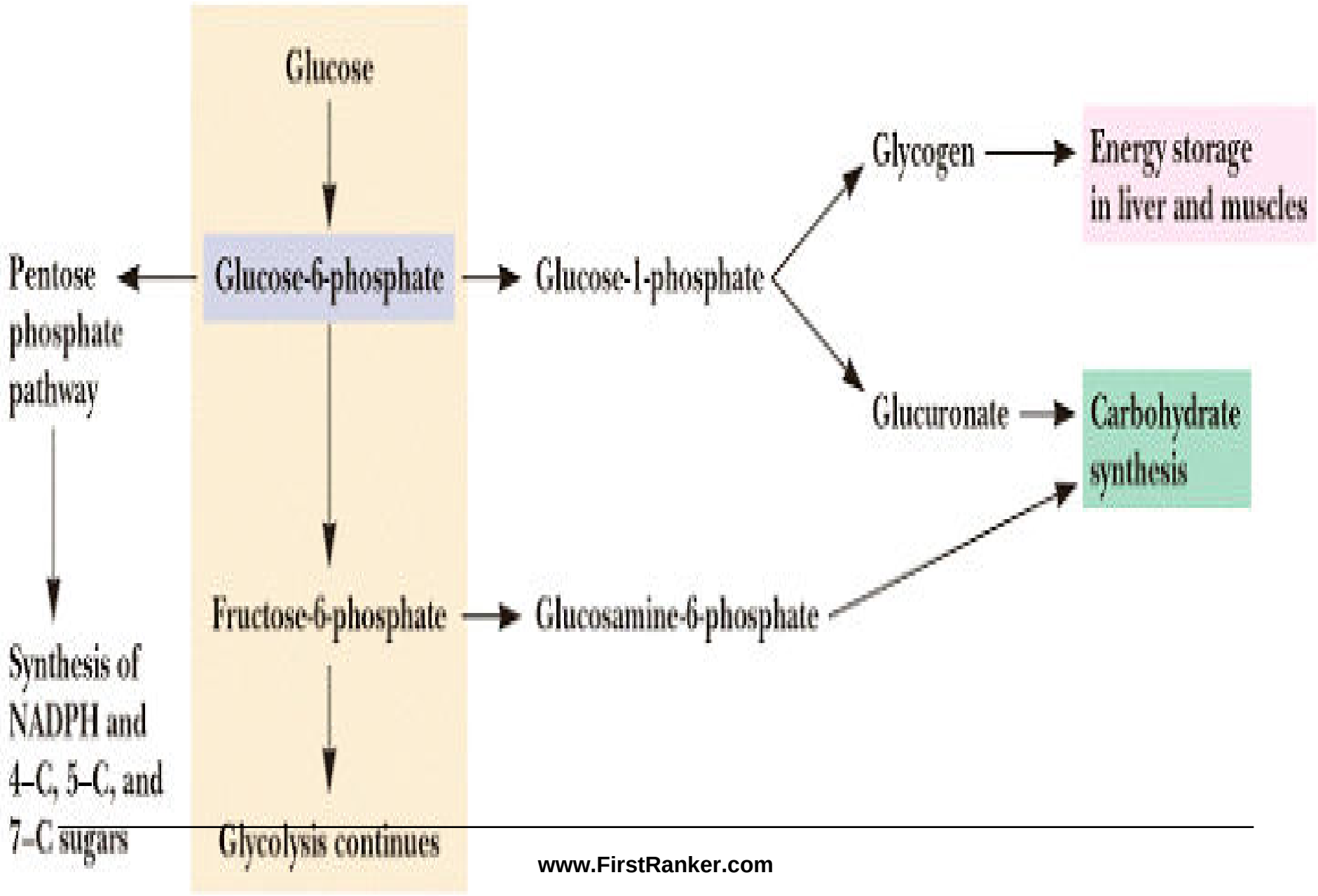
- In emergency fasting condition when blood Glucose lowers under influence of Glucagon body tries to regulate the blood Glucose by stimulating:
- **Glycogenolysis**

  (Breakdown of Stored Glycogen)
- **Gluconeogenesis**

  (Biosynthesis of Glucose).



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Pattern to Study A Metabolic Pathway

- Synonyms/Different Names of Pathway.
- What is the Pathway ? (In brief)
- Where the pathway occurs? (Organ/Cellular site)
- When pathway occurs? (well fed/emergency/aerobic/anaerobic)
- What type Of Pathway? (Catabolic/Anabolic)
- How the pathway Occurs? (Type of Rxn, Enzymes ,Coenzymes)

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- Why the Pathway occurred? (Significance)

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- Precursor, intermediates, byproducts and end products of Pathway.
- Energetics of the pathway (If Catabolic Pathway)
- Interrelation ships with Other Pathways.
- Regulation of Pathway :Modes of regulation.
- Regulatory hormone/ Regulatory Enzyme/Modulators.
- Inborn Error of the Metabolic Pathway

Complete Oxidation Of Glucose

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- The main aim of Glucose in cells is to oxidize (Remove Hydrogen) and catabolize to liberate energy.

- Glucose (C6) is completely oxidized to free CO_2, H_2O and Energy (ATP). Glucose is completely oxidized via:
- **Glycolysis**
  (1 Glucose ⟶ 2 Pyruvate and ATP)
- **PDH Complex reaction**
  (2Pyruvate ⟶ 2 Acetyl-CoA and ATP)
- **TCA cycle**
  (2 Acetyl –CoA ⟶ CO_2, H_2O and ATP)

GLYCOLYSIS

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Synonyms Of Glycolysis

- **Embden Meyerhof Parnas** (EMP) Pathway
- **Aerobic and Anerobic Oxidation Of Glucose.**
- **Oxidation Of Glucose to Pyruvate.**
- **Conversion of Glucose to Lactate.**

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What is Glycolysis?

- Major **Oxidative Pathway** of Glucose.
- Takes place in **cytosol of every cell** of human body.
- Glucose undergoes series of significant catabolic reactions in aerobic and anaerobic conditions to form Pyruvate and Lactate respectively.

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- **Glucose**(6C) ⟶ 2**Pyruvate + ATP**
  (Aerobic Glycolysis) (3C)

- **Glucose** ⟶ **2 Lactate +ATP**
  (Anaerobic Glycolysis) (3C)

- **Byproduct of Glycolysis is ATP.**

Nature /Type Of Glycolysis Pathway

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- Glycolysis is a **catabolic/ degradative pathway.**
- **Oxidation of Glucose** occurs in Glycolysis.
- **Removal of Hydrogen** from Glucose structure.
- Temporary acceptor of removed Hydrogen is **coenzyme NAD$^+$** which get transformed to **form** reducing equivalent **NADH+ H$^+$.**

Glycolysis-Energy Generating Pathway

- The NADH+ H$^+$ generated in the steps of Glycolysis enters ETC for its reoxidation and generation of ATP.

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When Glycolysis Occurs?

- **Glycolysis Occurs In**
- Cells when it needs energy .
- **Aerobic/Anaerobic condition** (Uniqueness).
- **Well fed condition** (Actively).

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- Erythrocytes needs **continuous** and **uninterrupted Glycolysis** for their survival.

Where Glycolysis Occurs?

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- Glycolysis Occurs in Cytoplasm of all body cells.

How Glycolysis Occurs?

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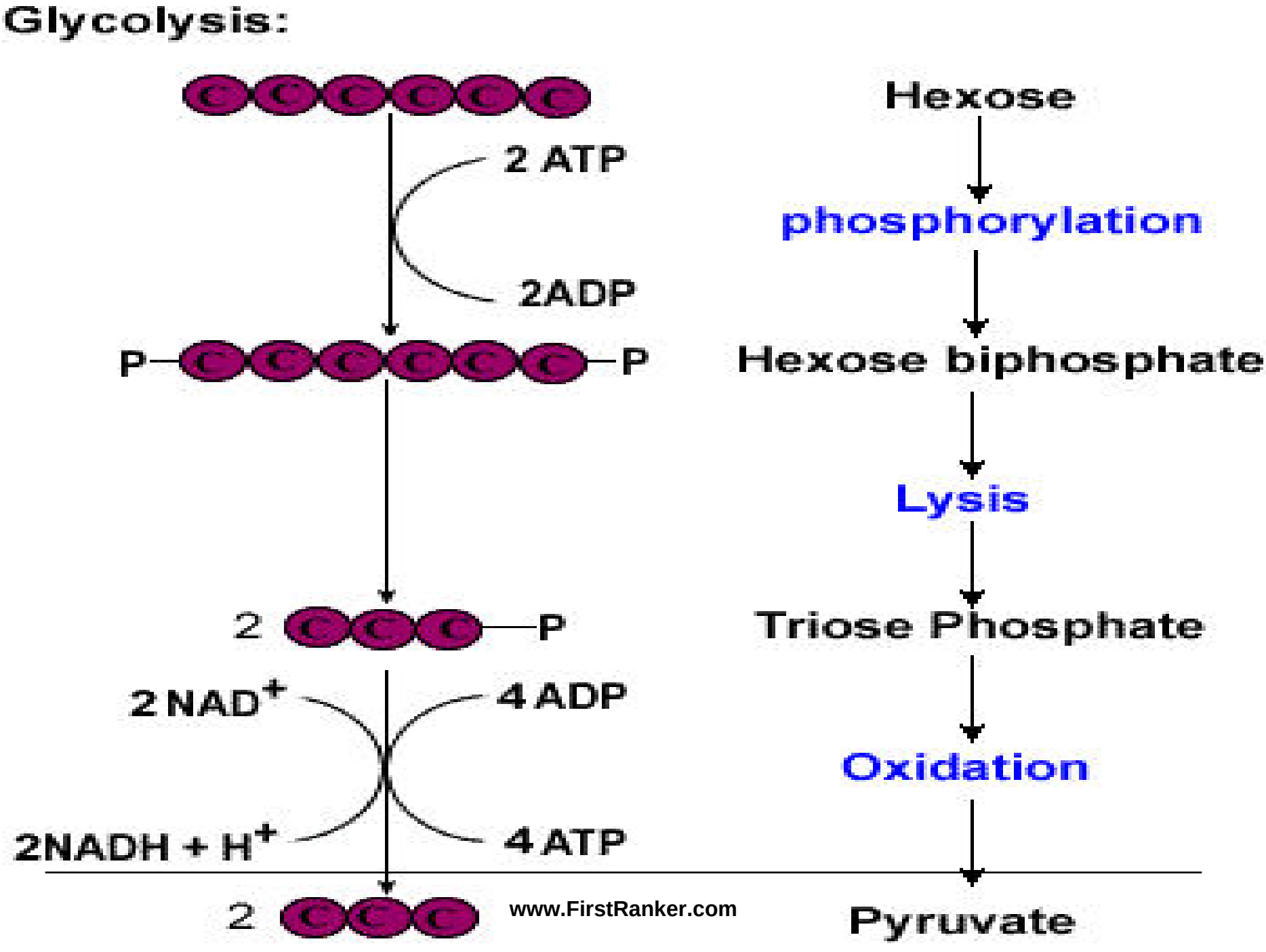
- Glycolysis occurs in **10 steps**.

- **Glycolysis is studied in 3 phases/3 stages:**

  - **Phase I- Energy Utilizing Phase**
  - **Phase II- Splitting Phase**
  - **Phase III- Energy Generating Phase**



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REACTION STEPS OF GLYCOLYSIS → 10 STEPS → 3 PHASES (HOW?)

GLUCOSE

IRREVERSIBLE RXN / PHOSPHORYLATION RXN — ATP, Mg^{++} → GLUCOKINASE / HEXOKINASE (*) → ADP

GLUCOSE-6-PHOSPHATE

ISOMERIZATION RXN ↔ PHOSPHO HEXOSE ISOMERASE

FRUCTOSE-6-PHOSPHATE

PHOSPHORYLATION RXN / IRREVERSIBLE RXN — ATP → PHOSPHO FRUCTO KINASE (PFK) (*) → ADP

FRUCTOSE-1,6-BIS PHOSPHATE

PHASE-II SPLITTING PHASE

LYASE — ALDOLASE-A

GLYCERALDEHYDE-3-PHOSPHATE ↔ DIHYDROXY ACETONE PHOSPHATE (PHOSPHO TRIOSE ISOMERASE)

OXIDATION & PHOSPHORYLATION RXN. — NAD^+ (⊖ ARSENITE; IODOACETATE) → GLYCERALDEHYDE-3-PO4 DEHYDROGENASE → $NADH+H^+$ — ETC undergoes → 3ATP (old) / 2.5 ATP (new)

1-3 BIS PHOSPHO GLYCERATE ← High Energy phosphate compd

SUBSTRATE LEVEL PHOSPHORYLATION RXN — ADP → PHOSPHO GLYCERATE KINASE → ATP

3-PHOSPHOGLYCERATE

MUTATION — PHOSPHOGLYCERATE MUTASE

2-PHOSPHO-GLYCERATE

DEHYDRATION → H_2O — ENOLASE (⊖ FLUORIDE)

PHOSPHOENOL PYRUVATE ← High Energy phosphate Compd.

SUBSTRATE LEVEL PHOSPHORYLATION RXN — ADP → PYRUVATE KINASE (PK) (Mg^{++}) (*) → ATP — IRREVERSIBLE RXN.

ENOL PYRUVATE → (Spontaneous rxn) → KETO PYRUVATE (3C-Keto acid)

PHASE-I ENERGY INVESTMENT PHASE

PHASE-III ENERGY GENERATING PHASE

Embden-Meyerhof pathway — Hexose monophosphate shunt

glucose

ATP / ADP — hexokinase

glucose-6-phosphate

GSH — Glutathione reductase — GSSG

$NADP^+$ — NADPH — G6PD — 6-phosphogluconate

glucose phosphate isomerase

fructose-6-phosphate

ATP / ADP — phosphofructokinase

fructose-1, 6-diphosphate

aldolase

glyceraldehyde-3-phosphate

$HbFe^{2+}$ / $HbFe^{3+}$ — NAD^+ / NADH — glyceraldehyde 3-phosphate dehydrogenase

1,3-bisphosphoglycerate — 2,3-bisphosphoglycerate mutase → 2,3-bisphosphoglycerate

ADP / ATP — phosphoglycerate kinase

3-phosphoglycerate ← 2,3-bisphosphoglycerate phosphatase

3-phosphoglycerate mutase

2-phosphoglycerate

enolase

phosphoenolpyruvate

ADP / ATP — pyruvate kinase

pyruvate

NADH / NAD^+ — lactate dehydrogenase

lactate

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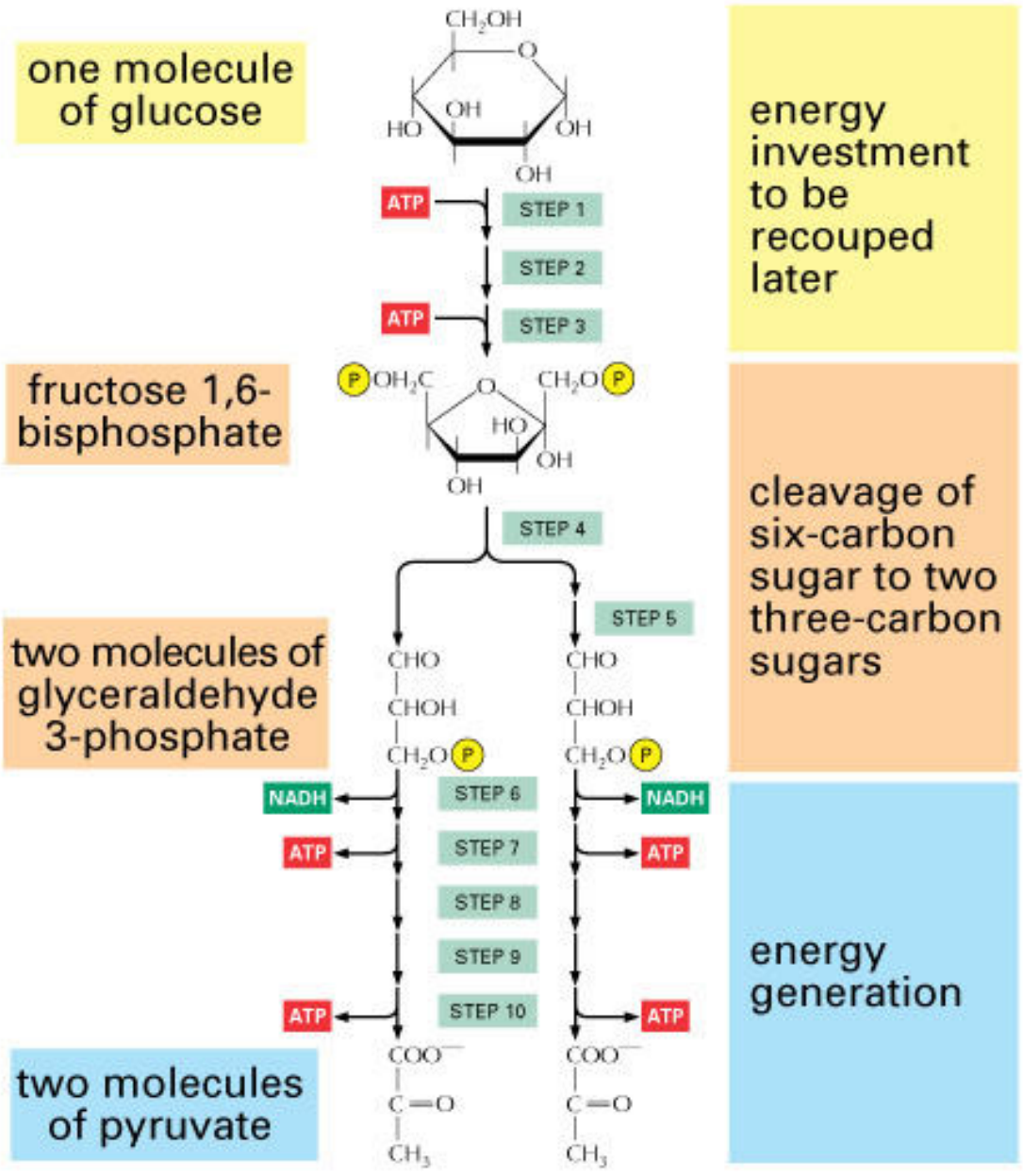
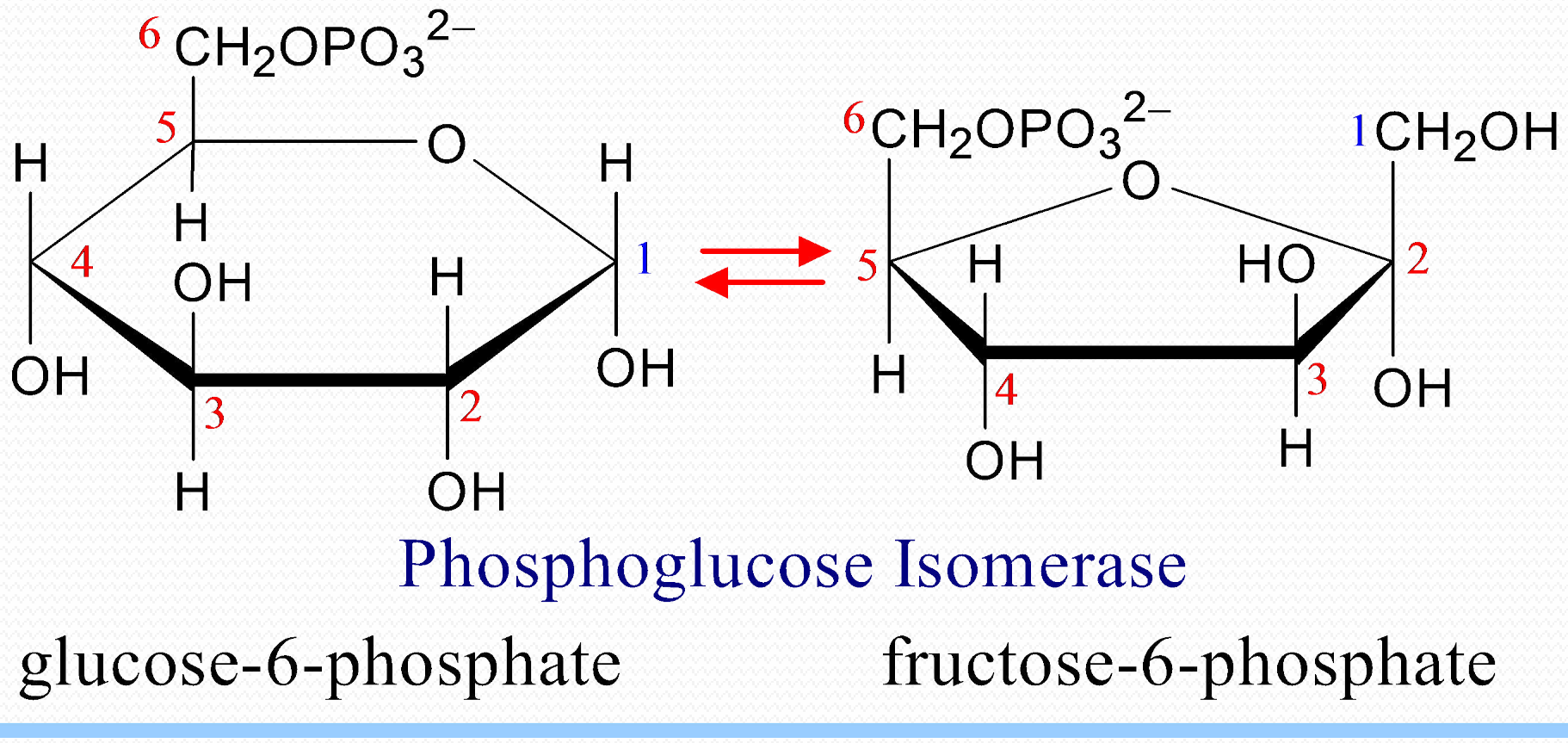


Figure 13-3 Essential Cell Biology, 2/e. (© 2004 Garland Science)



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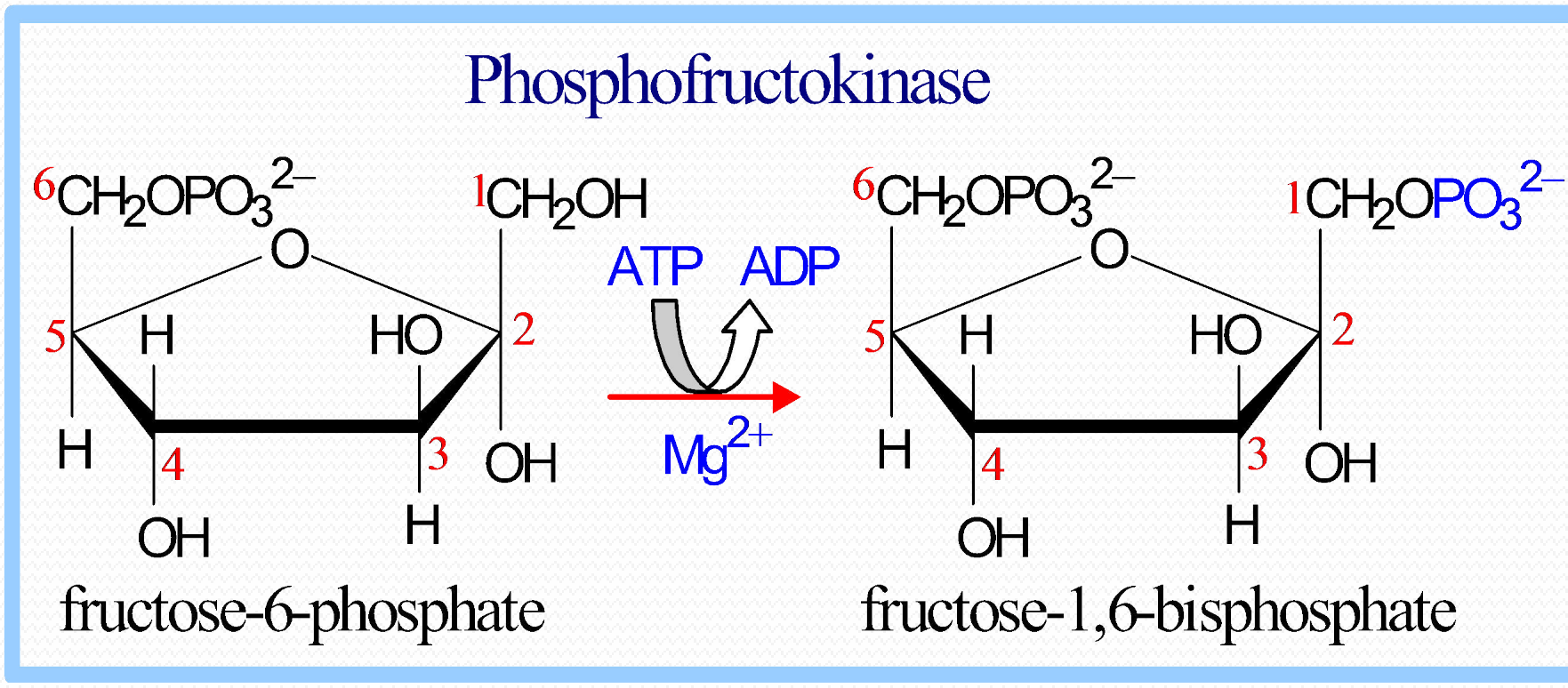
- Enzyme **Kinases**
- **Involves ATP**
- **Require Mg $^{++}$ ions** as cofactors.



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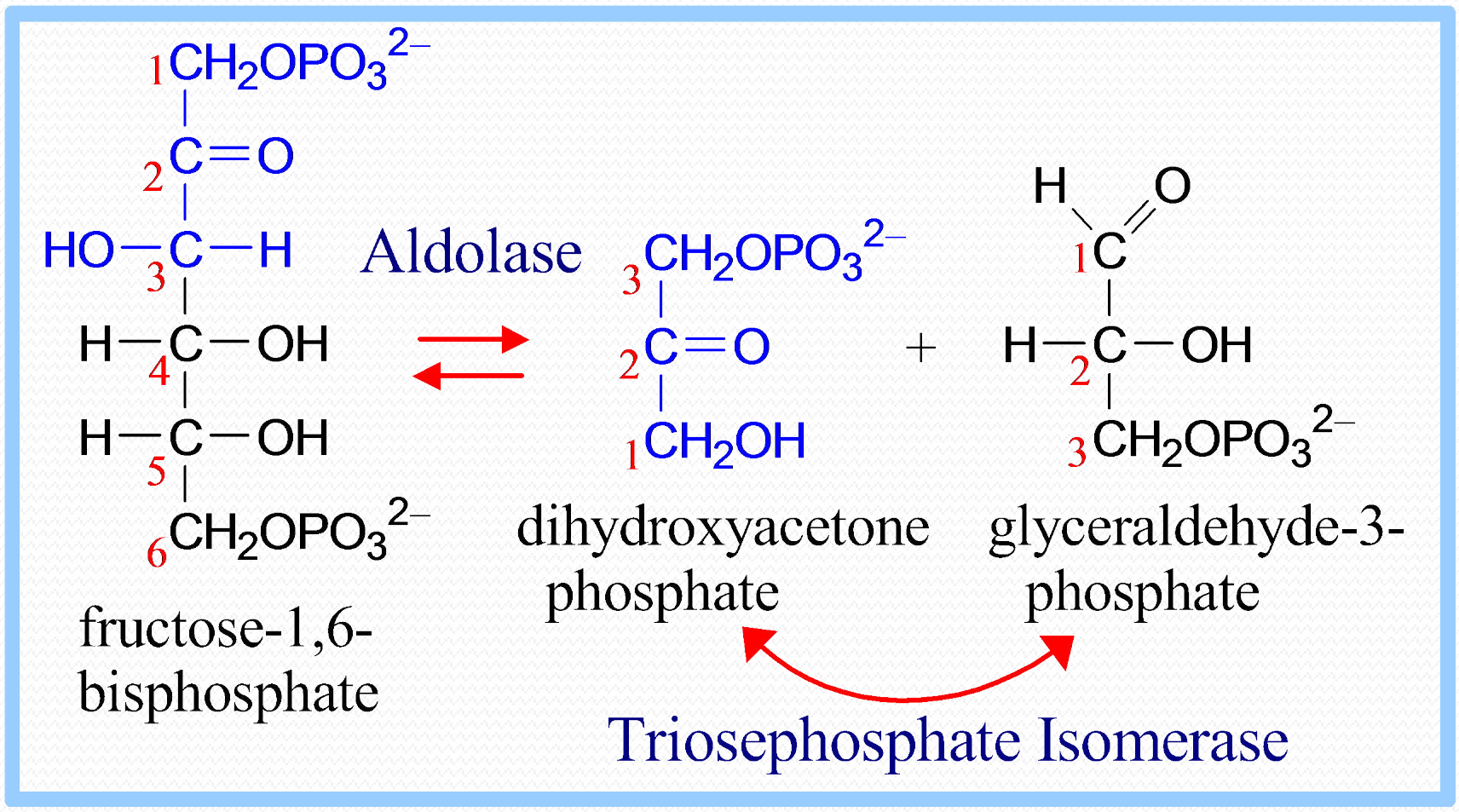

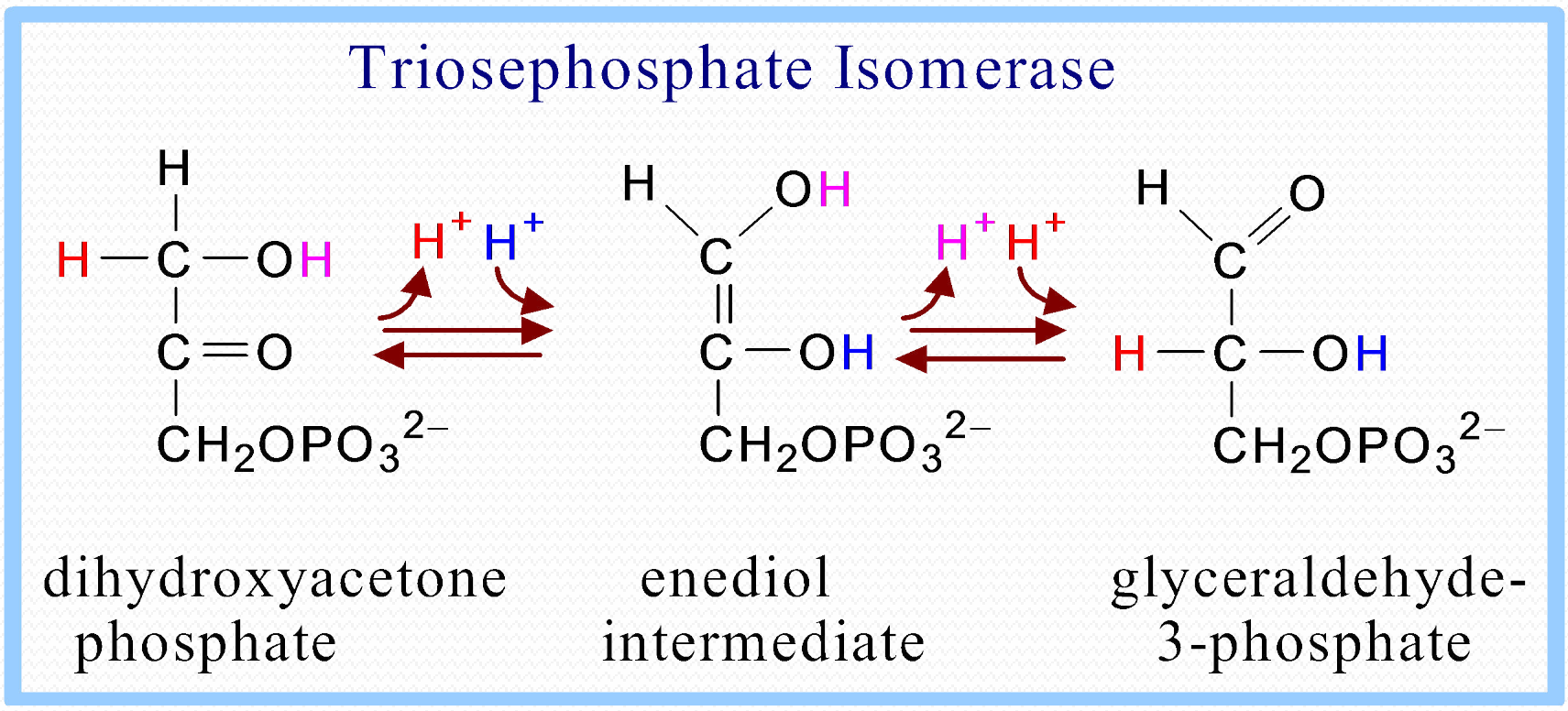

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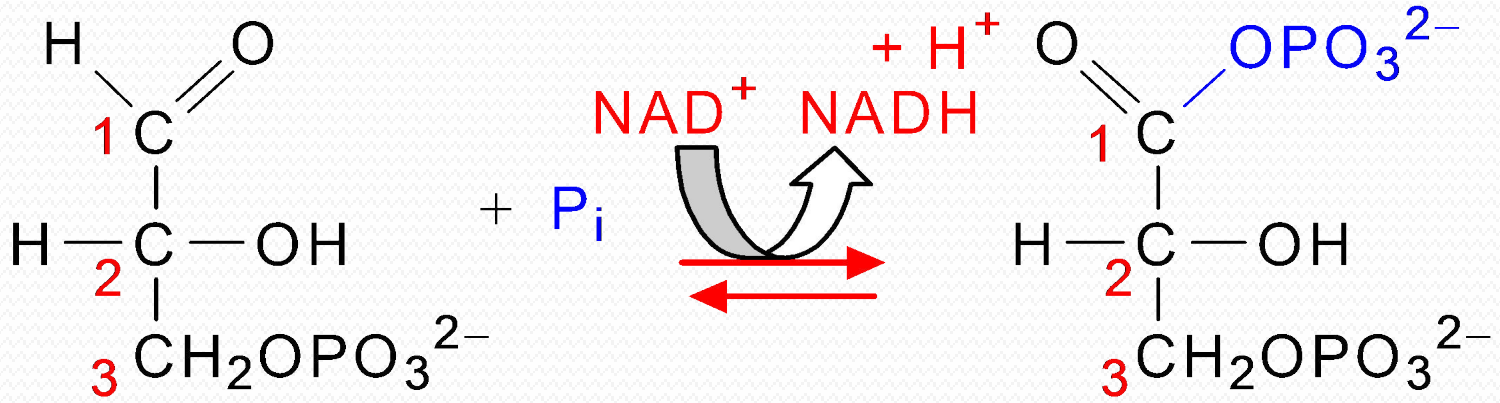
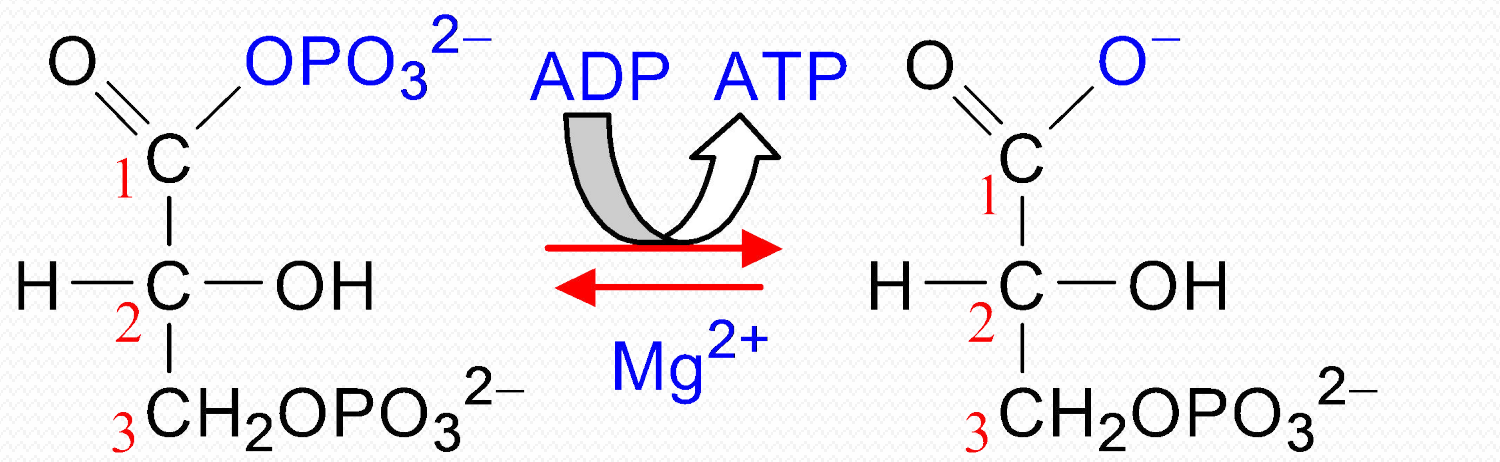
Glyceraldehyde-3-phosphate Dehydrogenase



Phosphoglycerate Kinase



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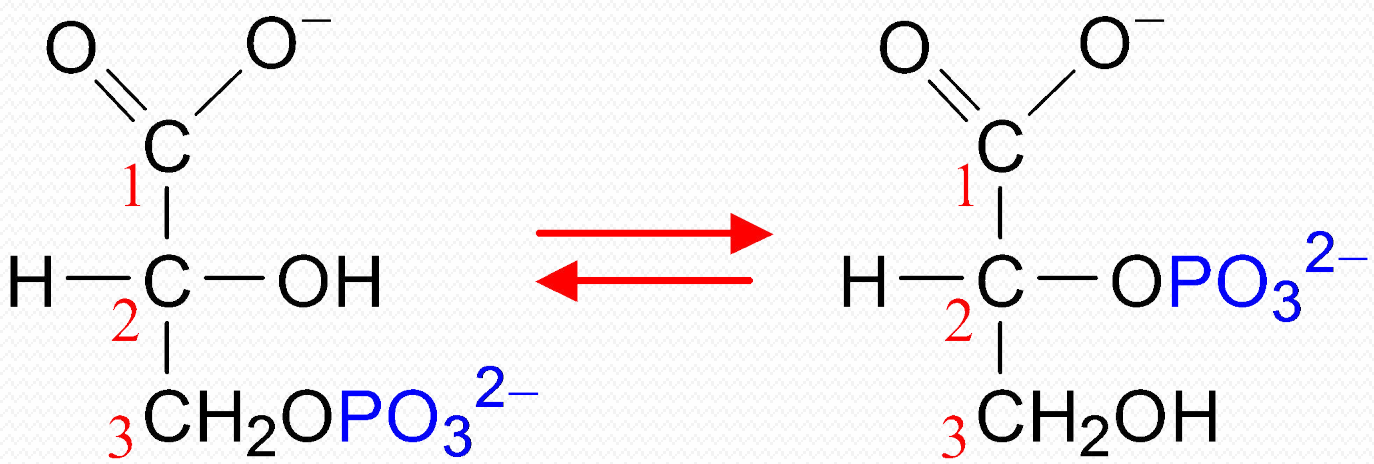
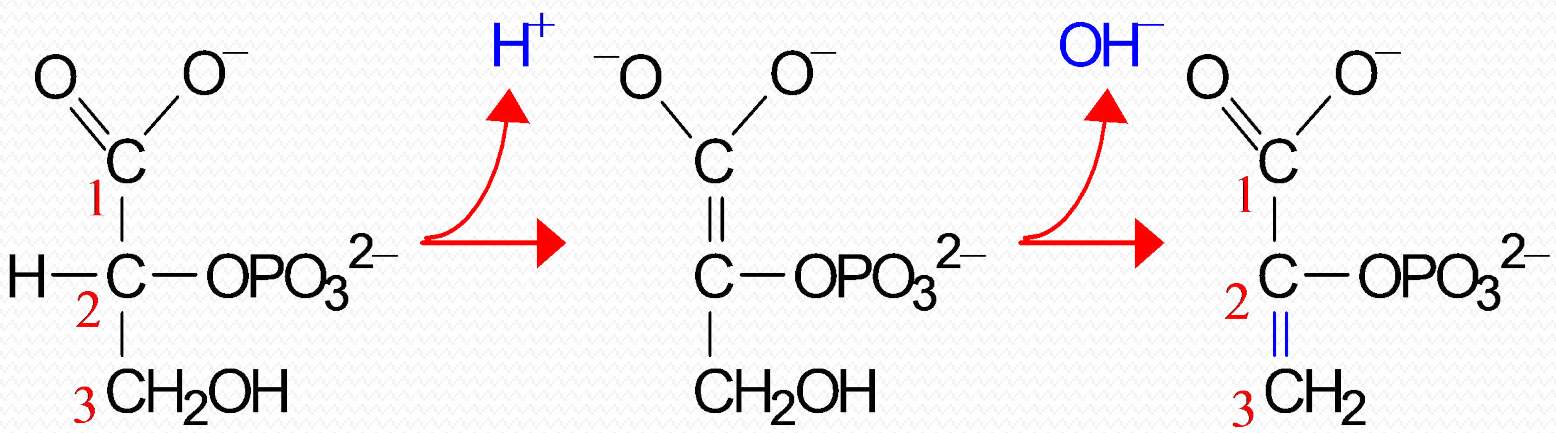
Phosphoglycerate Mutase



Enolase



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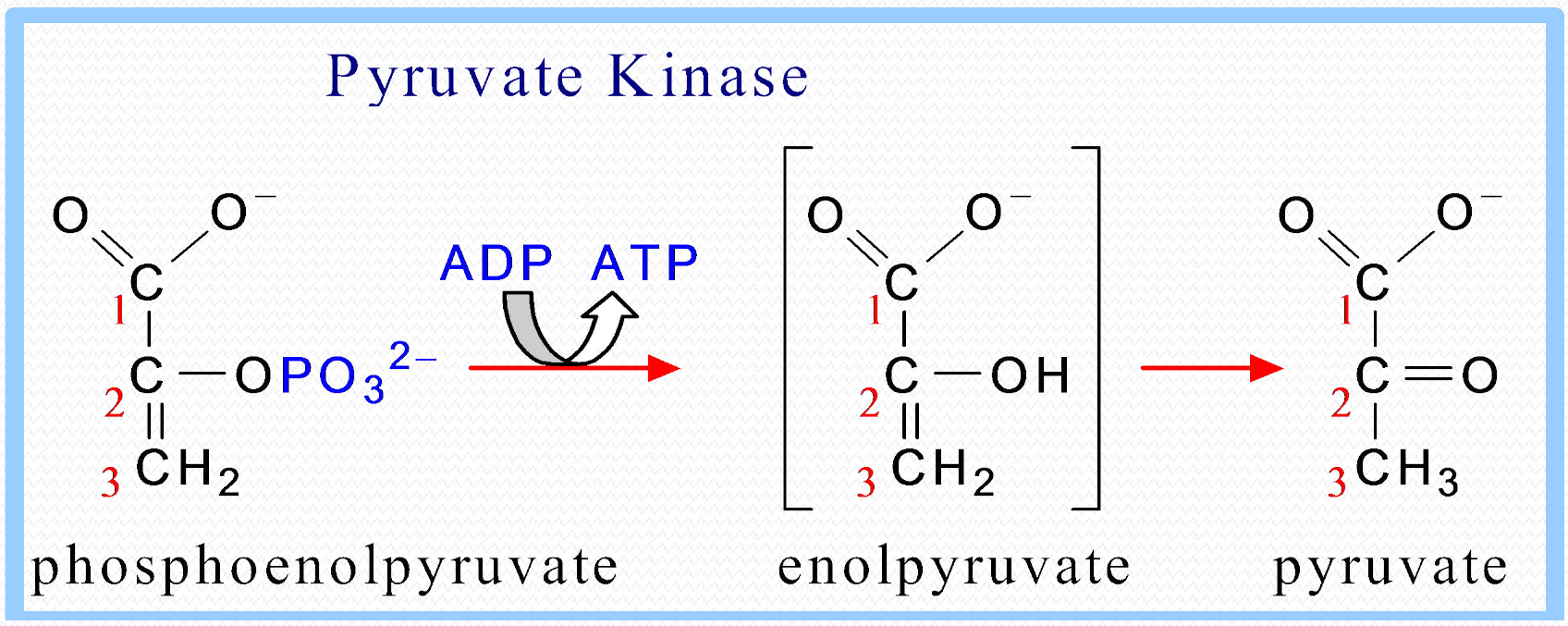

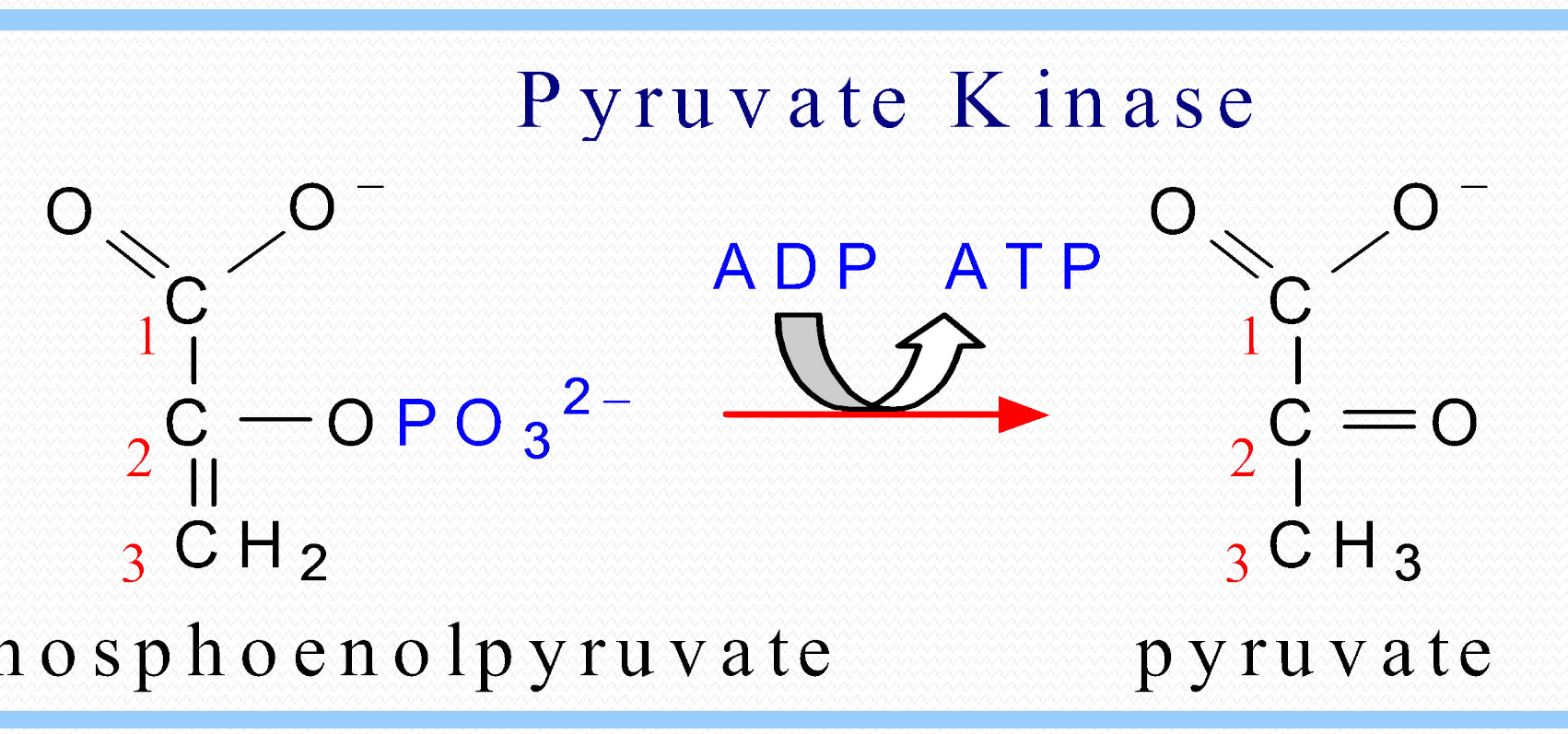

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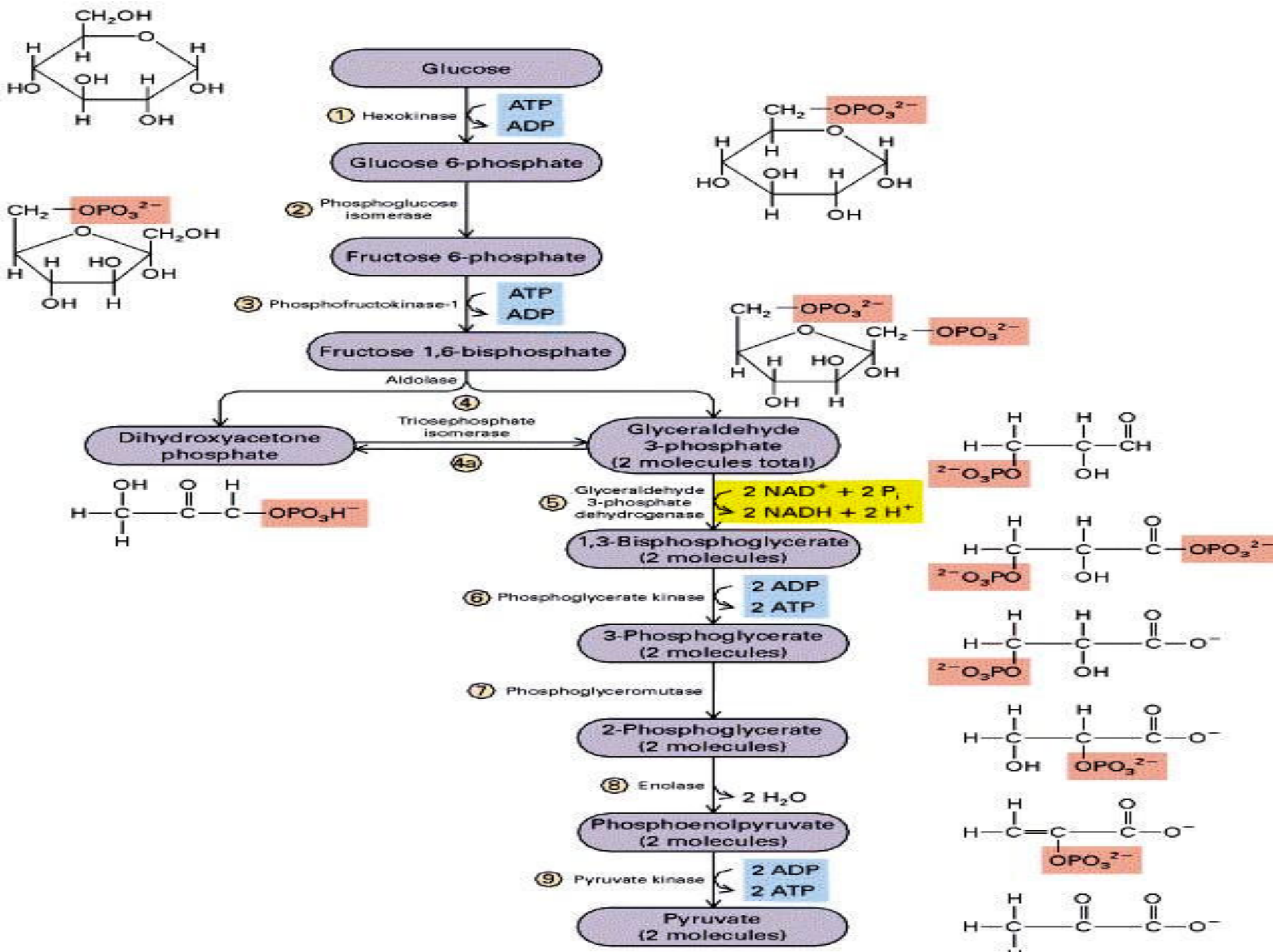

1. Phosphorylation Reaction
2. Isomerization Reaction
3. Phosphorylation Reaction
4. Lyase- Splitting Reaction

4 a. Isomerization Reaction.

5. Oxidation and Phosphorylation Reaction
6. Substrate Level Phosphorylation Reaction
7. Mutase Reaction
8. Dehydration Reaction
9. Substrate Level Phosphorylation Reaction

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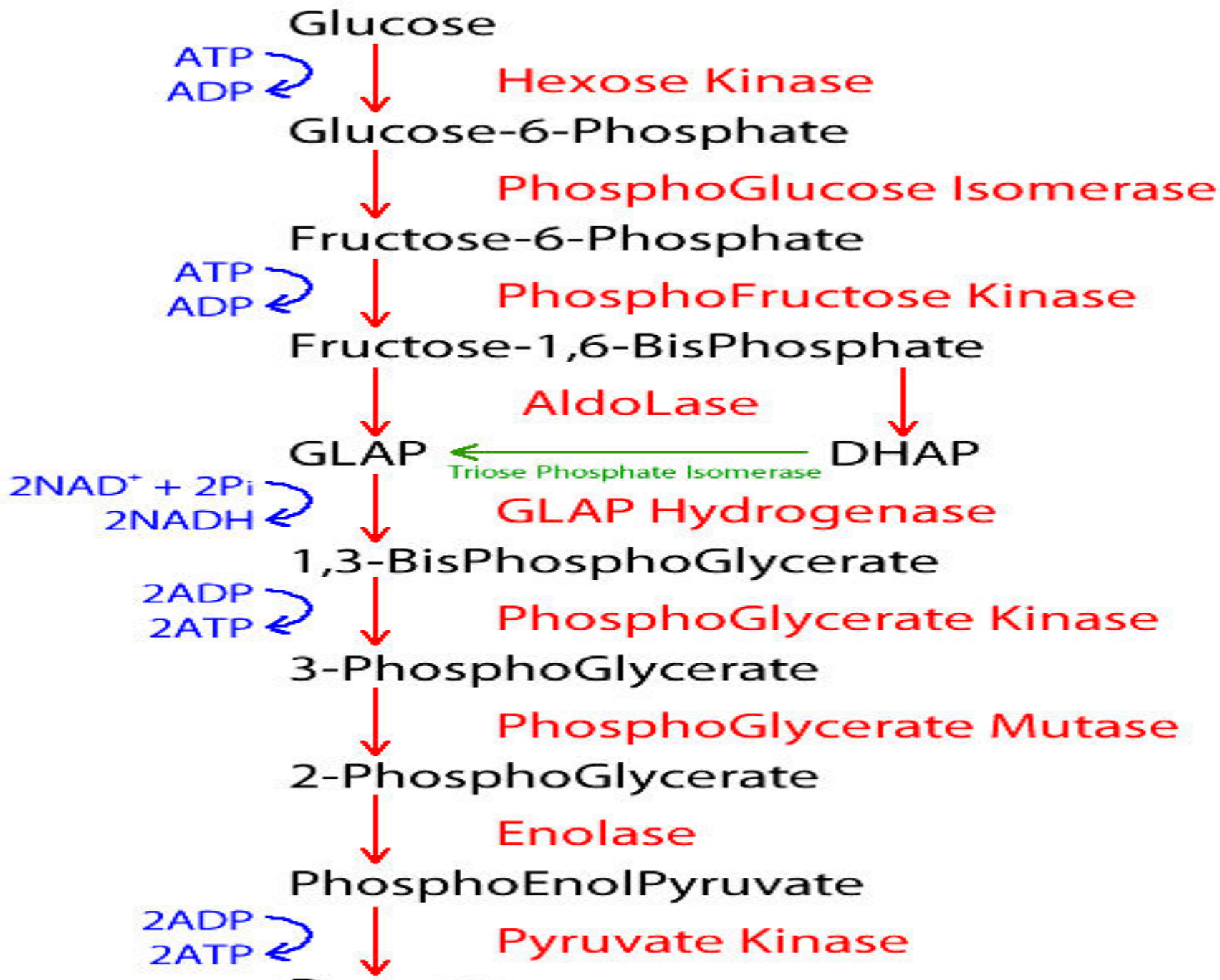

- **High Energy Compounds of Glycolysis:**
  - 1,3 Bis Phospho Glycerate.
  - Phospho Enol Pyruvate.

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- These high energy compounds have "high energy" bonds (~P) in their structures.
- Cleavage of these high energy bonds releases high energy .
- Which is used for phosphorylation of ADP + pi and generation of ATP at reaction/substrate level.

- Thus a high energy compound in a catabolic pathway is followed by a substrate level Phosphorylation reaction.

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- **Substrate Level Phosphorylation Reaction**
- Is a mode of generation of ATP at substrate level after the cleavage of high energy bond present in a high energy substrate.

- Glycolysis has **2 Substrate level phosphorylation reactions.**
- This mode of **generation of ATP** at reaction level is a **quick/immediate mode.**

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- 2Substrate Level Phosphorylating Enzymes of Glycolysis :
  - **Phospho Glycerate Kinase**
  - **Pyruvate Kinase**

- Glycolysis has
  - 3 irreversible reactions(1,3 and 9)
  - (1 oxidation reaction)-2NADH+H^+
  - 2 high energy compounds.
  - 2 substrate level phosphorylation reactions. (4ATPs)

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- **3 Irreversible Enzymes of Glycolysis**

  - **Glucokinase (GK)**
  - **Phospho Fructo Kinase (PFK)**
  - **Pyruvate Kinase (PK)**

Byproducts/ Energetics Of Glycolysis

- Reduced Coenzymes 2($NADH+H^+$) ⟶ 5ATP

  (1 $NADH + H^+$ $\xrightarrow{E.T.C}$ 2.5 ATP)

- 2 ATP's each from two substrate level phosphorylation rxns.(4 ATP's).

- **9 ATP's – 2 ATP's = 7 ATP's Net gain.**

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Enzyme Rxn Of Glycolysis	Number of ATP Utilized/Generated	
	Aerobic Condition	**Anaerobic Condition**
Glucokinase/Hexokinase	- 1 ATP	- 1 ATP
Phosphofructokinase(PFK)	- 1 ATP	- 1ATP
Glyceraldehyde-3-PO4 Dehydrogenase.	2(NADH+H+ enter ETC= +5 ATP)	2(NADH+H+ do not enter ETC= 0ATP)
Phosphoglycerate Kinase	+ 2ATP	+ 2 ATP
Pyruvate Kinase	+ 2ATP	+ 2 ATP
	Net + 7ATP's.	**Net + 2 ATP's.**

- 1 Glucose with **Aerobic Glycolysis** **7 ATP's.**
- 1 Glucose with **Anaerobic Glycolysis**

2 ATP's.

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- Intermediates and end products of Glycolysis serve as a **precursors** for biosynthesis :
  - **Fatty acid**
  - **Cholesterol**
  - **Amino acid**

Regulation Of Glycolysis

- Hormones regulating Glycolysis:
- **INSULIN**- Stimulates Glycolysis (Well fed Condition)
- **GLUCAGON** – Inhibist Glycolysis (Emergency Condition)

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- **Regulatory / Key Enzymes of Glycolysis :**

- **3 Irreversible** step catalyzing **Enzymes:**
  - **Glucokinase/Hexokinase**
  - **Phospho Fructo Kinase (PFK1)** (IMP)
  - **Pyruvate Kinase (PK)**

- Insulin and Glucagon stimulate and inhibit Key/Regulatory enzymes of Glycolysis respectively.

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Allosteric Activators of PFK

- AMP
- Fructose-2,6 Bis Phosphate (Produced by PFK2 activity)
- NAD^+
- Pi (Inorganic Phosphorous)

Allosteric Inhibitors Of PFK

- ATP
- Citrate
- NADH+ H^+
- H^+ ions (Low pH /Acidosis)

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Feed Forward Regulation

- Pyruvate Kinase is activated by Fructose-1,6 bisphosphate formed by PFK1 activity.
- This stimulates Glycolysis actively.

Inhibitors of Glycolysis

- **Fluoride** Inhibits Enzyme Enolase of Glycolysis.
- **Arsenite ,Iodoacetate** Inhibits Glyceraldehyde-3-PO4 Dehydrogenase.

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Significance Of Glycolysis:

- Glycolysis is an unique pathway operated in cytosol of each and every cell to generate chemical form of energy
- 7 ATP (Aerobic Condition)
- 2 ATP (Anaerobic condition).

- In Aerobic conditions Glycolysis provides energy (ATP) analogous to
  - **Cheque**

    (NADH+H^+ enters **Oxidative phosphorylation** /ETC) and
  - **Cash**

    (Substrate level Phosphorylation).

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- Intermediates of Glycolysis may serve as precursor for non essential amino acids.

- **Pyruvate** ⟷ (**Transaminase**) **Alanine**

Fates Of Pyruvate In Aerobic and Anaerobic Conditions

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- Pyruvate (3C) keto acid is an end product of Glycolysis.

Fate Of Pyruvate In Aerobic condition:

- Pyruvate is oxidatively decarboxylated to **Acetyl-CoA** (2C) by the activity of **Pyruvate Dehydrogenase (PDH) complex.**
- A reducing equivalent $NADH+H^+$ is released at this reaction.

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Fate of Pyruvate in Anaerobic Condition:

- **Pyruvate is reduced to Lactate** by the activity of **Lactate Dehydrogenase (LDH) .**
- **NADH +H^+** generated in Glycolysis and not entering in ETC, in anaerobic condition is **utilized in the reduction of Pyruvate to Lactate.**

- Lactate is said to be the dead end Of the Glycolysis.

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Significance of Pyruvate Reduction To Lactate

- **Utilizes** the **Glycolytic** generated **NADH+H.**
- Does **not accumulate** the **NADH+H$^+$** to **inhibit PFK** of Glycolysis.
- **Avoid interruption** of **Glycolysis** and continue it in **anaerobic condition**.

- **Physiologically during strenuous exercise.**
  - Muscle lacks enough oxygen.
  - Anaerobic Glycolysis forms major source of energy to exercising muscles.

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- **Lactate** serves as a **fuel** source for **cardiac muscle** as well as **brain neurons** .
- **Astrocytes**, which surround and protect neurons in the brain, **ferment Glucose** to **Lactate** and release it.
- **Lactate** taken up by adjacent neurons is converted to Pyruvate that is oxidized via Krebs Cycle.

- Lactic acidosis is noted when there is collapse in circulatory system.

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- Tissues in hypoxic condition produces Lactate.
- For ex in Ischemia, MI, Embolism , Shock.
- Lactate causes fatigueness of muscles.

- Lacticacidosis is a condition of **Metabolic Acidosis** where the blood pH is lowered.

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Lacticacidosis detects Oxygen Deficiency

- Oxygen debt leads to interrupt Glycolysis.
- Anaerobic Glycolysis.
- Low/No production of ATP.
- Lacticacidosis.

- **Oxygen debt** is related to patients morbidity or mortality.
- **Measuring Lactate levels** of blood allows rapid and **early detection of oxygen debt.**
- **Correction** of early **Oxygen debt** helps in **recovering the patients life**.

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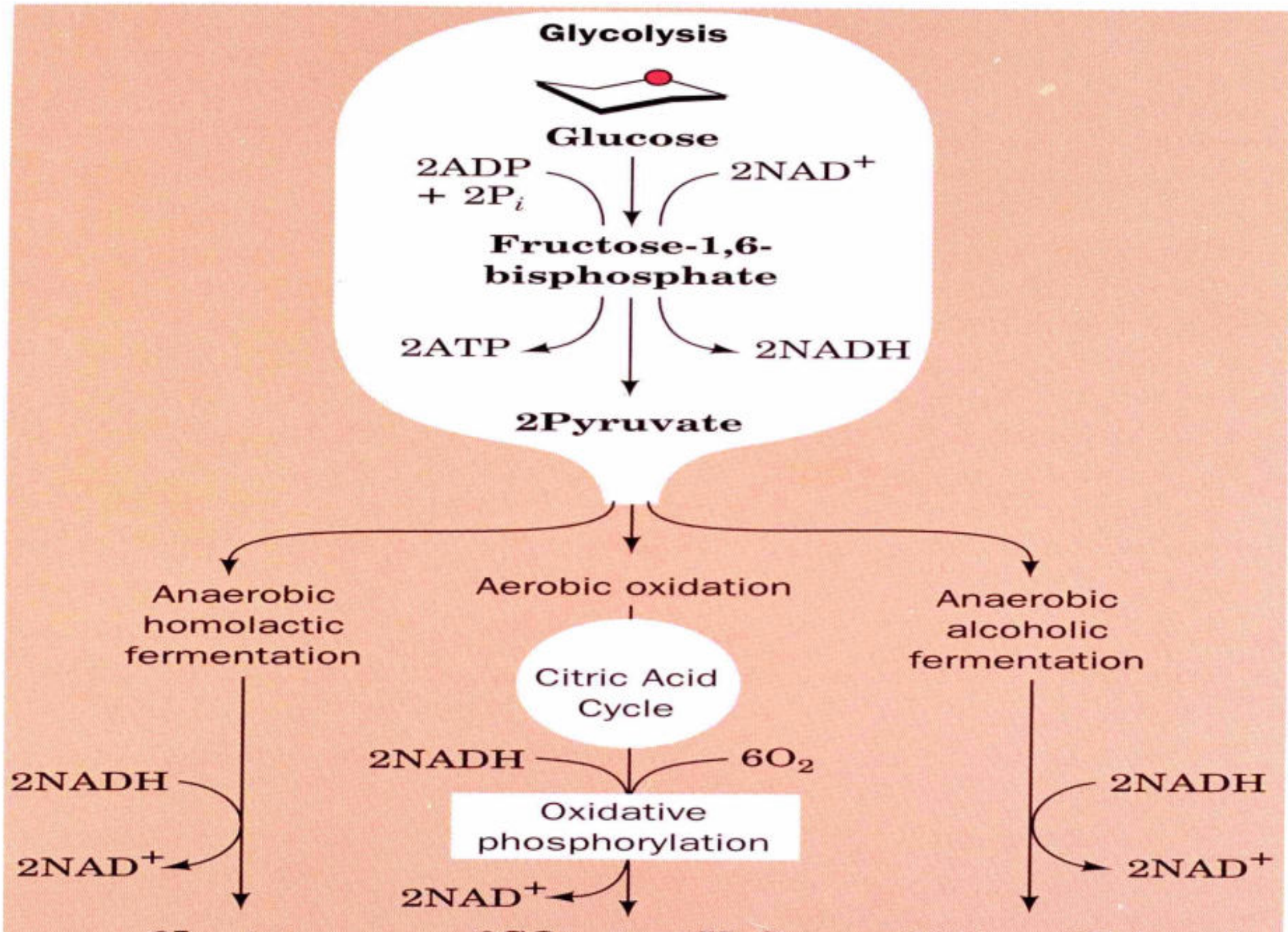

Inborn Error Of Glycolysis

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- **Pyruvate Kinase deficiency** in Erythrocytes leads to **Hemolytic Anemia** (Nonspherocytic Hemolytic Anemia).

- PK deficiency interrupts Glycolysis.
- Interrupted Glycolysis affects the RBC's and leads to its lysis.

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Glycolysis in Cancer

- In fast growing cancer cells **Glycolysis** proceeds at a **high rate** forming large amounts of **Pyruvate.**
- This Pyruvate is then reduced to **Lactate.**
- This produces relatively **acidic local environment in tumor.**

Rapaport Leubering Cycle

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Synonyms

- 2,3 Bis Phospho Glycerate Cycle /(**2,3BPG Cycle**)
- Shunt Glycolysis In Erythrocytes

Location/ Occurrence :

- 15-25% of Glucose enter via **2,3 BPG cycle** in the cytosol of mature Erythrocytes.

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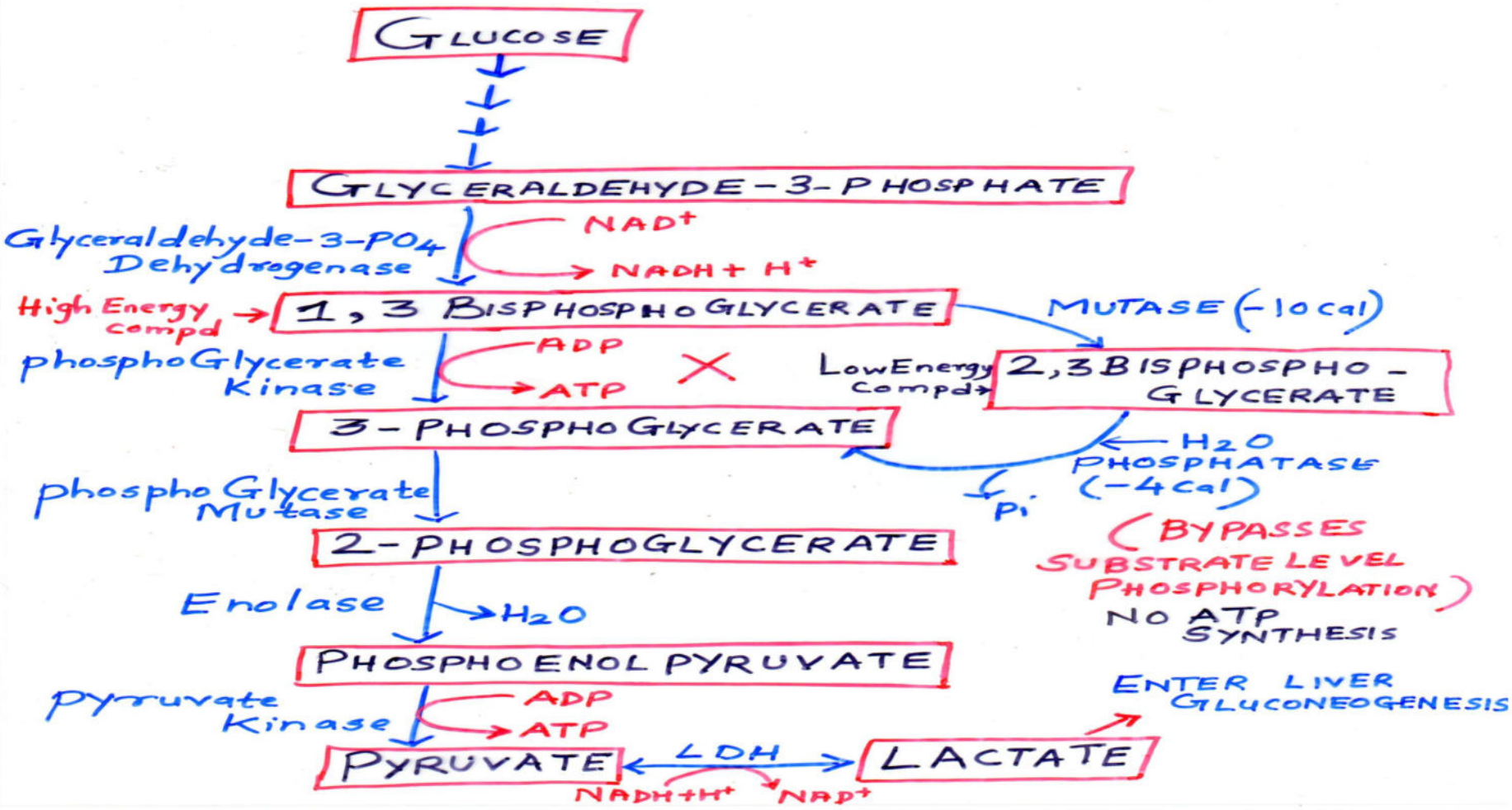
RAPAPORT LEUBERING CYCLE

- GLYCOLYSIS IN ERYTHROCYTES
- SHUNT PATHWAY OF GLYCOLYSIS
- 2,3 BPG cycle.

} SYNONYMS

15-25% OF GLUCOSE ENTER VIA 2,3 BPG CYCLE IN CYTOSOL OF MATURE ERYTHROCYTES.

SUPPLEMENTARY PATHWAY TO GLYCOLYSIS.



- End Product of Glycolysis in Erythrocytes is Lactate.

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- Mature **Erythrocytes has no Mitochondria.**
- Pyruvate obtained from Glycolysis could not be further oxidized in Erythrocytes.
- **Pyruvate is reduced to Lactate by LDH in Erythrocytes.**

Salient Features Of Rapaport Leubering Cycle

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- In Rapaport Leubering cycle
- A high energy compound **1,3 Bis Phospho Glycerate** is transformed to a low energy compound **2,3 Bis Phospho Glycerate.**

- 2,3 Bis Phospho Glycerate is dephosphorylated to 3 Phospho Glycerate and utilized.
- This **bypasses** the **substrate level phosphorylation** of Glycolysis

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- Rapaport Leubering Cycle **generates no ATP**.
- It dissipiates/waste energy as heat.
- It **does not accumulate ATP**

Energetics Of Glycolysis In RBC's

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Erythrocyte Glycolysis via 1,3 BPG

2 ATP

Erythrocyte Glycolysis via 2,3 BPG

0 ATP

Significance Of Rapaport Leubering Cycle

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- **Rapaport Leubering Cycle**
  - Maintains Glycolysis in continuous and uninterrupted in RBC's.
  - This in turn maintains cellular integrity of RBC's.
  - **Prevent hemolysis**.

- **2,3BPG of Rapaport Leubering cycle in RBC's:**
  - Has high affinity for Hemoglobin.
  - **Helps in unloading of Oxygen by OxyHb at tissues**.

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- **2,3BPG Increases In**
  - Hypoxic conditions
  - High altitudes
  - Fetal tissue
  - Anemic Condition

Inborn Error Of Rapaport Leubering Cycle

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Hexokinase Deficiency	Pyruvate Kinase Deficiency
Decreases 2,3 BPG concentrations.	Increases 2,3 BPG concentrations.
Decreases Unloading of Oxygen at tissues.	Increases Unloading of Oxygen at tissues.

Pyruvate Metabolism
OR
Formation and Fates Of Pyruvate

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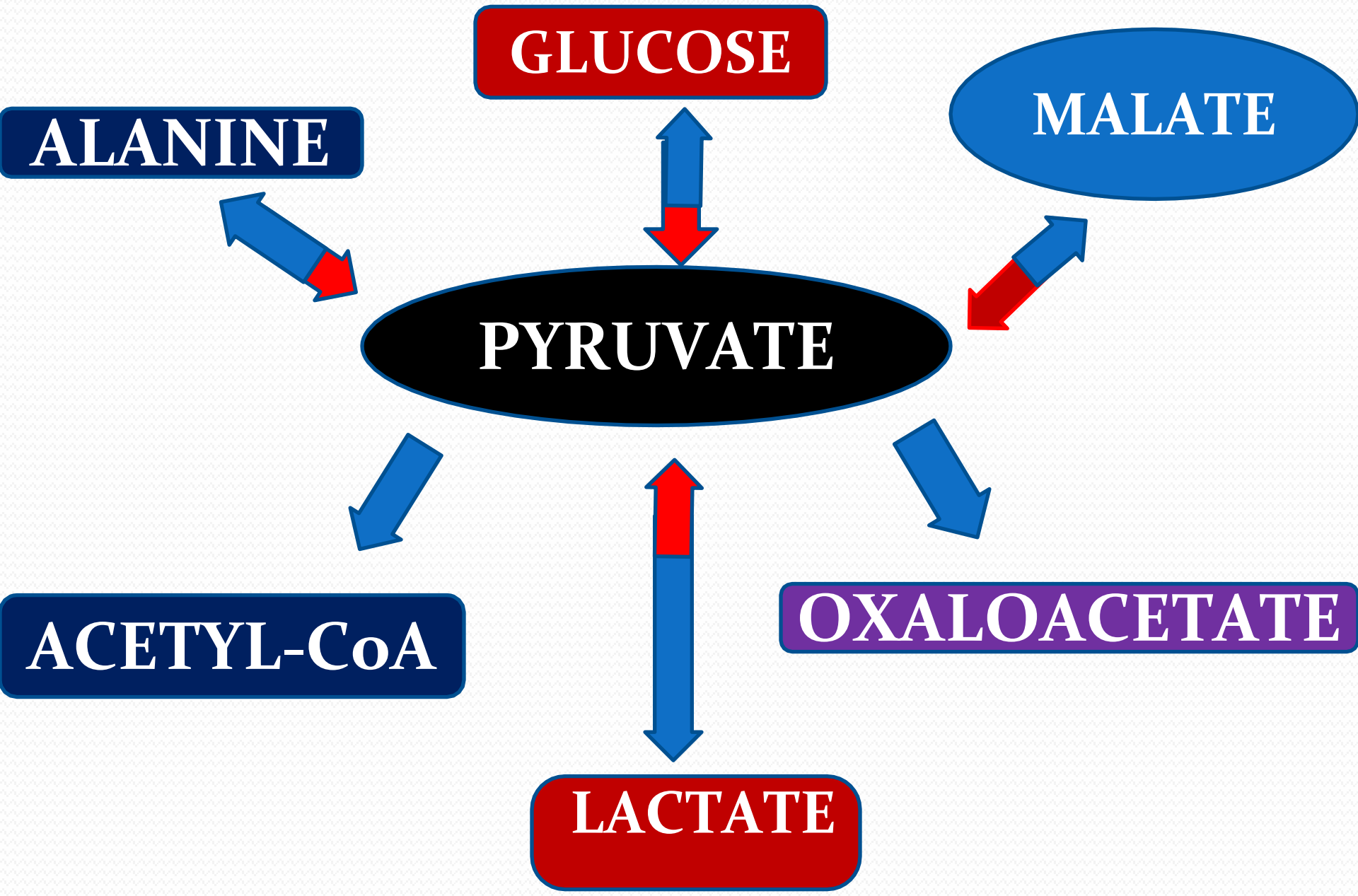

FATE AND FORMATION OF PYRUVATE / PYRUVATE METABOLISM

(24)

GLUCOSE (6C)

(Well fed Condition) Glycolysis

Gluconeogenesis (Emergency Condⁿ)

ALANINE ⇄ PYRUVATE (3C) ⇄ MALATE

ALT

Transamination Rxⁿ

Malic enzyme

Aerobic Condⁿ

Oxidative Decarboxylation Rxⁿ

PDH Complex

Irreversible Rxⁿ

CO_2

2C

ACETYL-COA

Anaerobic Condⁿ Reduced

LDH

LACTATE (3C)

Pyruvate Carboxylase

Biotin

CO_2

Carboxylⁿ Rxⁿ

Irreversible Rxⁿ

4C

OXALOACETATE

(Ketoacid)

PRECURSORS OF TCA cycle

UTILISED VIA TCA CYCLE

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- **PYRUVATE IS FORMED FROM**
- **Glucose (Glycolysis)**
- **Lactate (Oxidation-LDH)**
- **Malate (Malic enzyme)**
- **Alanine (Transamination-ALT)**

- **PVRUVATE IS CONVERTED TO**
- **Glucose (Gluconeogenesis)**
- **Lactate (Reduction-LDH)**
- **Malate (Malic enzyme)**
- **Alanine (Transamination-ALT)**
- **Acetyl-CoA (PDH Complex)**
- **Oxaloacetate (Carboxylation Rxn)**

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- Pyruvate Irreversibly forms
  - **Acetyl-CoA**
  - **Oxaloacetate**
- In Mitochondrial Matrix
- These are the **precursors of TCA cycle.**

Oxidative Decarboxylation Of Pyruvate To Acetyl-CoA By Pyruvate Dehydrogenase (PDH) Complex.

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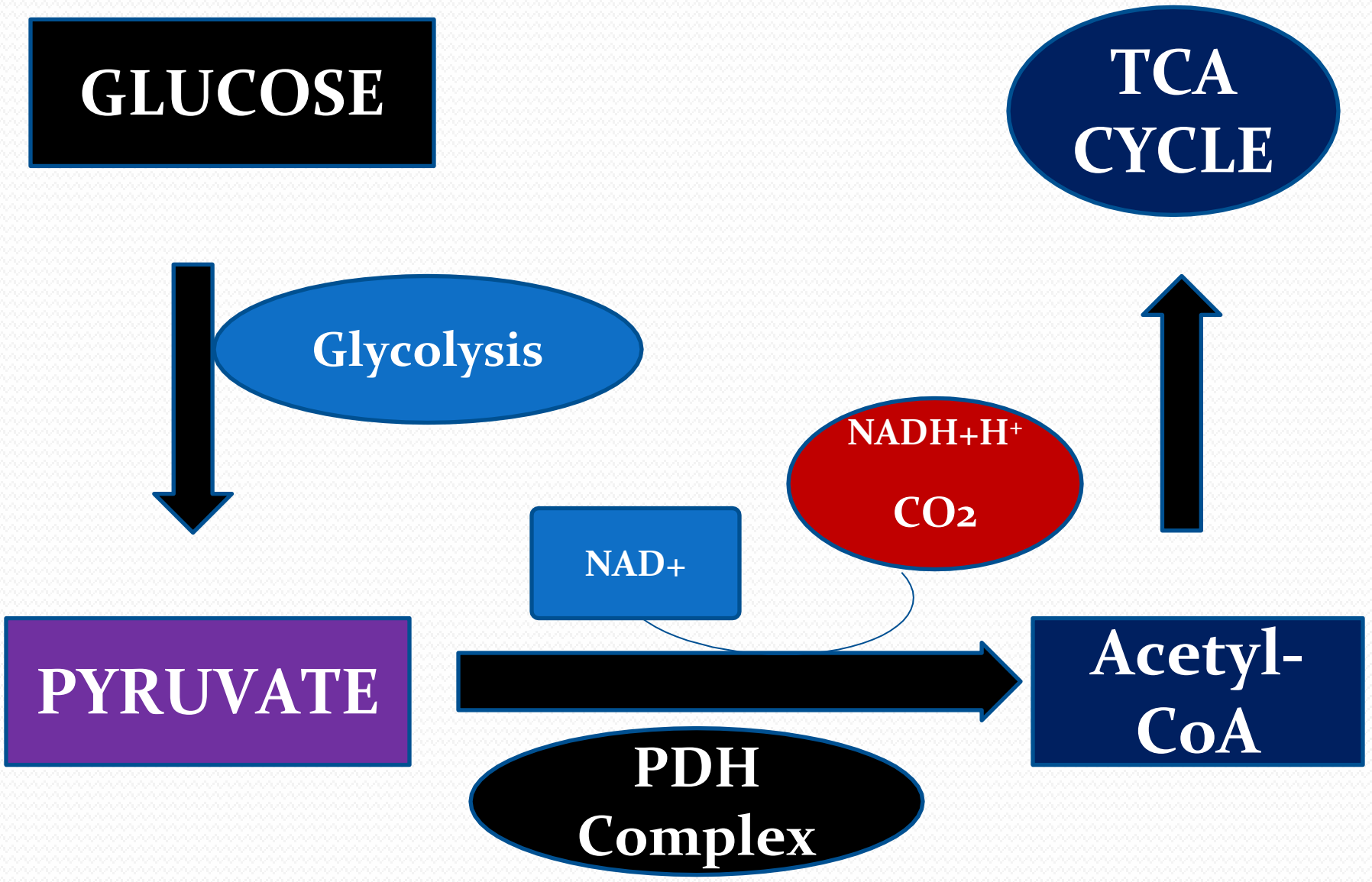

- Pyruvate is generated as an end product of Glycolysis in the cytoplasm.
- This is then transported into **Mitochondrial matrix**
- By a **Pyruvate transporter** located in the mitochondrial membrane.

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- Pyruvate, a 3 carbon keto acid
- Obtained from Glycolysis is oxidized (removal of Hydrogen) and decarboxylated (removal of CO_2)
- To form a 2 carbon, high energy compound **Acetyl-CoA** and
- Reducing equivalent NADH+ H^+.

- **Reducing equivalents NADH+H^+ released** at this step enter in E.T.C for it's reoxidation and generation of ATP's.
- Thus **this is an energy producing step**.

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- Oxidative Decarboxylation of Pyruvate to Acetyl-CoA
- Is biocatalyzed by **PDH complex(Multi Enzyme Complex).**

- Acetyl-CoA formed in PDH complex step, enters in TCA cycle for its complete oxidation.

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- Thus PDH complex reaction is a **connecting reaction** between Glycolysis and TCA cycle.

PDH Complex

- **Neuberg (1911)** discovered PDH complex.
- PDH Complex is a **Multi Enzyme complex.**
- PDH complex is composed of:
- **3 Enzymes and 5 Coenzymes.**

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- **Three Enzymes Of PDH Complex:**
  - **Pyruvate Dehydrogenase**
  - **Di Hydrolipoyl Dehydrogenase**
  - **Di Hydrolipoyl Transacetylase**

- **Five Coenzymes Of PDH Complex.**
  - **TPP (Derived from Vit B1)**
  - **FAD (Derived from Vit B2)**
  - **NAD^+ (Derived from Vit B3)**
  - **CoA-SH (Derived from Vit B5)**
  - **Lipoic acid/Lipoamide.**

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- **Associated Enzymes and Coenzymes Of PDH Complex:**

- **Pyruvate Dehydrogenase (E1)**
  (Coenzyme = TPP)

- **Dihydrolipoamide Acetyltransferase (E2)**
  (Coenzymes = Lipoamide, CoA)

- **Dihydrolipoamide Dehydrogenase (E3)**
  (Coenzymes = FAD, NAD^+)

Location Of PDH complex:

- PDH complex is located in Mitochondrial matrix.

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- Reaction biocatalyzed by PDH Complex is **completely** an **irreversible reaction.**

- **Due to irreversible nature of PDH complex reaction:**
  - Acetyl-coA obtained through β oxidation of Fatty acids cannot be converted to Pyruvate and used for Glucose production.
  - **Thus Fat is not converted to Carbohydrates in human body.**

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Working Of PDH Complex

- PDH Complex irreversibly biocatalyzes
- An **Oxidative Decarboxylation** of **Pyruvate** to **Acetyl-coA**
- At aerobic conditions in mitochondrial matrix.

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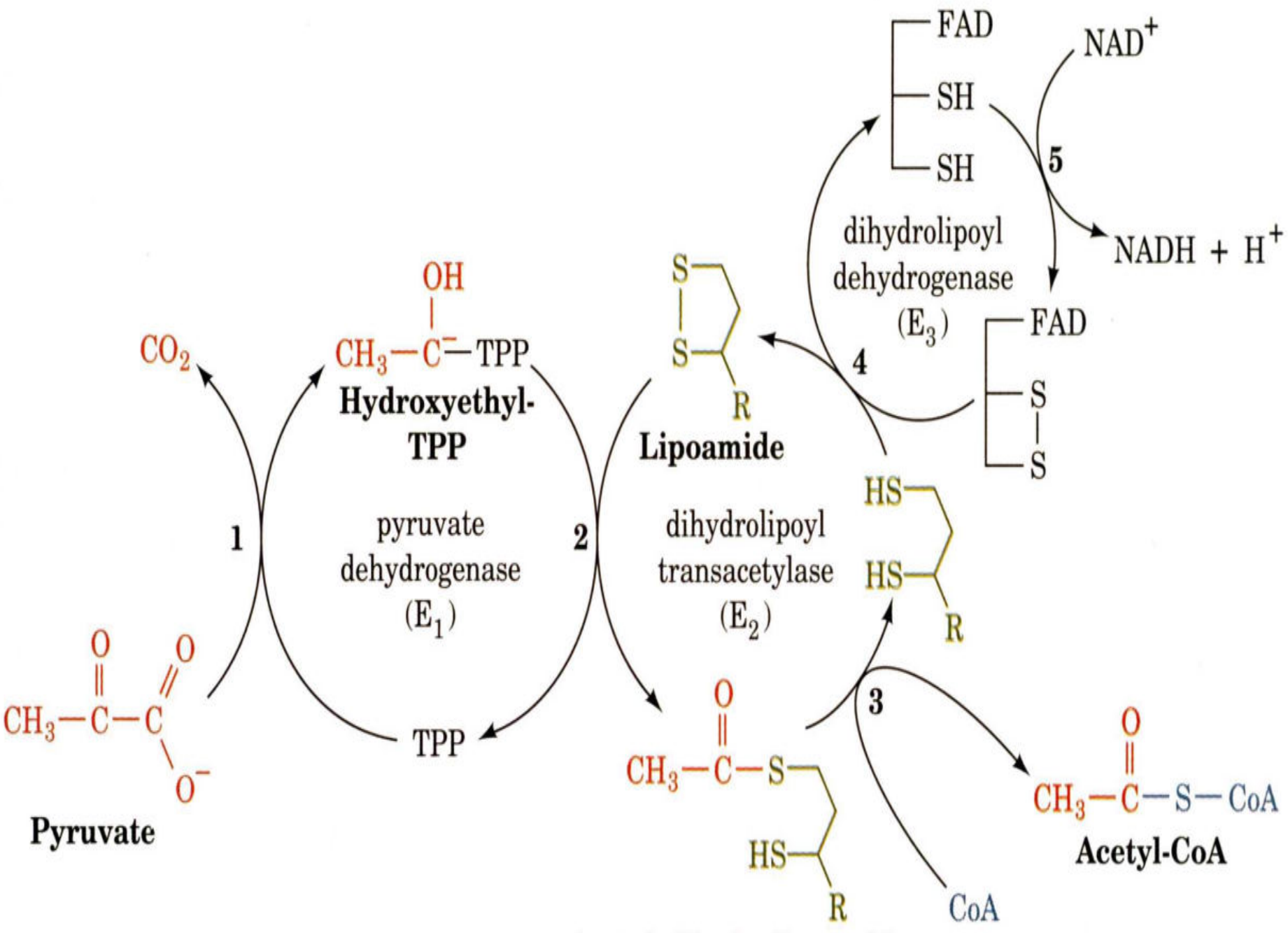
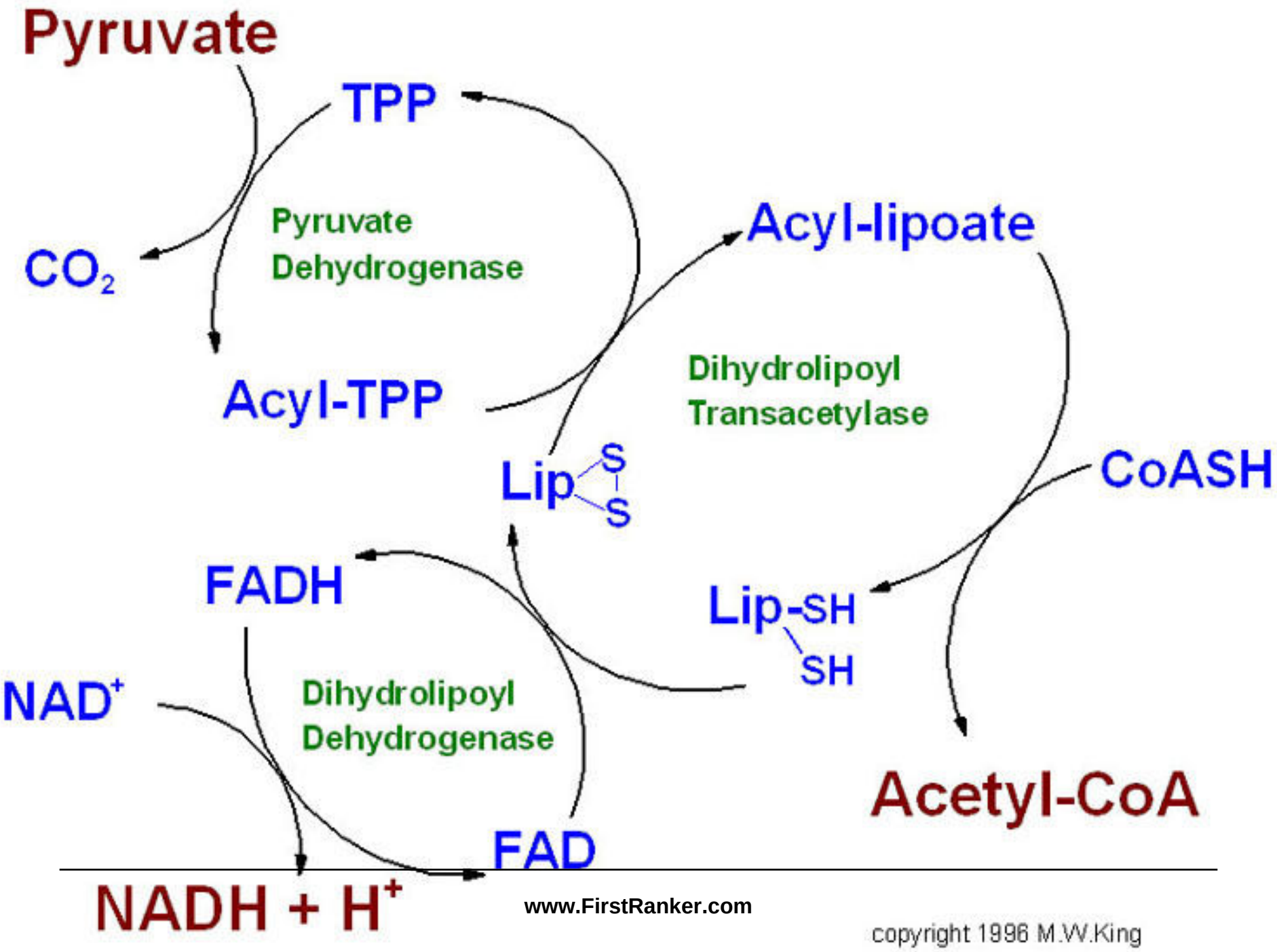


Acetyl-dihydrolipoamide



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Regulation Of PDH Complex

- PDH Complex is **stimulated by INSULIN.**

- PDH Complex is **inhibited by GLUCAGON.**

Activators Of PDH Complex.

- ADP
- NAD^+

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Inhibitors Of PDH Complex

- ATP
- NADH+ H^+
- Cyclic AMP
- Acetyl-CoA

Chemical Inhibitors Of PDH Complex

- Arsenic
- Mercuric Ions

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Deficiency Of PDH Complex And Its Consequences

- PDH Complex **deficiency is rare**
- **It blocks** the conversion of **Pyruvate to Acetyl-CoA**
- **Brings incomplete Oxidation Of Glucose**
- **Increases Pyruvate** concentration
- Increased **Pyruvate is reduced to Lactate**
- **Leads to Lactic acidosis**
- **Decreases** Acetyl –CoA, which Decreases **TCA cycle**
- **Decreases ATP level**
- **Low ATP levels affects cellular activities.**
- **Fatigue ,Weakness, Neurological Disorders.**

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TCA CYCLE

Synonyms OF TCA Cycle

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- Fate of Acetyl CoA
- Tri Carboxylic Acid Cycle (TCA Cycle)
- Citric Acid Cycle
- Krebs Cycle (Hans Kreb-1937)
- Amphibolic Pathway
- Common Metabolic Pathway
- Central Metabolic Pathway
- Final Oxidative Pathway

What Is TCA Cycle?

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- Common metabolite Acetyl-CoA
- Obtained from Glucose, Fatty acids and Amino acid metabolism
- Finally , commonly and completely oxidized via TCA cycle.

1 Acetyl-CoA +3NAD^+ + FAD + GDP + Pi

Over all TCA

2 CO_2+CoA + 3NADH +3H^++ 1$FADH_2$ + 1GTP

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- Acetyl-CoA a **central/common metabolite** is completely oxidized

- To liberate $2CO_2$, and reducing equivalents $3NADH+H^+$, 1 $FADH_2$ and 1GTP through TCA cycle.

10 ATPs generated on oxidation of 1 Acetyl CoA via TCA cycle

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Nature/Type Of Pathway

- **TCA is an Amphibolic Pathway.**
- It is connected to both Amphibolic and Catabolic Pathway.

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Condition In which Pathway Occurs

- TCA is purely carried out in an Aerobic condition.

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Location : Organ and Cellular Site

- TCA is carried out in **all cells which contain Mitochondria.**
- Cellular site for TCA is **Mitochondrial Matrix.**

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- TCA cycle des not operate in
- Mature Erythrocytes ,Cornea and Lens cells
- Since they are devoid of Mitochondria.

Reactions Steps OF TCA Cycle:

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- TCA cycle constitutes **10 steps.**

- Acteyl–CoA and Oxaloacetate(OAA) are **initators of TCA cycle.**

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Sources Of Acetyl CoA

- **Glucose Metabolism**
  (PDH Complex Reaction)
- **Fatty Acid Metabolism**
  (β Oxidation of Fatty acids)
- **Amino Acid Metabolism**

Sources Of Oxaloacetate(OAA)

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- **OAA** used in TCA is **majorly** obtained from **Glucose metabolism**

  (In a well fed condition)
- **OAA** comes **minorly** from **Amino acid** (ASP)

  [In an emergency condition].

- **Oxaloacetate** is a 4 Carbon Keto acid obtained **from Pyruvate** a 3 Carbon Keto acid on **Carboxylation reaction.**

- Pyruvate is carboxylated to Oxaloactate by an **irreversible** activity of an **enzyme Pyruvate Carboxylase**, ATP and Coenzyme Biotin.

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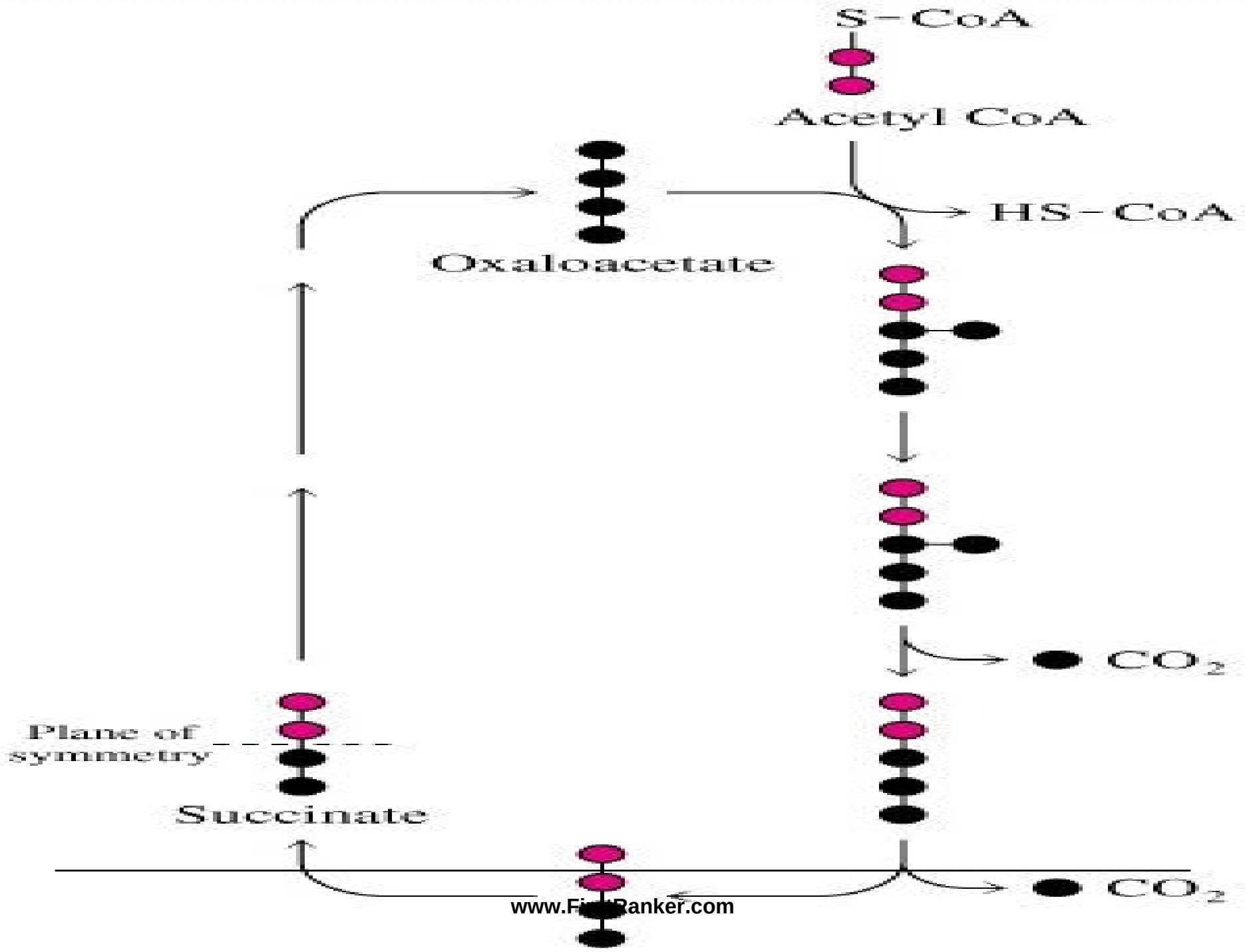
- In TCA cycle **Oxaloacetate used** up in first step is **regenerated** in last step.
- 2 carbon units lost in TCA cycle in the form of CO_2 is from OAA .
- The regenerated OAA gets 2 Carbon atoms from entered 2 carbon Acetyl-CoA.



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TCA Is An Amphibolic Pathway

Catabolic Role Of TCA Cycle

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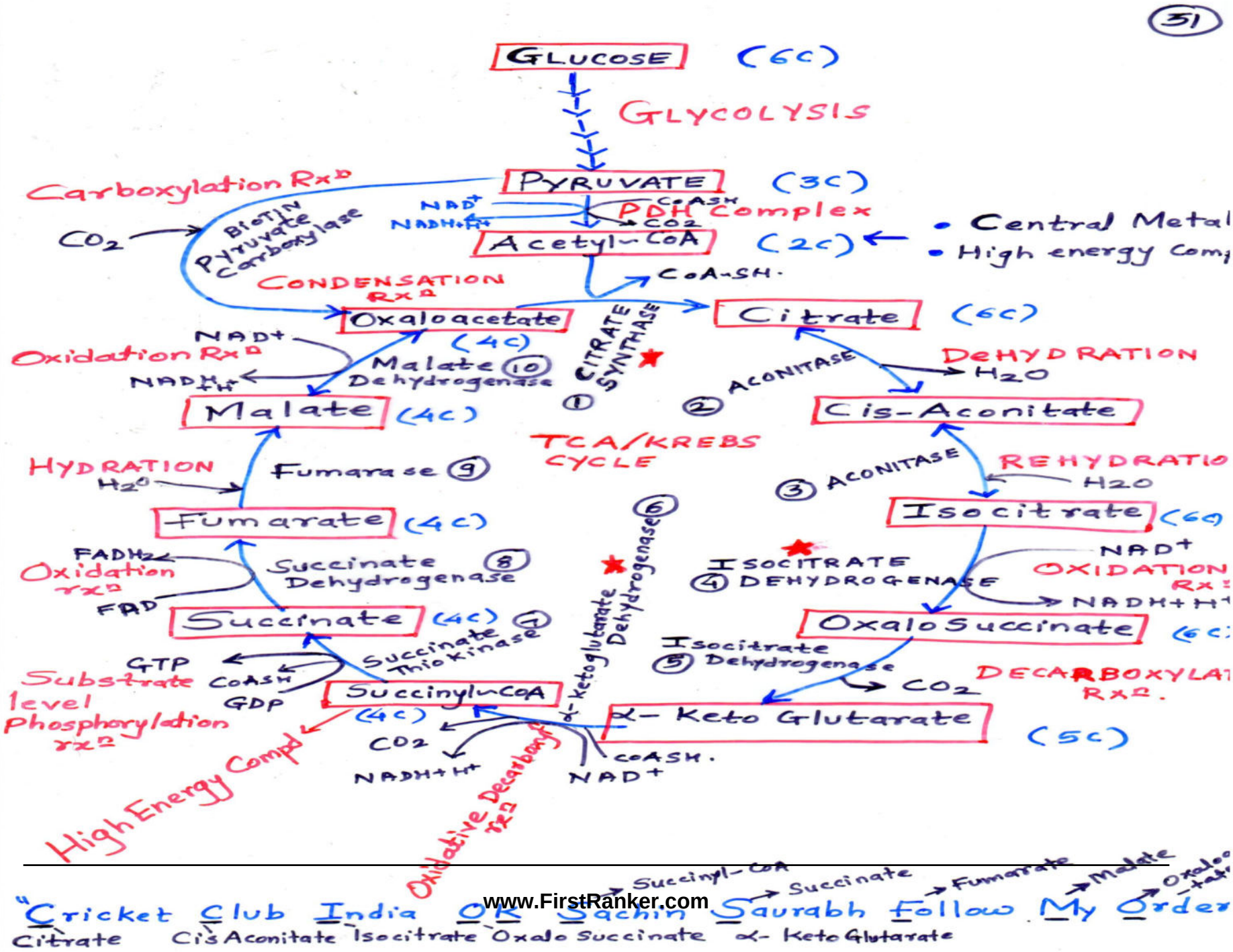
- TCA is associated to Carbohydrates ,Lipids, and Proteins for its complete metabolism.
- 65-70% of ATP is generated through TCA cycle.
- TCA is **a most energetic** metabolic pathway.



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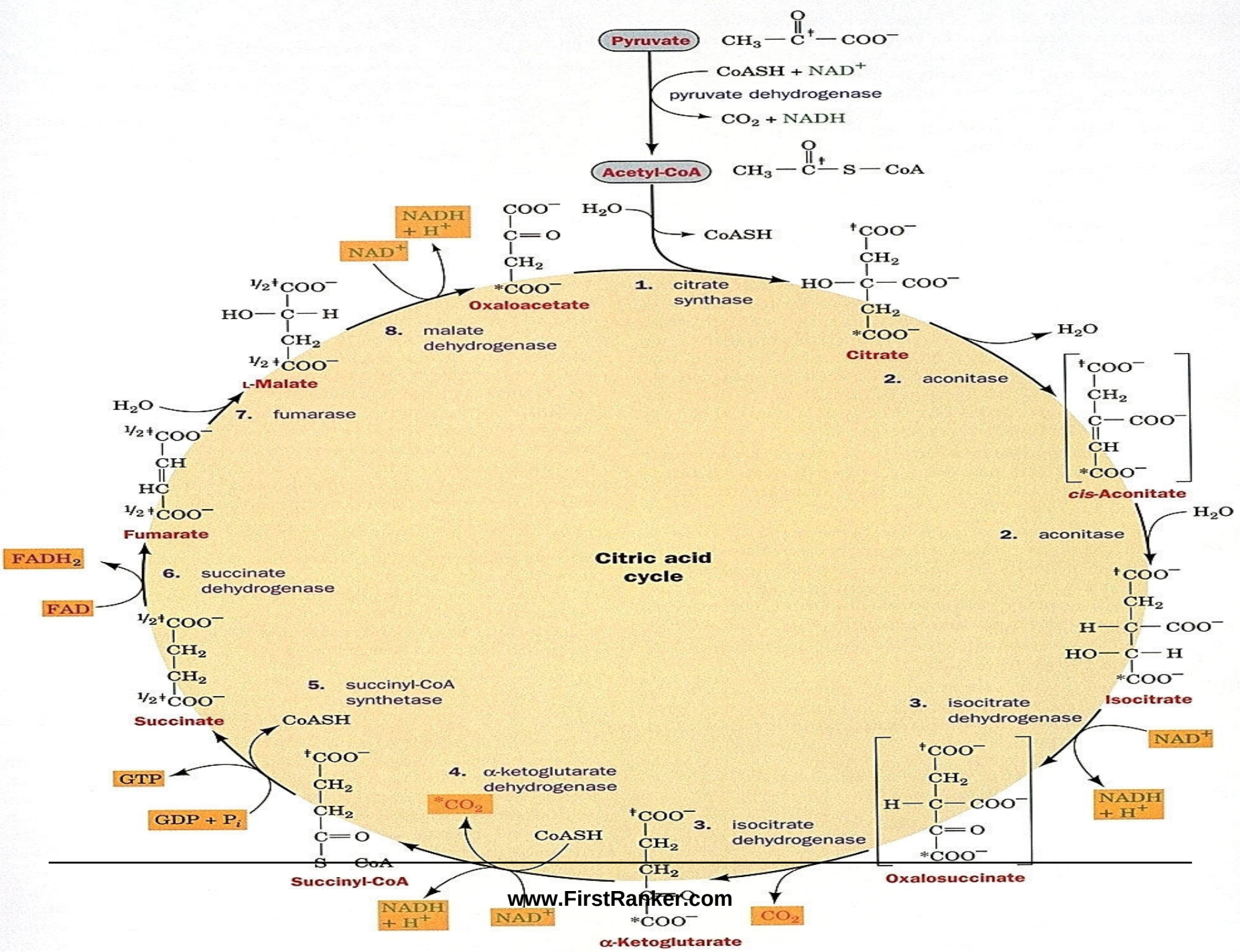
1. Aldol Condensation
2. Isomerization- **Dehydration and Rehydration**
3. Oxidation
4. Decarboxylation
5. Oxidative Decarboxylation
6. Substrate Level Phosphorylation
7. Oxidation
8. Hydration
9. Oxidation



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- Central metabolite Acetyl-CoA obtained from Glucose, Fatty acids, and Amino acid metabolism.
- Acetyl-CoA enters in TCA cycle and completely oxidized to free CO_2 and reducing equivalents which further enters ETC to generate ATPs.
- Since Acetyl-CoA is catabolized and produces energy.
- Thus TCA has catabolic and energy generating role.

- Succinate Dehydrogenase is the only enzyme of TCA embedded in the inner mitochondrial membrane.
- Succinate Dehydrogenase functions as **Complex II of ETC.**

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Alpha KDH Complex Is a Multi Enzyme Complex

- **3 Enzymes**

- Alpha Keto Glutarate Dehydrogenase
- Dihydrolipoyl Dehydrogenase
- Dihydrolipoyl Trans Succinylase

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- 5 Coenzymes
- TPP
- FAD
- NAD+
- Lipoamide
- CoA

Anabolic Role Of TCA

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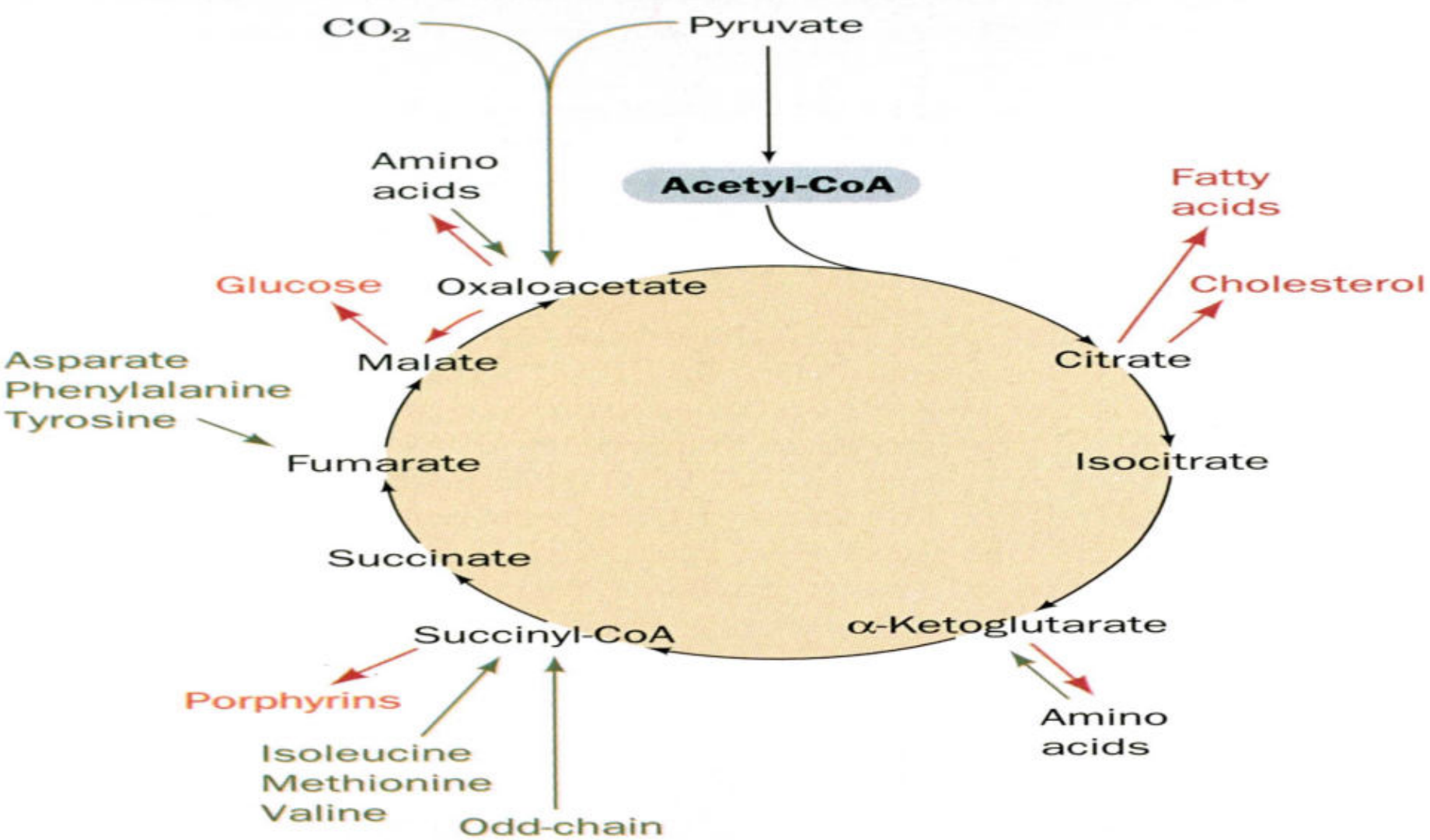
Citric acid cycle intermediates are always in flux



- In TCA Cycle there is continuous influx and efflux of intermediate metabolites as per cellular need.
- TCA is considered as a metabolic Traffic Circle.

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- Various intermediates of TCA cycle are connected to the biosynthesis of various functional biomolecules of human body.
- This role of TCA signifies Anabolic role .

- **Citrate** a 6 carbon moiety is a **first Tricarboxylic acid** produced in TCA.
- **Citrate** is a carrier of acetate carbons for De novo **biosynthesis of Fatty acids** in cytosol.

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- **Acetyl CoA** obtained from Glucose in a well fed condition is a **precursor of fatty acid biosynthesis**.

- Acetyl –CoA is **impermeable** to mitochondrial membrane.
- Impermeable Acetyl-CoA of mitochondria is brought out in the cytosol in a permeable form of Citrate.

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- **Citrate** in cytosol undergo lysis by **Citrate Lyase** to regenerate **Acetyl-CoA and OAA.**

- **Alpha Keto Glutarate** (α KG) a 5 carbon Keto acid, an intermediate of TCA is involved in **Transamination reaction of Aminoacids.**
- α KG is an **acceptor of an amino group** from another amino acid involved in Transamination reaction.

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- α KG on Transamination forms its corresponding amino acid **Glutamic acid.**
- Thus **α KG is a precursor** for biosynthesis of **non essential amino acid** in human body.

- Oxaloacetate of TCA is also transaminated to a non essential amino acid **Aspartate.**
- Intermediates of TCA are **Glucogenic precursors**
- In an emergency conditions they are used for **biosynthesis of Glucose.**

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- Succinyl –CoA, a high energy compound ,an intermediate of TCA cycle is followed by Substrate level Phosphorylation reaction to **generate GTP** at reaction level.
- Succinyl-CoA is a precursor for **Heme biosynthesis** .
- Succinyl-CoA is involved in **Ketolysis** where it is a CoA donor for **Thiophorase reaction.**

- Intermediates of TCA cycle are connected to Biosynthesis of
  - **Lipids**
    (Lipogenesis)
  - **Glucose**
    (Gluconeogenesis)
  - **Aminoacids**
    (Nutritionally Nonessential)

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- **TCA cycle** is termed as **open cycle-** Since an intermediates of TCA cycle enter and leave the cycle as per the cellular need.

- TCA Cycle is analogus/ Illustrated as- "**Heavy Traffic Circle**" in a National Highway with many connecting roads.
- Since many intermediates of TCA cycle are interconnected to other metabolic pathways.

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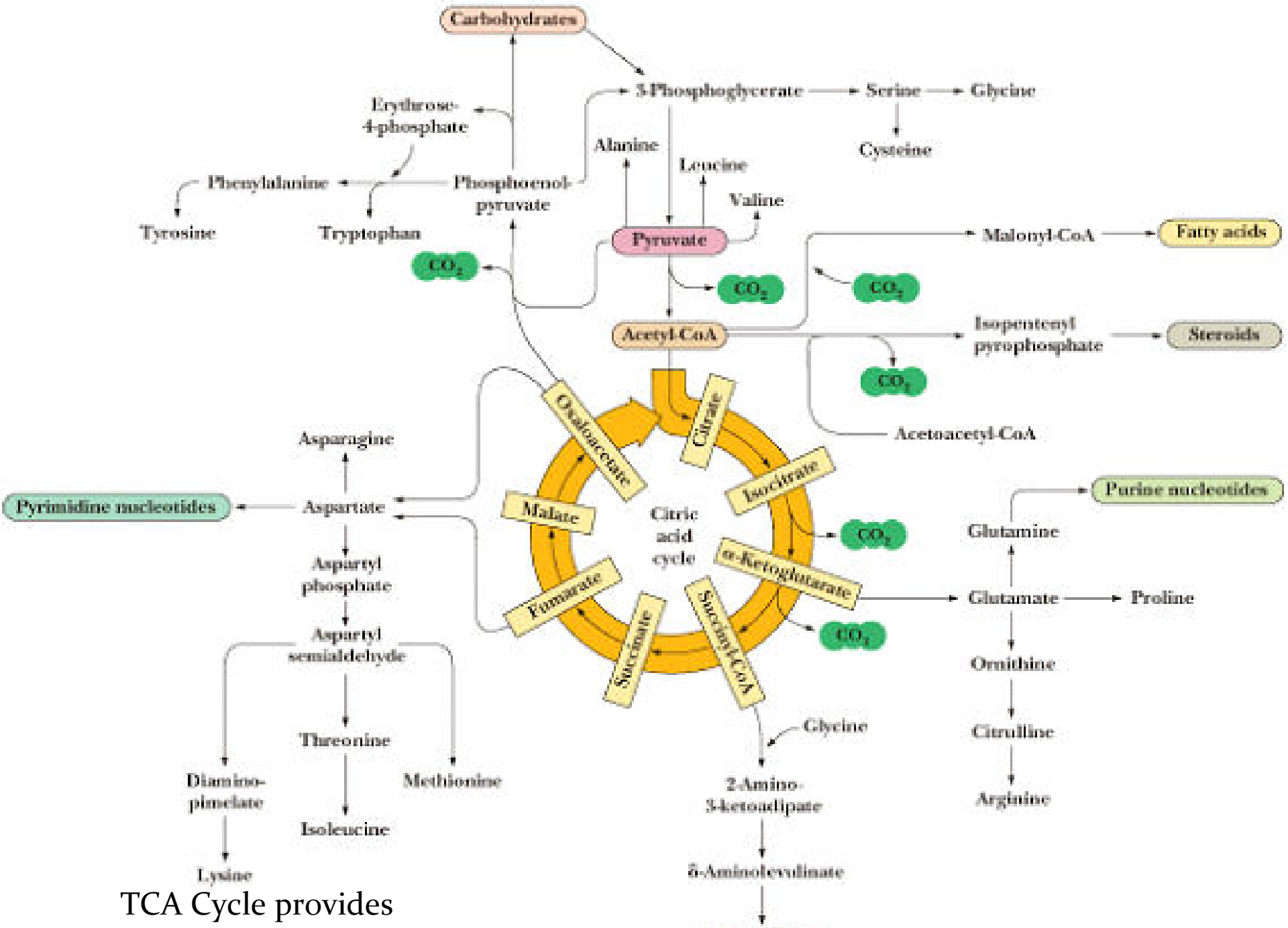

TCA Cycle provides intermediates for many

Energetics Of Per Turn TCA Cycle

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Enzymes Generating Reducing Equivalents

- Isocitrate Dehydrogenase ----------$NADH+H^+$
- αKetoglutarate Dehydrogenase -------$NADH+H^+$
- Malate Dehydrogenase----------$NADH+H^+$
- Succinate Dehydrogenase ----------$FADH_2$
- Succinate Thiokinase ----------GTP

- In per turn of TCA cycle 1 Acetyl-CoA enters to catabolize and generate 3$NADH+ H^+$ 1 $FADH_2$ and 1 GTP.

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- 3 NADH+ H^+ when enters ETC it generates 7.5 ATPs
- 1 FADH2 when enters ETC generates 1.5 ATPs.
- 1 Substrate level phosphorylation generates 1 GTP.
- Net 10 ATP's are generated per turn of TCA cycle.

Significance of TCA

- TCA Cycle is the largest generator of ATP among the metabolic pathways.

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Reduced Coenzymes Fuel ATP Production

- Isocitrate Dehydrogenase 1 NADH=2.5 ATP
- α- Ketoglutarate Dehydrogenase 1 NADH=2.5 ATP
- Succinate Thiokinase 1 GTP=1 ATP
- Succinate Dehydrogenase 1 FADH2=1.5 ATP
- Malate Dehydrogenase 1 NADH=2.5 ATP

- Total of 10 ATPs gained from oxidation of 1 Acetyl-CoA per TCA turn.

- **GTP formed in TCA cycle is used in following step of Gluconeogenesis:**
- Conversion of Oxaloacetate to PhosphoenolPyruvate (PEP) in presence of enzyme PEP Carboxykinase and GTP.

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Regulation Of TCA Cycle

- Hormone Insulin in well fed condition stimulates and activates key / regulatory Enzymes of TCA cycle.
  - **Key Enzymes of TCA cycle :**
  - **Citrate Synthase**
  - **Isocitrate Dehydrogenase (IDH)**
  - **α Keto Glutarate Dehydrogenase (KDH)**

- Activators of key Enzymes- ADP,AMP

- Inhibitors Of key Enzymes- ATP, NADH+ H^+, Succinyl-CoA

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- Citrate of TCA inhibits PFK of Glycolysis.
- Citrate stimulate Fructose -1,6 Bisphosphatase of Gluconeogenesis.
- Citrate activates Acetyl CoA Carboxylase of Fatty acid biosynthesis.

- **Regulation Of TCA by availability of ADP:**
- Low levels of ADP in cells indirectly inhibit TCA cycle.
- ADP is required for synthesis of ATP through oxidative phosphorylation (ETC).
- Low/Limited ADP are insufficient to reoxidize reducing equivalents NADH+ H^+ ,$FADH_2$ generated during TCA.
- This accumulates NADH+ H^+ ,$FADH_2$ which are inhibitors of key enzymes of TCA cycle.

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Chemical Inhibitors OF TCA cycle

INHIBITOR and Type	ENZYME INHIBITED
Fluoroacetate (Non Competitive)	Aconitase
Arsenite (Non Competitive)	α Keto Glutarate Dehydrogenase.
Malonate (Competitive)	Succinate Dehydrogenase

- TCA enzyme defects has reported to suffer from severe neurological damage due to impaired ATP formation in CNS.

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Hyperammonaemia Impairs TCA

- High ammonia levels in blood are toxic to body since they **deplete the levels of α-Keto Glutarate**.

  (an intermediate of TCA cycle)
- Low levels α-Keto Glutarate, **affects the operation of TCA cycle and production of ATPs.**

- Vitamin B Complex deficiencies affects Glucose metabolism and has low ATP production.
- Vitamin B complex members are modified to Coenzymes required in enzyme catalysis of metabolic reactions.
- One should take care to supplement adequate Vitamin B complex through ingestion of fresh fruits and vegetables.

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- Beri Beri and
- Wernicke Korsakoff Syndome (In alcoholics)
- Due to Thiamine (TPP) deficiency.
- TPP is a member of multienzyme complex PDH and Alpha KDH.
- Low TPP= low ATP
- Low Nervous tissue , Cardiac Functions.

- Pellegra is due to Niacin deficiency.
- Niacin deficiency affects the concentration of coenzymes NAD^+ and NADP.
- NAD^+ and NADP deficiency affects metabolism by low ATP production.

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Leigh Syndrome

- Leigh Syndrome is a rare disorder
- Also referred as **Sub acute Necrotizing Encephalomyelopathy**
- Progressive **neurological disorder**
- **Defect in mitochondrial ATP production**
- Mutations in PDH Complex/ATP Synthase of ETC.

Anaplerotic Reactions/ Anaplerosis

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- Anabolic reactions connected to TCA cycle utilizes the intermediates of this cycle.
- The drawn up intermediates should be replenished.
- If not replenished ,TCA cycle will stop to operate.

- The biochemical reactions which replenish or add up/fill up the intermediates of TCA cycle and maintain its operation are termed as **anaplerotic reactions.**

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The Anaplerotic Reactions

The "filling up" reactions

- PEP Carboxylase - converts PEP to Oxaloacetate
- Pyruvate Carboxylase - converts Pyruvate to Oxaloacetate
- Malic enzyme converts Pyruvate into Malate

Anaplerotic Reactions

Pyruvate —(Pyruvate Carboxylase; CO_2 ATP, ADP Biotin)→ **Oxaloacetate**

Pyruvate ⇄(Malic Enzyme; NADP, $NADPH+H^+$) **Malate**

Glutamate ⇄(GDH) **α Keto Glutarate**

Aspartate ⇄(AST) **Oxaloacetate**

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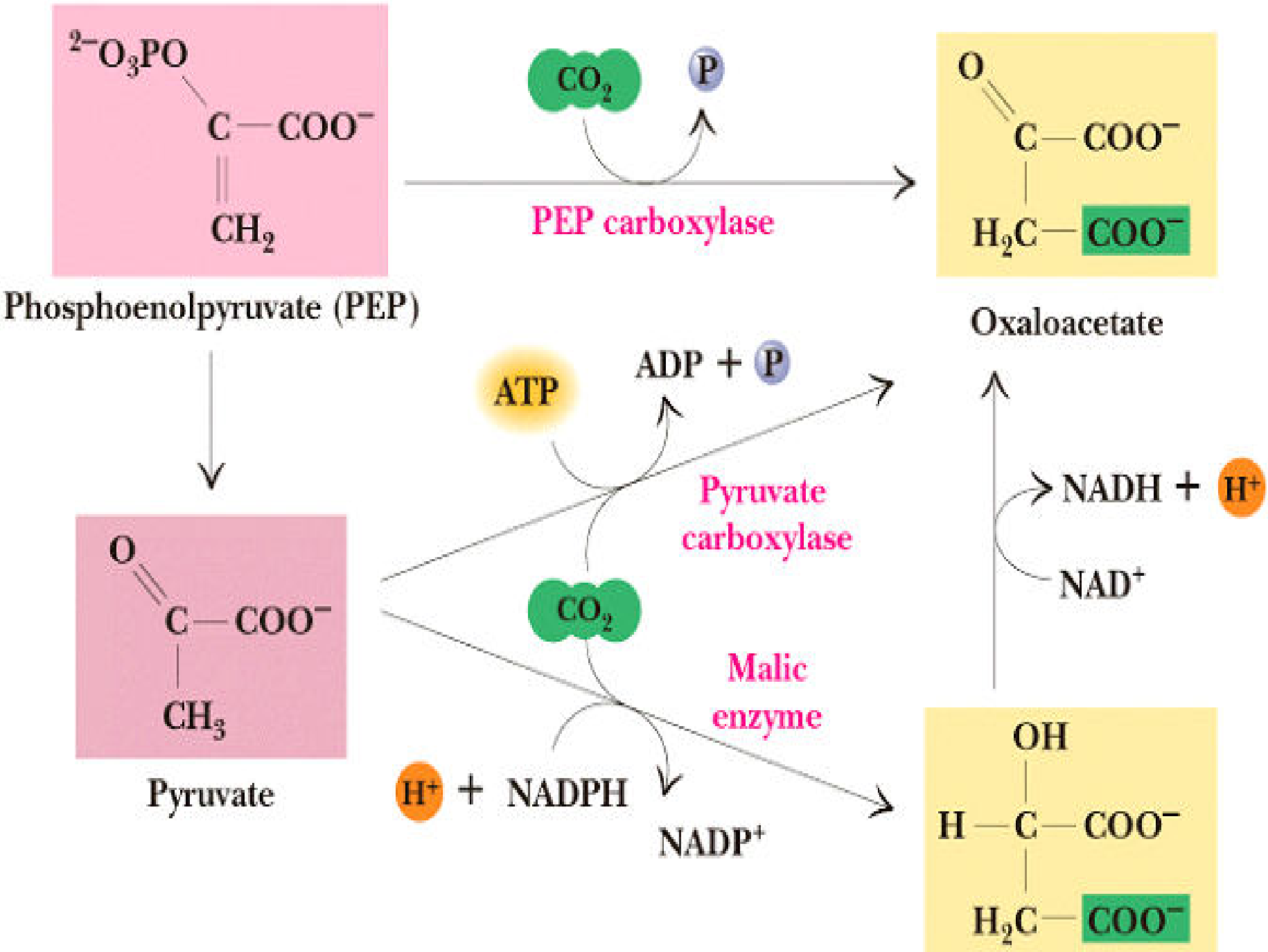

Energetics Of Complete Oxidation of Glucose

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1 molecule of Glucose on complete oxidation in body cells liberate 32 ATP's.

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Glycogen Metabolism

Glycogenesis And Glycogenolysis

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GLYCOGENESIS	GLYCOGENOLYSIS
Glycogenesis is biosynthesis of Glycogen from free and excess of Glucose in well fed condition in the cytoplasm of Liver and Muscles.	Glycogenolysis is breakdown of Glycogen to Glucose in emergency condition in the Liver and Muscles.
Glycogenesis is an anabolic process to store free excess Glucose in the form of condensed , compact, globular, and granular form as –Glycogen.	Glycogenolysis is a catabolic degradative process to utilize the stored Glycogen after its cleavage to release Glucose ,which on further oxidation generate ATPs in emergency conditions.

Where Glycogen Metabolism Occurs?

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Site/Location Of Glycogen Metabolism

- **Organs for Glycogen Metabolism:**
- Liver and Muscles.
- **Cellular Site :**
- Cytoplasm

- **In Liver**
- **Rate of Glycogen Synthesis**- 6-8%
- **Amount Stored**- 75-150 gm.

- **In Muscles**
- **Rate of Glycogen Synthesis**- 1-2 %
- **Amount Stored**- 250-400 gm.

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- 1% of Glycogen stored in cardiac/heart muscles.

- **Storage of Glycogen in tissues is limited.**

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When Glycogenesis Operated?

- Glycogenesis takes place after a **well fed condition**.
- After a **heavy Carbohydrate meals.**
- When there is **free and excess of cellular Glucose.**
- **Under** the influence of **Insulin.**

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How Glycogenesis Occur?

Steps Of Glycogenesis

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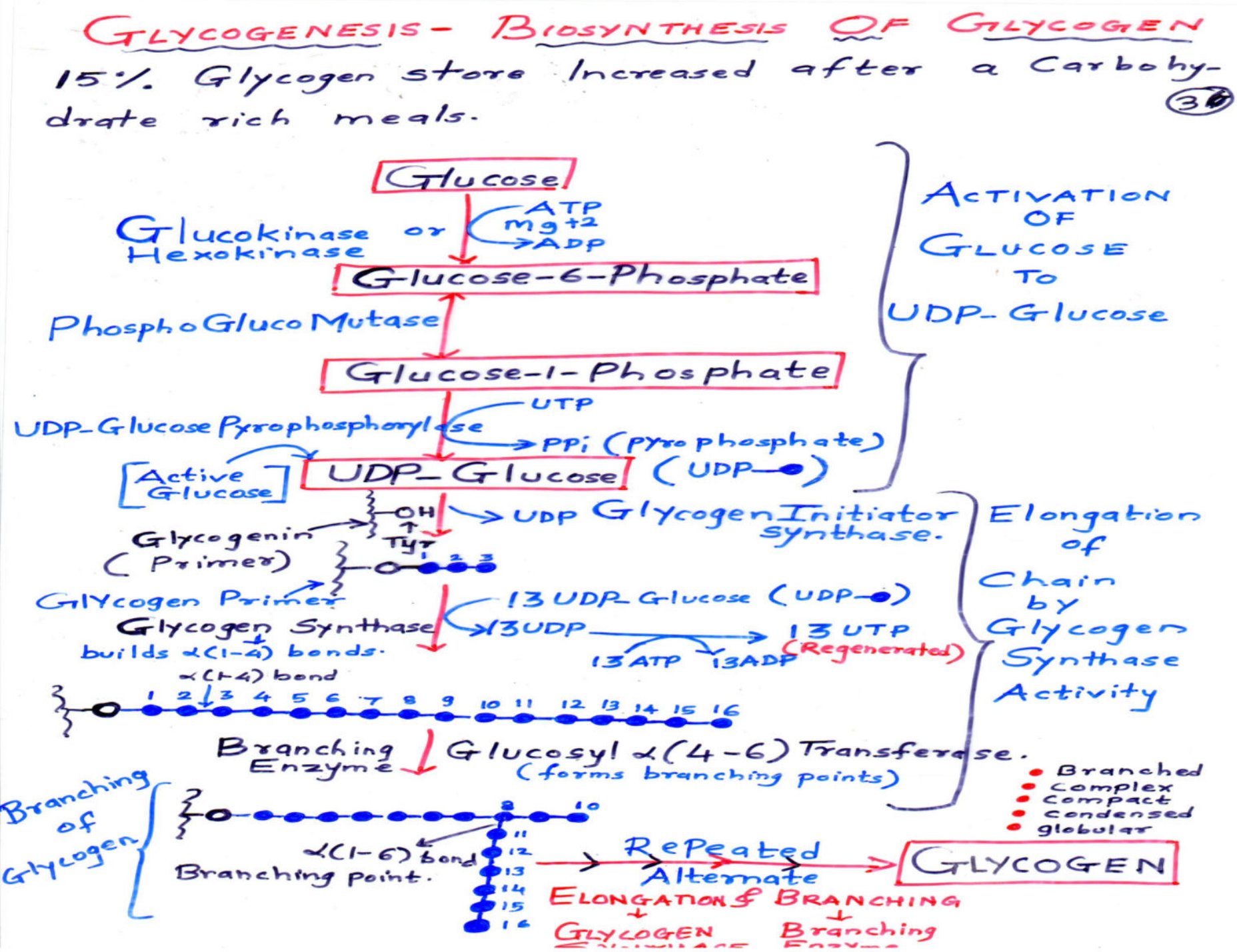

- **Process of Glycogenesis involves following Steps:**

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- **Activation of Glucose** to
- **UDP-Glucose.**

(Energetic Compound)

- **Glycogen synthesis depends on sugar nucleotides**

UDP-Glucose

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Glycogenesis Needs

Glycogen Primer

- A Glycogen Primer is required to initate the process of Glycogenesis

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- **Glycogen Primer** at a **very first time** of Glycogenesis in a body is a Protein **Glycogenin.**

- **Glycogenin catalyzes primer formation.**

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- **Glycogenin** is a protein scaffold on which **Glycogen molecule is built.**
- First Glucose is linked to a Tyrosine –OH of Glycogenin.

- Glycogenin by auto glucosylation using UDP-Glucose form a Glycogen primer.

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- **Glycogen primer in an adult body:**
- Is a residual of Glycogen molecule left out after Glycogenolysis in tissues.

Glycogen Synthase

- **Glycogen Synthase is the main enzyme of Glycogenesis.**
- **It forms α-(1→ 4) glycosidic bonds in Glycogen.**
- **Glycogen Synthase requires 4 to 8 Glucose units on Glycogenin for its activity.**

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- **UDP- Glucose is linked to non reducing ends of Glycogen Primer** by **Glycogen Synthase** activity to grow the linear chain.

- **Glycogen Synthase** transfers Glucosyl units from UDP-Glucose to C-4 hydroxyl at a nonreducing end of a Glycogen strand/Glycogen primer.

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- After stipulated growth of linear chain,
- Branching enzyme **adds a branching point.**

- **Alternate activities of Glycogen Synthase and Branching Enzyme occurs**
- To link UDP-Glucose units to form a complex, compact and condensed structure of Glycogen.

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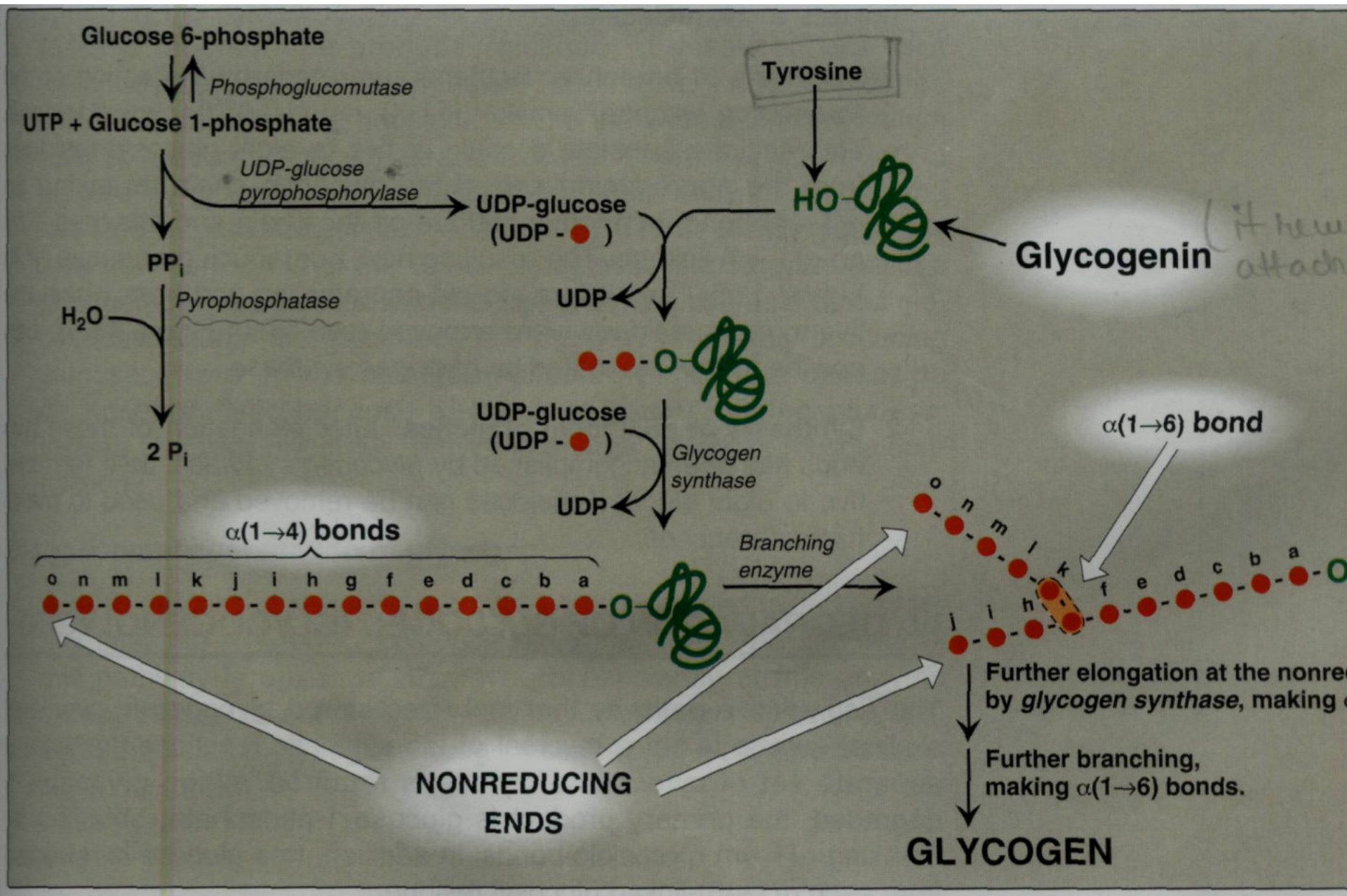

Figure 11.5

Glycogen synthesis.

- **During Glycogenesis.**

- Glycogen Synthase -builds α(1-4) glycosidic bonds.

- Branching Enzyme – Glucosyl α(4-6) Transferase builds α(1-6) glycosidic bonds.

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- More branching points in a Glycogen molecule
- Increases the number of non reducing ends
- Which can be elongated by addition of new Glucose residues to it
- By Glycogen Synthase activity.

- UDP released during Glycogenesis is converted to UTP at an expense of ATP.

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Significance Of Glycogenesis

- Glycogenesis stores free and excess Glucose in condensed, compact and granular form which:
- Reduces osmotic effect
- Occupy less space.

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Glycogenolysis

Site Of Glycogenolysis

- Cytoplasm of Liver and Muscles.
- Where Granules of Glycogen stored.

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When Glycogenolysis Occur?

- **Glycogenolysis occur in the body when:**
- Stored Glycogen needs to be utilized.
- Blood or cellular Glucose lowers.
- There is fasting or starvation.
- There are long hours between meals.

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Steps Of Glycogenolysis

- Glycogenolysis is not a just reversal of Glycogenesis.
- A different sets of enzyme used.

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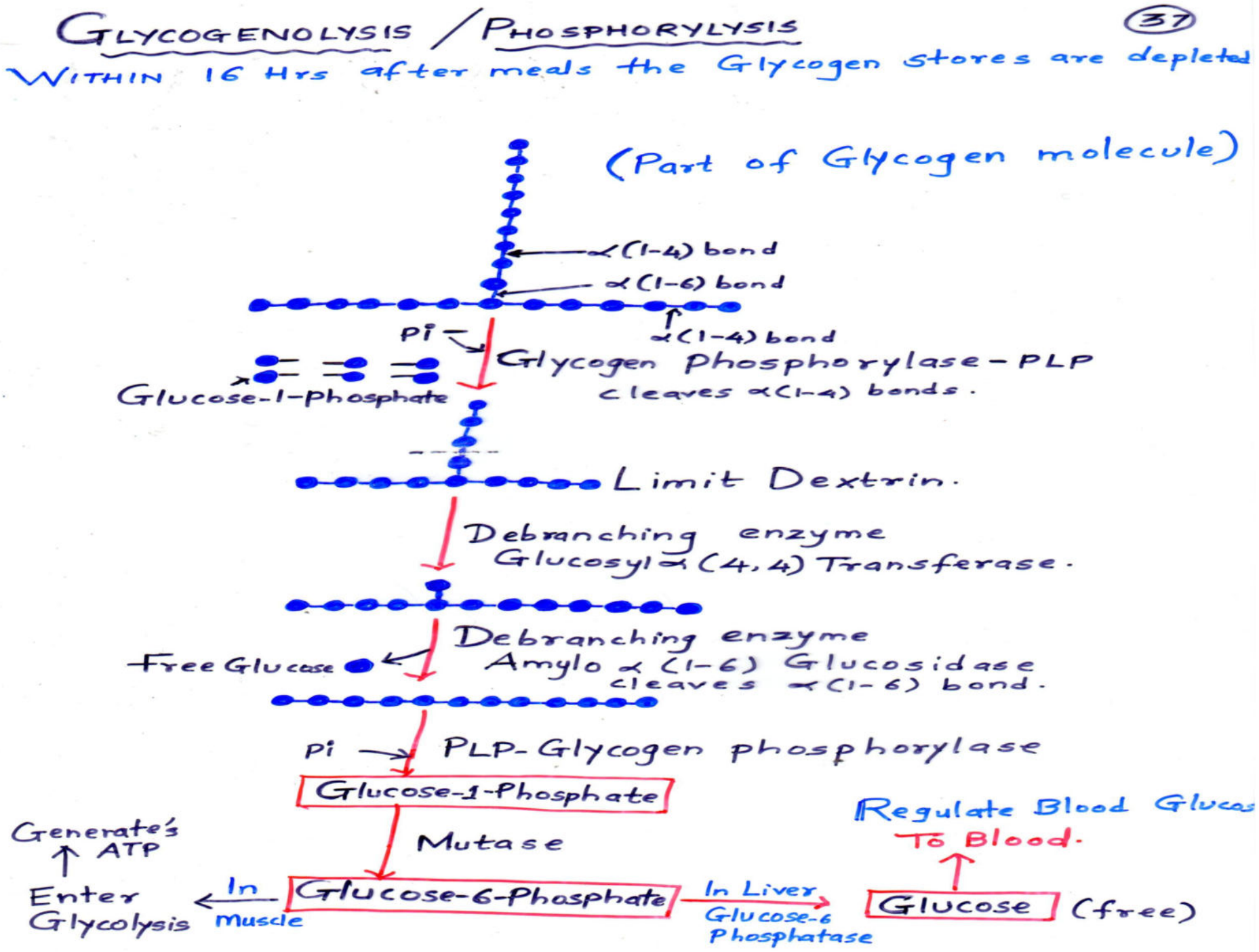

- Glycogenolysis involves cleavage of α(1-4) and α(1-6) glycosidic bonds of Glycogen.
- Enzyme **Glycogen Phosphorylase** cleaves α(1-4) glycosidic bonds.
- **Debranching Enzymes** removes α(1-6) glycosidic bonds.

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- **Glycogen Phosphorylase is a main enzyme of Glycogenolysis.**
- **Glycogen Phosphorylase cleaves Glycogen at non-reducing end to generate Glucose-1-phosphate**

- **Glycogen Phosphorylase cleaves α(1-4) glycosidic bonds linking Glucose from the non reducing ends of glycogen molecules**
- **This is a Phosphorolysis, not a hydrolysis**
- **Metabolic advantage: product is a sugar-P - a "sort-of" Glycolysis substrate**

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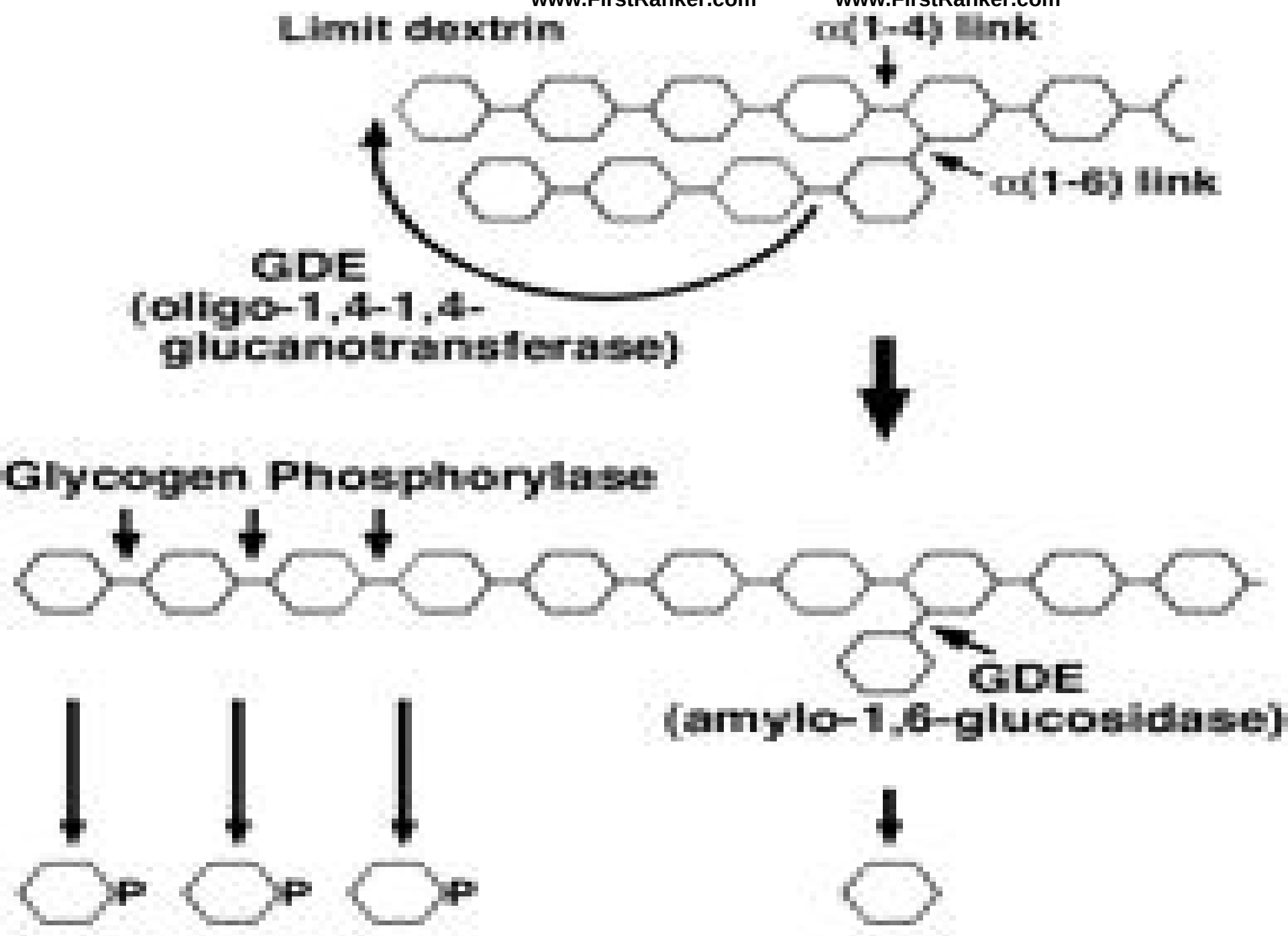

End Products Of Glycogenolysis

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- **During Glycogenolysis**

- Enzyme Glycogen Phosphorylase by its activity releases Glucose -1-PO4.

- **Debranching by bifunctional (two) Enzymes.**

- **Glucosyl α(4 , 4) Transferase.**
- **Amylo α(1-6) Glucosidase**

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- Debranching Enzyme **Amylo α(1-6) Glucosidase**
- Acts on exposed branching point **α(1-6)bond** of Glycogen and releases **free Glucose.**

- The number of free Glucose units released during Glycogenolysis depends upon
- The number of branching points hydrolyzed by Debranching enzyme activity.

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Glucose-1-PO_4 : Free Glucose

8: 1

Released during Glycogenolysis

Muscle Glycogenolysis	Liver Glycogenolysis
In Muscles Enzyme **Glucose-6-Phosphatase is naturally absent.**	In Liver Enzyme **Glucose-6 Phosphatase is naturally present.**
Glucose-6-PO_4 ends as an end product of Glycogenolysis which further enters Glycolysis and get metabolized within muscle cells.	In Liver Glucose-6-PO_4 of Glycogenolysis is transformed to free Glucose (permeable) by Glucose-6-Phosphatase activity.
Muscle Glycogenolysis has no role in blood Glucose regulation	Free Glucose formed from Liver Glycogenolysis comes out in blood and helps in blood Glucose regulation.

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Significance Of Glycogenolysis

- Muscle Glycogen is extensively degraded in exercising muscles to provide energy for it's activity.

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- Liver Glycogenolysis operates to
- Generate free Glucose from breakdown of stored Glycogen.
- Liver Glycogenolysis add free Glucose to blood.
- Regulates blood glucose levels.
- Correct fasting Hypoglycemia
- Supply sufficient Glucose to Brain and Erythrocytes.
- Try to maintain good function of brain and RBC's in fasting condition

- Stored Glycogen in Liver on Glycogenolysis ,supply Glucose in a rapid and mobilizable form.

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- Liver Glycogenolysis regulates blood Glucose levels in early stages of fast.

- Liver Glycogenolysis corrects fasting Hypoglycemia.

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Regulation OF Glycogen Metabolism

- Regulation means good coordination of Glycogenesis and Glycogenolysis as an when required by the body to maintain blood Glucose in normal range.
- Glycogen metabolism is regulated by stimulation or inhibition of regulatory/key enzymes of Glycogen metabolism under hormonal influence.

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- Glycogenesis and Glycogenolysis are reciprocally regulated

- **In well fed condition**
  - Glycogenesis is onn
  - Glycogenolysis is off
- **In fasting condition**
  - Glycogenolysis is onn
  - Glycogenesis is off

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Modes Of Regulation

- **Hormonal Regulation**

  (Covalent Modification Of Key Enzymes of Glycogen Metabolism)
- **Allosteric regulation**
- **Influence Of Calcium** on Glycogen Metabolism.

Hormonal Regulation

- **Insulin In well fed condition**
  - Stimulates Glycogenesis
  - Inhibits Glycogenolysis

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- **Glucagon and Epinephrine In emergency condition :**
  - Stimulates Glycogenolysis
  - Inhibits Glycogenesis

- Glucagon and Epinephrine
- Acts via second messenger cyclic AMP by cascade of reactions
- Regulates the enzymes and pathway of Glycogen metabolism

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- **Glucagon** has **no effect** on Muscle Glycogenolysis.
- Epinephrine and Calcium stimulates Muscle Glycogenolysis.

- **Regulatory Enzyme Of Glycogenesis:**
  - **Glycogen Synthase**
- **Regulatory Enzyme Of Glycogenolysis:**
  - **Glycogen Phosphorylase.**

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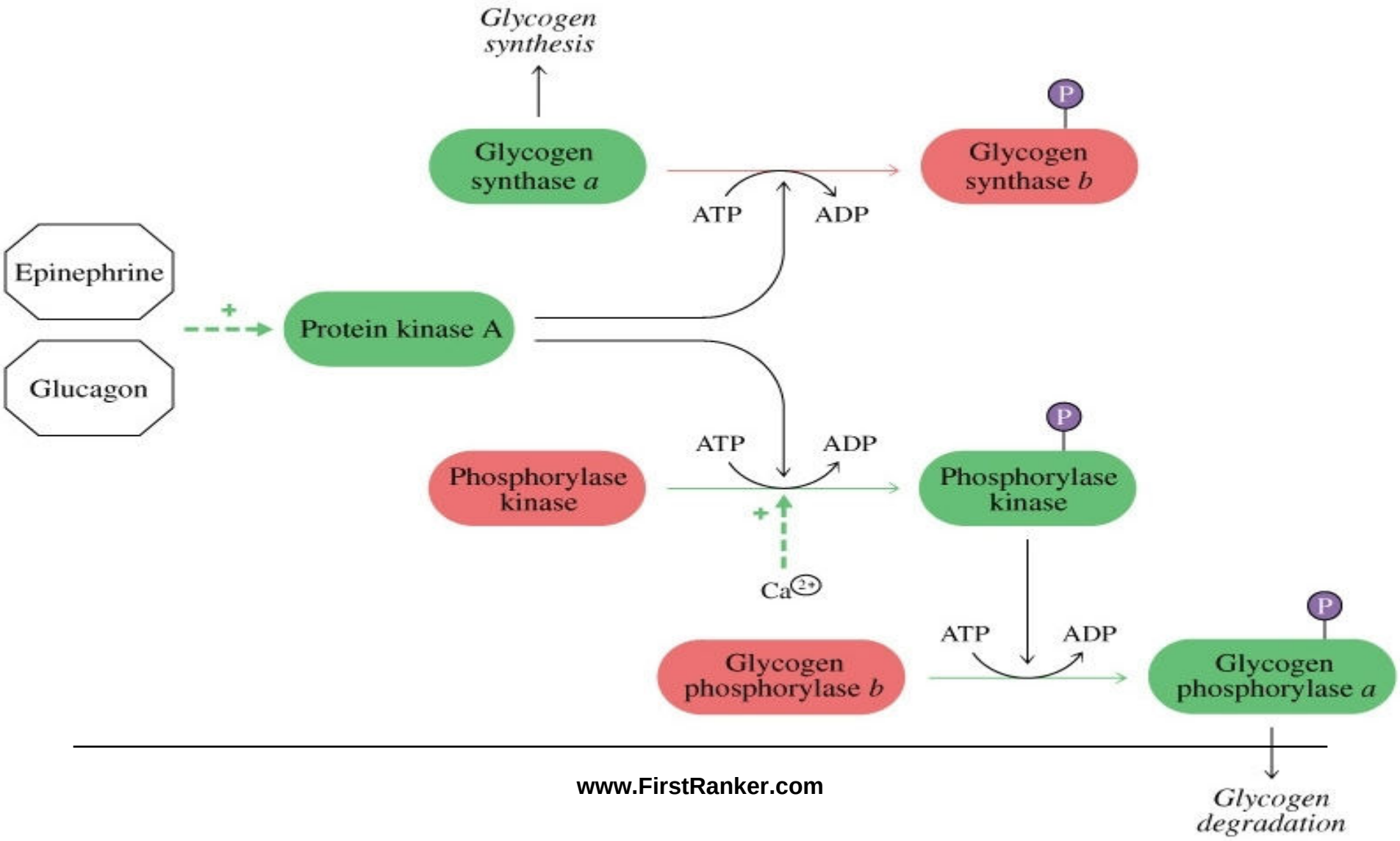
Covalent Modification Of Enzymes

Glycogen Phosphorylase	Glycogen Synthase
❖ "A" Form Active Form **Phosphorylated Form**	"A" Form Active Form **Dephosphorylated Form**
❖ "B" Form Inactive Form **Dephosphorylated Form**	"B" Form Inactive Form **Phosphorylated Form**

Effect of glucagon and epinephrine on glycogen phosphorylase glycogen synthase activities



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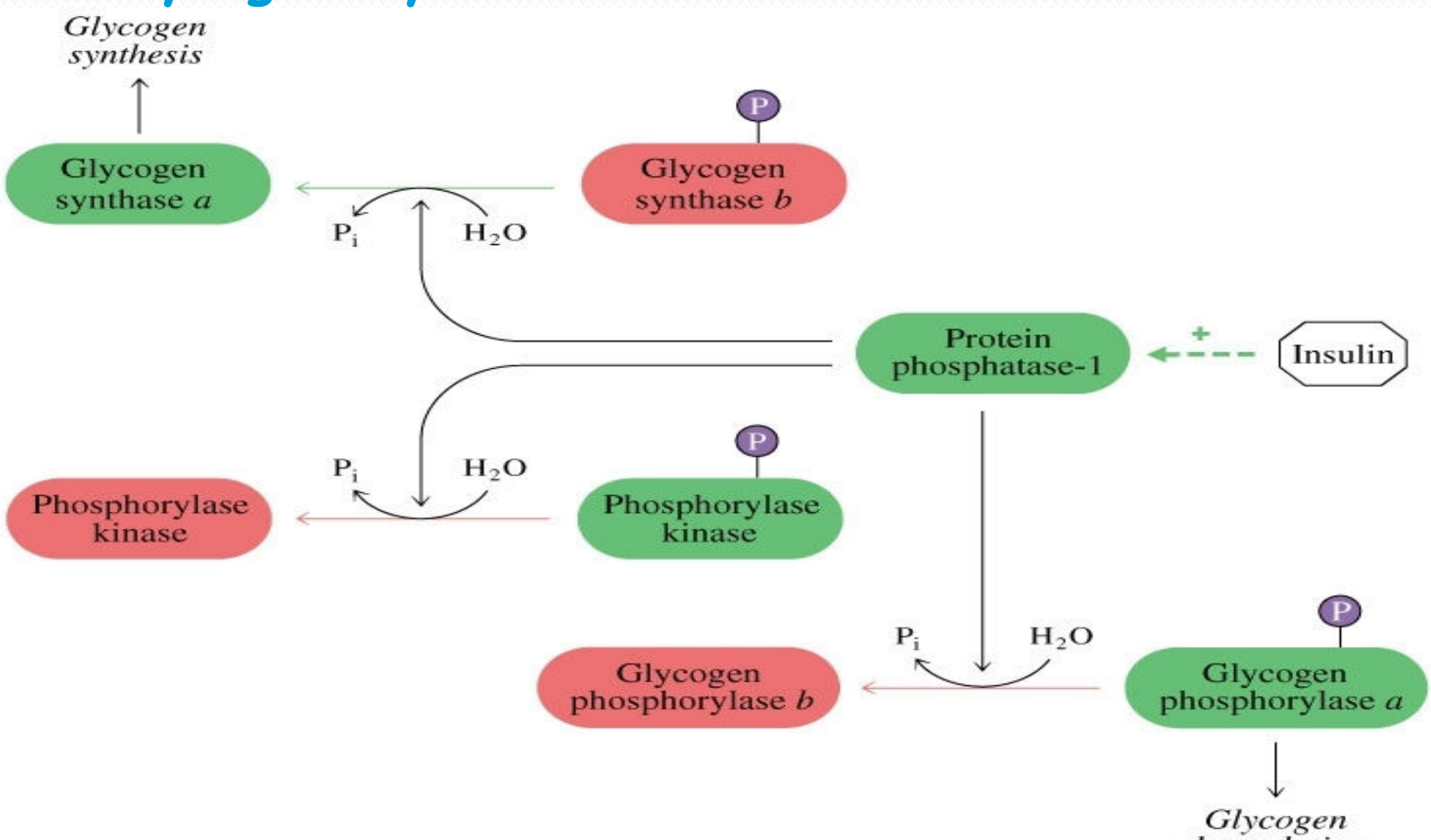
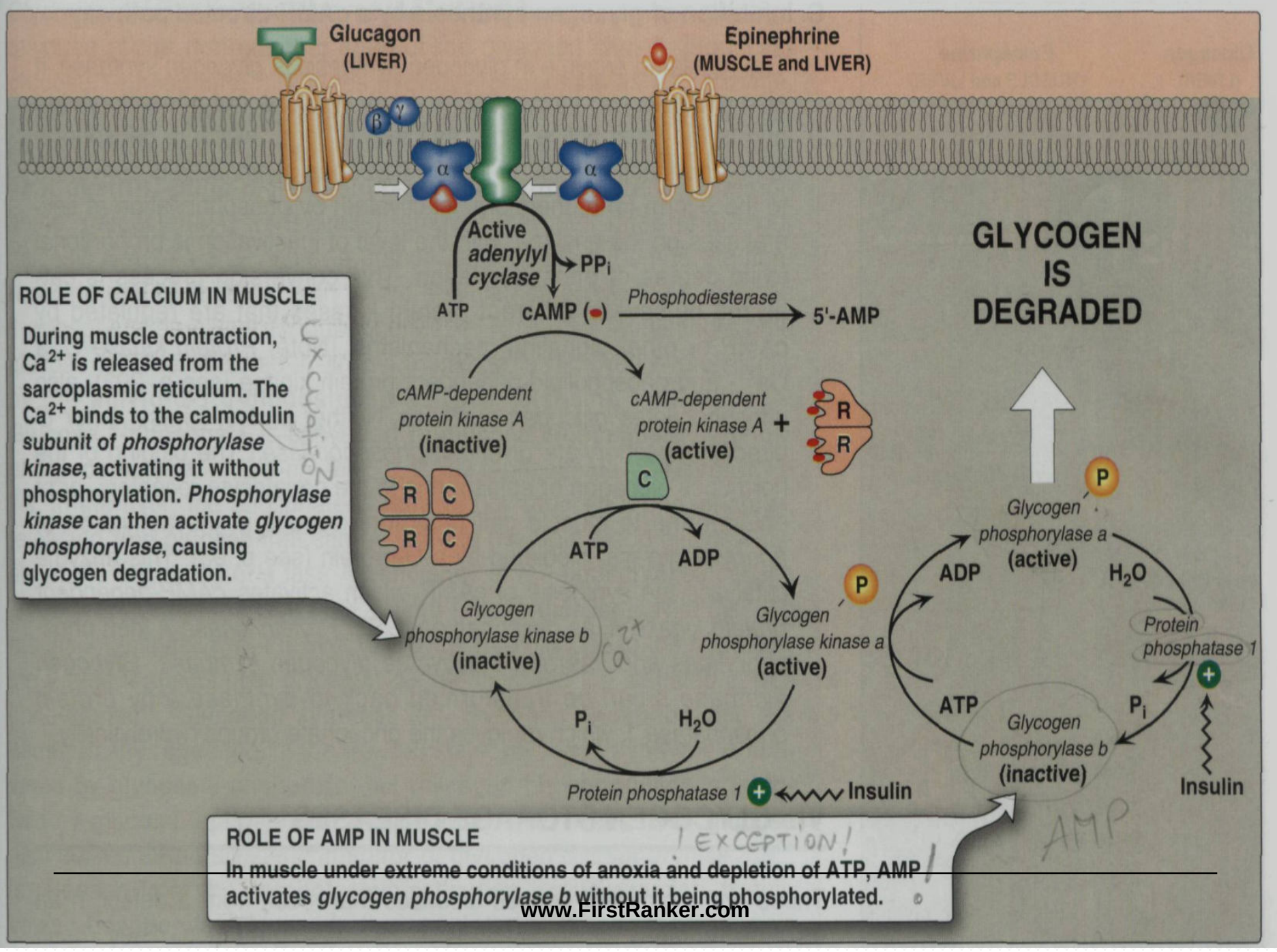
Effect of Insulin on Glycogen Phosphorylase Glycogen Synthase activities





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- In emergency condition when Blood Glucose level go subnormal.

↓

Glucagon (secreted)

↓

cAMP → → → → Phosphorylates Glycogen Synthase 'b' Inactive form

↓

Inhibits Glycogenesis.

↓

Cascade of Reactions

↓

Activates - Proteinkinase

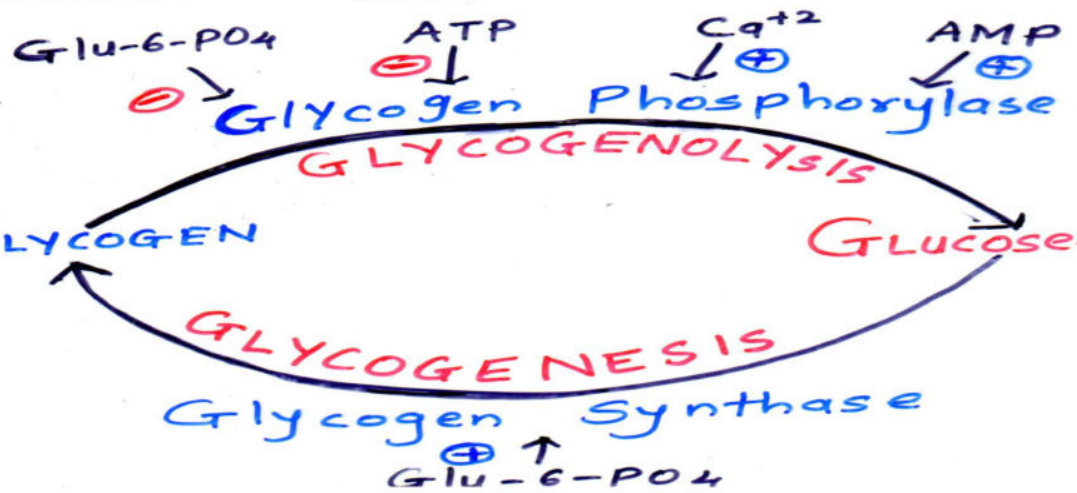
↓

Phosphorylates Glycogen phosphorylase 'a' - Active form

↓

Stimulates Glycogenolysis

ALLOSTERIC REGULATION OF GLYCOGEN METABOLISM



Influence of Calcium in Regulation of Glycogen metabolism.

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- Calcium stimulates Liver and muscle Glycogenolysis

- Calcium inhibits Liver and muscle Glycogenesis.

- Calcium binds to Calmodulin, which then activates an enzyme **muscle Phosphorylase Kinase b** and **Liver Phosphorylase Kinase b.**

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- Calcium activated Phosphorylase Kinase b stimulates and activates Glycogen Phosphorylase.

- Thus Calcium indirectly activates Glycogen Phosphorylase
- Calcium Stimulates Glycogenolysis.

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	Glycogen Synthesis	*Glycogen Degradation*
Well-fed state	Increased	Decreased
Fasting	Decreased	Increased
Hyperglycemia	Increased	Decreased
Hypoglycemia	Decreased	Increased
Elevated		
Insulin	Increased	Decreased
Glucagon	Decreased	Increased
Epinephrine	Decreased	Increased
Cyclic adenosine monophosphate	Decreased	Increased
Enzyme phosphorylation		
Glycogen synthase	Decreased	. . .
Glycogen phosphorylase	. . .	Increased

Glycogen Storage Disorders OR Inborn Errors Of Glycogen Metabolism

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- Glycogen Storage Disorders are inherited/congenital metabolic defects concerned with Glycogenesis and Glycogenolysis.

- **Cause:**
- Enzyme defects of Glycogen metabolism.
- **Type:**
- Generalized/Tissue specific

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- **Consequences of Glycogen Storage Disorders:**

- **Abnormal form** or **amount** of Glycogen is deposited in Muscles ,Liver or both.
- **Affects** the **functional activities** of these tissues.
- No correction of fasting hypoglycemia.
- No supply of energy to muscles during emergency conditions.

Types Of Glycogen Storage Disorders

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Type of Glycogen Storage Disorder	Name of Glycogen Storage Disorder	Enzyme Defect
Type I	Von Gierke's Disease	Liver Glucose-6-Phosphatase
Type II	Pompe's Disease	Lysosomal α(1-4) Glucosidase
Type III	Cori's Disease	Debranching Enzyme
Type IV	Anderson's Disease	Branching Enzyme
Type V	Macrdle's Disease	Muscle Glycogen Phosphorylase
Type VI	Her's Disease	Hepatic Glycogen Phosphorylase
	Lewi's Disease	Glycogen Synthase
Type VII	Tauri's Disease	Phospho Fructo Kinase

Disorders Related to Glycogenesis

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Lewis Disease	**Glycogen Synthase Deficiency**
Andersons Disease	**Branching Enzyme Glucosyl α (4-6) Transferase deficiency.**

Disorders Related to Glycogenolysis

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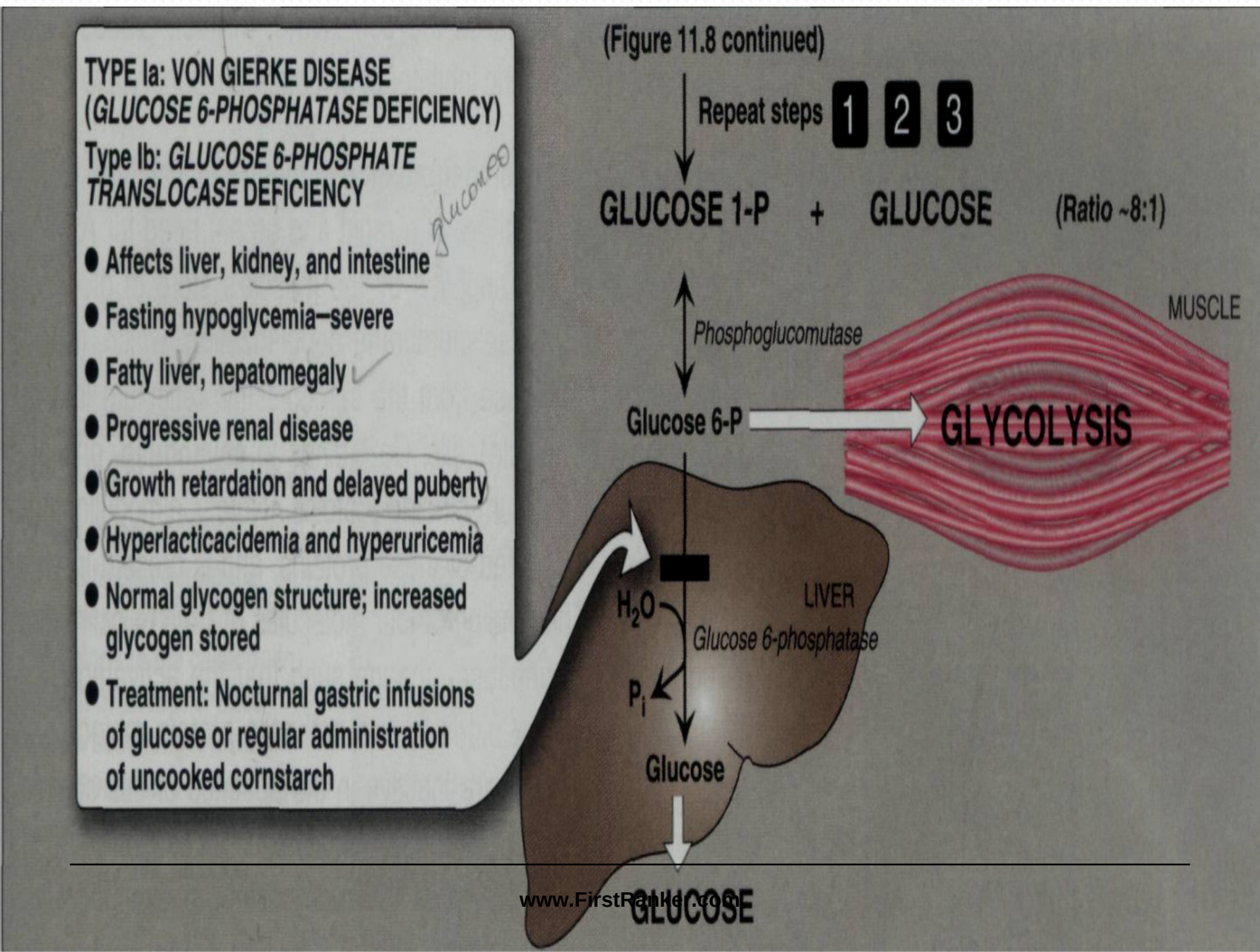
Von Gierkes Disease

- **Enzyme Defect:**
  - **Liver Glucose-6-Phosphatase deficiency**

- **Biochemical Alterations and Manifestations:**
  - Hypoglycemia
  - Hyperlipidemia
  - Hyperuricemia
  - Lacticacidemia
  - Mental retardation
  - Convulsions



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- **Pompe's Disease**

- **Enzyme Defect:**
- **Lysosomal α (1-4) Glucosidase/Acid Maltase**

- **Biochemical Alterations and Manifestations:**

  - Glycogen accumulates in Lysosomes of skeletal and cardiac muscles and affect its function.
  - Cardiomegaly
  - Congestive Heart Failure
  - Weakness of respiratory muscles.

- **Cori's Disease (Limit Dextrinosis)**

- **Enzyme Defect:**
  - **Debranching Enzyme Amylo α(1-6) Glucosidase deficiency.**

- Limit Dextrin gets deposited in Liver and Muscles.

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Macrdle's Disease

- **Enzyme Defect:**
- **Muscle Glycogen Phosphorylase deficiency.**

- **Biochemical alterations and manifestations:**
  - No Glycogenolysis in muscles.
  - Abnormal Glycogen storage in muscles.
  - Excersise Intolerance.
  - Muscle cramps
  - Myoglobinuria.

Her's Disease

- **Enzyme Defect:**
- **Hepatic Glycogen Phosphorylase deficiency.**

- **Biochemical alterations and manifestations:**
  - No Glycogenolysis in liver.
  - Abnormal Glycogen storage in hepatocytes.
  - No correction of fasting Hypoglycemia.
  - Hepatomegaly
  - Mild Ketosis.
  - Frequent feedings of Carbohydrate required.

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- **Tauri's Disease**

- **Enzyme Defect:**
- **Phospho Fructo Kinase deficiency.(Of Glycolysis)**

- **Biochemical alterations and manifestations:**
  - Muscle Glycogenolysis is linked with muscle Glycolysis.
  - PFK deficiency of Glycolysis accumulates Glucose-6 -PO_4 in muscles.
  - Glucose-6-PO_4 allosterically stimulates Glycogenesis and inhibits Glycogenolysis which accumulates Glycogen abnormally.

List Of Glycogen Storage Disorders

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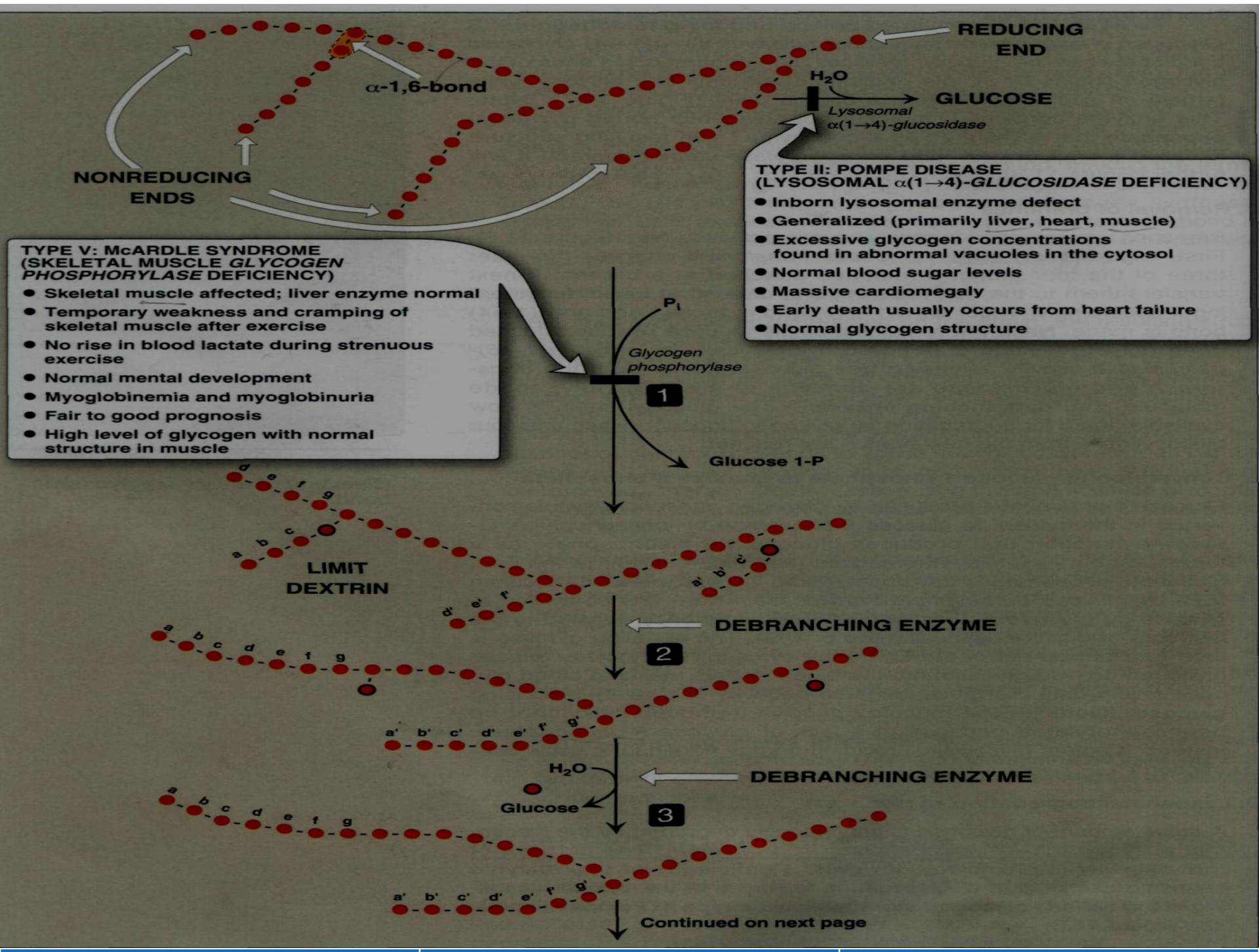

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Type V	Macrdle's Disease	Muscle Glycogen Phosphorylase
Type VI	Her's Disease	Hepatic Glycogen Phosphorylase
	~~Lewi's Disease~~	~~Glycogen Synthase~~.

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Pneumonic To Remember

Very Private Conversation At My Home Lawn Table.

Hexose Mono Phosphate Shunt

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Synonyms

- HMP Shunt
- Pentose Phosphate Pathway (PP Pathway)
- 6-Phosphogluconate Pathway
- Direct Oxidative Pathway
- Dicken's Horecker Pathway
- NADPH+H^+ Generating Pathway.

- HMP Shunt is an **alternative oxidative pathway of Glucose**.
- It's a **multifunctional pathway**.
- It **has no involvement of ATP**.
- Do **not require Oxygen**.

- NADPH+H^+ is generated.

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- **HMP shunt is more anabolic in nature and generates:**
  - **Reducing equivalents- $NADPH+H^+$**
  - **Pentose Sugar- Ribose-5-Phosphate.**

- In HMP shunt **6 molecules of Glucose-6-PO_4 makes its entry.**
- 1 molecule of Glucose is oxidized ($6CO_2$+ 12 $NADPH+12H^+$)
- **5 molecules of Glucose are regenerated** (Glyceraldehyde-3-PO_4 and Fructose-6-PO_4).

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- **$NADPH+H^+$** generated in HMP shunt **supports Lipogenesis.**
- Where in well fed condition free and excess Glucose is transformed to **Fatty acid and Cholesterol**.

- **$NADPH+H^+$** generated in HMP shunt do not enter in ETC and do not produce ATPs.

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Where HMP Shunt Operates?

Organs and Cellular Site Of HMP Shunt

- **Cytoplasm of Following Tissues:**
  - Liver (30%)
  - Erythrocytes (30%)
  - Gonads (10%)
  - Adrenal Gland (10%)
  - Adipose Tissue (10%)
  - Lactating Mammary Gland (10%)

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Condition Of Operation Of HMP

- HMP shunt operates in a **well fed condition** after a heavy rich Carbohydrate meals.

Reactions Of HMP Shunt

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$$6(\text{Glucose-6-PO}_4)+12\text{NADP}^+ +6\text{H}_2\text{O}$$

HMP Shunt

$$6\text{CO}_2+12\text{NADPH}+12\text{H}^+ +$$

$$2(\text{Glyceraldehyde-3-PO}_4)+4(\text{Fructose-6-PO}_4)$$

- In HMP Shunt 6(Glucose-6-PO_4)=

  36 Carbon atoms.
- 6CO_2 and 12 NADPH+H+ generated=

  1 Glucose oxidation
- 30 Carbons are regenerated in the form of
  - 2(Glyceraldehyde-3-PO_4)

    { 2x3= 6 Carbons}
  - 4(Fructose-6-PO_4)

    {4x6=24 Carbons}

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Reactions of HMP Shunt:

Glucose-6-PO4 (6C)

★ Glucose-6-PO4 Dehydrogenase (G-6-P-D) — NADP+ OXIDATION → NADPH+H+

6-Phospho Gluconolactone

Hydrolase — H_2O HYDRATION

6-Phospho Gluconate

6-Phospho Gluconate Dehydrogenase — NADP+ OXIDATION & CO_2 → NADPH+H+ DECARBOXYLATION

Ribulose-5-Phosphate (5C)

PHASE-I OXIDATIVE PHASE

Epimerase OR Aldo-Keto Isomerase. Isomerization

Xylulose-5-PO4 (5C) | Ribose-5-PO4 (5C)

2C of X-5-P to R-5-P → TPP Transketolase

Glyceraldehyde-3-PO4 (3C) | Sedoheptulose-7-PO4 (7C)

3C of S-7-P to G-3-P → Transaldolase

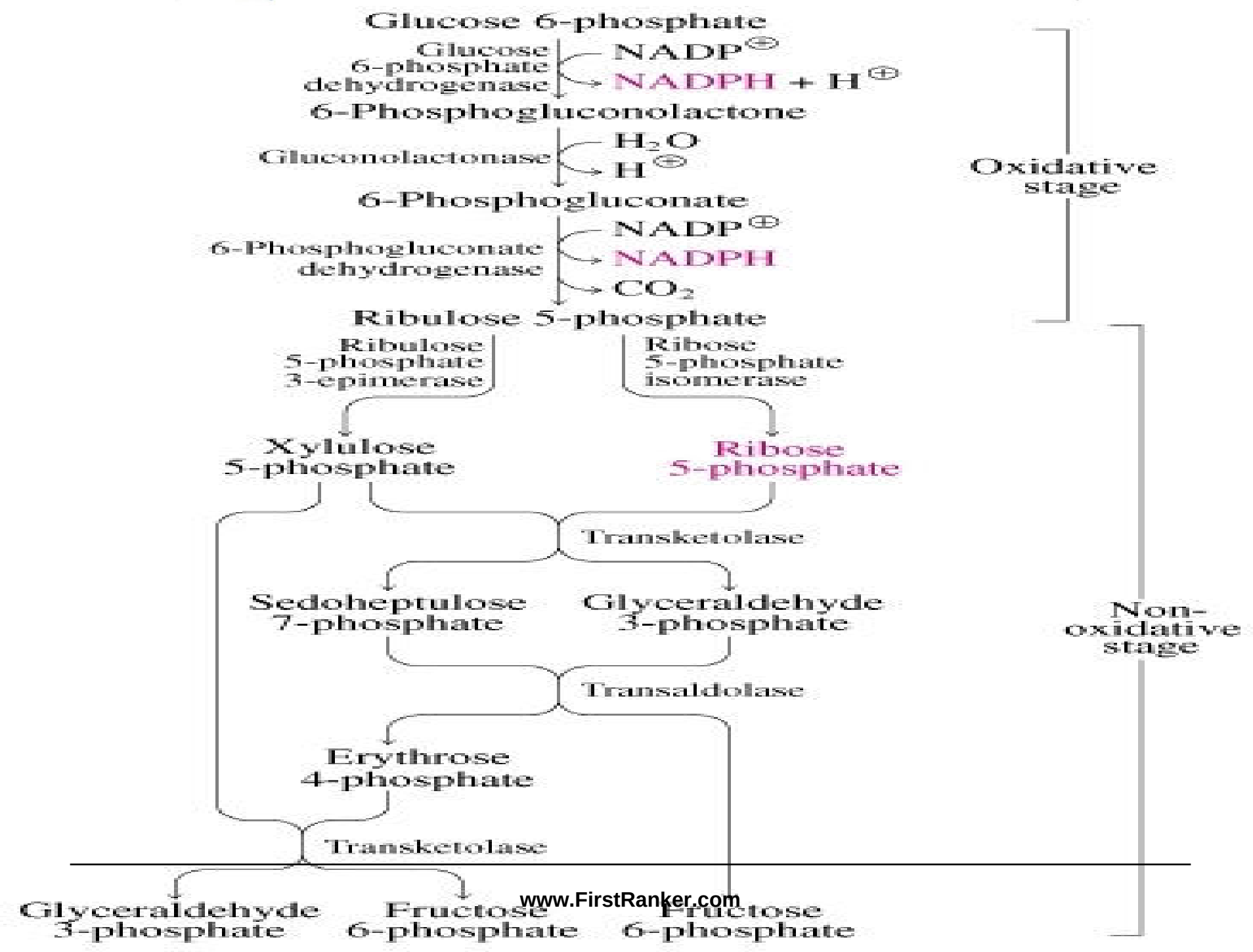
Erythrose-4-PO4 (4C) | Fructose-6-PO4 (6C)

Glyceraldehyde-3-PO4 (3C) — TPP — Transketolase — Fructose-6-PO4 (6C)

2C of X-5-P to E-4-P

PHASE-II NON-OXIDATIVE PHASE

Fructose-6-PO4 → Enter Glycolysis and get metabolized.



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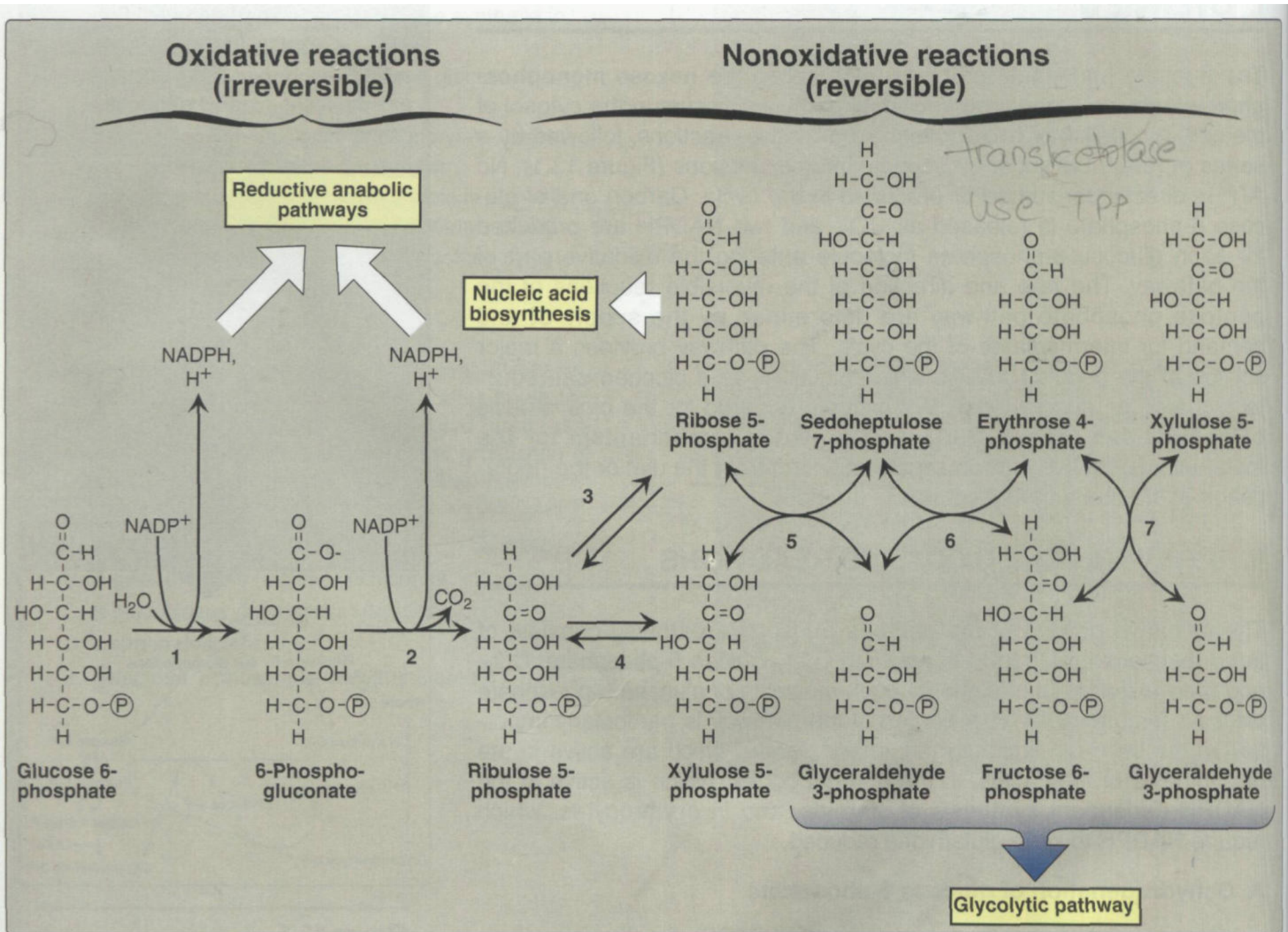

- HMP shunt includes two irreversible oxidative reactions $NADP^+$ dependent.
- Series of reversible non oxidative sugar-phosphate inter (3-7 carbon).

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- **Transketolase** transfers C2 units: TPP requiring enzyme
- **Transaldolase** transfers C3 units
- Two enzymes control the rearrangement of carbon skeletons which result in the production of Glyceraldehyde-3-phosphate and Fructose-6-phosphate.

NADPH Producing Enzymes In HMP Shunt

- Glucose-6-P Dehydrogenase
- 6-P-Gluconate Dehydrogenase

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Regulatory Enzyme Of HMP

- **Glucose-6-PO_4 Dehydrogenase** (G6PD) is a regulatory enzyme of HMP Shunt.
- Insulin in well fed condition stimulates this enzyme and enhances the operation of HMP Shunt.
- NADPH+ H^+ inhibits Glucose -6- Phosphate Dehydrogenase.

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Significance Of HMP Shunt

- HMP Shunt predominantly and uniquely produces reducing equivalent – $NADPH+H^+$

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- **Uses of NADPH+H$^+$**

- NADPH+H$^+$ is used as a coenzyme for reduction reactions catalyzed by enzyme **Reductases** during reductive biosynthesis of :
  - **Fatty acids**
  - **Cholesterol**
  - **Steroidal Hormones**
  - **Certain Amino acids (GDH activity)**

Role Of NADPH+H$^+$ In RBC's

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- **NADPH+H$^+$** in RBC's serve as a coenzyme for enzyme **Glutathione Reductase.**

- **Glutathione Reductase** of RBC's in turn keeps an enzyme **Glutathione Peroxidase**(H_2O_2 detoxifying enzyme) **in reduced** and **active state**.

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- **NADPH+ H^+** in RBC's indirectly helps in **detoxification of H_2O_2**
- This allows **no accumulation** of **H_2O_2** within RBC's.
- In turn **maintains cell membrane integrity** and **prevent hemolysis.**

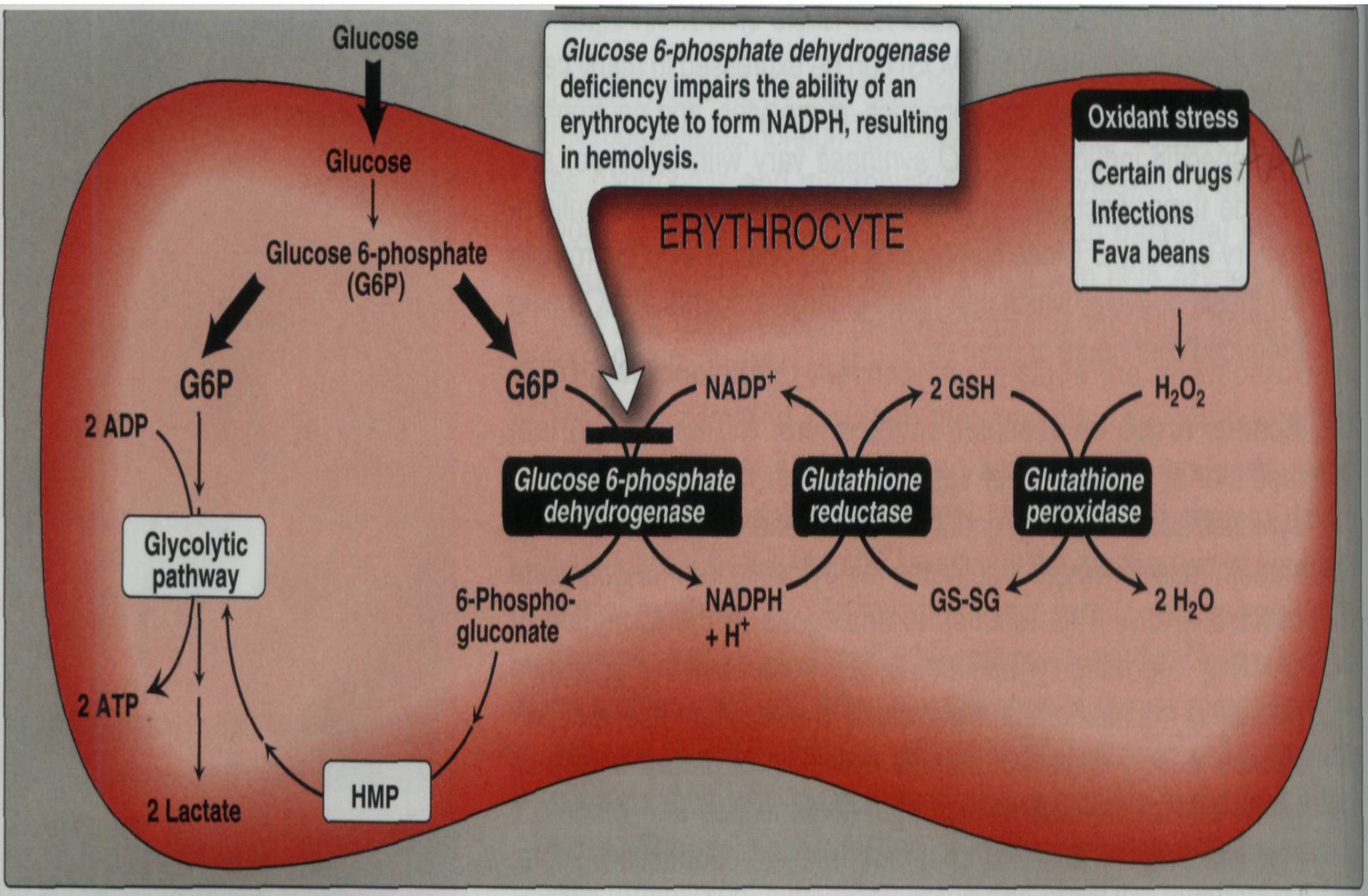

Figure 13.10
Pathways of glucose 6-phosphate metabolism in the erythrocyte.

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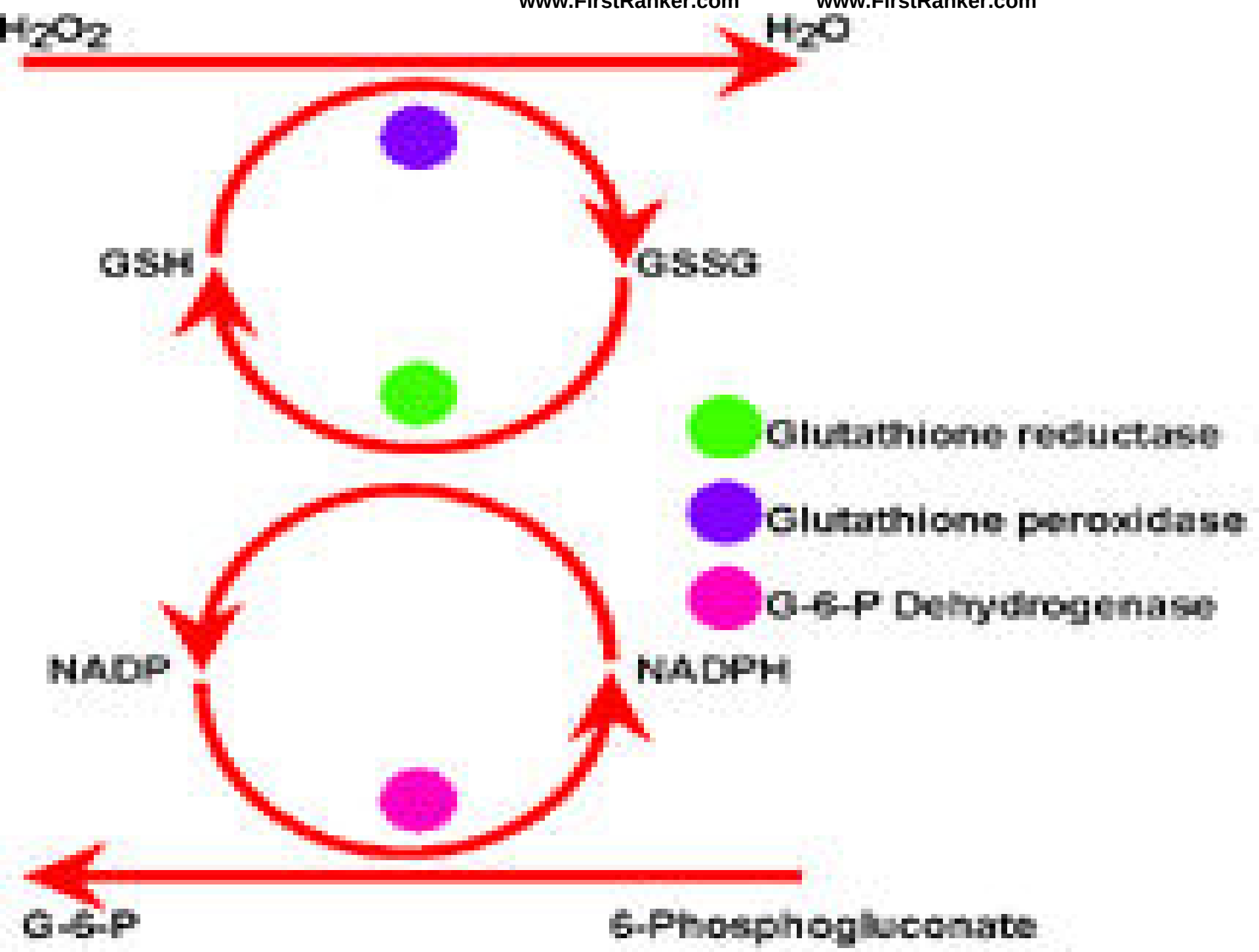

- **NADPH+ H^+** in RBC's keeps the **Hemoglobin iron in Ferrous** (Fe^{+2}) state and **prevents** from formation of **Methemoglobinemia**

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- **NADPH+ H^+** is used in **detoxification** of certain **drugs**(Mono Oxygenase System)through Cytochrome P450 system.

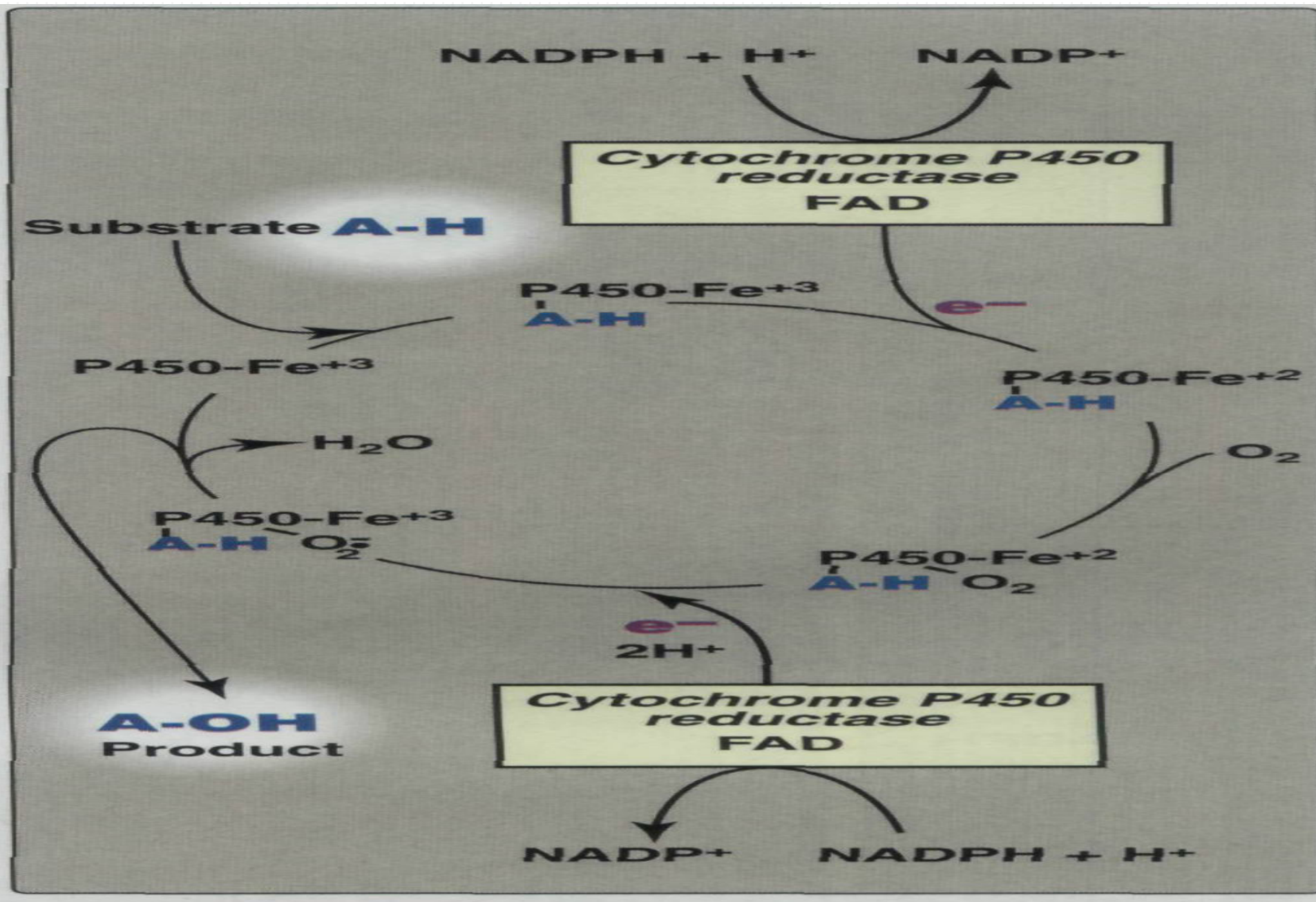

Figure 13.7 Cytochrome P450 monooxygenase cycle.

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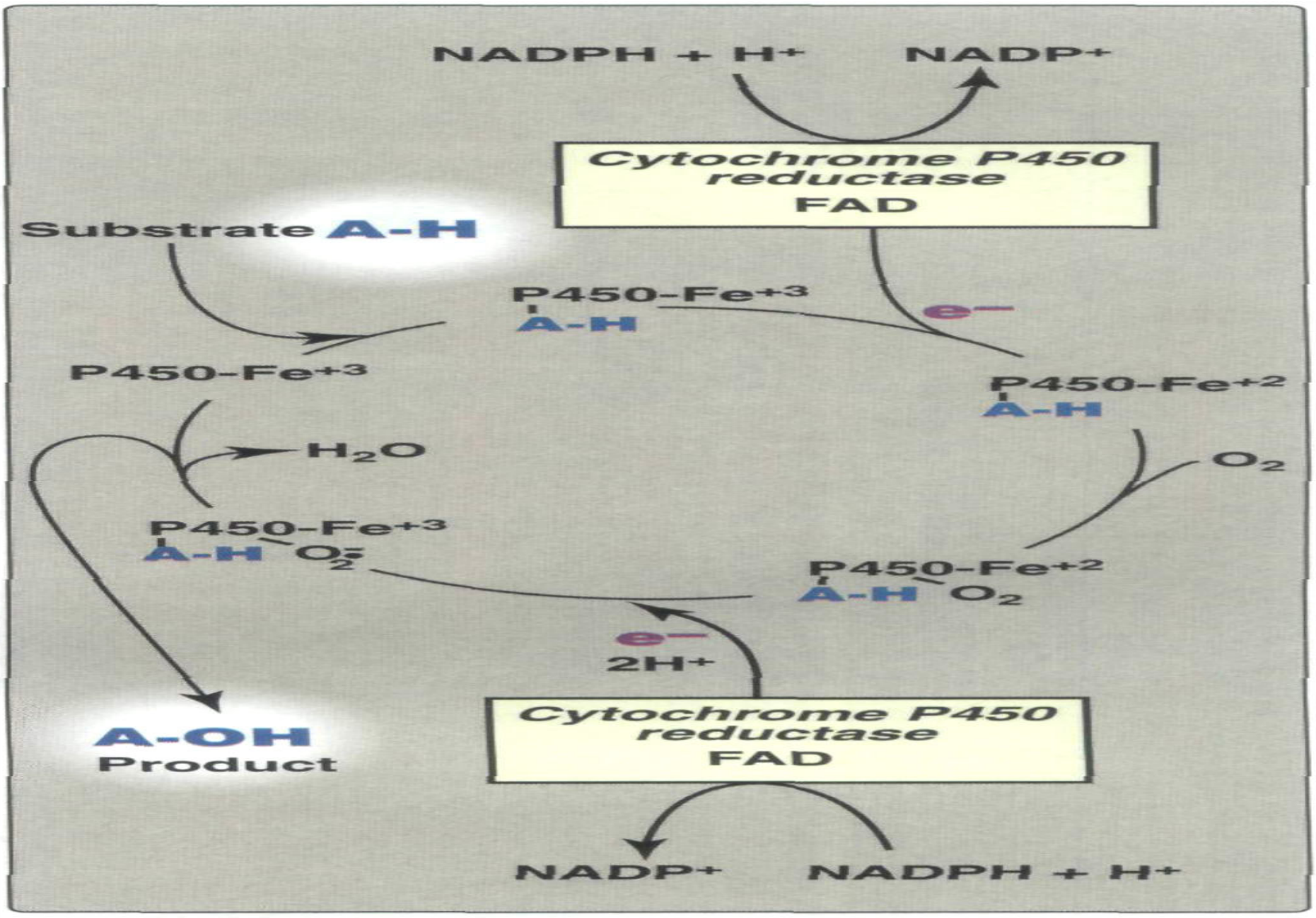

Figure 13.7
Cytochrome P450 monooxygenase cycle.

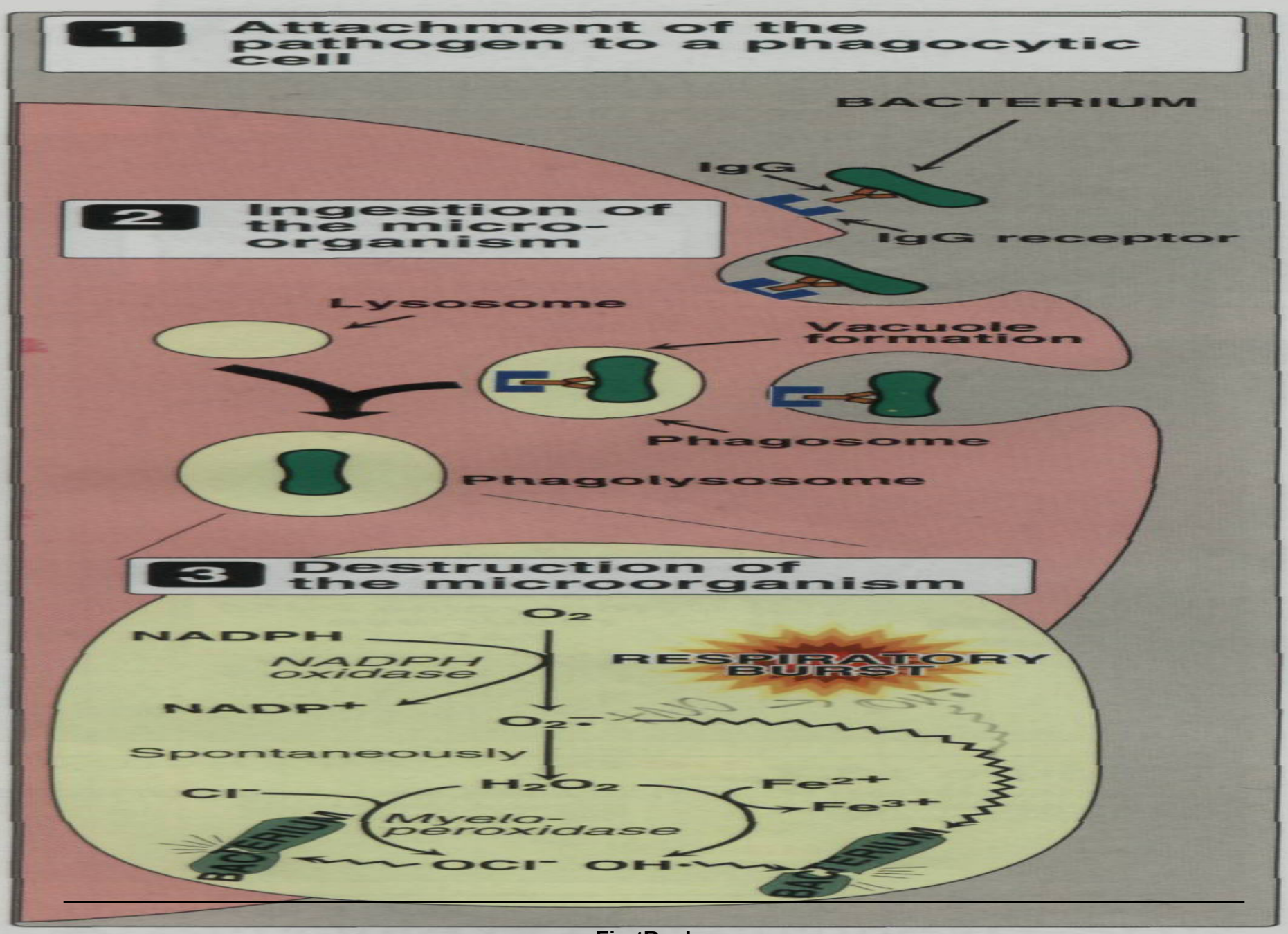

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Figure 13.8
Phagocytosis and the oxygen dependent pathway of microbial

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Enzymes Requiring $NADPH+H^+$

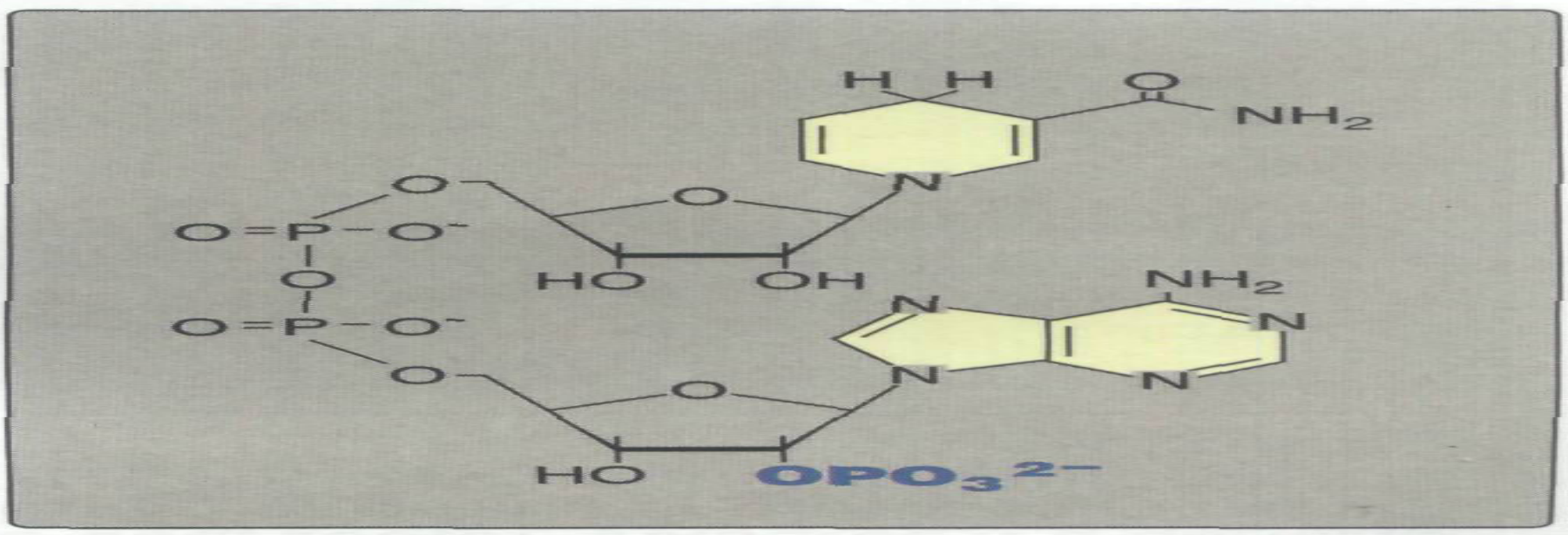

Figure 13.4
Structure of NADPH+H.

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- De novo Biosynthesis Of Fatty acids
  - Keto Acyl Reductase
  - Enoyl Reductase
- Cholesterol Biosynthesis:
  - HMG CoA Reductase
- In R.B.C's
  - Glutathione Reductase
  - Methemoglobin Reductase

- In Detoxification Process:
  - Bilirubin Reductase
  - Cytochrome P450 Reductase

- Uronic Acid Pathway
  - L- Xylulose Reductase
  - L- Gulonate Reductase

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- **Ribose-5-PO_4** another important byproduct of HMP Shunt is used for biosynthesis of Nucleotides, and certain nucleotide coenzymes-ATP,NAD,FAD and CoA

- HMP Shunt is an unique multifunctional pathway which involves interconversions of sugars:
  - 3 carbon (Glyceraldehyde-3-PO_4)
  - 4 carbon(Erythrose-4-PO_4)
  - 5 carbon (Ribose-5-PO_4)
  - 6 carbon (Fructose-6-PO_4)
  - 7 carbon(Sedoheptulose-7-PO_4)

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Inborn Error of HMP Shunt OR Glucose-6-Phosphate Dehydrogenase Deficiency

- Glucose -6-PO_4 Dehydrogenase(G.6.P.D) is the regulatory or key enzyme of HMP shunt.
- Persons with **G.6.P.D deficiency** suffer from **Hemolytic Anemia and Hemolytic Jaundice.**

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- G.6.P.D deficiency is **sex linked inherited.**
- **G.6.P.D deficiency** blocks HMP shunt and **decreases the levels of NADPH+H$^+$**
- Low levels of NADPH+H$^+$ in cells impairs the cell membrane integrity.
- **Lysis of RBC's- Hemolytic Anemia and Hemolytic Jaundice.**

Consequences Of G.6.P.D Deficiency In RBC's

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- **G.6.P.D deficiency in RBC's :**

- Decreases NADPH+H+ concentration.
- Lowers Glutathione Reductase activity.
- Lowers the active reduced form of Glutathione Peroxidase.
- Decreases detoxification of H_2O_2.
- Increases H_2O_2 levels in cell.(Toxic free radical).
- Increases Peroxidation of membrane PUFA's.
- Looses cell membrane integrity.
- Lysis of RBC membrane(Hemolysis).
- Hemolytic Anemia ,Hemolytic Jaundice, Methemoglobinemia.

- **Individuals with G.6.P.D deficiency are Resistant to Malaria.**
- **The Reasons for it are:**
- Low life span of R.B.C's.(Due to abnormal hemolysis)
- Incomplete life cycle of Malarial Parasites in such defective R.B.C's.

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- Persons with **G.6.P.D deficiency on** ingestion of Oxidant Drugs –Primaquine, Antipyretics (produces more H_2O_2) aggravate the condition and leads to **Hemolytic anemia.**

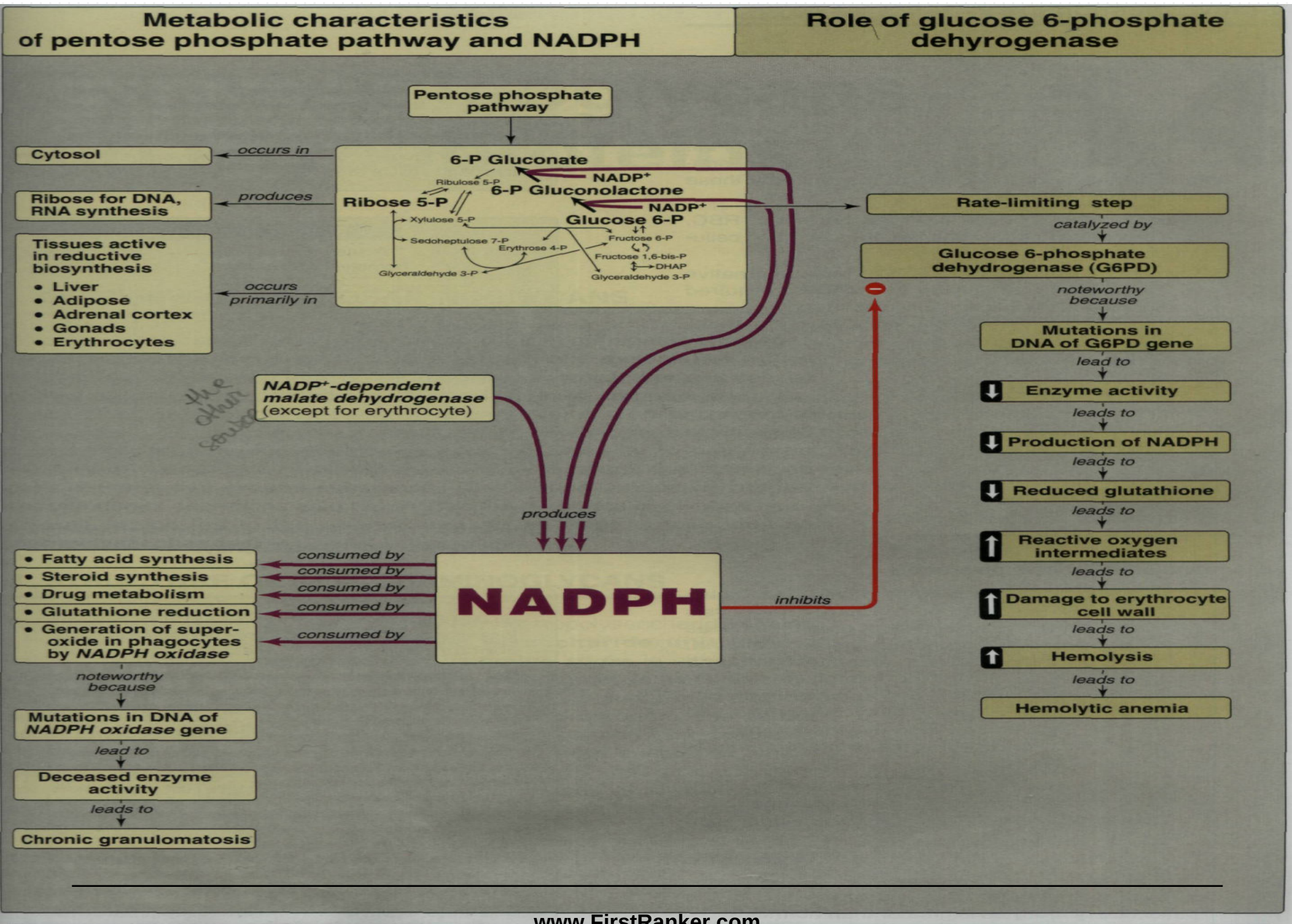

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Figure 13.14
Key concept map for the pentose phosphate pathway and NADPH.

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Gluconeogenesis

Synonyms

- Neo Glucogenesis.
- Biosynthesis of Glucose.
- Conversion of Pyruvate to Glucose.
- Metabolism Of Lactate.

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What Is Gluconeogenesis?

- **Gluconeogenesis is**
- Anabolic process
- Carried out in the Cytosol of Liver,
- In an emergency condition
- Under the influence of hormones Glucagon and Epinephrine
- **Biosynthesis of Glucose from non Carbohydrate precursors.**

Gluconeogenesis is the process whereby precursors such as Lactate, Pyruvate, Glycerol, and Glucogenic Amino acids are converted to Glucose.

Fasting requires all the Glucose to be synthesized from these non-carbohydrate precursors.

Most precursors must enter the **Krebs cycle at some point to be converted to Oxaloacetate.**

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- Humans consume 160 g of Glucose per day
- 75% of that is used up in the brain
- Body fluids contain only 20 g of Glucose
- Glycogen stores yield 180-200 g of Glucose
- The body must still be able to make its own Glucose

Where Gluconeogenesis Occur?

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Organs and Cellular Site For Gluconeogenesis:

- **Organs operating Gluconeogenesis:**

- Liver (Predominantly)
- Renal Cortex (1/10)

- **Cellular Site:**

- Mitochondria and Cytoplasm.

When Gluconeogenesis Operated?

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- **Gluconeogenesis predominantly takes place**

- **When blood Glucose is low.**
- **When cellular Glucose is deprived.**
- **In between meals.**
- **In response to Glucagon.**

- **Physiologically In fasting/Starvation conditions.**

- **Pathologically In Diabetes Mellitus**

(In D.M low levels of Insulin and high levels of Glucagon)

- Gluconeogenesis provides Glucose in slow and sustained manner in response to fall in blood Glucose.

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Glucogenic/Non carbohydrate Precursors

- The **source of Pyruvate and Oxaloacetate** for Gluconeogenesis during fasting or carbohydrate starvation is
- Mainly from **Amino acid catabolism**.

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- **Pyruvate** (Predominant precursor)
- **Lactate**(Anaerobic and Erythrocyte Glycolysis)
- **Propionyl-CoA**

  (βoxidation of odd chain fatty acid and Amino acid catabolism)
- **Glycerol** (Lipolysis, TAG breakdown)
- **Glucogenic Amino acids**

  (Ala, Asp, Ser, Gly, Tyr, Trp, His)
- **Intermediates of TCA cycle**

How Gluconeogenesis Occur?

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Steps Of Gluconeogenesis

- **Glycolysis** converts Glucose to Pyruvate.
- **Gluconeogenesis** converts Pyruvate to Glucose.

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- Gluconeogenesis and Glycolysis are **not exactly same** but **differs** in their **irreversible steps.**
- The reversible enzymes of both the pathways are same.

- **In Gluconeogenesis**

- **Seven steps of Glycolysis are retained.**
- **Three steps are replaced.**

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Three irreversible enzymes of Glycolysis.

- Glucokinase
- Phosphofructokinase
- Pyruvate Kinase

These 3 steps are bypassed in Gluconeogenesis.

- Glucose-6-Phosphatase
- Fructose-1,6-Bis Phosphatase
- PEP Carboxy Kinase (GTP dependent)
- Pyruvate Carboxylase(Requires ATP and Biotin)

Oxaloacetate is the starting material for Gluconeogenesis

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- Conversion of Pyruvate to PEP
- Is in two irreversible steps
- With two enzymes
- Requiring ATP and GTP

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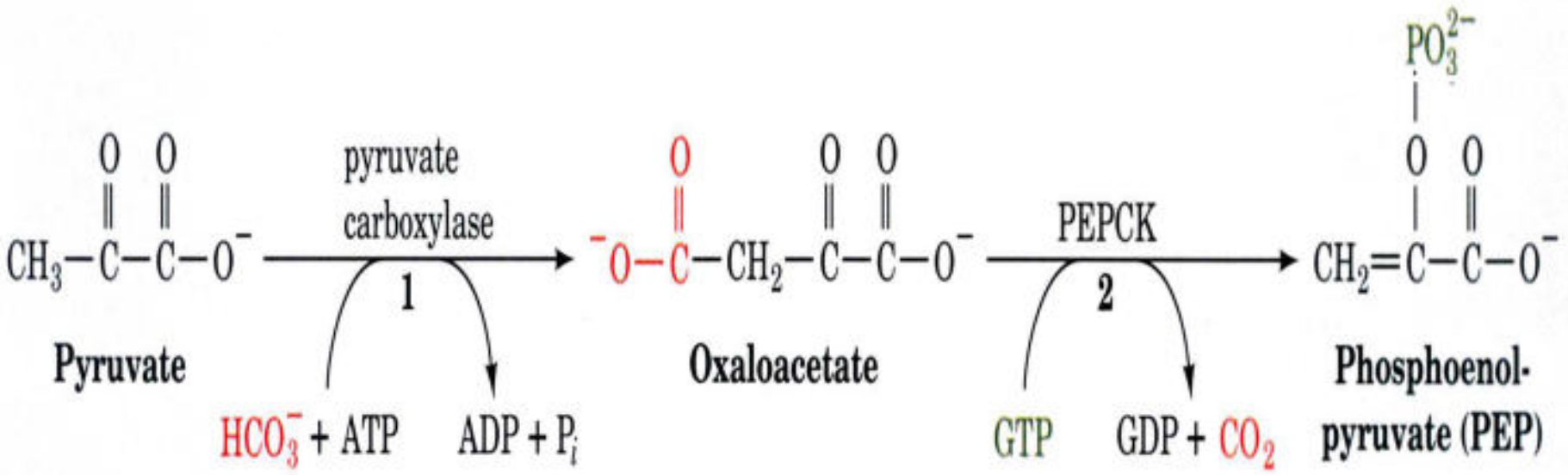
Pyruvate is converted to Oxaloacetate before being changed to PhosphoenolPyruvate

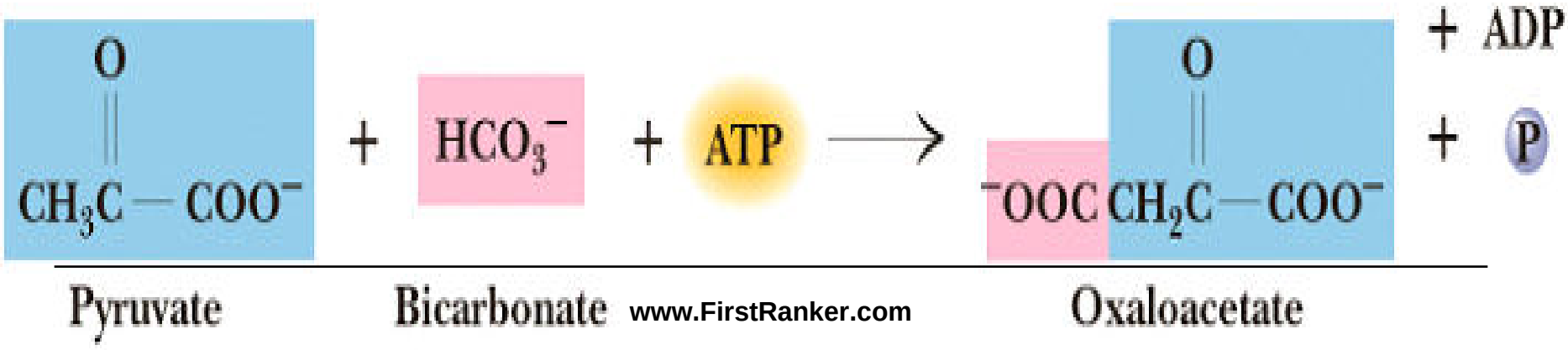


1. Pyruvate Carboxylase catalyses the ATP-driven formation of Oxaloacetate from Pyruvate and CO_2

2. PEP Carboxykinase (PEPCK) converts Oxaloacetate to PEP that uses GTP as a phosphorylating agent.

Pyruvate Carboxylase

- The reaction requires ATP and bicarbonate as substrates
- Biotin cofactor
- Acetyl-CoA is an allosteric activator
- Regulation: when ATP or acetyl-CoA are high, Pyruvate enters gluconeogenesis



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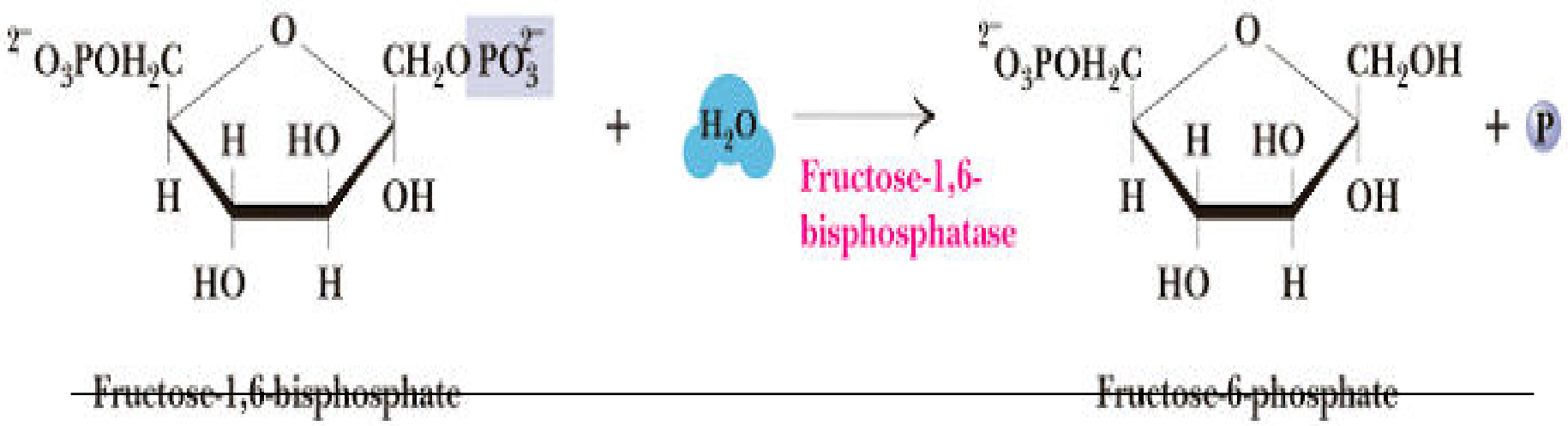
PEP Carboxykinase

- Not an allosteric enzyme
- Rxn reversible in vitro but irreversible in vivo
- Activity is mainly regulated by control of enzyme levels by modulation of gene expression
- Glucagon induces increased PEP Carboxykinase gene expression

Fructose-1,6-Bisphosphatase

- **Allosteric regulation:**
  - **Citrate stimulates**
  - **Fructose-2,6--Bisphosphate inhibits**
  - **AMP inhibits**



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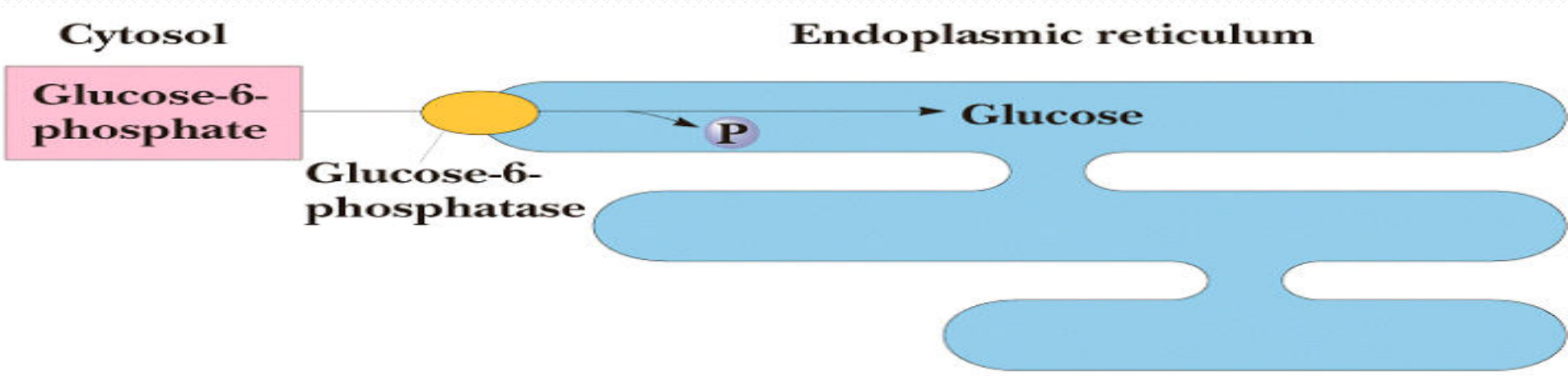
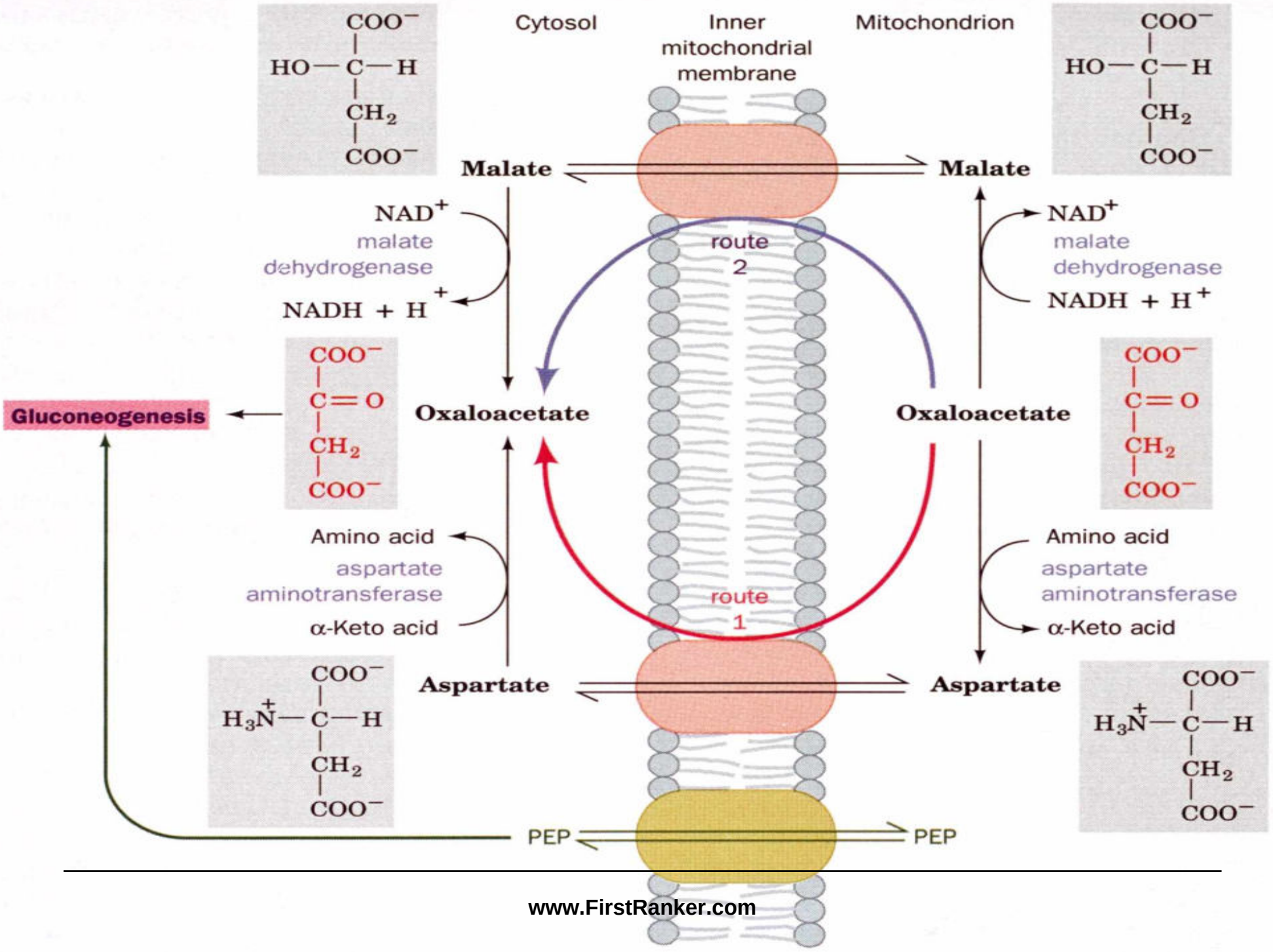
Glucose-6-Phosphatase

- Presence of G-6-Pase in ER of liver and kidney cells makes gluconeogenesis possible
- Muscle and brain do not do gluconeogenesis
- G-6-P is hydrolyzed as it passes into the ER
- ER vesicles filled with glucose diffuse to the plasma membrane, fuse with it and open, releasing glucose into the bloodstream.





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ATP Use In Gluconeogenesis

- 2 ATPs are used in Pyruvate Carboxylase reaction of Gluconeogenesis.
- 2 GTPs are used in PEP Carboxykinase step of Gluconeogenesis generated in TCA cycle.
- 2 ATPs are used in Phospho Glycerate Kinase activity.

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- Net 6 ATP's are utilized during Gluconeogenesis for biosynthesis of 1 Glucose molecule from 2 molecules of Pyruvate.

Entry Of Glucogenic Precursors For Gluconeogenesis

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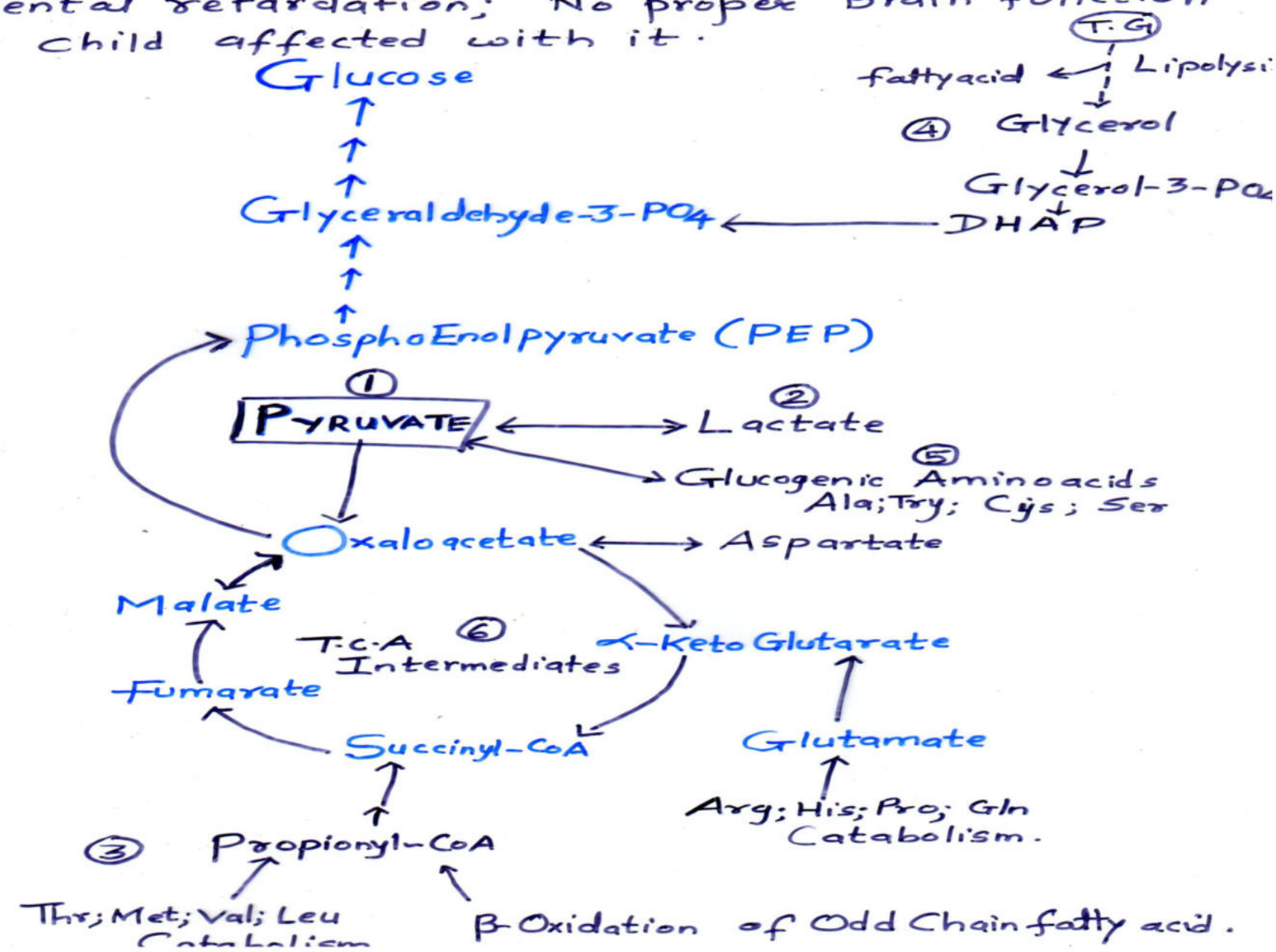
Inborn Error of Gluconeogenesis : (61)

Cause - Pyruvate Carboxylase Deficiency.

Blocks - Gluconeogenesis

- ★ Does not correct Hypoglycaemia
- ★ Mental retardation; No proper Brain function in child affected with it.



Regulation Of Gluconeogenesis

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Regulatory Enzymes Of Gluconeogenesis

- **Four irreversible enzymes** of **Gluconeogenesis** are its regulatory enzymes.
  - **Pyruvate Carboxylase**
  - **PEP Carboxy Kinase.**
  - **Fructose-1,6-Bis Phosphatase.**
  - **Glucose-6- Phosphatase.**

- Gluconeogenesis and Glycolysis are reciprocally regulated ,i.e if one pathway is active another is relatively inactive.

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- In a well fed condition **Insulin inhibits Gluconeogenesis.**
- In emergency condition **Glucagon stimulates Gluconeogenesis.**

- To prevent the waste of a futile cycle, Glycolysis & Gluconeogenesis are **reciprocally regulated**.

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- **Glucagon** via cAMP cascade of reactions brings covalent modification of enzymes.
  - **Pyruvate Carboxylase.**
  - **PEP Carboxy Kinase.**
- **Stimulate Gluconeogenesis.**
- Simultaneously **Glucagon Inhibits Pyruvate Kinase of Glycolysis.**

Substrate Availability and Regulation Of Gluconeogenesis

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- Increased availability of Glucogenic precursors viz Lactate ,Glycerol, products of Glucogenic amino acids influences the rate of Gluconeogenesis.

Excess Acetyl-CoA in emergency condition Allosterically Stimulates Gluconeogenesis

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- In fasting or emergency condition .
- Glucose metabolism decreased.
- Lipid metabolism increased.
- Increased Lipolysis.
- Increased βOxidation of Fatty acids.
- Increased Acetyl-CoA.
- Acetyl-CoA stimulates Pyruvate Carboxylase for OAA synthesis.
- Simulates Gluconeogenesis.

Acetyl-CoA regulates Pyruvate Carboxylase

Increases in Oxaloacetate concentrations increase the activity of the Krebs cycle and Acetyl-CoA is an allosteric activator of the Carboxylase.

However when ATP and NADH concentrations are high and the **Krebs cycle is inhibited, Oxaloacetate goes to Glucose.**

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- **Pyruvate Carboxylase**

(Pyruvate → Oxaloactate) is allosterically **activated by acetyl CoA**.

- [Oxaloacetate] tends to be limiting for Krebs cycle.
- When Gluconeogenesis is active in Liver, Oxaloacetate is diverted to form Glucose.
- Oxaloacetate depletion hinders acetyl CoA entry into Krebs Cycle.
- The increase in [acetyl CoA] activates Pyruvate Carboxylase to make Oxaloacetate.

Reciprocal Regulation By Fructose-2,6-bisphosphate

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- The allosteric regulator **Fructose-2,6-bisphosphate** is synthesized & degraded by a **bi-functional enzyme** that includes 2 catalytic domains:

- **Fructose-2,6-bisphosphate** is synthesized from excess Glucose in well fed condition.

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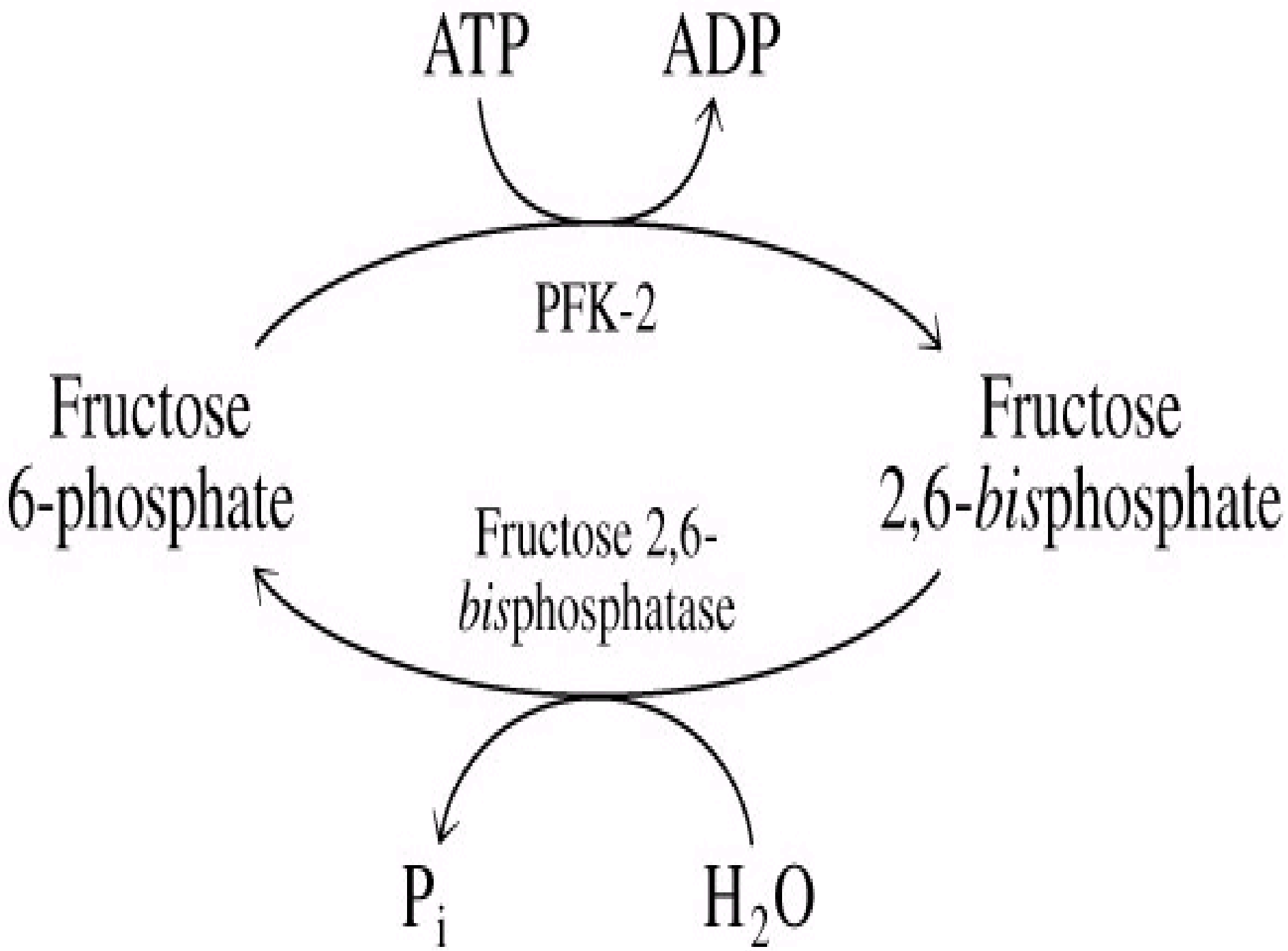

(II) Allosteric Effect Of Fructose-2,6-Bis-Phosphate :

Glucagon
↓
c-AMP
⊖
Phospho Fructo Kinase-2
ATP ADP
Fructose-6-PO4 ⇄ Fructose-2·6 Bis Phosphate
Pi Fructose-2·6 Bis-phosphatase
⊕
c-AMP
↑
Glucagon

Glycolysis
⊕ ↑
Phospho Fructo Kinase (PFK)
⊕
Fructose-2·6 Bis Phosphate
In well fed Condition
⊖
Fructose-1-6 Bis phospha-tase
⊖
Gluconeogenesis

★ Thus Fructose-2-6 Bis phosphate is Allosteric activator of PFK of Glycolysis.
Allosteric inhibitor of Fructose-1-6 Bis Phosphatase of Gluconeogenesis.

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- **Fructose-2,6-bisphosphate stimulates Glycolysis.**

  Fructose-2,6-bisphosphate allosterically **activates** the Glycolysis enzyme **PhosphoFructokinase 1(PFK1)**.

- **Fructose-2,6-bisphosphate** allosterically **inhibits** the **Gluconeogenesis** enzyme **Fructose-1,6-bisphosphatase**.

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Low blood [glucose]

↓

Increased glucagon secretion

↓

Increased [cAMP]

↓

Increased enzyme phosphorylation

↓

Activation of FBPase-2 and inactivation of PFK-2

↓

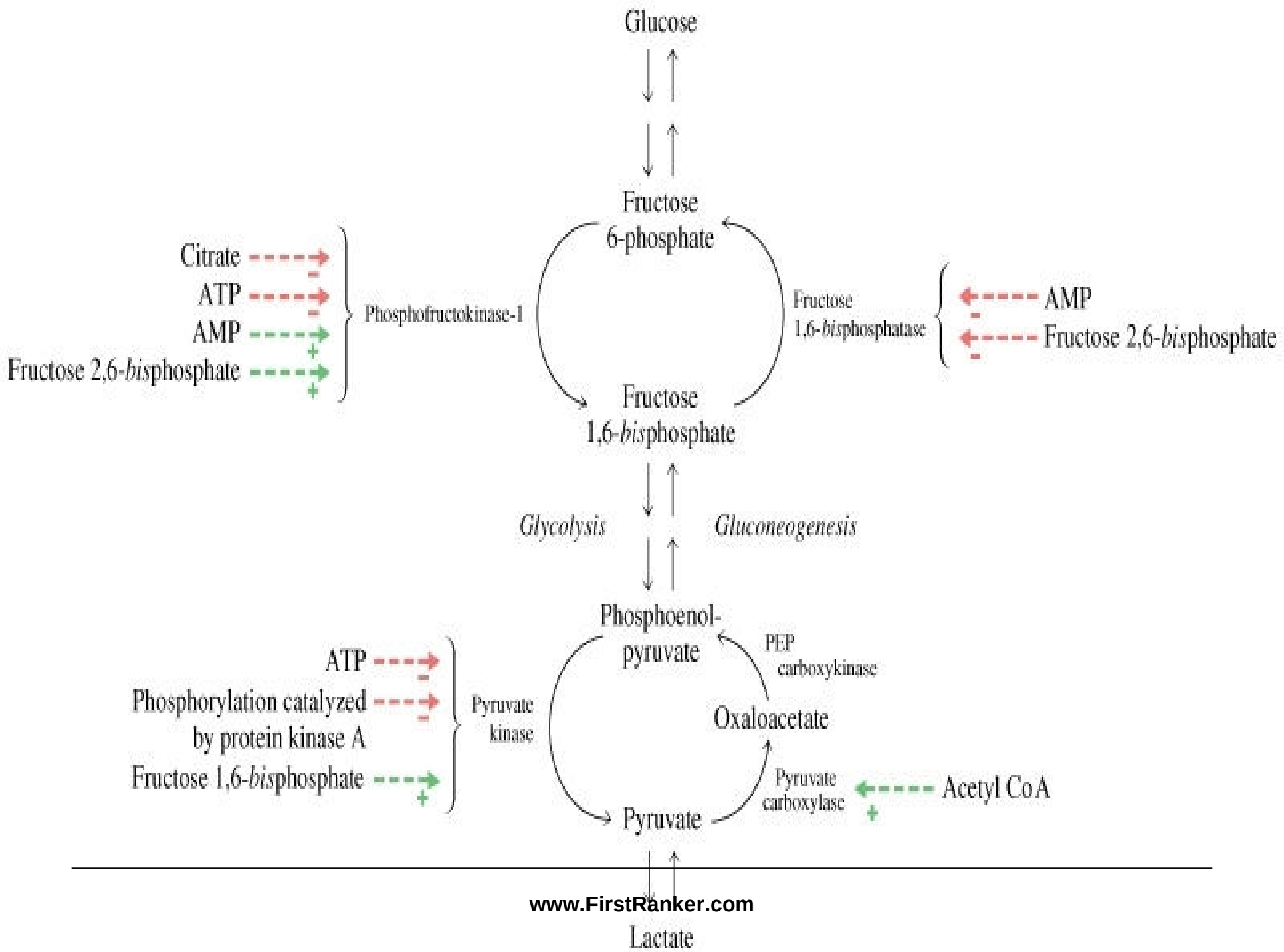
Decreased [F2,6P]

↓

Inhibition of PFK and activation of FBPase

↓

Increased gluconeogenesis



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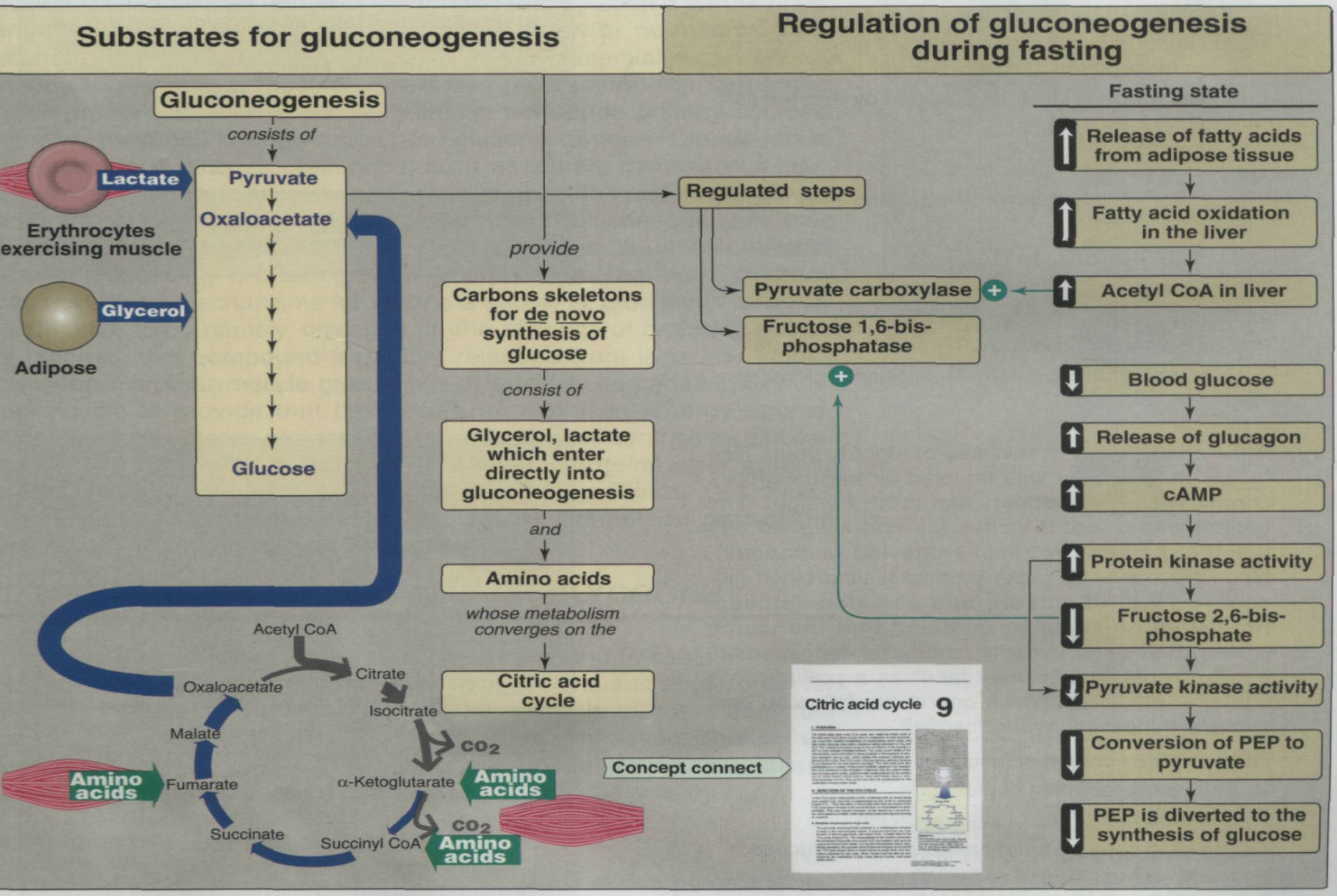

Figure 10.9
Key concept map for gluconeogenesis.

Significance Of Gluconeogenesis

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- Glucose is a primary source of energy.
- Brain and Erythrocytes are totally dependent upon Glucose for its energy in all states.
- Blood Glucose in fasting condition should be maintained to 70-110 mg%.
- Gluconeogenesis operates in critical emergency conditions when blood Glucose go below subnormal.

- Gluconeogenesis endogenously produces Glucose in Liver using non carbohydrate precursors **and regulate blood Glucose levels.**

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- Thus Gluconeogenesis **corrects fasting Hypoglycemia** and try to maintain the fasting blood Glucose of 70-110 mg%.
- Gluconeogenesis helps in supply of Glucose to Brain and Erythrocytes in emergency condition and maintain their functions.
- Gluconeogenesis by its operation **metabolizes Lactate, Propionyl CoA, and Glycerol obtained from other metabolic pathways.**

Cori's Cycle and Glucose Alanine Cycle

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- Cori's cycle metabolizes Muscle Lactate produced in anaerobic condition.

- The **Cori Cycle** operates during **exercise**.
- **Lactate** produced from Pyruvate in muscles in anaerobic condition ,passes via the blood to the **Liver**, where it may be converted to **Glucose by Gluconeogenesis.**

- The Glucose may travel back to the **muscle** to fuel **Glycolysis**.

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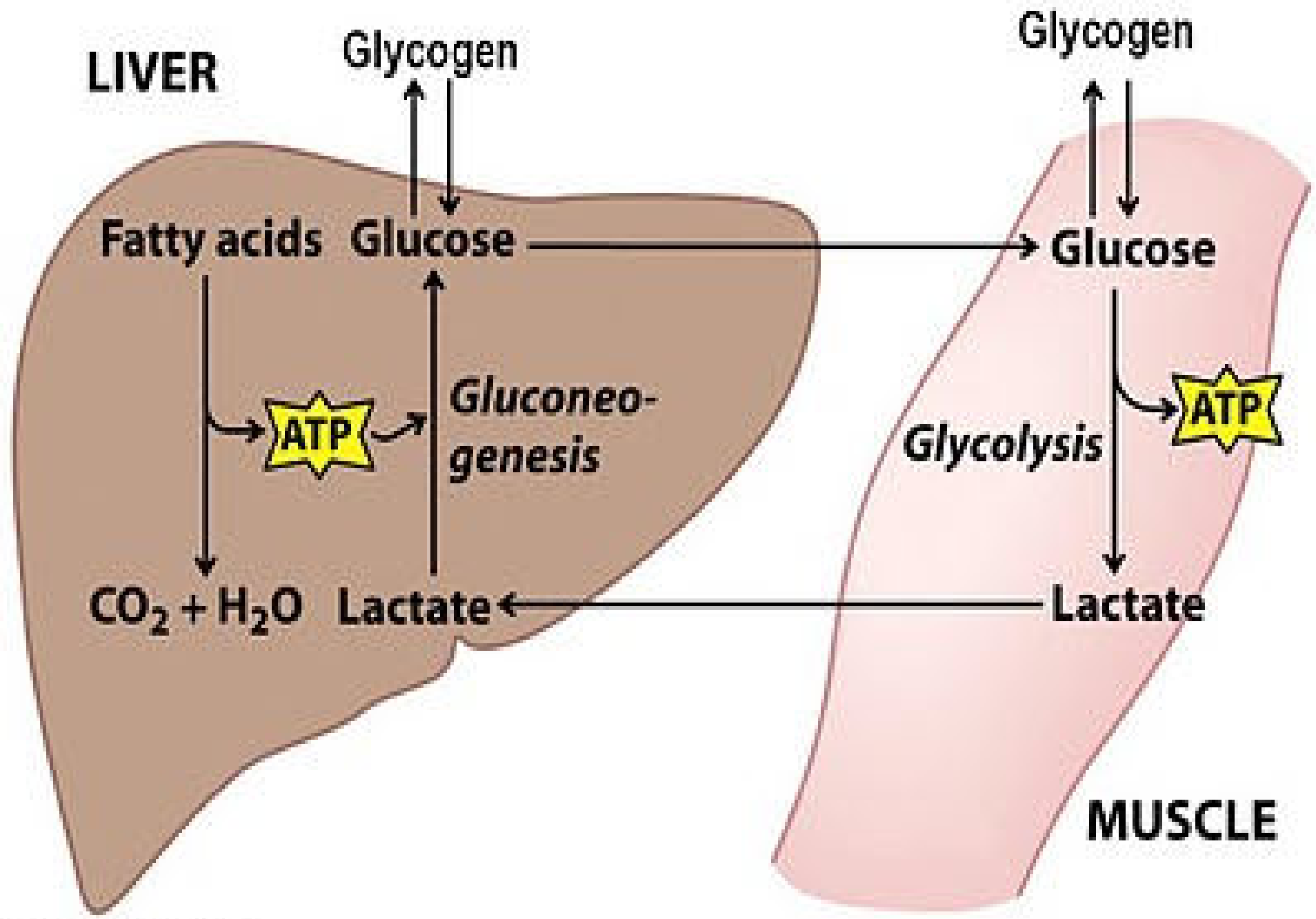

Principles of Biochemistry, 4/e
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Glucose Alanine Cycle (Cahill Cycle)

- Glucose Alanine Cycle is important during starvation.
- Glucose Alanine cycle is intimately related with Cori's cycle.

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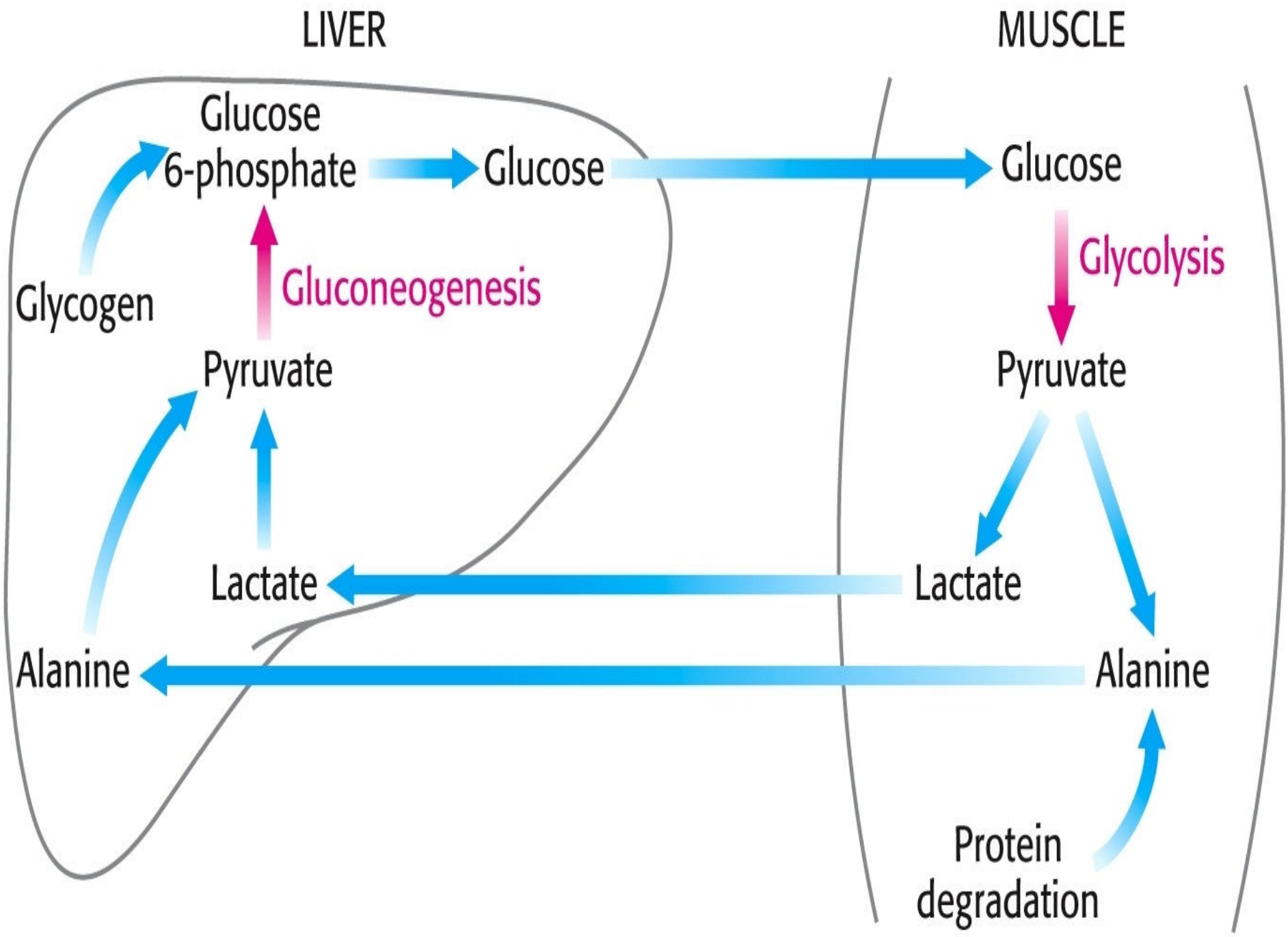

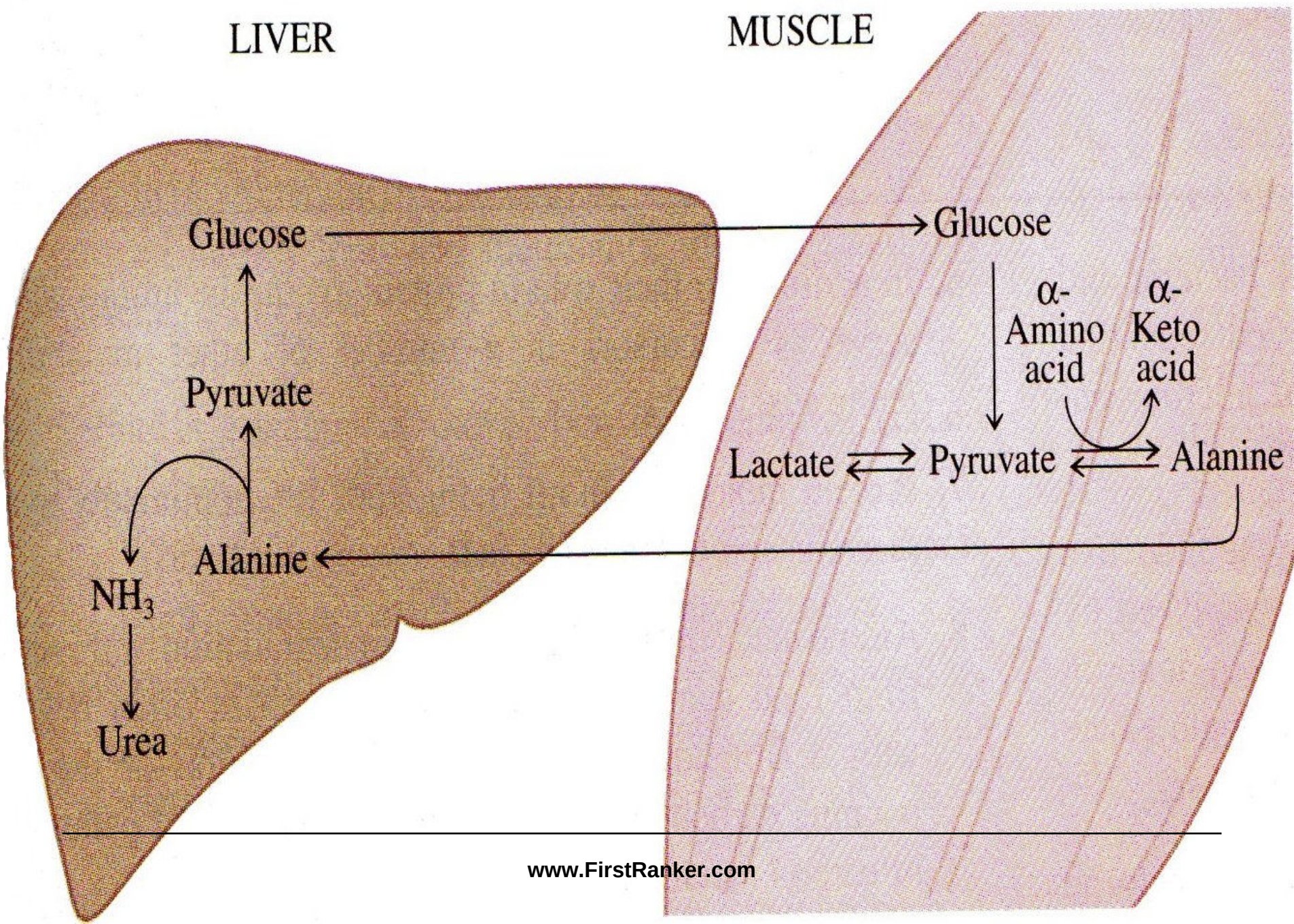

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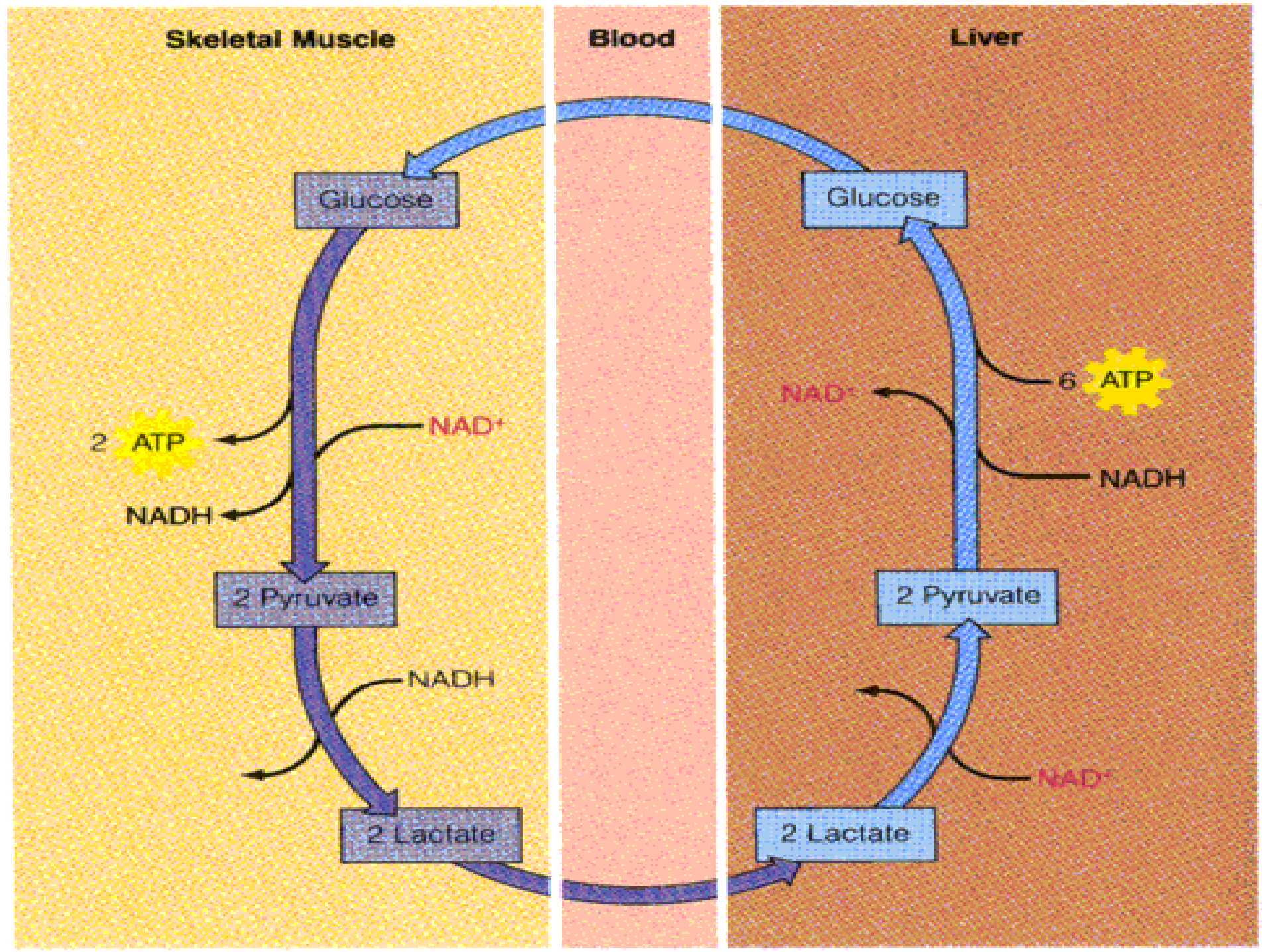

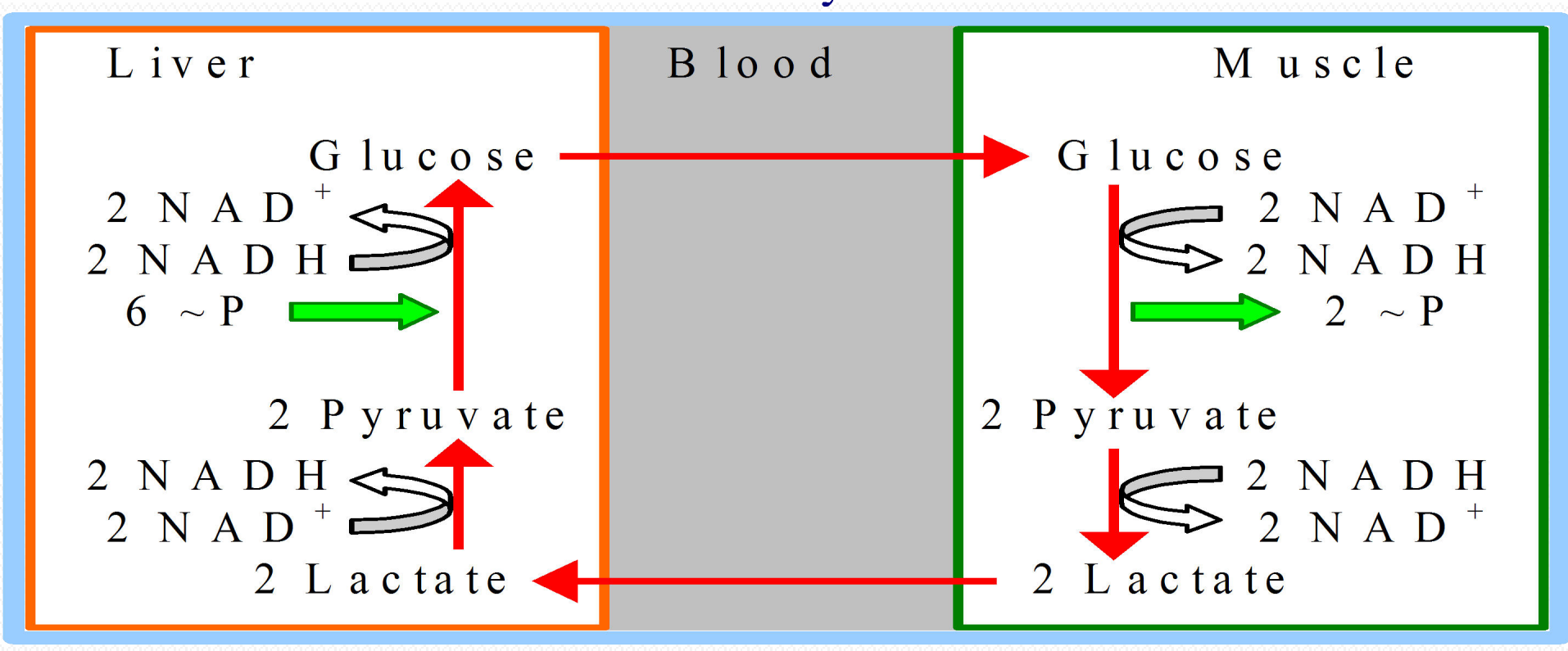

The Cori cycle **costs 6 ~P** in liver for every **2 ~P** made available in muscle. The **net cost is 4 ~P.**

Although costly in ~P bonds, the Cori Cycle allows the organism to accommodate to large fluctuations ~~in energy needs of skeletal muscle between rest and~~ exercise.

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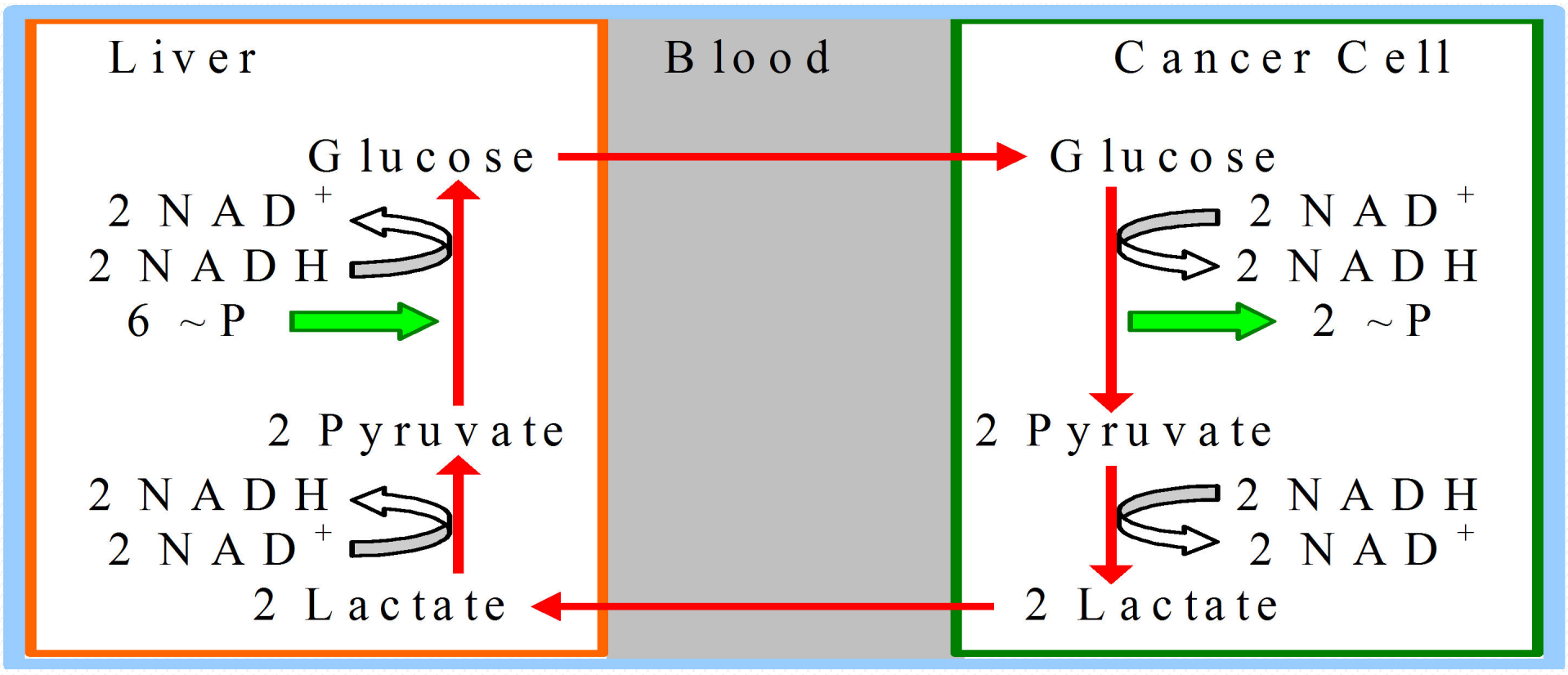

Energy dissipation by the **Cori Cycle**, which expends **6 ~P** in liver for every **2 ~P** produced via Glycolysis for utilization within the tumor, is thought to contribute to the **weight loss** that typically occurs in late-stage cancer even when food intake remains normal.

GN Ratio or DN Ratio

- Glucose Nitrogen Ratio
- Dextrose Nitrogen Ratio

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- During Starvation Muscle Proteins are degraded to release Glucogenic precursors(G).
- Nitrogenous Urea end product of Protein catabolism excreted out through urine(N).

- GN ratio =3.65
- 1 gm of Urea nitrogen produced will form 3.65 gm of Glucose.
- Protein contains 16% Nitrogen.
- 58% of Protein is Glucogenic

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- G N ratio gives idea of amount of body Protein degradation which provide precursors for Glucose production in emergency conditions.

- **GN ratio is enhanced in**
- Insulin deficiency
- Increased body Protein degradation
- Starvation
- Pyrexia
- Hyperthyroidism
- Cancer

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Uronic Acid Pathway

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Significance Of Uronic Acid Pathway

- Uronic Acid Pathway is minor Oxidative Pathway of Glucose.
- Uronic Acid Pathway oxidizes Glucose to Glucuronic acid.
- UDP-Glucuronate is an activated molecule produced in Uronic Acid Pathway which has specific roles in the body.

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Functions of UDP-Glucuronate:

- UDP-Glucuronate is a repeating unit of Mucopolysaccharides/ Glycosaminoglycans of human body.
- UDP-Glucuronate is component of Glycolipids-Cerebrosides and Gangliosides.
- UDP-Glucuronate serve as a **conjugating agent** for detoxification reactions in Liver.

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- Bilirubin in Liver is conjugated with 2 molecules of UDP-Glucuronate to form **Bilirubin di Glucuronide** [**conjugated Bilirubin**]

Inborn Error Of Uronic Acid Pathway

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- **Essential Pentosuria** is an inborn error of Uronic Acid Pathway.
- Essential Pentosuria is also a member of Garrod's Tetrad.
- **Enzyme Defect:**
  - **Xylitol Dehydrogenase/L-Xylulose Reductase.**
- Abnormally **L-Xylulose**(Pentose) accumulated in blood and excreted out in urine.

Galactose Metabolism

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Sources of Galactose

- **Dietary Exogenous Source of Galactose:**
  - Lactose- **Milk and Milk Products.**
  - Digestion of Lactose by **Lactase** liberates Galactose and Glucose.
- **Bodies Endogenous Source of Galactose:**
  - Breakdown product of GAG's, Glycoprotein and Glycolipids.

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- Infants major food is milk.
- Galactose is equally present along with Glucose in their GIT.

Absorption And Fate Of Galactose

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- Galactose from an intestinal lumen is **actively absorbed** with **relative coefficient** of absorption of **110.**
- Galactose absorbed in intestinal mucosal cells diffuse into **Hepato Portal circulation and carried to Liver.**
- **Galactose in Liver is metabolized and transformed to Glucose.**

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Conversion Of Galactose To Glucose In Liver Cells :

Galactose

PHOSPHORYLATION — ATP / ADP — Galactokinase

Galactose-1-PO4

UDP-Glucose — Gal-1-PO4 Uridyl-transferase

Glu-1-PO4 → Glu-6-PO4 → Glycolysis

UDP-Galactose → Lactose (Lactating women), GAG's, Glycolipids.

Transferase

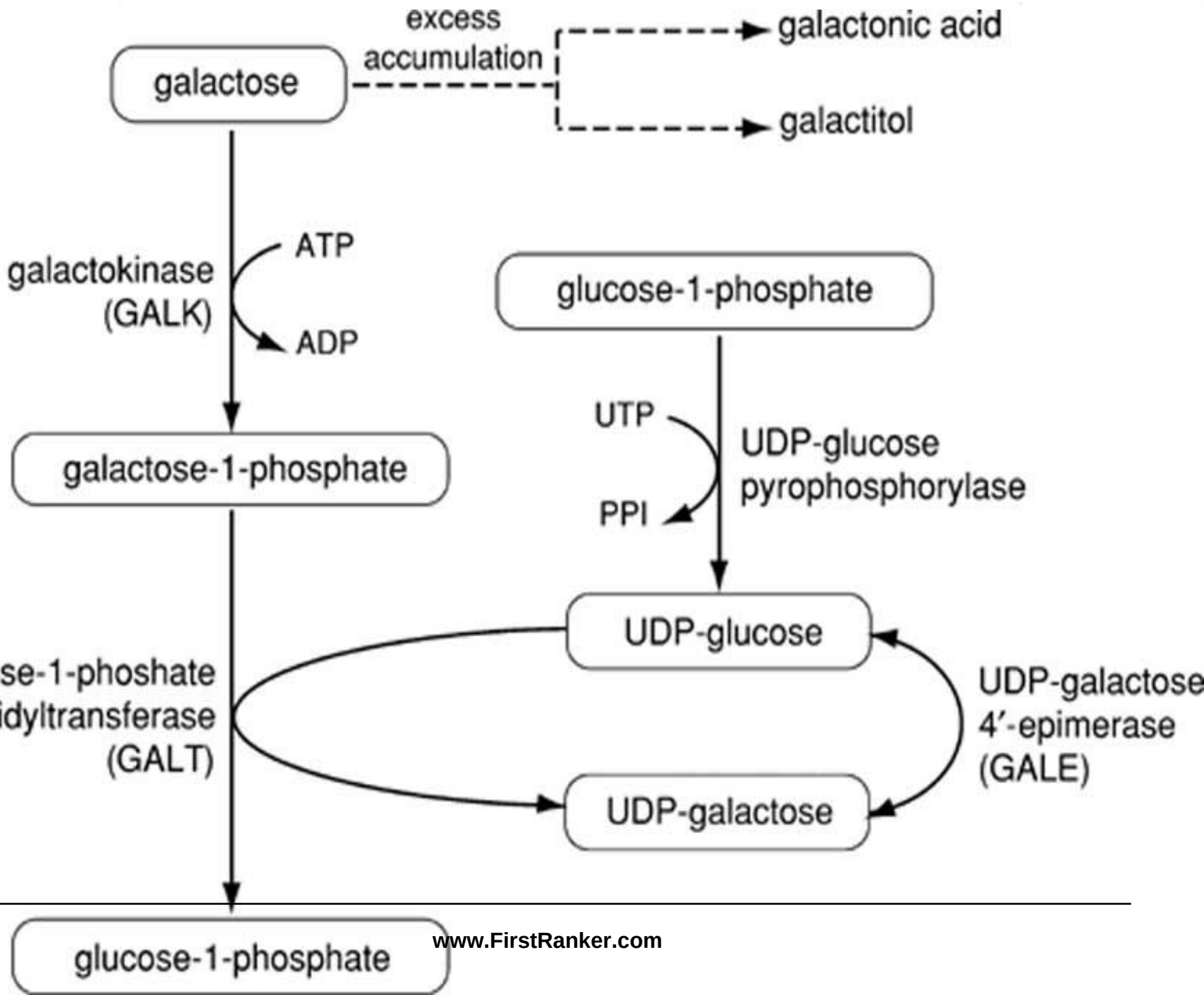
Epimerization

UDP-Hexose-4-Isomerase or Epimerase

UDP-Glucose

Enters Glycogenesis.

Glycogen



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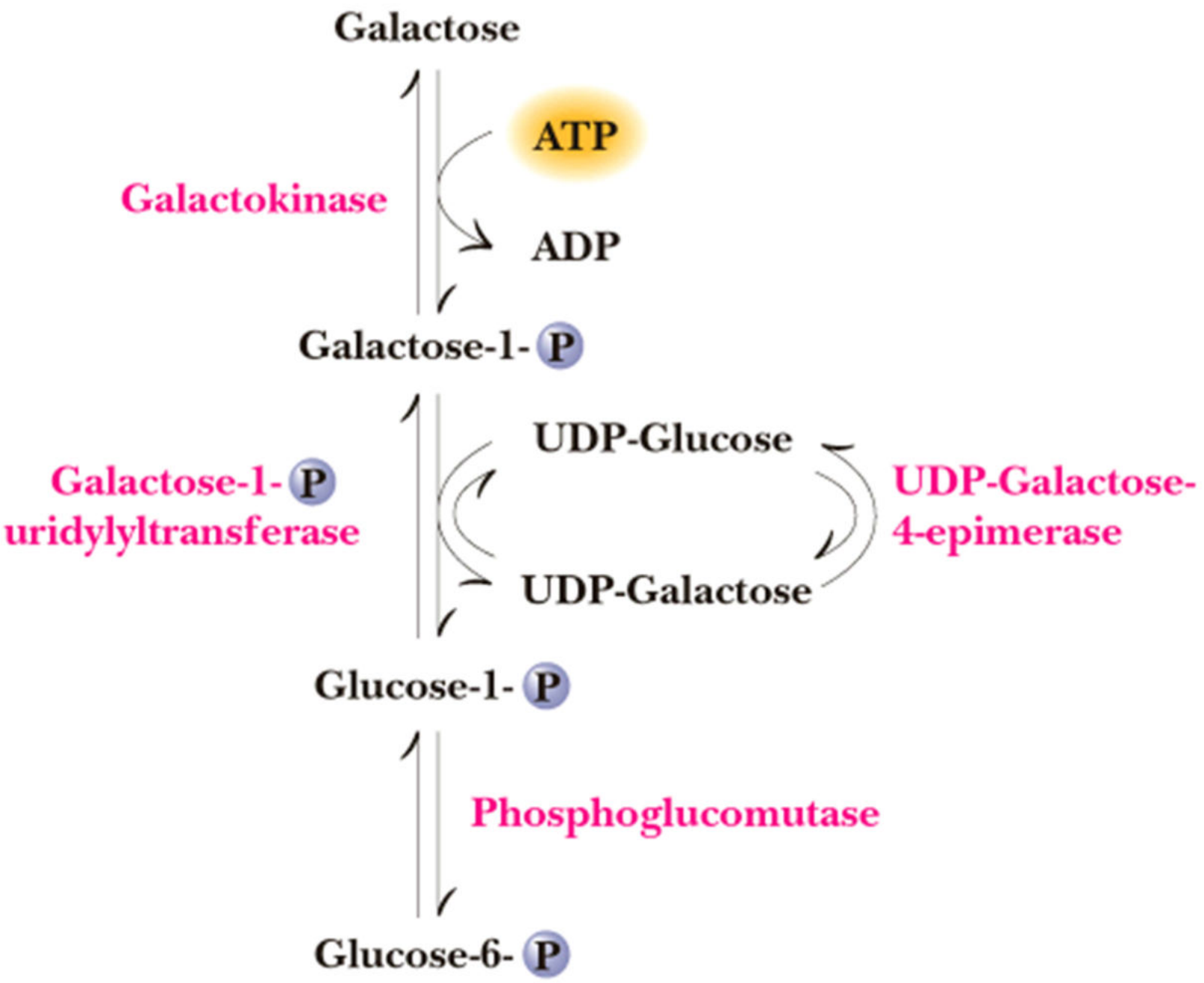

Inborn Errors Of Galactose Metabolism

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Galactosaemia

- **Enzyme Deficient: Galactokinase**
  - **Biochemical Alterations:**
- Galactose not metabolized to Glucose.
- No phosphorylation of Liver Galactose to Galactose-1-PO4.
- Free Galactose(permeable) from Liver, move out in blood.
- **Galactosemia**-Increased levels of Galactose in blood.
- **Galactosuria**-Galactose excreted in urine.

Galactosemia Leads To Cataract

- In Galactosemia the high levels of blood Galactose rich to eyes and get accumulated.
- In the lens cells the accumulated **Galactose is reduced to Galactitol.**
- **Galactitol in lens cause opaqueness of lens.**
- Causing Cataract.

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Classical Galactosemia

- **Enzyme Deficient:**

Galactose-1-PO_4 Uridyl Transferase.

- **Biochemical Alterations and Clinical Manifestations:**
- Blocks the conversion of Gal-1-p04 to UDP-Galactose.
- Accumulation of **Galactose-1-p04 in Hepatocytes.**
- Hepatomegaly
- Splenomegaly
- Loss of Weight
- Weakness
- Hepatic Jaundice.
- Mental Retardation

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- Infants (Milk fed) whose principle dietary carbohydrate is Galactose are more affected during inborn error of Galactose metabolism.

Fructose Metabolism

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Sources Of Fructose

- Fructose is present in free form in **Fruits and Honey.**
- Fructose is a component **of Sucrose.**
- Sucrose digestion by **Sucrase** liberates free Glucose and Fructose.
- Endogenously Fructose is richly present in **seminal fluid.**

Absorption and Fate Of Fructose

- Fructose from intestinal lumen is absorbed by **facilitated diffusion.**
- From intestinal mucosal cells it is carried to Liver by **Hepato Portal circulation.**

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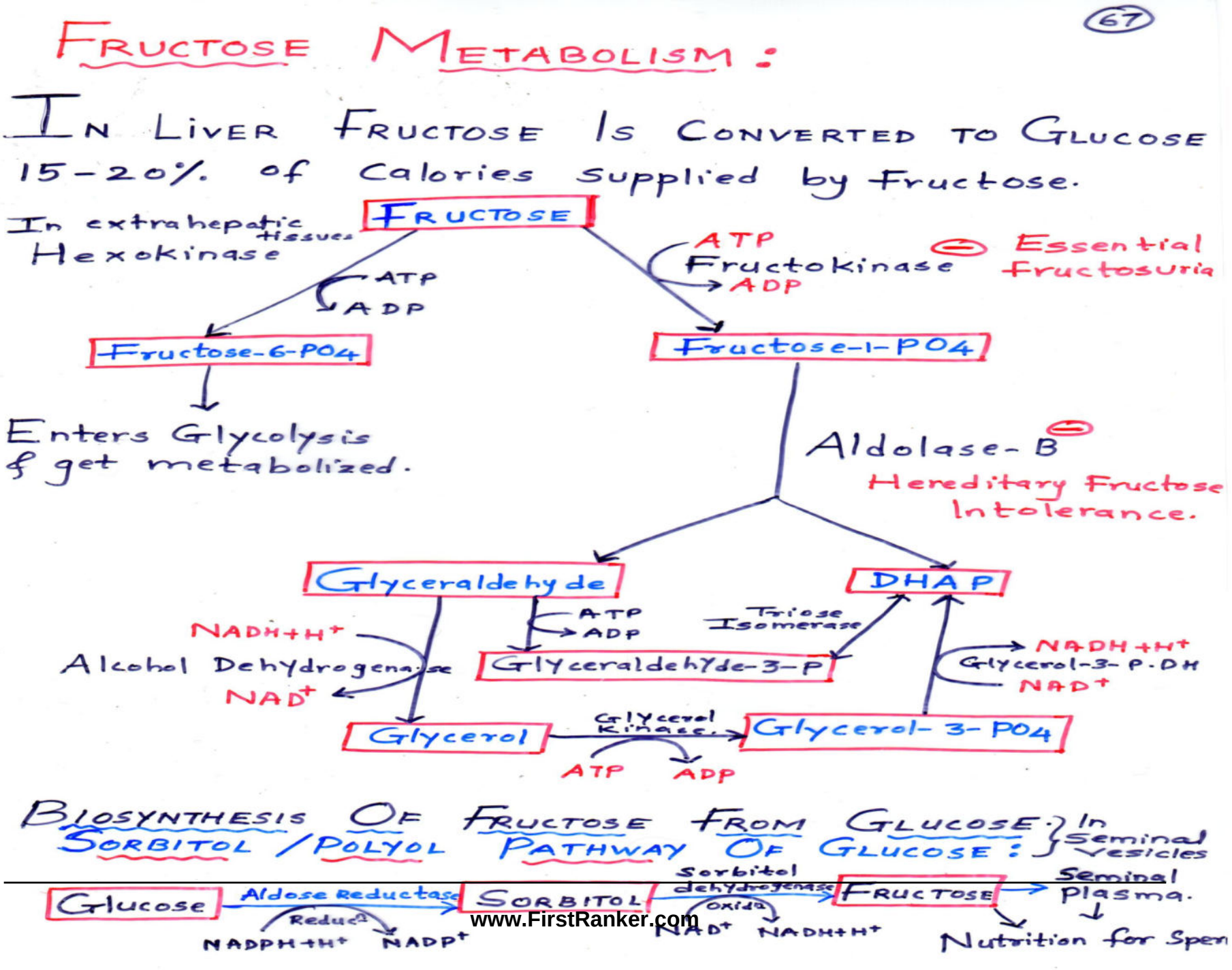
- **In liver Fructose is metabolized to Glucose and utilized.**



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Inborn Errors Of Fructose Metabolism

Essential Fructosuria

- **Enzyme Defect: Liver Fructokinase**
- **Biochemical Alterations and Manifestations:**

- Blocks the phosphorylation of Fructose to Fructose-1-PO4.
- Free Fructose is permeable ,come out of Liver.
- High levels of Fructose in blood and urine.
- Fructosuria.
- Asymptomatic.
- Restrict Sucrose and Fructose in diet.

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Hereditary Fructose Intolerance/Fructose Poisoning

- **Enzyme Defect:**
- Aldolase- B
- **Inheritance:**
- Autosomal recessive
- **Incidence:**
- 1 in 20,000 births

- **Biochemical Alterations and Clinical Manifestations:**
- Fructose-1-PO_4 not further metabolized and accumulates in hepatocytes.
- Affects normal functioning of Liver.
- Depletion of inorganic Phosphorous(pi).
- Decreases Glycolysis ,Glycogenesis and Gluconeogenesis.

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- Classical manifestations of hereditary Fructose intolerance:
- Hypoglycemia
- Hepatomegaly.
- Hepatic Jaundice.
- **Diagnosis:**
- Benedict's and Selivanoff's Test.
- **Management:**
- Diet free of Sucrose and Fructose.

Homeostasis Of Blood Glucose
OR
Factors Regulating Blood Glucose

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What is Homeostasis?

- **Homeostasis** is a physicochemical process in the body, where the **altered levels** are tried to **maintained to normal levels**.

- **Biochemical homeostasis** means **keeping** the **biochemical constituents within normal range**.

- **Homeostasis of blood Glucose** means **keeping the blood Glucose within normal range.**

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- Normal homeostatic mechanism maintains bodies health.

- **Defect in homeostatic mechanisms leads to:**
- **No corrections of altered levels** of biochemical constituents.
- Biochemical constituents vary from normal range **leading to hyper and hypo values.**
- **Leads to Metabolic disorders.**

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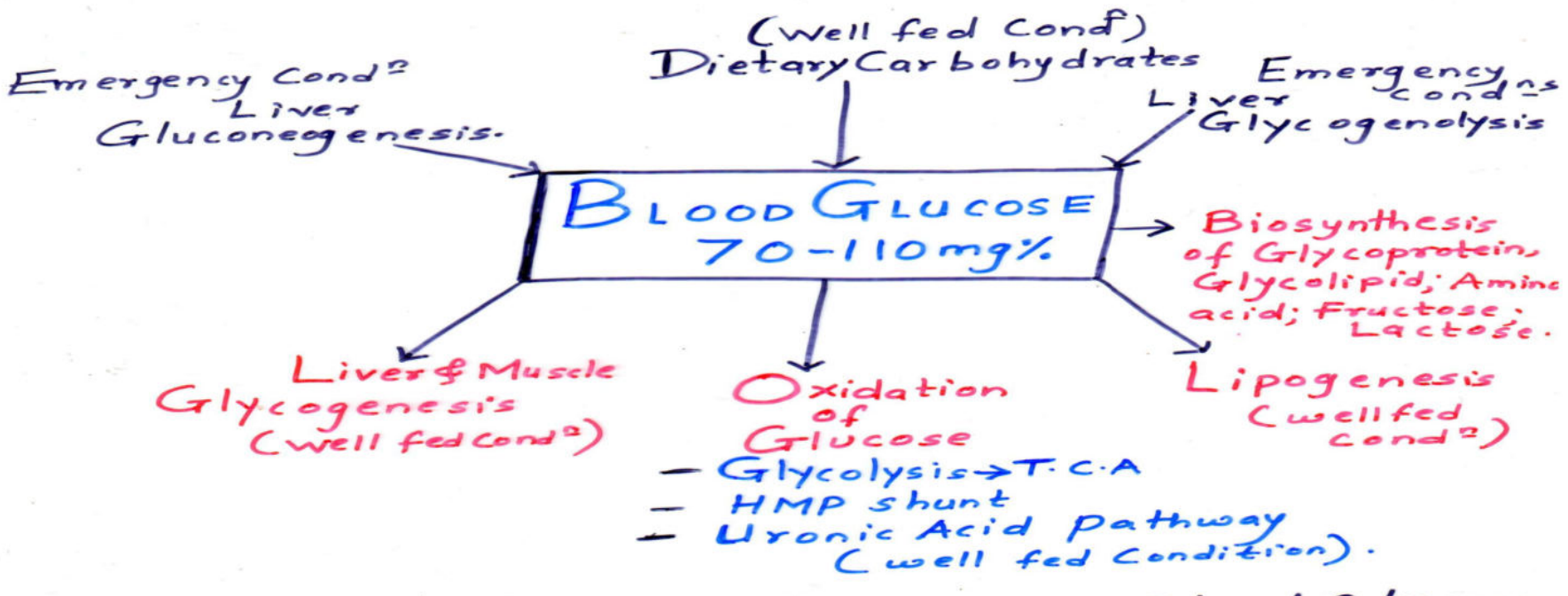
Normal Ranges Of Blood Glucose:

- **Fasting Blood Glucose(F)= 70-110 mg%**
  (After 10-12 hours of fast)
- **Post Prandial(PP) Blood Glucose= 120-160mg%**
  (1 ½ -2 hours after meals)
- **Random Blood Glucose= 80-140 mg%.**
  (Any Time of the day)

The Ways By Which Glucose Added And Utilized From Blood :



Homeostatic factors Regulating Blood Glucose

(I) **Hormones :**

* **Hypoglycemic / Antidiabetogenic Hormones**
  Insulin → Lowers BGL.
* **Hyperglycemic / Diabetogenic Hormones**
  Glucagon; Epinephrine; Glucocorticoi
  Growth Hormone; Thyroid Hormone
  ↑ Increases BGL

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Homeostatic Factors Regulating Blood Glucose:

Hormones

- **Blood Glucose Regulating Hormones:**

- **Hypoglycemic/ Blood Glucose Lowering Hormone/ Anti Diabetogenic :**

  - **INSULIN**

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- **Hyperglycemic/ Blood Glucose Increasing Hormones Diabetogenic :**
  - **Glucagon**
  - **Epinephrine (Adrenaline)**
  - **Thyroid Hormone**
  - **Growth Hormone**
  - **Glucocorticoids.**

Organs And Metabolic Pathways Operating In It:

- Liver (Glucostatic Organ)
- Muscles
- Adipose Tissue
- Kidney.

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- Healthy normal functioning of organs and the related metabolic pathways is essential for normal blood Glucose regulation.

INSULIN

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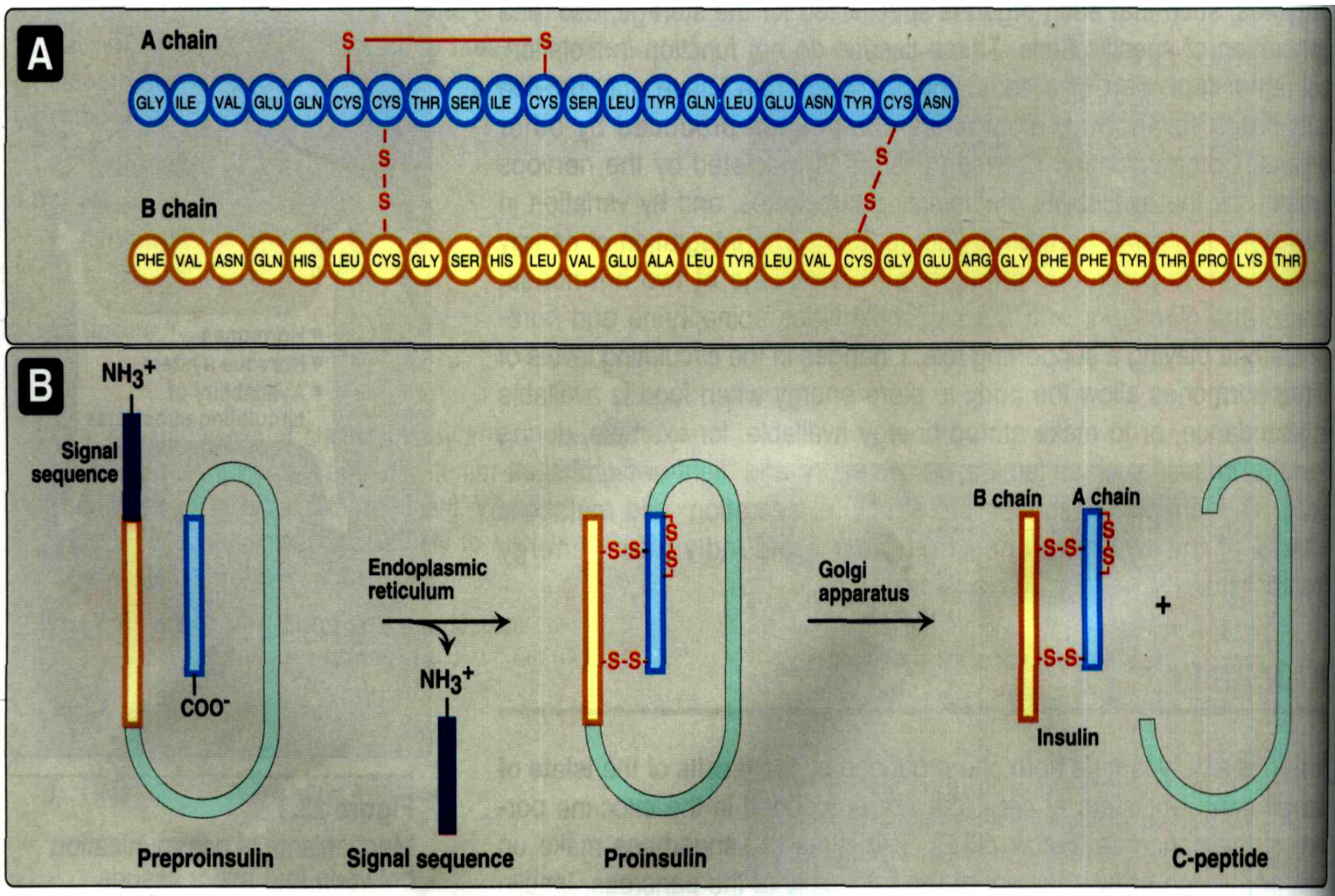

Figure 23.3
A. Structure of insulin. B. Formation of human insulin from preproinsulin.

Incretin - Gut Hormones Stimulates Insulin Secretion.

- Gut hormones **GIP** (Glucose dependent Insulinotropic Peptide) and **GLP-1** (Glucagon Like Peptide-1) produced in response to Glucose in intestine.
- **Incretin** reach and activate the Pancreas for robust Insulin secretion, in anticipation of the rise in blood Glucose , after meals.

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- Hormone Insulin get secreted by **β cells of Islets of Langerhans of Pancreas** in response to increased blood Glucose levels in a well fed condition:

- Insulin helps in **transportation of Glucose in peripheral tissues.**
- Stimulates all the **key or regulatory enzymes** of metabolic pathways which metabolizes the entered Glucose in cells.

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- **Insulin by its activity stimulates and increases Glucose utilizing pathways in well fed condition:**
  - **Glycolysis.**
  - **Glycogenesis**
  - **Lipogenesis**
  - **HMP Shunt**
  - **Uronic Acid Pathway**

- **Insulin by its activity simultaneously inhibits and decreases Glucose producing pathways:**
  - **Glycogenolysis**
  - **Gluconeogenesis**

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Counter Regulatory Hormones

- **Glucagon** (From α cells of islets of Langerhans)
- Epinephrine (Hypothalamic Glucoreceptors, mediated by ANS)
- Growth Hormone (Anterior Pituitary)
- Cortisol (Adrenal Cortex- mediated by ACTH)
- All these hormones opposes the action of insulin on Glucose use.

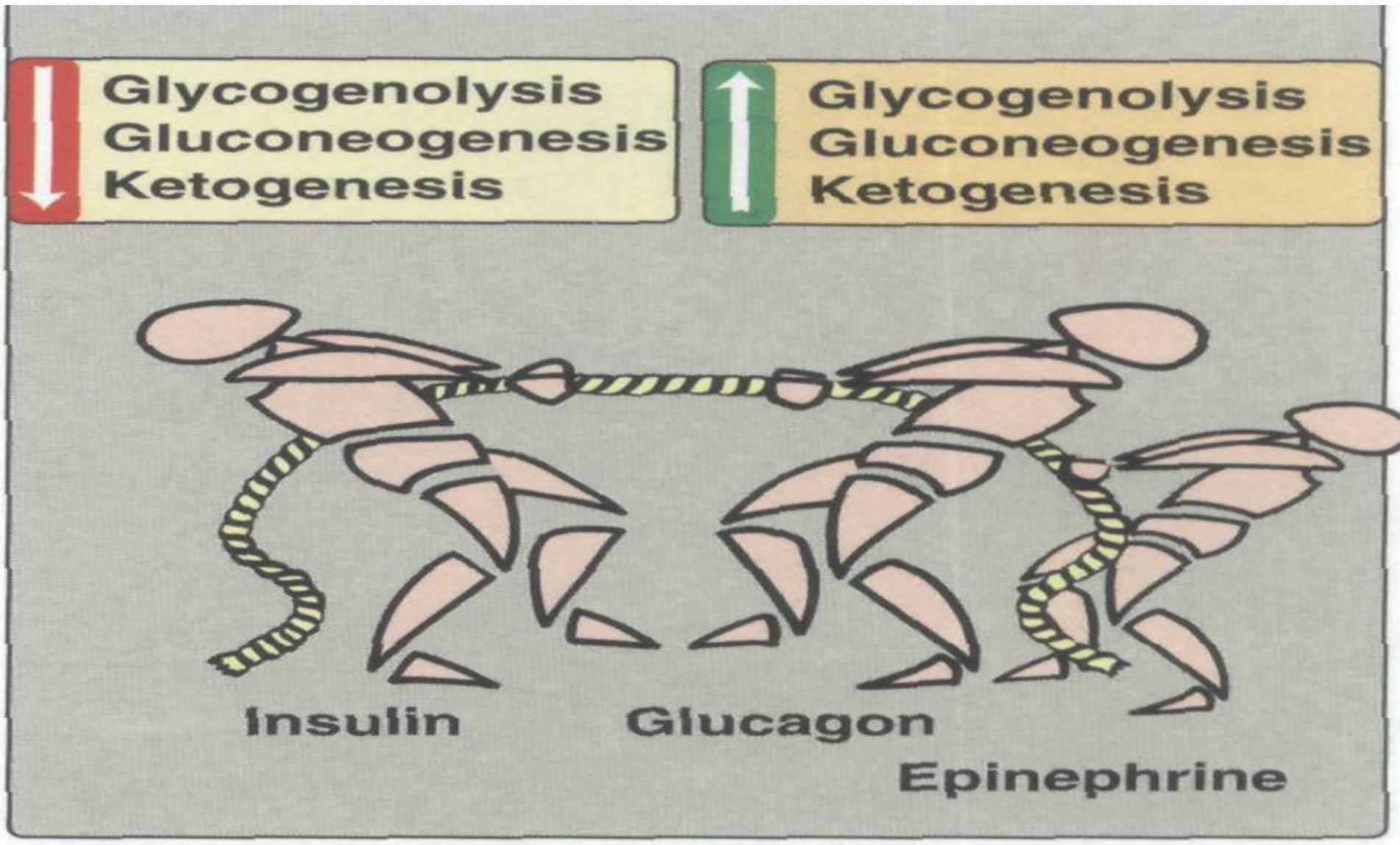

Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

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- Glucagon and Epinephrine are most important in the acute and short term regulation of blood Glucose levels.
- Glucagon stimulates Liver Glycogenolysis and Gluconeogenesis.

- Epinephrine stimulates Glycogenolysis and Lipolysis.
- Epinephrine inhibits insulin secretion.
- Epinephrine inhibits insulin mediated uptake of Glucose by peripheral tissues.
- Epinephrine is not so essential if Glucagon is functioning.

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- Cortisol and Growth Hormone are important in the long term management of Glucose metabolism.

Insulin	Glucagon
Insulin is a polypeptide hormone composed of 51 amino acids	Glucagon is a polypeptide hormone composed of 29 amino acids.
Structure has two polypeptide chains 21 and 30 amino acids.	Structure has one polypeptide chain
Insulin is synthesized and secreted by beta cells of Islets of Langerhans of Pancreas.	Glucagon is secreted by alph cells of Islets of Langerhans of Pancreas.
Insulin is secreted in response to high blood Glucose and Aminoacid levels.	Glucagon is secreted in response to low blood Glucose

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Insulin	Glucagon
Epinephrine inhibits Insulin secretion	Epinephrine stimulates Glucagon secretion.
Insulin by its activity lowers the blood Glucose. **Insulin Glucose utilizing hormone**	Glucagon by its activity raises the blood Glucose. **Glucagon is Glucose producing hormone**
Insulin stimulates all pathways of Glucose operating in a well fed condition which metabolizes cellular Glucose	Glucagon stimulates Glycogenolysis and Gluconeogenesis in emergency fasting condition.

Insulin	Glucagon
Insulin deficiency leads to persistent Hyperglycemia	Glucagon deficiency leads to persistent hypoglycemia
Insulin for its action do not use cyclic AMP.	Glucagon for its activity uses cyclic AMP.
Insulin stimulates Glycogenesis, Lipogenesis, Protein biosynthesis.	Glucagon stimulates Glycogenolysis, Lipolysis, Protein degradation.

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Homeostatic Mechanism Of Blood Glucose:

In a well fed condition after heavy meals

↓

Glucose added to blood

↓

Increased blood Glucose (Transient Hyperglycemia)

↓

Insulin secreted

↓

Mediates Glucose uptake by peripheral tissues (GluT4 Insulin dependent)

↓

Regulates the increased blood Glucose

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In a fasting condition /Between meals

↓

Blood Glucose is utilized

↓

Decreased blood Glucose(Transient Hypoglycemia)

↓

Glucagon and Epinephrine secreted

↓

Stimulates Glucose producing pathways of Liver
Glycogenolysis and Gluconeogenesis Increased
Glucose added to blood

↓

Regulates the decreased blood Glucose

Significance Of Blood Glucose Regulation

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- A constant source of blood Glucose is an absolute requirement for human life.
- Glucose is the greatly preferred energy source for Brain, Erythrocytes.
- Glucose is essential for exercising muscles.

- **Homeostatic mechanism of blood Glucose :**
- Corrects transient hyperglycemia after a well fed state.
- Corrects transient hypoglycemia in a fasting condition.
- Maintain a constant normal range of blood Glucose in specific conditions of body.
- Helps in continuous supply of Glucose to tissues which are totally dependent on Glucose.
- Try to keep the Brain and Erythrocytes vital and active

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Disorders Of Blood Glucose Regulation

- **Causes of abnormal blood Glucose regulation:**
  - **Defects in Hormonal** secretion and their activities.
  - **Diseased organ** system.
  - **Deranged metabolic** pathways associated to Glucose.

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- **Defect in factors regulating blood Glucose:**
- **Does not correct transient** Hyperglycemia and Hypoglycemia.
- **Leads to persistent** Hyperglycemia and Hypoglycemia.

Persistent Hyperglycemia

- Persistent hyperglycemia is characterized with chronic abnormal high levels of blood Glucose.
- **Persistent Hyperglycemia is noted in:**
  - **Diabetes mellitus.**
  - **Stress, Anxiety**
  - **Hyperadrenalism**
  - **Hyperthyroidism**
  - **Hyperpituitarism**

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Persistent Hypoglycemia

- Persistent hypoglycemia is characterized with abnormal low levels of blood Glucose.
- **Persistent Hypoglycemia is noted in:**
  - **Prolonged Starvation**
  - **Tumors of pancreas**
  - **High dose of insulin during insulin therapy**
  - **Alcoholism**

Types Of Hypoglycemia

- Insulin –Induced Hypoglycemia
- Post Prandial Hypoglycemia
- Fasting Hypoglycemia
- Alcoholic Intoxication-Hypoglycemia

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- **Insulin induced hypoglycemia-**
- High dosage of Insulin while treating Type I Diabetes mellitus.
- Glucagon is administered subcutaneously or intramuscularly to unconscious patients who have lost the ability to coordinate swallowing.

- **Post prandial Hypoglycemia-**
- Caused by **exaggerated insulin release after meals.**
- Transient hypoglycemia with mild adrenergic symptoms.
- Manage the condition by advising the patients to take frequent small meals rather than usual three large meals.

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- **Fasting Hypoglycemia-**

- In fasting condition.
- In pancreatic tumors- large insulin secretions.
- Hepatic damage- low Glycogenolysis and Gluconeogenesis
- Adrenal insufficiency
- Show Neuroglycopenic symptoms
- Convulsions and Coma

Alcoholic Intoxication-Hypoglycemia

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- Persons in fasting condition(depleted stores of Glycogen) intoxicated with alcohol.
- Alcohol metabolism produces abundance of NADH+H+
- Alcohol metabolism inhibits Gluconeogenesis.
- Decreases the Glucose synthesis.

Consequences of Hypoglycemia

- **Transient hypoglycemia** can cause **cerebral dysfunction.**
- **Persistent ,prolonged hypoglycemia** causes **brain death.**

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Symptoms Of Hypoglycemia

- **Adrenergic Symptoms:**

  (Due to elevated epinephrine , when abrupt fall in blood Glucose at 65 mg%)

  - Anxiety
  - Palpitation
  - Headache
  - Confusion
  - Tremors
  - Sweating

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- **Neuroglycopenic Symptoms:**

  (Due to impaired delivery of Glucose to brain, when blood glucose drops gradually at 50 mg%)

  - Slurred Speech
  - Seizures
  - Coma
  - Death

- **Hypoglycemia is more serious than hyperglycemia.**
- Brain does not get sufficient Glucose in hypoglycemic conditions.
- **One should manage hypoglycemia more rapidly to avoid brain dysfunction.**

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Correction Of Hypoglycemia

- Hypoglycemia is a medical emergency which should be immediately attended and resolved to have proper brain function.
- Administration of Glucose intravenously resolves the symptoms of hypoglycemia within minutes.

Hyperglycemia	Hypoglycemia
Blood glucose increased above normal range.	Blood Glucose decreased below normal range.
Caused due to insufficiency or inefficiency of Insulin.	Caused due to excess activity of Insulin.
Predominant in Diabetes mellitus.	Noted in Insulinomas
Hyperglycemia is less severe and do not affect brain function.	Hypoglycemia is more serious , affects normal function of brain.
Hyperglycemia may lead to Glycosuria.	Hypoglycemia condition shows no Glycosuria.

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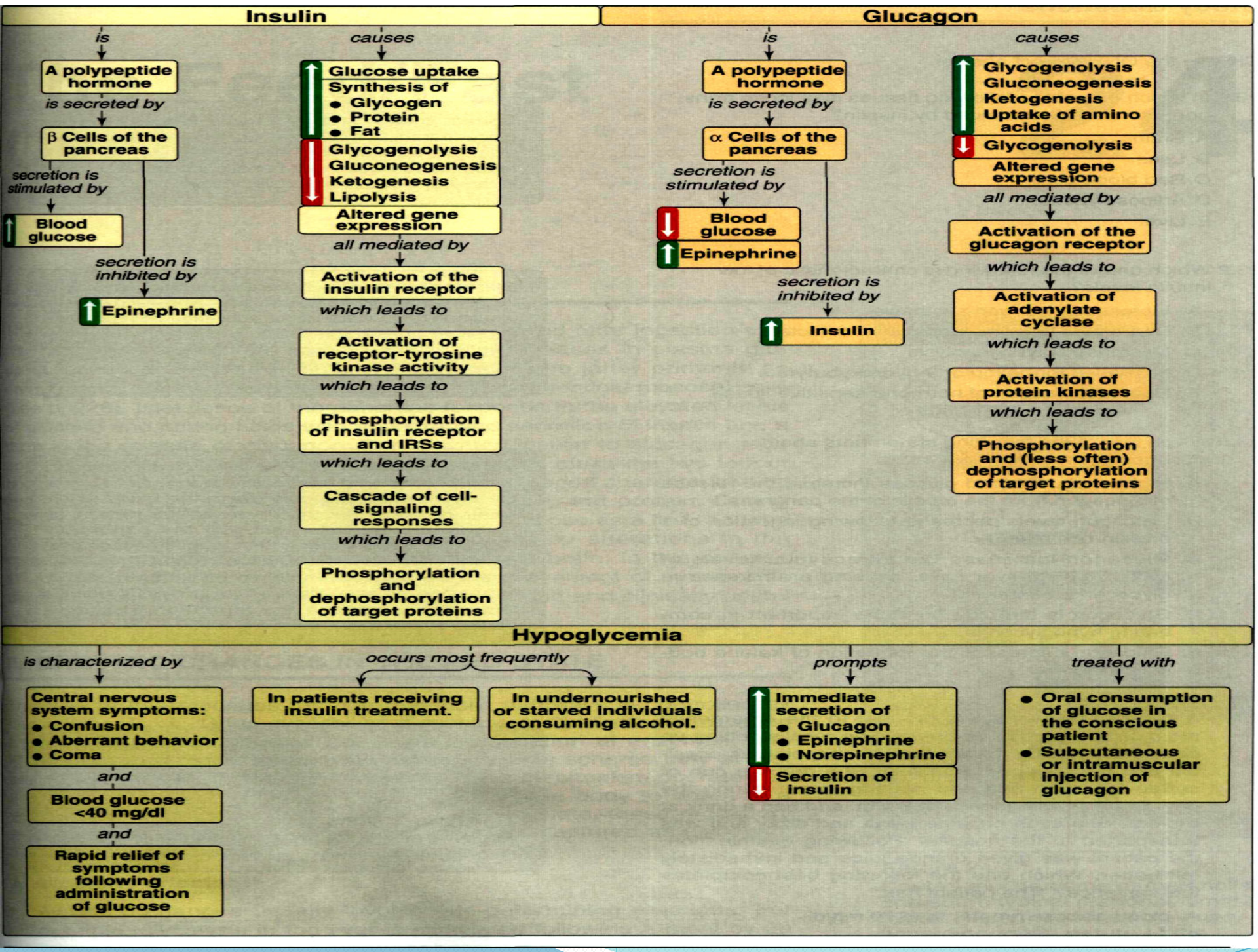

Diabetes Mellitus (DM)

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What is Diabetes mellitus?

- **Diabetes mellitus is**
- Most common (3rd leading cause of death)
- Heterogeneous, wide spread
- **Endocrine, metabolic disorder**
- Characterized by **chronic persistent hyperglycemia.**

Causes/Etiological Factors:

- **Basic cause for Diabetes mellitus is :**
  - **Insulin insufficiency**
  - **Insulin inefficiency**

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- Diabetes Mellitus is a **disorder due to defect in blood Glucose regulation.**

- Hormone **Insulin** which regulates blood glucose levels is **affected in Diabetes mellitus.**

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- Low/No insulin activity in DM **does not transport Glucose** within peripheral cells leading to persistent hyperglycemia.

Multiple and Complex Etiological Factors Of Diabetes Mellitus:

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- Hereditary
- Race
- Nutritional Status
- Stress
- Drug Interaction
- Endocrine Dysfunction
- Infections
- Autoimmunity
- Occupational
- Living Style
- Various other Environmental Factors

- Modern Life style ,food habits, stress ,and polluted environment are likely to increase the number of sufferers of Diabetes Mellitus.

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Geographical Distribution/ Prevalence Of DM

- Diabetes mellitus is a substantial **global health problem.**
- **Widely spreaded** in every part of world.
- More than 20 million people are sufferers of DM world wide.

Classification/Types Of DM

- **WHO Classification of Diabetes mellitus:**
  - **Type 1/IDDM/Juvenile Onset DM**
  - **Type 2/NIDDM/Maturity Onset DM**
  - **Gestational Diabetes mellitus(GDM)**

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Type 1 Diabetes Mellitus

- **Type 1 DM**
- Juvenile Onset
- Initiated by environmental factor/ viral infection.
- Abrupt onset
- Cellular mediated **autoimmune destruction of the beta cells of the pancreas**
- **Absolute deficiency of insulin secretion.**
- Insulin dependence
- Ketosis tendency
- Presence of islet cell autoantibodies, insulin auto antibodies in blood circulation.

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Type 2 Diabetes Mellitus

- **Type 2 DM**
- Maturity Onset Diabetes
- Has resistance to Insulin
- Insulin secretory defect
- Not absolute insulin deficiency
- Strong genetic predisposition
- Prone to obese and sedentary life persons
- Milder type

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Character	IDDM	NIDDM
Prevalence	10-20%	80-90%
Age Of Onset	< 20 Years	> 30 Years
Body Weight	Normal/Low	Obese/Over weight
Genetic Predisposition	Moderate	Very Strong
Defect	Insulin deficiency- Destruction of β cells of Pancreas	Insulin inefficiency- Insulin Resistance , defect in Insulin receptors.

Character	IDDM	NIDDM
Plasma Insulin	Low or absent	Normal / Increased
Auto Antibodies	Frequently found	Rare
Severity	More severe	Mild
Treatment	Insulin Doses	Hypoglycemic Drugs.
Acute Complications	Diabetic Ketoacidosis Ketosis common.	Hyperosmolar Coma Ketosis Rare.

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	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	900,000 = 10% of diagnosed diabetics	10 Million = 90% of diagnosed diabetics
GENETIC PREDISPOSITION	Moderate	Very strong
DEFECT OR DEFICIENCY	β Cells are destroyed, eliminating production of insulin	Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin
FREQUENCY OF KETOSIS	Common	Rare
PLASMA INSULIN	Low to absent	High early in disease; low in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar coma
TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, +/– insulin

Gestational Diabetes Mellitus (GDM)

- Glucose intolerance during pregnancy.
- Affects approximately 4 % of pregnant women.
- Caused due to metabolic and hormonal changes during pregnancy
- Women with GDM frequently return to normal postpartum.

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- Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy .

- Gestational diabetes is caused when the **insulin receptors do not function properly.**
- GDM Leads to perinatal complications.
- GDM Increases risk to suffer from DM in later life.

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- Perform a diagnostic oral glucose tolerance test (OGTT) without prior plasma or serum glucose screening.

- Sample drawn after 100-gram glucose drink (glucose load)
- Time of Sample Collection Target LEVEL
- Fasting* (prior to glucose load) 95 mg/dL (5.3 mmol/L)
- 1 hour after glucose load 180 mg/dL (10.0 mmol/L)
- 2 hours after glucose load 155 mg/dL (8.6 mmol/L)
- 3 hours after glucose load* 140 mg/dL (7.8 mmol/L)
- INDICATION: If two or more values meet or exceed the target level, gestational diabetes is diagnosed.

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- Women with GDM has large gestational age (macrosomic)

- Infants born to mothers with untreated GDM has following complications:
  - **High birth weight (< 4 kg)**
  - **Respiratory Distress syndrome**
  - **Hypoglycemia**
  - **Hypocalcaemia**
  - **Hyperbilirubinemia**

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- Remember that women diagnosed with GDM can develop diabetes later onn in their life.
- Hence they are advised to undergo annual screening to enable early diagnosis or to rule out the condition.

Risk Factors to Develop DM

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- The development of type 2 diabetes is caused by a combination of **lifestyle and genetic factors.**
- While some are under personal control, such as **diet and obesity.**
- Others, such as increasing **age, female gender, and genetics** are not under personal control.

- A **lack of sleep** has been **linked** to type 2 **diabetes**. This is believed to act through its effect on metabolism.

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- The **nutritional status of a mother during fetal development** may also play a role, with one proposed mechanism being that of altered DNA methylation.

- A number of **lifestyle factors** are known to be important to the development of type 2 diabetes, including:
  - **Urbanization**
  - **Stress**
  - **Obesity**(defined by a **body mass index of greater than thirty**)
  - **Excess body fat**
  - **Lack of physical activity/Lack of exercise** is believed to cause 7% of DM cases.

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- **Dietary Factors**

- **Very poor diet increases risk of DM.**
- Very excess consumption of **sugar-sweetened drinks** in excess is associated with an increased risk of DM.
- Eating **lots of white rice** appears to also play a role in increasing risk of DM.

- The type of fats in the diet are also important:
- Dietary **Saturated fats and trans fatty acids increases the risk of DM.**
- Dietary **Polyunsaturated and monounsaturated fat decreasing the risk of DM.**

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Biochemical Alterations In DM

- In **Type -1 Diabetes mellitus there is destruction of beta cells of islets of Langerhans** which leads to **absolute deficiency of insulin.**

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- In **Type -2 Diabetes mellitus** membrane Glucose transporter **GluT4 is reduced** which leads to insulin resistance.

Metabolism Deranged In DM

- Diabetes mellitus **chiefly alters** and affects **Carbohydrate metabolism**
- which in turn affects the interdependent
  - **Lipid Metabolism**
  - **Protein Metabolism**
  - **Water and Mineral Metabolism**

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- **Diabetes mellitus exhibits Starvation of peripheral cells (Scarcity In Plenty).**

Chronic Persistent Hyperglycemia In DM

- Due to low or poor/decreased Insulin activity in Diabetes mellitus.
- **Decreased uptake** of blood Glucose by peripheral tissues.
- **Underutilization Of Glucose.**

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- Due to more/increased Glucagon activity.
- Over production of Glucose.
- Chronic persistent hyperglycemia.

Decreased Utilization of Cellular Glucose In DM

- As **Insulin is low** in its activity in DM.
- There is **decreased stimulation** of following **pathways:**
  - **Decreased Glycolysis**
  - **Decreased TCA cycle**
  - **Decreased Glycogenesis**
  - **Decreased Lipogenesis**
  - **Decreased HMP shunt.**

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Increased Lipolysis, Gluconeogenesis and Ketogenesis In Type 1 DM

- Low insulin in body of DM
- More Glucagon in body of DM
- Glucagon stimulates :
  - **Increased Lipolysis**
  - **Increased Gluconeogenesis**
  - **Increased Ketogenesis**
  - **(Incomplete Fatty acid Oxidation)**

Renal Osmotic Glycosuria In DM

- Blood Glucose levels when crosses renal threshold value for Glucose=180 mg%.
- The presence of high Glucose in renal tubules exerts an osmotic effect.
- Reduces reabsorption of water.
- Excretion of Glucose along with water - Glucosuria **(Osmotic Diuresis).**

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Decreased Protein Synthesis and Increased Protein Breakdown In DM

- Low insulin activity **inhibits protein biosynthesis** and **stimulates muscle protein breakdown** in a body suffering from Diabetes Mellitus.
- The Glucogenic Aminoacids released from Protein breakdown produces Glucose in Liver via Gluconeogenesis.
- **Excess Protein breakdown makes the person emaciated and loose weight.**

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Increased Serum TAG, Cholesterol and Ketone bodies In D.M

- Hypertriglyceridemia in DM is due to:
- Increased Lipolysis
- Decreased Lipoprotein Lipase activity.

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- **"Fat Burns Under The Flame Of Carbohydrate"**
- For complete oxidation of body fat there needs a sufficient cellular Carbohydrate metabolism.

- Low cellular Carbohydrate metabolism in DM, exhibit **incomplete metabolism of Fats.**

- In Diabetes mellitus there is less cellular Carbohydrate metabolism
- Excess but incomplete fatty acid oxidation
- More production of Ketone bodies which are partial oxidized products of fat metabolism.

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- More deficiency of Insulin.
- More deprivation in cellular Glucose metabolism.
- More incomplete/partial fat oxidation.
- More Ketone bodies production.
- Accumulation of Ketone bodies in blood- **Ketonemia.**
- Ketone bodies excreted in Urine- **Ketonuria.**

Uncontrolled DM shows Ketosis

- **Uncontrolled Diabetes Mellitus** is a serious condition of DM.
- Very low Insulin activity.
- Very deranged metabolic activity.
- Ketonemia + Ketonuria =Ketosis
- Kassumals breathing-Acetone Breath.
- Acidosis-Ketoacidosis.
- **Diabetic Ketoacidosis.**

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Water Electrolyte and Acid Base Imbalance In DM

- Osmotic Diuresis in Diabetes Mellitus
- Water Loss- Dehydration.
- Electrolyte Loss
- Ketoacidosis- Acid Base Imbalance.

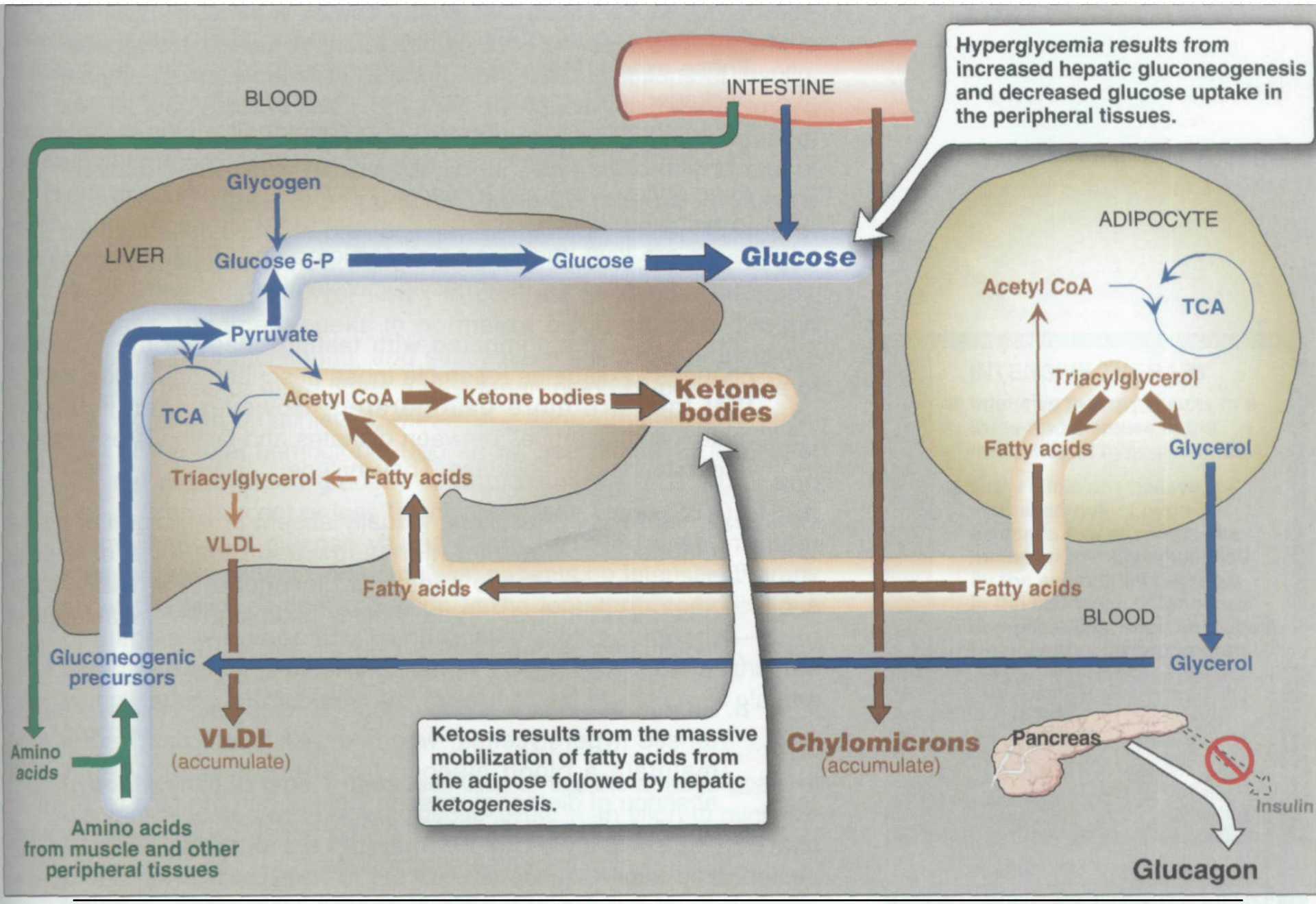

Figure 25.3
Intertissue relationships in type 1 diabetes.

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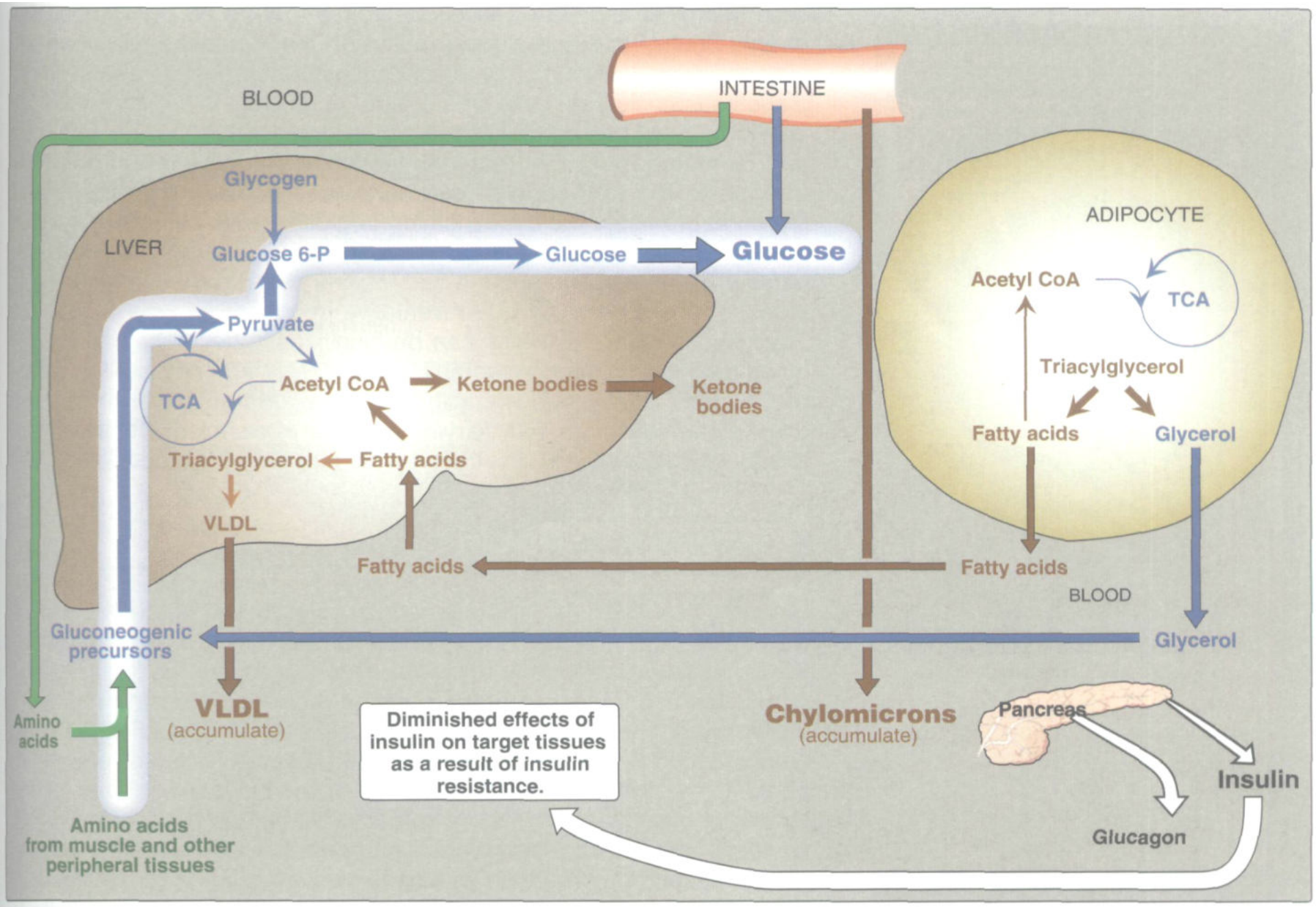

Figure 25.10
Intertissue relationships in type 2 diabetes.

Clinical Manifestations Of DM

- **Polyuria - Osmotic Diuresis.**
- **Polydypsia - Thirst (Due to Dehydration).**
- **Polyphagia – Cellular Starvation – (Stimulate Hunger centre)**
- **Weakness**
- **Lethargy**
- **Weight Loss.**
- **In serious conditions Coma.**

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- Other symptoms that are commonly present at diagnosis include:
- A history of **blurred vision**
- **Itchiness and Burning sensation.**
- Peripheral neuropathy
- Recurrent **vaginal infections**, and **fatigue.**

- **Fatty Liver is noted in Type 2 Diabetes mellitus**
- Increased influx of fatty acids in Liver.
- Decreased VLDL formation in Liver.
- Decreased mobilization of lipids out from Liver.

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Increased Protein Glycation in DM

- Due to increased circulating blood Glucose.
- There is increased glycation of body proteins.
- This interferes normal function and turn over of Proteins.

- **Glycation of Hemoglobin** (HbA1c), affects oxygen transport.
- **Glycation of Albumin** affects its transport function.
- **Glycation of Apolipoprotein –B** , affects LDL metabolism and increases atherogenesis.
- Decreases elasticity of blood vessels.

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- Advanced Glycation End(AGE) Products increases **free radical generation.**
- Enhanced **Oxidative Stress** in Diabetes mellitus.

Complications Of Diabetes Mellitus

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- Individual suffering from Diabetes mellitus with **poor Glucose control** for many years **develop** from its **Complications.**

- A person with Diabetes mellitus with **good control** of his **blood Glucose** is at **low risk for complications of DM.**

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- Diabetes mellitus **developed with serious complications**, making it a **dreadful disease**.

Causes for DM Complications:

- **High Glucose** in blood circulation and body fluids, **exerts high osmotic effect** in blood vessels and renal tubules.
- Osmotic Diuresis in **renal tubules**.
- **High Sorbitol**(Reduced form of Glucose) accumulates in eyes and causes Cataract.

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- **Poor energy supply** to tissues make the **organ system weak.**
- **Defective Immune System**.
- More susceptible and compatible environment **for bacterial growth.**

- High circulation of blood lipids- **hyperlipidemias increases risk of Atherosclerosis.**
- High levels of Ketone bodies in blood and urine- **Ketosis.**

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Long standing complications develop in insulin independent tissues like

- **Brain** (Brain Dysfunctions and Stroke)
- **Erythrocytes** (Low Oxygen Transport and Unloading of Oxygen)
- **Eye Lens** (Diabetic Cataract)
- **Peripheral Nerves** (Diabetic Neuropathy)
- **Kidney** (Diabetic Nephropathy)
- **Liver** (Fatty Liver)

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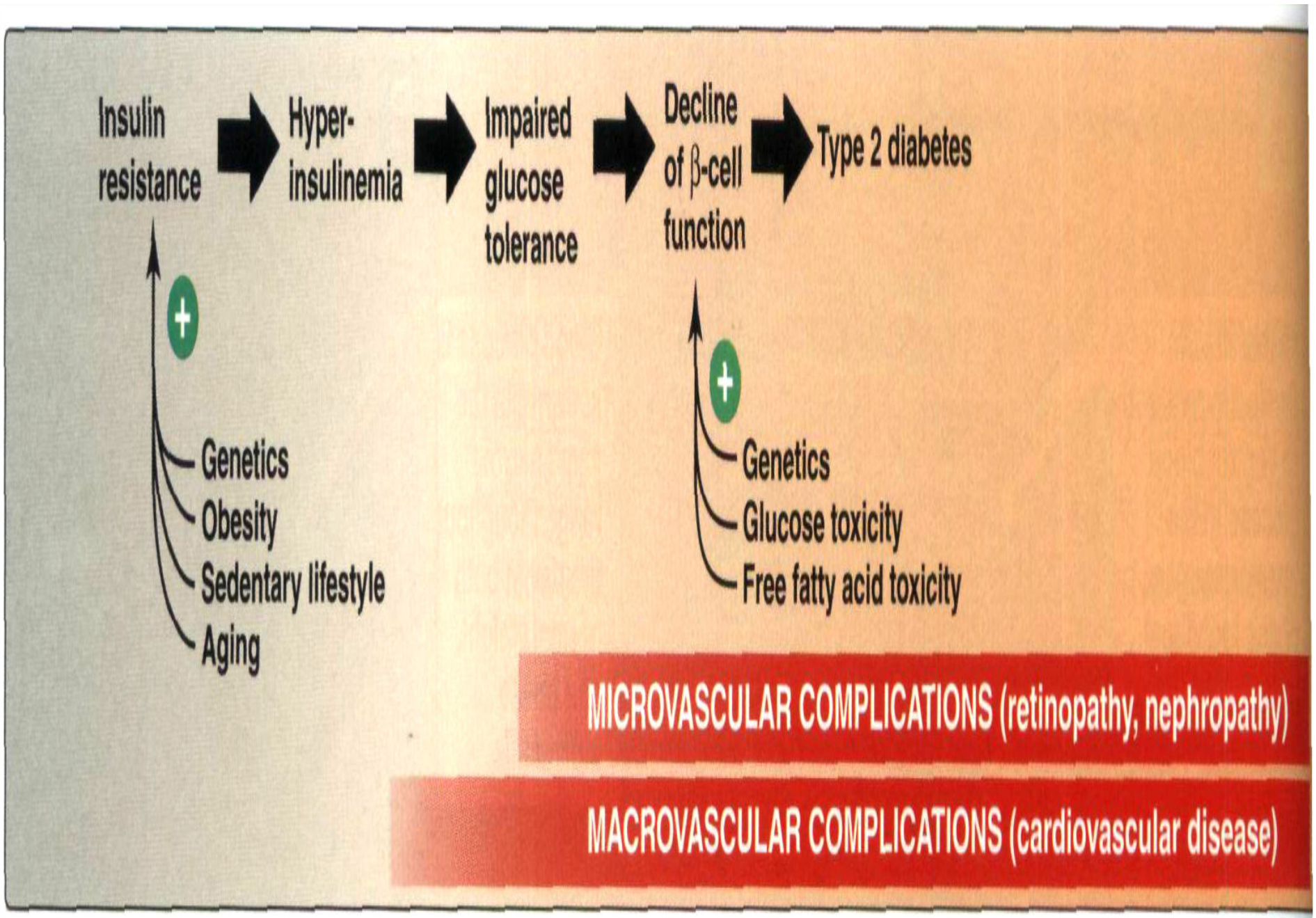

Delayed Complications Of DM

- **Cardio Vascular Disorders**
  - Atherosclerosis
  - Myocardial Infarction (**Painless MI Attack**)
- **Retinopathy**
- **Cataract**
- **Stroke**
- **Autonomic and Sensory Motor Dysfunction**
- **Nephropathy**
- **Foot Ulcers –Gangrene**

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- Type 2 Diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy.

- **Two to four times** the risk of cardiovascular disease, including ischemic heart disease and stroke in persons suffering from DM.

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- 20-fold increase in **lower limb amputations**, and increased rates of hospitalizations.

- In the developed world, and increasingly elsewhere, type 2 Diabetes is the largest cause of **non traumatic blindness** and **kidney failure.**

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- It has also been associated with an increased risk of neurological disorders:
  - **Cognitive dysfunction** and dementia through disease processes such as
  - **Alzheimer's disease** and vascular dementia.

- Other complications include:
- **Sexual dysfunction**
- **Frequent infections**

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Acute Complication Of DM

- Diabetic Ketoacidosis (Type 1DM)
- Hyper Osmolar Nonketotic Coma (Type 2 DM,BGL> 900mg%)

- People with type 2 diabetes mellitus may rarely present with Nonketotic Hyperosmolar coma (a condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure)

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Diagnosis Of Diabetes Mellitus

- **Urine Analysis**

Glucose –

Semi Quantitative Benedict's Test- Checks Glucosuria.

Ketone Bodies-

Rothera's Test- Checks Ketonuria.

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- **Blood Glucose Estimation:**
  - **GOD -POD Method.**
- **Fasting Blood Glucose**
- **Post Prandial Blood Glucose**
- Diabetic cut off for DM is 126mg% in the fasting sample on two different occasions.

- **Glucose Tolerance Test (GTT)**

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Diagnostic Tests to assess Long term complications of Diabetes mellitus:

- **Blood Urea**
- **Serum Creatinine**
- **Urinary Protein**
- **Microalbuminuria**

(300 mg/24 hr of urine)

- Urinary Albuminuria > 300 mg/day is mos diagnostic for **Diabetic Nephropathy.**

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- **Lipid Profile-**

- **Serum TAG**
- **Serum Cholesterol-**
- **Serum LDL and HDL**
- Results of Lipid profile assess the risk of macrovascular complications CVD in **Diabetes Mellitus**.

Diagnostic Tests To Assess Long Term And Short Term Glucose Control

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- **Estimation of Glycosylated Hemoglobin** (HbA1c)
- Gives index of Glucose control in DM in last **4-6 weeks.**

(Half life of RBC's 120 days).

- **Methods to measure Glycated Hemoglobin:**
- **Methods based on structural differences:**
  - Immunoassays
  - Affinity Chromatography
- **Methods based on charge differences:**
  - Ion exchange Chromatography
  - Isoelectric focusing
  - HPLC

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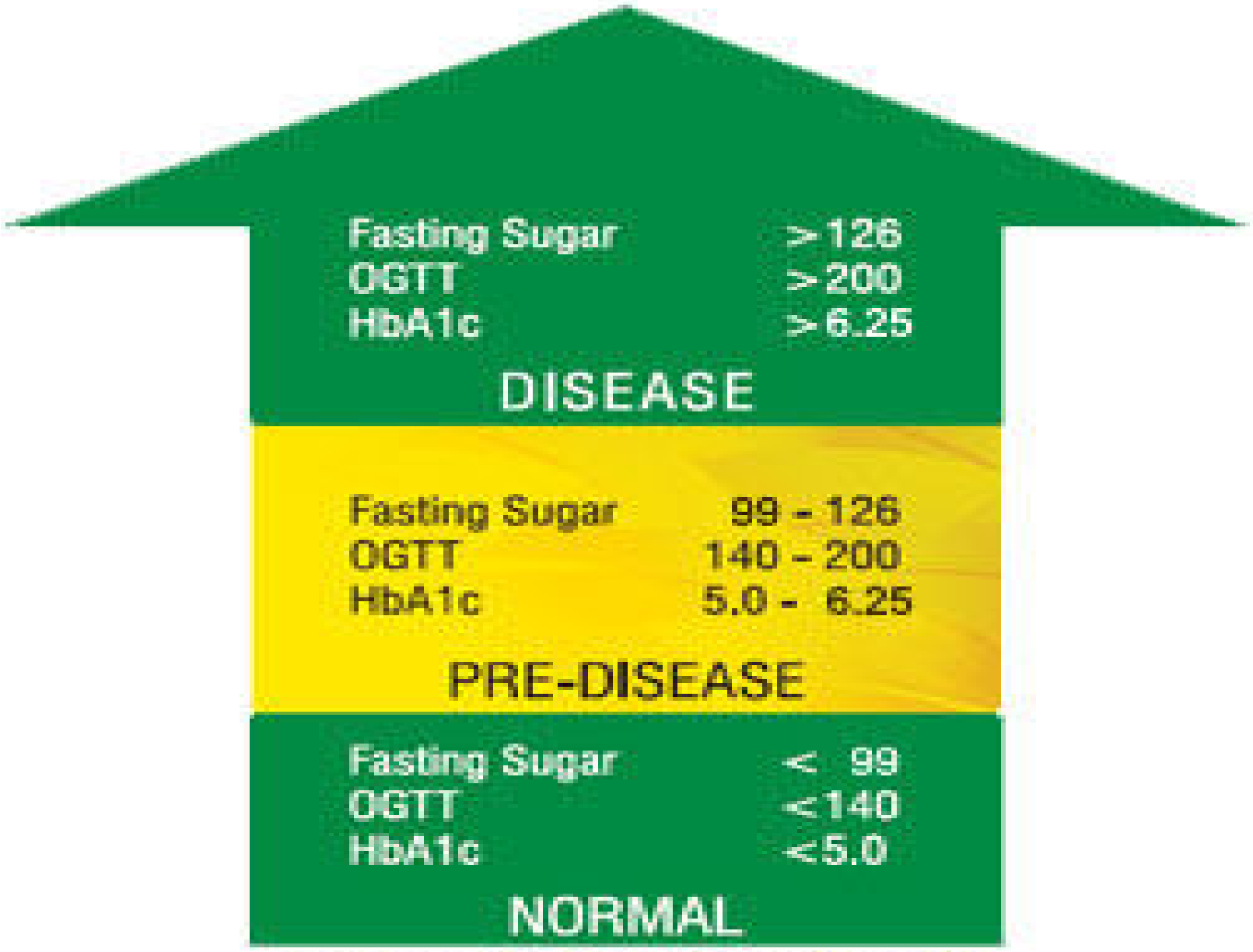

- **Fructosamine** – Quantitation of Glycosylated Proteins.
- Gives index of Glucose control in DM in last 2-3 weeks.
- (Half life of Albumin 20 days).

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- **Estimation of Blood**
  - **Insulin levels**
  - **Islet Autoantibodies**
  - **Insulin Autoantibodies**

Self Monitoring Of Glucose

- In cases of Type 1 D M patients
- For **tight blood Glucose control**
- To minimize complications of DM.
- By Accu Check-Glucometer
- By Uri Stics -
- Glucostics , Albustics , Ketostics.

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Treatment Of DM

- Diabetes mellitus is **not a curable disease.**
- Treatment or Management of Diabetes mellitus is
- **Controlling the blood Glucose levels within normal range.**

Management Of IDDM

- Diet Control- Foods with low Glycaemic Index.
- Weight to be improved- Good Protein diet.
- Insulin therapy- Adjust Insulin dose w.r.t BGL.

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- **Monitoring of the patients during Insulin therapy:**
- Insulin therapy lowers serum potassium levels (**Hypokalemia**) check and correct for it.
- High doses of Insulin may lead to hypoglycemia have a check.

Management Of NIDDM

- Diet Control.
- Exercise to loose weight.
- Use of Hypoglycemic Drugs

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Hypoglycemic Drugs

- **Sulfonylureas**- Glipizide (Glucotrol), Glyburide (Diabeta), Tolazamide (Tolinase)
- **Meglitinides**-Replaglinide (Prandin)
- **Biguanides**- Metformin (Glucophage)
- **Butamide**
- **Thiazolidinediones (TZDs)**-Rosiglitazone (Avandia)
- **Incretin mimetic**- Exenatide

Oral Medication Mechanisms:

- Increases insulin production.
- Improves insulin receptor sensitivity.
- Inhibits Gluconeogenesis.
- Inhibits Carbohydrate absorption from GIT.

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Prevention Of Diabetes Mellitus

- **Onset of Type 2 Diabetes can be delayed or prevented through:**
- Proper nutrition – **Balanced diet**
- Diet high in green leafy vegetables
- Limiting the intake of sugary drinks
- **Regular Exercise**

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- Balanced lifestyle may reduce the risk by over half
- Avoid stressful life- being **Spiritual,Organized and Ethical.**

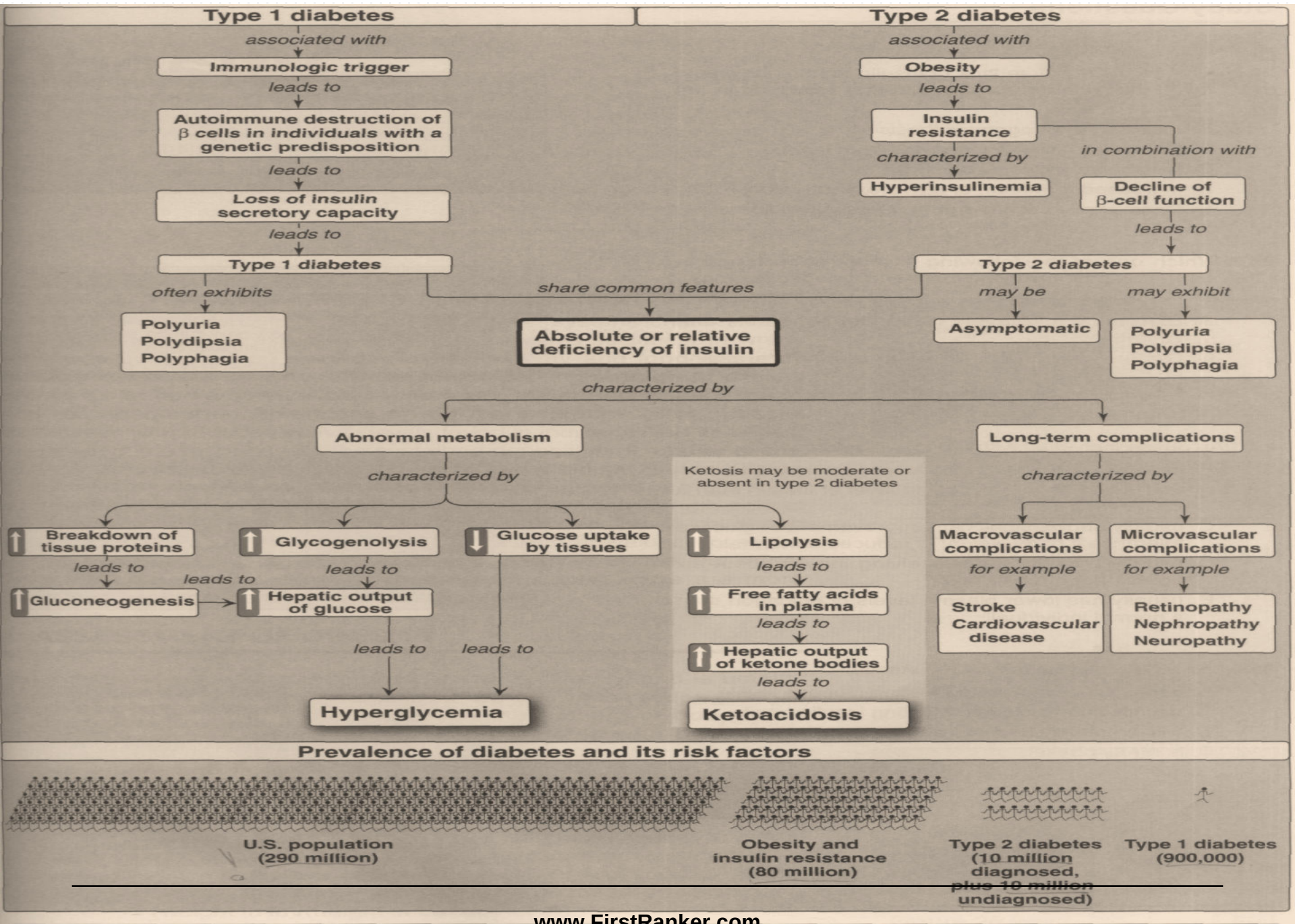

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Figure 25.13
Key concept map for diabetes.

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Glycosuria

- Glycosuria is a pathological condition
- Detectable amount of sugar is excreted out through urine.

Causes For Glycosuria:

- Increased levels of blood sugar over their renal threshold values.
- Defect in renal tubules lowering the renal threshold values of sugars.
- **Renal threshold value for Glucose = 180 mg%.**

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Types Of Glycosuria

- **Glucosuria** (Most Common)
- **Fructosuria**
- **Galactosuria**
- **Pentosuria**

- **Diabetic/ Hyperglycemic Glycosuria**
- **Alimentary Glycosuria**

  (GIT absorption defect)
- **Emotional Glycosuria**

  (In anxiety, stress, anger)
- **Renal Glycosuria**

  (Renal tubular defect, low renal threshold value)

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Detection And Confirmation Of Glycosuria:

- Semi Quantitative Benedicts Test on Urine Specimen.

Observations Of Semi Quantitative Benedicts Test	
No change in test color	Negative Test- No Glycosuria
Green color Precipitate (Cu_2O)	0.5 % Glucose present
Yellow color Precipitate	1% Glucose present
Orange color Precipitate	1.5 % Glucose present
Red color Precipitate	2% or more Glucose present.

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Glucose Tolerance Test (GTT)

What Is GTT?

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- **Glucose Tolerance Test (GTT)**
- Is a special investigation
- Carried out in a Clinical Biochemistry Laboratory
- To check the bodies tolerance towards a high dose (75gm) of Glucose in a fasting condition.

- **Normal Tolerance** –
  - Normal Blood Glucose
  - No Glycosuria

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- **Decreased Tolerance** –
  - Increased Blood Glucose
  - May have Glycosuria

- **Increased Tolerance** –
  - Decreased blood Glucose
  - No Glycosuria

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Indications Of GTT
OR
When GTT Is Prescribed ?

- **In a case which is unclear-** Has symptoms of Diabetes Mellitus but normal BGL.
- To diagnose Gestational DM(GDM) during pregnancy.
- To find out severity of DM
- To rule out renal Glycosuria.

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Types Of GTT

- **Oral GTT**

- Oral dosage of Glucose given during test.

- **Intravenous GTT**

- In GIT disordered persons, Glucose dose is infused intravenously.

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- **Mini GTT**

- The duration of GTT is reduced to 1 ½ hrs.

- **Corticosteroid Stressed GTT**

- GTT is tested after dosage of corticosteroids.

Preparation of a Person for GTT

OR

Advice Given To a Person Prior to GTT

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- **A week prior to the appointed date for GTT, the person is advised for:**
  - Eat **normal Carbohydrate diet**
  - **Do Not fast or starve**
  - **Do no strenuously exercise**
  - **Drink no Alcohol**
  - **Take no medications**

- The person is advised to come in fasting condition (10-12 hrs fast) on the test date.

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Procedure Of Oral GTT

- Collect a fasting blood and urine specimen from the person undergoing GTT.
- Label the collected fasting samples (F)

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- Note the time
- Give an oral dose of Glucose 75 gm with 250 ml water/1.5 gm per kg body wt.
- May flavor with lemon to avoid vomiting.

- From the time of dosage with an interval of 30 minutes collect the blood and urine specimens up to 2 1/2 hrs or 150 minutes.
- Label each collected specimen.
- Analyze all the collected specimens.

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- Blood specimens are analyzed to estimate Glucose concentration (Using GOD-POD method).
- Urine specimens are checked for qualitative presence/absence of Glucose (Benedicts Test)
- Record the readings of blood Glucose for every specimen
- Plot a GTT curve on graph paper and interpret the results.

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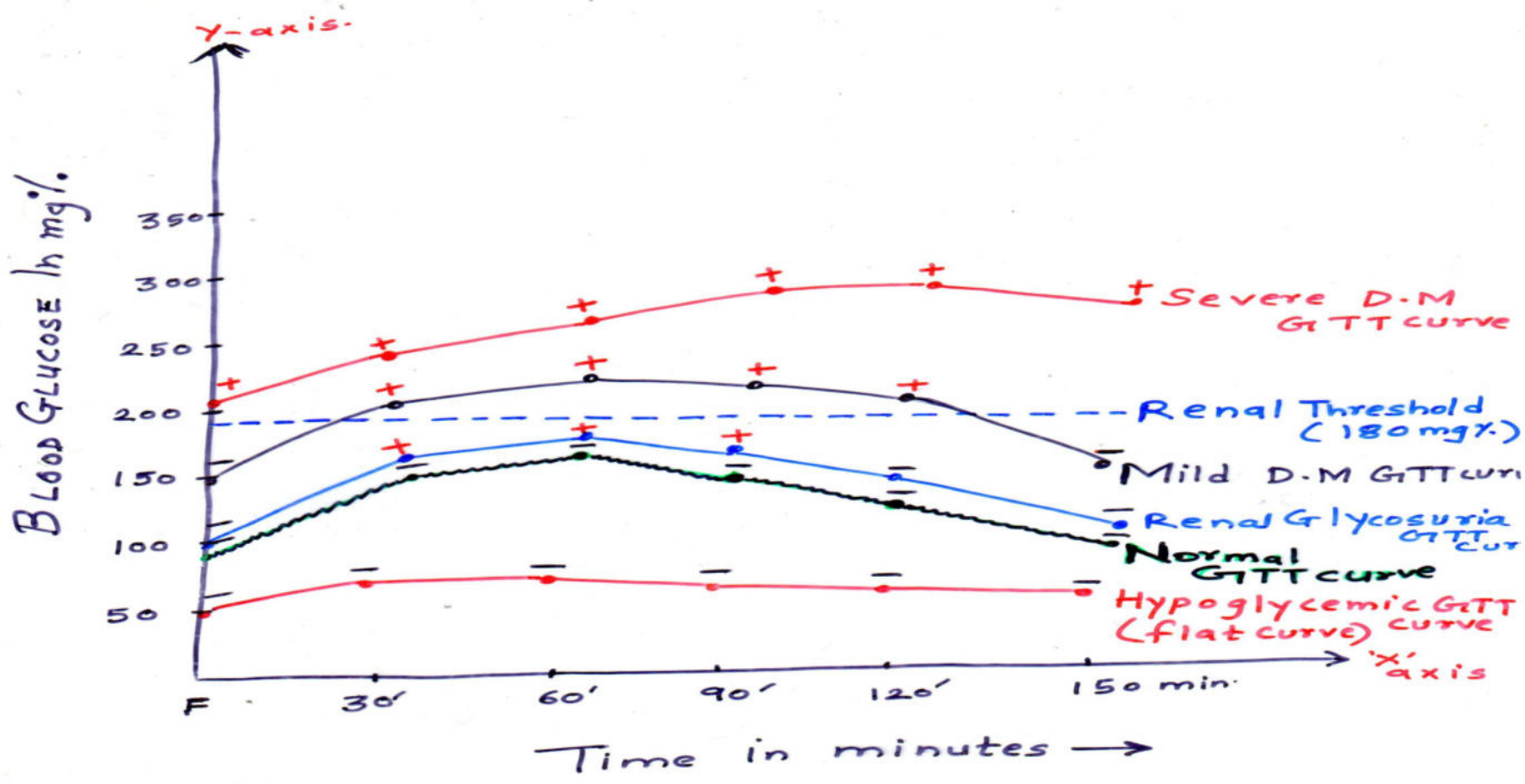
Types And Interpretations Of GTT Curve



Normal Tolerance → Normal Person.

Impaired Tolerance → Abnormal.

* Decreased Tolerance → In Diabetes mellitus (due to Low Insulin activity). (Hyperglycemic curve)
* Increased Tolerance → Insulinomas (Pancreatic Tumors. (Due to high Insulin activity). (Hypoglycemic curve)

Plot a GTT Curve

Specimens	Blood Glucose	Urine Glucose
Fasting	75 mg%	Absent
30 minutes	100 mg%	Absent
60 minutes	120 mg%	Absent
90 minutes	145 mg%	Absent
120 minutes	1 20 mg%	Absent
150 minutes	85 mg%	Absent

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Plot a GTT Curve

Specimens	Blood Glucose	Urine Glucose
Fasting	160 mg%	Absent
30 minutes	170 mg%	Absent
60 minutes	200 mg%	Present
90 minutes	240 mg%	Present
120 minutes	230 mg%	Present
150 minutes	180 mg%	Present

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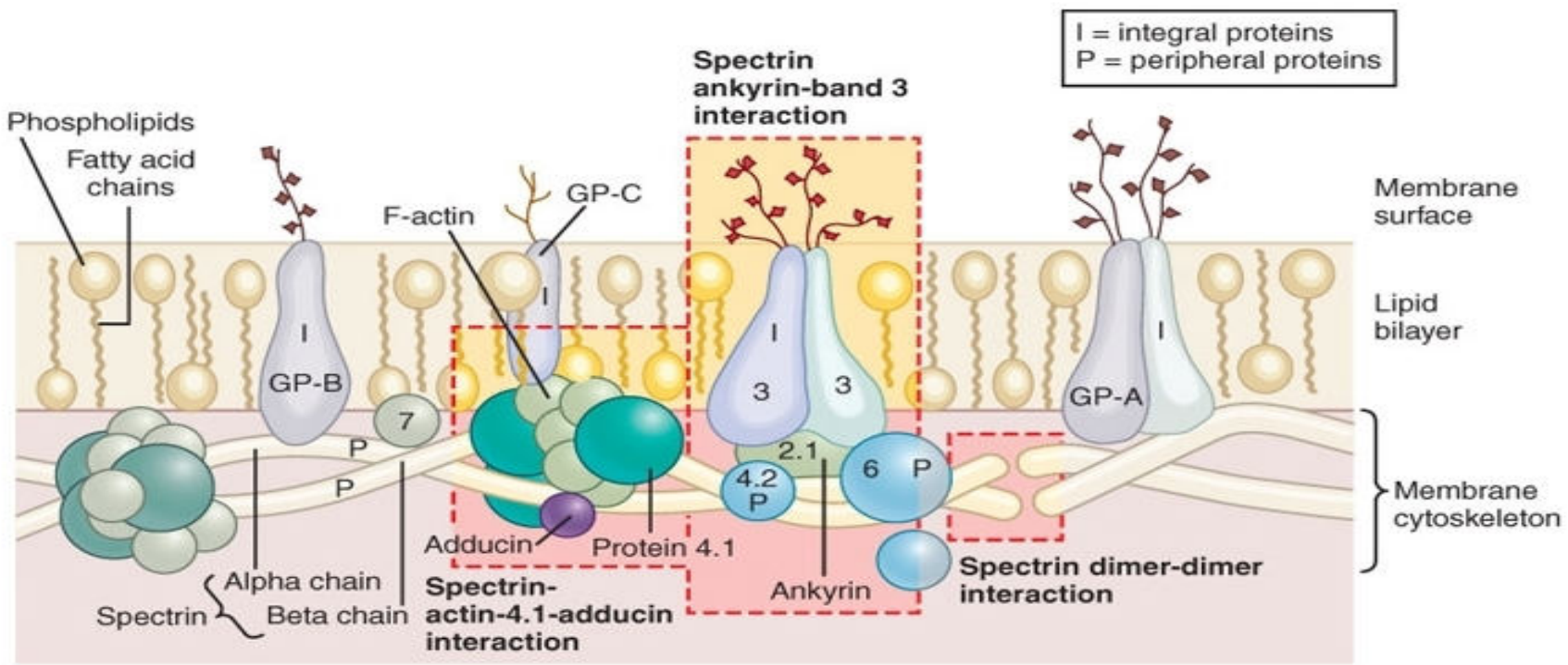
Question

- Why there is need of continuous and uninterrupted Glycolysis in RBC's?
- To maintain RBC membrane integrity and avoid destruction and lysis of RBC's.

RBC membrane structure



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The RBC membrane

- Located in the membrane are proteins that function as **cationic pumps.**

- The RBC maintains its volume and water homeostasis by controlling the intracellular concentrations of Na^+ and K^+ via these **cationic pumps** which **require ATP.**
- **ATP is also required in** the **Ca^{++} pump system** that **prevents excessive intracellular build-up of Ca^{++}.**

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- **In ATP depleted** cells there is an **intracellular build up of Na^+ and Ca^{++} and a loss of K^+ and water.**
- This leads to dehydrated, rigid cells that are destructed/ lysed and culled by the spleen.

- Any abnormality that increases membrane permeability or **alters cationic transport** may lead to decreased RBC survival.

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- The major peripheral protein in RBC's is Spectrin
- It **binds with** other peripheral proteins such as **Actin** to form a skeleton of microfilaments on the inner surface of the membrane.
- This strengthens the membrane and gives it its elastic properties.

- For **Spectrin** to participate in this interaction, it must be phosphorylated by a **protein kinase** that **requires ATP.**
- Thus, a **decrease in ATP**
- **Decreased Phosphorylation of Spectrin.**

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- **Unphosphorylated Spectrin** can no longer bind to Actin to give the membrane its elastic properties.
- This then leads to a loss in membrane deformability and a decreased RBC survival time.

Pasteur And Crabtree Effects

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- Study findings of Glucose metabolism (Catabolism) in Yeast **Saccharomyces cerevisiae** under both aerobic and anaerobic condition.

- Experimental findings of Glucose metabolism in Yeast cells in different concentrations of:
  - **Oxygen**
  - **Sugar**

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- Yeast's are ubiquitous unicellular fungi.
- Most yeast cells are of facultative fermentative.

Types of Yeast

- **Non fermentative** –Has exclusively respiratory metabolism (aerobic), **not capable of alcohol fermentation.**
- **Obligate fermentative**- Natural respiratory mutants metabolize Glucose **only** through **alcoholic fermentation.**
- **Facultative fermentative**- Fully respiratory or fermentative metabolism or **both respiratory and fermentative mechanism.**

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Yeast Sugar Metabolism

- Yeast sugar metabolism depends on:
- Growth condition
  - Type and concentration of Sugar
  - Oxygen concentration

- Metabolic flux occurs on the Pyruvate branch point.
- Pyruvate is oxidized via TCA in aerobic condition.
- Pyruvate is reduced/ fermented to Lactate or ethanol in anaerobic condition.

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Pasteur effect

Word origin: named after its discoverer Louis Pasteur.

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- In 1861 Louis Pasteur figured out
- In the absence of oxygen, yeast consumes more glucose than in the presence of oxygen.
- A phenomenon that has become known as Pasteur effect in the literature.

- Pasteur effect explains the inhibiting effect of oxygen on the process of fermentation.

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- Oxygen inhibits Glycolysis.
- Oxygen limits the use of Glucose.
- In aerobic Glycolysis more ATP produced inhibits PFK of Glycolysis.
- In aerobic condition no fermentation occurs.
- In aerobic condition there is no production of Ethanol/Lactate.

- This shift from slow aerobic to rapid anaerobic consumption of glucose was first noted by Pasteur.
- This shift also happens anytime you are unable to provide oxygen to your own mitochondria- they consume Glucose faster in an attempt to produce ATP via the less efficient fermentation to lactate, and lactic acid accumulates in your muscles.

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- He found that aerating yeasted broth caused the yeast cell growth increased while fermentation rate decreased.
- A switch from anaerobic to aerobic conditions results in the decrease in the rate of carbohydrate breakdown in yeasts.
- Citrate and ATP, allosteric inhibition of the PFK 1 enzyme explains the Pasteur effect.

- Pasteur effect is defined as **inhibition of fermentation** pathway by respiration (Oxygen).
- Oxygen inhibits fermentation(Ethanol/Lactate production) and reduces the rate of Glycolysis.

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- Fermentation occurs in anaerobic conditions.

- Later studies reported several misinterpretations related to the results of Pasteur effect.
- Stated that results of Pasteur were an artefact due to anaerobic growth impairment.
- Anaerobic fermentation occurred in yeast entered in stationary or resting phase.
- Anaerobic fermentation occurred in sugar limiting continuous culturing and at resting cell condition.
- Production of alcohol occurs when cells are in growth / lag phase.

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- In presence of high concentration of Glucose ,the Pasteur effect does not work.
- Under this condition the degradation of Glucose is via fermentation to produce ethanol in aerobic condition.

Crabtree Effect

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- Named after the English Biochemist

Herbert Grace Crabtree.

- Crabtree effect is the converse of the Pasteur effect.

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- The Crabtree effect(1929) describes the phenomenon whereby the
- Yeast, Saccharomyces cerevisiae, produces ethanol (alcohol) **aerobically** in the **presence of high external glucose concentrations** rather than producing biomass via the Tricarboxylic acid cycle.

- Crabtree effect defines occurrence of alcoholic fermentation under aerobic conditions.
- Saccharomyces cerevisiae catabolize Glucose mainly by fermentative process.

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- When oxygen supply is kept constant and Glucose concentration is increased, the oxygen consumption by cells falls.
- Cells with high rate of Glycolysis consumes pi and NAD^+ which limits their availability to operate oxidative phosphorylation.
- Here ETC/ oxidative phosphorylation decreases and that decrease oxygen consumption.

- At high Glucose concentration the rate of aerobic fermentation is also increased.
- At high concentration of Glucose there is inhibition of synthesis of ETC enzymes by high fermentation rates.
- High rate of Glycolysis **reduces** the **respiratory chain** and induces fermentation to produce alcohol.
- Catabolite repression of ETC enzymes.

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Mechanisms Explaining Crabtree Effect

- Catabolite Repression
- Catabolite Inactivation
- Limited Respiration Capacity

Catabolite Repression

- When Glucose/ initial product of Glucose metabolism suppress the synthesis of various enzymes of respiration(Still unclear).

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- High concentration of sugar disrupts the structure of yeast mitochondria.
- Respiration is stopped Ethanol fermentation occurs.

Catabolite Inactivation

- Glucose in high concentration inhibits the key enzymes of respiratory track.

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- Crabtree effect in Yeast cell can be observed when the growth medium containing Glucose in concentration above 5mM.

- Increasing concentrations of Glucose accelerates Glycolysis (the breakdown of glucose) which results in the production of appreciable amounts of ATP through substrate-level phosphorylation.
- This reduces the need of oxidative phosphorylation done by the TCA cycle via the electron transport chain and therefore decreases oxygen

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- The effect can be easily explained, as the yeast being facultative anaerobes can produce energy using two different metabolic pathways.

- While the **oxygen concentration is low**, the product of Glycolysis, (Pyruvate), is **turned into ethanol** and carbon dioxide, and the energy production efficiency is low

  (2 moles of ATP per mole of glucose).

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- If the oxygen concentration grows, Pyruvate is converted to acetyl CoA that can be used in the citric acid cycle, which increases the efficiency to 32 moles of ATP per mole of Glucose.
- Therefore, about 15 times as much glucose must be consumed anaerobically as aerobically to yield the same amount of ATP.

- Under anaerobic conditions, the rate of Glucose metabolism is faster, but the amount of ATP produced (as already mentioned) is smaller.

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- When exposed to aerobic conditions, the ATP production increases and the rate of Glycolysis slows, because the ATP produced acts as an allosteric inhibitor for Phosphofructokinase 1, the third enzyme in the Glycolysis pathway.

- So, from the standpoint of ATP production, it is advantageous for yeast to undergo Krebs Cycle in the presence of oxygen, as more ATP is produced from less Glucose.

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- **When Glucose concentration is high in aerobic condition:**
- **Yeast fermentation** in aerobic condition has **limited capacity.**
- High Glucose concentration
- Increases Glycolysis
- Increased Pyruvate concentration
- Limits the yeast to use Pyruvate in line of TCA and oxidative phosphorylation.
- Pyruvate is fermented to Ethanol.

- **When Glucose concentration is high in anaerobic condition:**
- **Yeast fermentation** in anaerobic condition has **unlimited capacity**.
- Use all Pyruvate generated from Glycolysis to **Ethanol unlimitedly.**

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- Crabtree phenomena occurs in tumor cells where cell is in the aerobic condition metabolizes Glucose excessively via Glycolysis and produces Lactate.

QUESTIONS

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I) Long Answer Questions.

Q.1 Give principle carbohydrates present in the diet & its rich food sources. Describe the digestion & absorption of different carbohydrate forms.

- Q.2 Define Glycolysis. Describe reactions, Energetics, significance, regulation of Glycolysis.

OR

Describe E.M.P. pathway

(Conversion of Glucose to Pyruvate).

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- Q.3 Describe Glycogen metabolism & its regulation.
  - OR
- Describe Glycogenesis and its regulation
- Describe Glycogenolysis and its regulation.

Q.4 Describe T.C.A. cycle/Kreb's cycle/Amphibolic pathway/Common metabolic pathway.

- OR

How Acetyl-CoA is oxidized in the body & give its significance.

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- Q.5 Describe H.M.P. Shunt & Give its significance.
- OR
- Describe Pentose Phosphate Pathway.
- Q.6 Define Gluconeogenesis. Describe the reactions of Gluconeogenesis.
- State the fate of the Glucogenic precursors .How Gluconeogenesis is regulated.

- Q.7 Describe Diabetes Mellitus with respect to clinical types, causes, biochemical alterations, clinical manifestations, diagnosis & management.

- Q.8 Homeostasis of blood glucose level by hormonal & metabolic factors.

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II) Short Notes

- Lactose Intolerance
- Dietary cellulose & its importance.
- Role of Insulin in Carbohydrate metabolism.
- Fates of dietary Glucose entered in the Liver cells.
- Difference between Insulin & Glucagon.
- Glycogen storage disorders/Inherited disorders of Glycogen Metabolism.
- Difference between EMP & HMP pathways.
- G-6 P. D. deficiency.
- Uronic Acid Pathway & its significance.
- Metabolic fate of Fructose

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- Rapaport Leubering Cycle/Glycolysis in Erythrocytes.
- Oxidative Decarboxylation of Pyruvate/Pyruvate Dehydrogenase Complex.
- Glycogenolysis in Muscles & Liver.
- Cori's Cycle/Metabolism of Lactate.

- Metabolic fate of Galactose
- Galactosemia.
- Glycosuria.
- Difference between Hyperglycemia & Hypoglycemia
- Glucose Tolerance Test.
- Inborn errors of Carbohydrate Metabolism.

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- Glucose Transporters
- Glucose Alanine Cycle
- Glycaemic Index of Foods and their importance
- G: N /D:N ratio
- Differentiate between IDDM and NIDDM

- Role of HMP Shunt in Erythrocytes.
- $NADPH+H^+$ requiring enzymes.
- Site & significance of Rapaport Leubering cycle.

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- **Short Answer Questions**

- Define substrate level phosphorylation. Give examples of it.
- Calculate the Energetics of Glycolysis in Aerobic & Anaerobic condition.
- Write formation and fates of Pyruvate in the body.

- Calculate the Energetics of complete oxidation of 1 glucose molecule.
- **Give the Regulatory enzymes of following pathways -**
  - **Glycolysis**
  - **HMP Shunt**
  - **Gluconeogenesis**
  - **Glycogenesis**
  - **Glycogenolysis**

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- Glycosidases & their role/Glycosidases their action & products in GIT.
- Enumerate disorders of carbohydrate metabolism with respect to biochemical defect & biochemical alterations.

- Write the enzymes & coenzymes of PDH and KDH complex.
- Enumerate the diagnostic tests for Diabetes mellitus.
- Give four factors, which regulate blood glucose.

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- Write various pathways of carbohydrate metabolism with respect to occurrence/ location (where), condition (when), significance (why).
- Pasteur and Crabtree effect

Case Studies

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Case Study 1

- A 58 year old obese man with frequent urination is seen by his primary care physician. The following laboratory tests were performed.
- Random blood Glucose= 225 mg%
- Urine Glucose 2+
- Urine Ketones Negative

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Questions

- What is probable diagnosis of this patient?
- What other tests should be performed to confirm this?
- After diagnosis what test should be performed to monitor his condition?

Case Study 2

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- An 18 yr male who had an history of Diabetes mellitus was brought to an emergency department because of excessive drowsiness , vomiting and diarrhea .His Diabetes had been well controlled with 40 units of Insulin daily until several days ago . When he developed excessive thirst an Polyuria. For past three days he also had headache, myalgia, and low grade fever . Diarrhea and Vomiting began one day ago.

Questions

- What is the probable diagnosis of this patient based on the data presented?
- What laboratory tests should be performed to manage this patients condition?
- Why are urine ketones positive?
- What methods are used to detect urine ketones? Which ketone body is detected?

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Case Study 3

- A 14 yr old male student was seen by his physician. His chief complaints were fatigue, weight loss, and increase in appetite , thirst and frequency of urination . For the past three to four weeks he had been excessively thirsty and had to urinate every few hours. He began to get up 3 to 4 times a night to urinate . The patient has family history of Diabetes mellitus.
- Fasting Blood Glucose=160 mg%
- Glycosuria and Ketonuria detected.

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Questions

- Based on the preceding information can this patient be diagnosed with Diabetes mellitus?
- What further tests might be performed to confirm the diagnosis?
- According to ADA what criteria are required for the diagnosis Of Diabetes mellitus?
- Assuming this patient has diabetes which

Diagnostic Criteria For DM

Random Blood Glucose + Symptoms of DM	**> 200 mg%**
Fasting Blood Glucose	>126 mg%
Post prandial Blood Glucose	> 200 mg%

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Case Study 4

- A 13 year old girl collapsed on a play ground at school. When her mother was contacted she mentioned that her daughter had been loosing weight and making frequent trips to the bathroom in the night. The emergency squad noticed a fruity breath. On entrance to emergency dept her vital signs were as follows:
- B.P -98/50
- Body Temp 99 degree
- Respirations Rapid

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Urine PH	5.5
Urine Protein	Negative
Urine Glucose	4+
Urine Ketones	Present
Blood Glucose	500 mg%
Blood Urea	30 mg%
Serum Creatinine	0.4 mg%

Questions

- Identify the patients most likely type of Diabetes mellitus?
- What is the cause of fruity breath?

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Case Study 5

- A 28 year old woman delivered a 9.5 lb infant .

The mothers history was incomplete and she claimed to have had no medical care through her pregnancy . Shortly after birth the infant became lethargic and flaccid.

Blood Glucose = 25 mg%

Ionized Calcium= 4.9 mg%

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Questions

- Give the possible explanation for the infants large birth weight and size.
- If the mother was gestational Diabetic why was her baby hypoglycemic?
- If the mother had been monitored during pregnancy what laboratory tests should have been performed?

Case Study 6

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- Laboratory tests were performed on a 50 year old lean white woman during an annual physical examination . She has no family history of Diabetes or any history of elevated Glucose levels during Pregnancy.

Fasting Blood Glucose	90 mg%
Serum Cholesterol	140 mg%
HDL	40 mg%
Serum Triglycerides	90 mg%

Questions

- What is probable diagnosis of this patient?
- Describe the proper follow up for this patient?

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Case Study 7

- For 3 consecutive months, a fasting Glucose and Glycosylated Hemoglobin were performed on a patient. The result are as follows:

	Quarter 1	Quarter 2	Quarter 3
Fasting Blood Glucose	280 mg%	85 mg%	91 mg%
Hb A1c	7.8 %	15.3 %	8.5 %

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Questions

- In which quarter was the patients Glucose the best regulated
- Do the fasting Glucose and Glycosylated Hb match? Why or Why not?

Case Study 8

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- A 25 yr old healthy female patient complains of dizziness and shaking 1 hour after eating a large heavy carbohydrate meal . The result of random Glucose test performed showed 55 mg%.

- However he had lost consciousness on that occasion; his mother had made him drink a heavily sugared milk thinking that the child was feeling weak. This seemed to have alleviated symptoms.

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Questions

- Identify the characteristic of Hypoglycemia in the case study?
- What tests should be performed next to determine the problem?

Case Study 9

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- A 5 year old child was brought to the medical OPD in a comatose state . He had felt headache and dizziness only a few hours before. His father noticed profuse sweating and some abnormal behavior at that time and rushed him to the hospital. A similar episode had occurred two months earlier after the child had a glass of sugarcane juice .

- Presently physical examination showed tachycardia and rapid breathing . Liver was markedly enlarged, being palpable 4 cm below coastal margin .Blood and urine samples were analyzed .

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- Blood glucose was 52mg% , no other abnormality was found in the test result. The child was given intravenous dextrose to treat hypoglycemia. He responded well and the hypoglycemia symptoms were promptly disappeared .

- Two days later, Liver biopsy reports revealed large deposits of Fructose-1-PO_4 within hepatocytes.

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Questions

- What is the probable biochemical defect in this child ? Suggest a biochemical test to evaluate the above diagnosis.
- Provide biochemical explanation for the child's sign and symptoms
- Would you expect liver function to be normal or sluggish in this child? Give reason.
- Suggest how to manage this condition?

Case Study 10

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- A 23 year old male developed fever about two weeks back. He had bouts of shivering temperature of 40. 4 degree centigrade and started treatment with Primaquine after identification of the parasites in a blood smear.

- The fever subsided the next day the following symptoms aggravated and he felt fatigue, dizziness breathlessness on slightest exertion headache and insomnia and paresthesia of the fingers and toes.

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- Three days later , the patient noticed dark black coloured urine. On examination he showed pallor of the skin and the mucous membrane, yellow sclera . Jaundice, tachycardia(heart rate 110/min) and systolic murmurs were prominent and spleen was enlarged.

Investigations	Patients result	Reference range
Hemoglobin	10.2 gm%	11-14 gm %
Reticulocyte count	6.3 %	Up to 2 %
Serum Total Bilirubin	8.3 mg%	0.1 -1 mg %
Urine bile pigment	Absent	

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- The red cells , on microscopic examination , were found to contain small inclusion bodies(Heinz bodies).

Questions

- What is the probable diagnosis?
- What type of anemia and Jaundice developed in patient?
- State the biochemical basis of the problem?
- Which metabolic pathway is affected in this disordered state?

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Case Study 11

- A premature infant of 2.3 kg body weight, born to Diabetic mother, was shifted to nursery after the attending of paediatrician noticed . The noted symptoms were muscle twitching ,tremors profuse sweating.

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- Soon after, the infant had convulsions and lapsed into comatose state. Blood analysis showed .
- Blood Glucose =38 mg%

Questions

- What is the probable diagnosis?
- Why there is muscle twitching in infant?
- Could the Diabetes in mother is responsible for the infants condition?
- Why there is loss of consciousness?

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THANKYOU

Quantitative Estimation Of Blood Glucose

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Glucose

- Chemically Glucose is a Monosaccharide-
- Aldo Hexose $C_6(H_2O)_6$
- Glucose is a chief sugar of body and blood.
- It is a primary source of energy .
- In blood the predominant form is β D Glucose
- Brain ,RBC's lens cells are totally dependent on Glucose.

- Main metabolic fates of Glucose is
- To completely oxidize to liberate CO_2 ,H_2O and ATP.
- When Glucose is excess, it is converted to Glycogen and Fat and stored as reservoir of energy.
- Blood Glucose is regulated by the hormonal influence.
- Insulin hormone lowers the blood Glucose.
- Glucagon and Epinephrine increases blood Glucose.

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Aim Of An Experiment

- Estimate the amount of Glucose present in the given test specimen

Collection of Blood Sample

- Intravenous blood is withdrawn
- Collected in Tube containing Sodium Fluoride(NaF) and Potassium Oxalate (1:3 mixture)
- NaF is antiglycolytic agent- Inhibits Enolase of Glycolysis.
- Potassium Oxalate- Anticoagulant.

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- **Specimens used for Glucose estimation:**
  - **Whole blood**
  - **Plasma**
  - **Serum**

Conditions Of blood Samples

- **Fasting Blood Sample (FBS):**
  - **Blood sample collected in fasting condition after 10 -12 hrs of fast.**
- **Post Prandial Blood Sample (PP Sugar):**
  - **Blood sample collected after 2 hrs of meals.**
- **Random Blood Sample (RBS):**
  - **Blood sample collected any time.**

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Methods Used

- **True Glucose Method-Based on Enzyme Use.**
  - **GOD-POD Method**
  - **Hexokinase**
- **Based on Reducing Property Of Sugar.**
  - **Folin Wu Method**
  - **Ortho Toluidine Method**

Principle Based On Reducing Property

- In hot and alkaline medium Glucose is transformed to Enediol which reduces the cupric ions to cuprous ions and form the precipitate of Cuprous oxide.
- Cuprous oxide then reduces Phosphomolybdate to Molybdenum blue.

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- The intensity of blue color produced is directly proportional to the amount of reduction reaction brought by reducing sugar.
- The Optical Density of colored solution is measured calorimetrically.

- A Glucose standard of 100 mg% is run similarly for comparison and calculation of unknown concentration of Glucose present in test specimen.

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- Methods based on reducing property of sugar are **not true glucose methods**.
- Actual Glucose concentration of blood specimen cant be estimated out by these methods.
- In these methods other reducing substances present in blood samples also reduce and give the reaction.
- Result values are higher than actual Glucose concentration.

Principle Of GOD-POD Method

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- Glucose present in a test specimen is acted upon by an enzyme Glucose Oxidase (GOD) which oxidizes Glucose to Gluconic acid and H_2O_2.
- The enzyme Peroxidase (POD) then act on H_2O_2 to liberate water and nascent oxygen.
- Nascent oxygen then reacts with a chromogen 4-Aminoantipyrine to form a pink color complex.

True Glucose Methods

- The enzymatic based methods for Glucose estimation are true Glucose methods.
- The enzyme specifically act on Glucose and measure the amount more accurately.

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Protocol

S. No	Test	Standard	Blank
Distilled water	1.8 ml	1.8 ml	2 ml
Plasma	0.2 ml	-------	--------
Glucose Standard	-------	0.2 ml	--------
Glucose Reagent	3 ml	3 ml	3 ml

- Mix all the contents of the tube .
- Incubate the tubes at 37 degree centigrade for 15 minutes.
- Read the O.D readings by adjusting the filter to green (520 nm).
- Record the O.D readings of Test, Standard and Blank.

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Calculation

$$\text{Blood Glucose in mg\%} = \frac{\text{O.D of T}}{\text{O.D of S}} \times 100$$

Results

- The blood Glucose of given test sample = mg%

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Clinical Interpretation

Normal Ranges

- Fasting Blood Glucose= 70-110 mg%
- Post Prandial Glucose = 110-140 mg%
- Random Glucose = 80-140 mg %

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Conditions Of Hyperglycemia

- **When estimated blood Glucose is above the normal range it is hyperglycemia.**
  - **Diabetes mellitus (Common Condition)**
  - **Stress, Anxiety , Anger , Fear**
  - **Hyper Thyroidism**
  - **Hyper Pituitarism**
  - **Hyper Adrenalism**

Conditions Of Hypoglycemia

- When the estimated blood Glucose is below the normal range it is hypoglycemia.
  - **Insulin Over dose**
  - **Pancreatic Tumors (Insulinomas)**
  - **Prolonged Starvation**
  - **Hypo Adrenalism**
  - **Hypo Pituitarism**
  - **Hypo Thyroidism**

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Roll No's- Even No's

- Observations
- O.D of Test= 0.30
- O.D of Standard= 0.28
- Calculate Blood Glucose in mg%
- Interpret your results.

Roll No's- Odd No's

- Observations
- O.D of Test= 0.60
- O.D of Standard= 0.28
- Calculate Blood Glucose in mg%
- Interpret your results.

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Thank You

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