Integrated Metabolism

OR

Intermediary Metabolism

OR

Interrelationship Between Various Metabolic Pathways

OR

Interdependence Of Metabolic Pathways

To Better Understand Metabolism Of Various Biomolecules

- Metabolism of each **chief biochemical was** **studied individually and separately.**

- **This was just for convenience** and **better understanding** of

- Various metabolic pathways associated with each biochemical constituent.

What is Integrated Metabolism?

- **Various metabolic reactions, pathways and processes** of important biochemical moieties of human body viz:
  - **Carbohydrates**
  - **Lipids**
  - **Proteins**
  - **Nucleic acids**
  - **Hemoglobin**
- **Takes place in different cells and cellular compartments** of **specific tissues and organs.**
- **For maintaining normal health ,growth and reproduction.**

The Metabolic Pathways Of Cells Takes Place

- **Synergistically**
- **Closely Interrelated/Integrated**
- **With Interdependence**
- **In a Regulated manner**
- **With good coordination**

- **In the cellular compartments of the body**
  - **Various metabolic pathways** related to different metabolic moieties
  - **Takes** place **synergistically, as per the cellular conditions**.

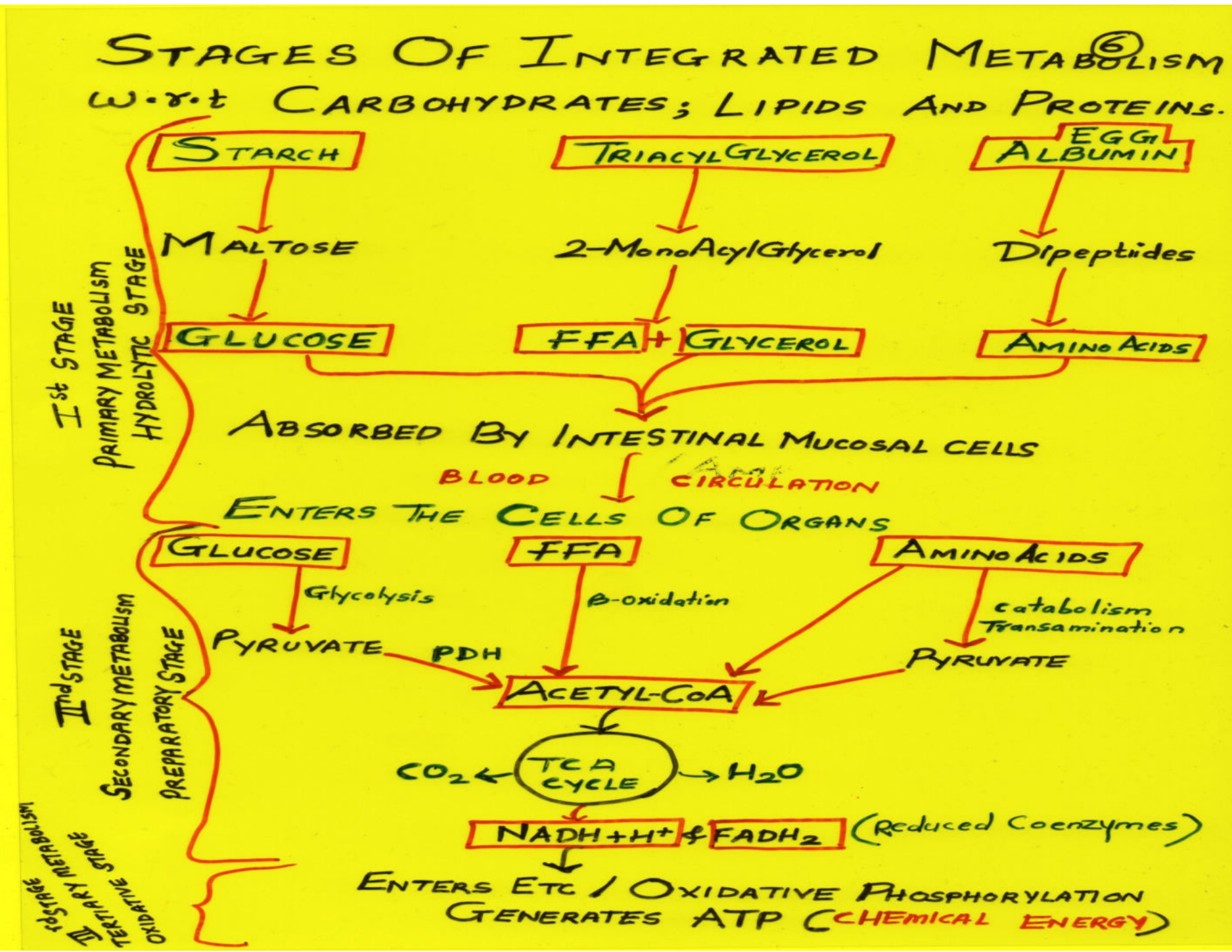
Factors Regulating Metabolism

- **Hormones** are the key regulators of Enzymes
- **Regulatory Enzymes** are stimulated or inhibited by specific hormones
- **Enzymes are regulated by:**
  - **Allosteric Regulation**
  - **Covalent Modifications**

Metabolism Is Regulated By

- **Availability of Substrates Regulate Metabolism :**
  - **Ratio of ATP and AMP**
  - **Citrate levels**
  - **Fructose 2,6 Bisphosphate levels**

- **Low and high levels of ATP** stimulate and inhibit the regulatory enzymes of Glycolysis and TCA.
- **Increased levels of Citrate** stimulates enzyme Acetyl CoA Carboxylase of De Novo biosynthesis of Fatty acid.
- **Increased Fructose 1,6 Bisphosphatase is**
  - **Allosteric stimulator of PFK of Glycolysis**
  - **Allosteric inhibitor of Fru1,6Bis Phosphatase of Gluconeogenesis.**



Evidences Of Metabolic Interrelationships

Interrelationships Of Carbohydrate with Lipid Metabolism

Free Excess Glucose In Well Fed Condition Is a Source For Lipogenesis

- **Pyruvate** end product **of Glycolysis** is **oxidatively decarboxylated** to **Acetyl-coA**
- **Acetyl-coA is then utilized** via **TCA cycle**
- **Acetyl-coA of Glucose when excess** is diverted and used for **biosynthesis** of **Fatty acids and Cholesterol.**

- **Glyceraldehyde-3-phosphate** an intermediate of **Glycolysis of Glucose , i**s a **source for Glycerol** production.

- **Glycerol** obtained **from Glucose** is utilized during **Lipogenesis ,for biosynthesis of Triacylglycerol and Phospholipid biosynthesis.**

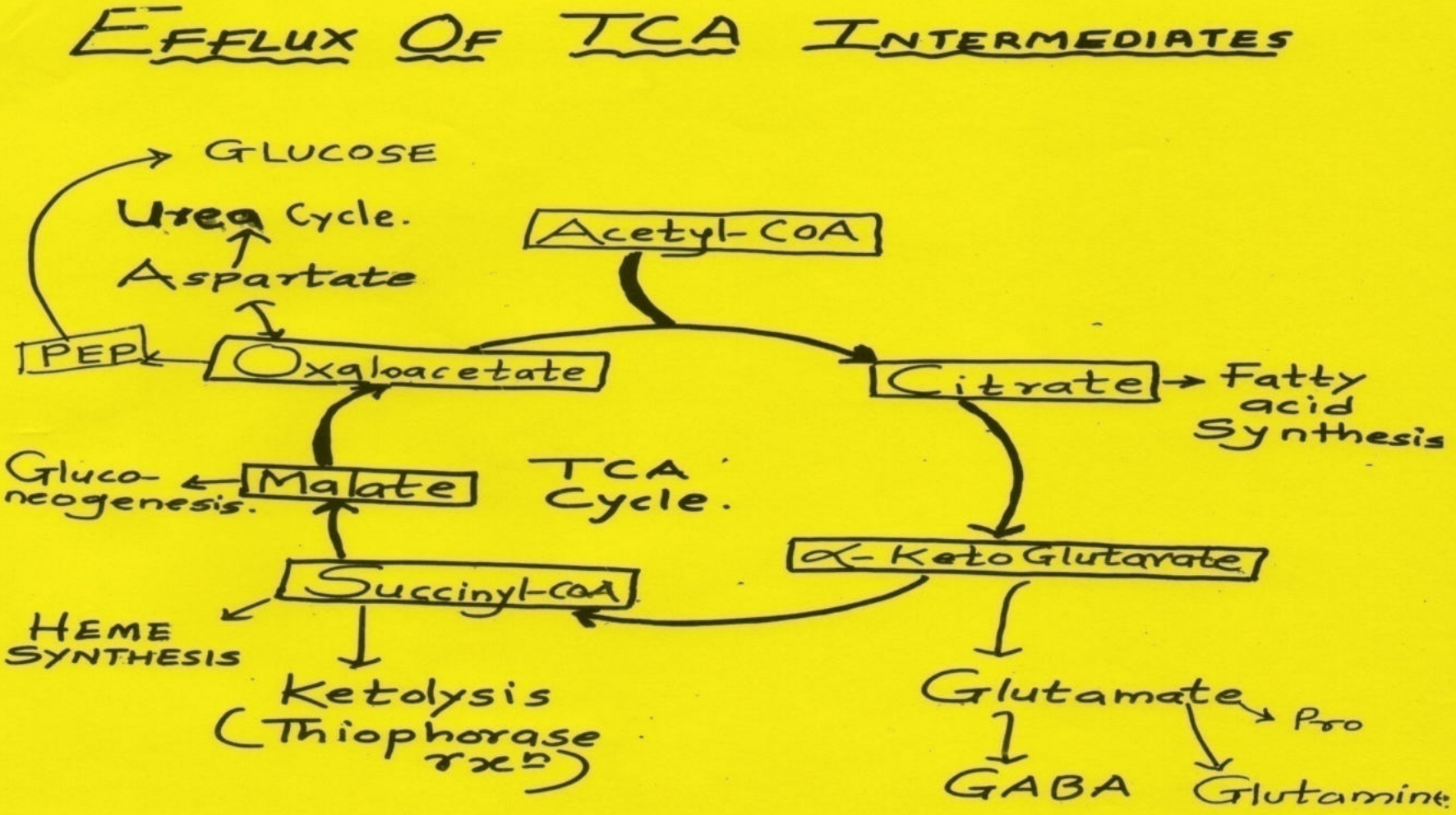
- When **Carbohydrates** taken in excess **can be converted to TAG which is**

- **Stored as reserve source** of energy in Adiposecytes

Interrelationships Of TCA Cycle

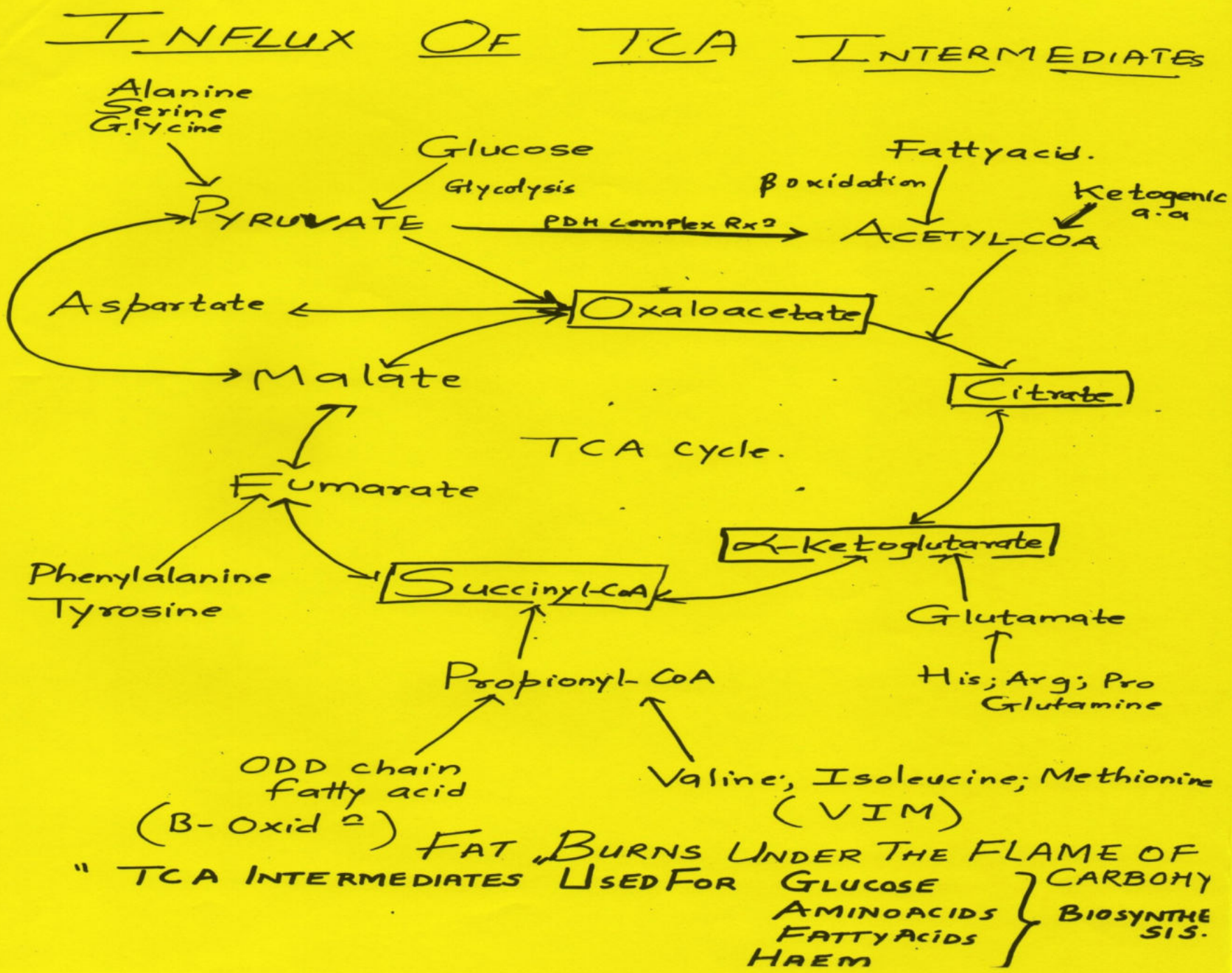
TCA Cycle
Is an
Excellent example
of
Integrated Metabolism

- The **TCA cycle intermediates** are very significant
- These intermediates are **influxed** and **effluxed** as per the cellular need and maintain **biochemical Homeostasis.**



Efflux of TCA Intermediates

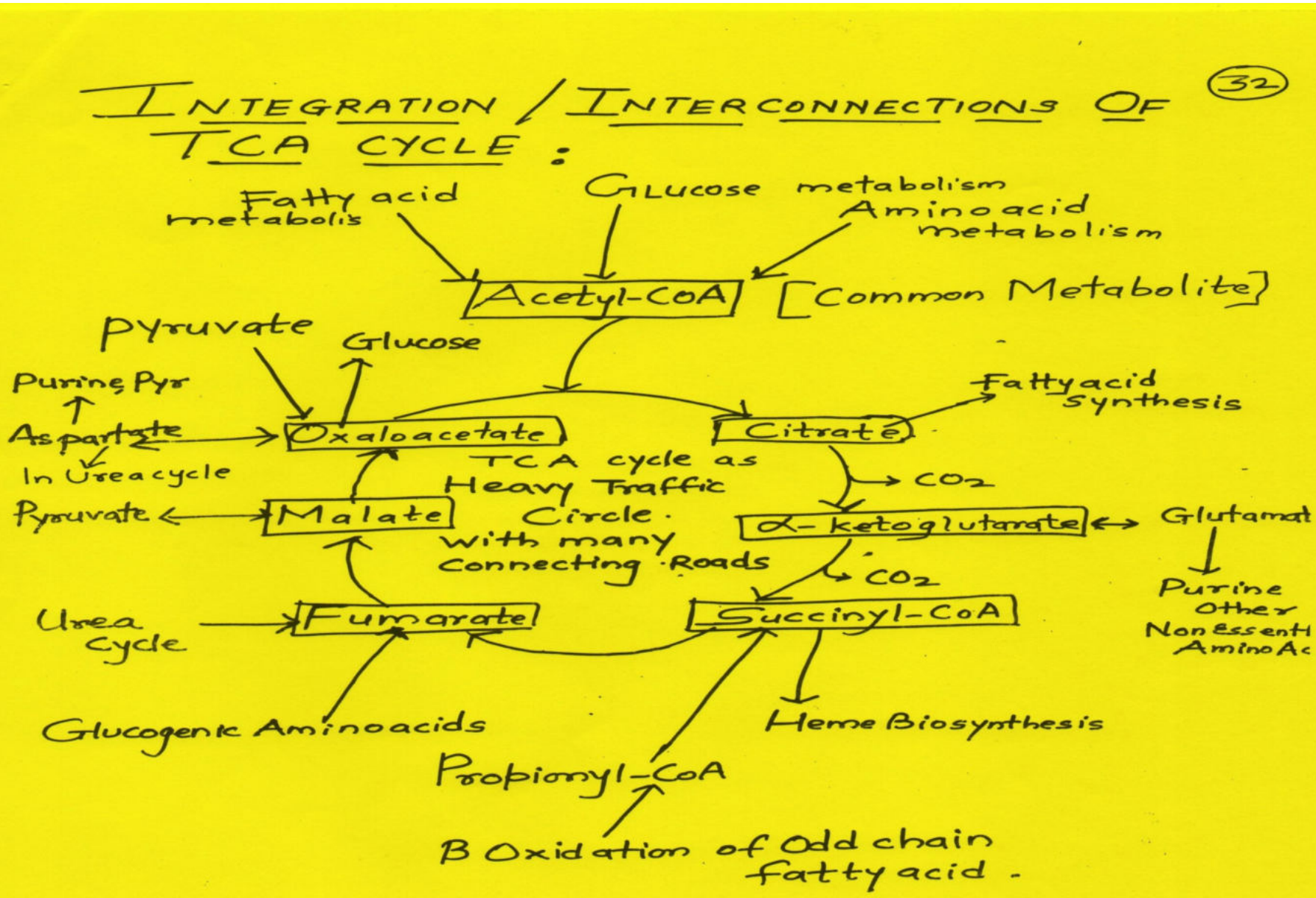
- **Citrate** – Denovo Biosynthesis of Fatty acids.
- **OAA** is reversibly transaminated to Aspartate.
- **α Ketoglutarate** reversibly transaminated to Glutamate.
- **Succinyl CoA** is effluxed for Heme biosynthesis and Ketolysis.



Influx of TCA Cycle Intermediates

- **αKetoglutarate** is added by Glutamate by it's Glutamate Dehydrogenase activity.
- **Succinyl -CoA** is obtained from **Propionyl-CoA** which is a source from B-oxidation of **odd chain fatty acid**
- Catabolism of **Valine, Isoleucine & Methionine** (VIM) amino acids **forms Succinyl-CoA.**

- **Fumarate** is influxed through **Phenylalanine & Tyrosine metabolism**
- **Fumarate** also through **Urea cycle** by Argininosuccinase activity.

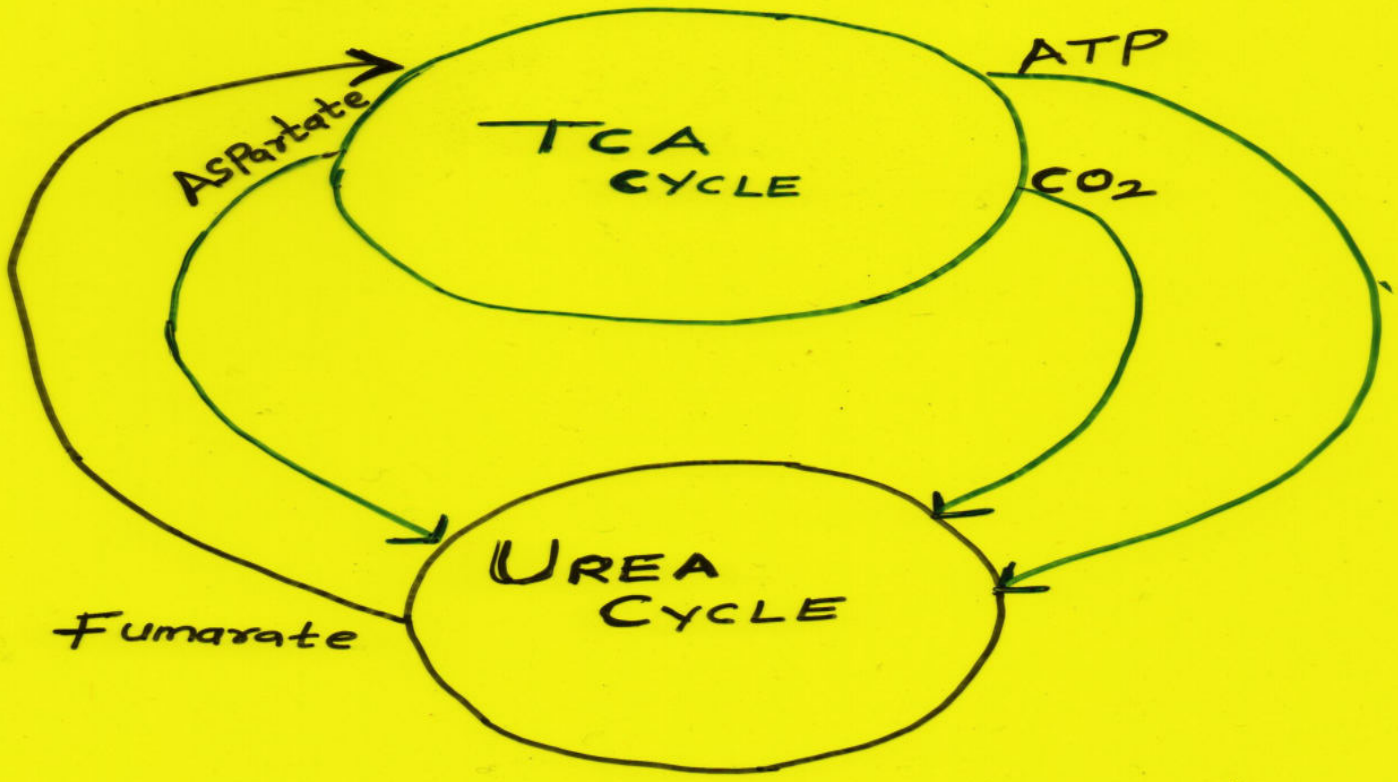


Points To Remember

- **TCA intermediates are used for the biosynthesis of:**
  - **I. Glucose**
  - **II. Amino acids**
  - **III. Fatty acids**
  - **IV. Heme**

Interrelationship Of TCA with Urea Cycle

Interrelationship Between TCA And Urea Cycle



1. CO_2 From TCA cycle → Urea cycle
2. ATP FROM TCA → Urea Cycle
3. OAA ⟷ ASP → Urea cycle
4. Fumarate released in Urea cycle → TCA cycle.

Interrelationship Of Lipid and Carbohydrate Metabolism

- **Fat burns under the Flame of Carbohydrates**

- For **complete oxidation of Fatty acids**

- Their **needs** presence of **sufficient amount of cellular Glucose.**

- **In a well fed conditions**

- The **major source of OAA is Glucose.**

- **Oxaloacetate** is an **essential initiating metabolite for the TCA cycle.**

- **OAA serve as a flame for oxidation of Acetyl CoA via TCA cycle.**

- **Cellular deprivation of Glucose** leads to **incomplete oxidation of Fatty acids**.
- **Accumulates Acetyl-CoA** in Mitochondrial matrix.
- **Impermeable Acetyl-CoA is then transformed to permeable ketone bodies via ketogenesis**.

Interrelationship Of Carbohydrates And Protein Metabolism

- **Intermediates of Carbohydrate** metabolism can be a **source of**

- Carbon skeleton for **biosynthesis of non Essential amino acids.**
  - ❖**Pyruvate to Alanine**
  - ❖**OAA to Aspartate**
  - ❖**αKetoglutarate to Glutamate**

β-oxidation of Fatty acid and it's Interrelationship

- The reduced **coenzymes FADH2 & NADH+H$^+$** generated during it's pathway are

- **Integrated with ETC /oxidative phosphorylation to generate ATP.**

- **Acetyl-CoA** formed as an end product **of β oxidation of fatty acids**

- Is integrated with **TCA cycle for it's complete oxidation**.

- **Acetyl-coA** can be **a source** for **Ketone bodies** production via Ketogenesis.

- To **small extent** in **normal metabolic conditions** and **excess in emergency conditions.**

Remember
Fatty acids
cannot be converted to Glucose In Human Body

- **Acetyl-CoA** obtained from Beta-oxidation of fatty acids **cannot** be reversibly **converted to Pyruvate**
- **Since PDH complex is irreversible in action**.
- **Thus there is no net conversion of Fatty acids (Fat) to Glucose (Carbohydrates).**

- However **Propionyl-CoA** end product of β oxidation of **odd chain fatty acid**
- Serve as a **source for Glucose production** after conversion into **Succinyl-CoA** (intermediate of TCA cycle)
- **Succinyl-CoA in turn** can be a source for **Heme synthesis and Ketolysis**.

- **Fatty acids are also not a source for Amino acids Biosynthesis in human body .**

Interrelationship With ETC

- Reduced coenzyme **NADH+H$^+$ generated** in **Glycolysis**
- By action of **Glyceraldehyde– 3 – Phosphate Dehydrogenase**
- **Enter in ETC for its reoxidation and ATP generation.**

HMP Shunt and It's Interrelationships

- Glucose is alternatively oxidized through HMP shunt to generate:

  – **$NADPH+H^+$** **(**reducing equivalents)

  – **Ribose-5- phosphate**

- **NADPH+H+ are integrated to:**
  - ***Biosynthesis of Fatty acids**
  - ***Biosynthesis of Cholesterol**
  - ***Drug metabolism**

- The **Ribose-5-phosphate** (pentose sugar) of HMP shunt is integrated for
  - **Biosynthesis** of **Purine & Pyrimidine Nucleotides**.

Amino acids are interrelated for Purine and Pyrimidine biosynthesis

- **Gly , Asp, Gln** for Purine Biosynthesis
- **Asp and Gln** for Pyrimidine Synthesis

Amino acids are Source For Glucose In Human Body

- **Glucogenic amino acids** are source for production of **Glucose** via Gluconeogenesis.

- **100 gm of Proteins can produce approx 60 gm of Glucose in human body.**

- **Amino acid Glycine** is connected to **Heme biosynthesis.**

- **Glycerol** released during lipolysis of **TAG is integrated**

- **With Gluconeogenesis to produce Glucose**.

Interrelationships of Uronic acid pathway

- **Glucuronic acid** of Uronic acid pathway is **integrated** with **Phase II conjugation reactions** of **detoxification process**.
  - **Glucuronic acid** is involved in **Bilirubin and other drug metabolism.**

- Glucuronic acid is involved in **Mucopolysaccharide biosynthesis.**

- **ATP produced during oxidative phosphorylation** are **connected to:**
  - **I. Nerve impulse conduction**
  - **II. Muscular activity**
  - **III. Active transport mechanism**
  - **IV. Biosynthetic Reactions**
  - **V. Activation Reactions**

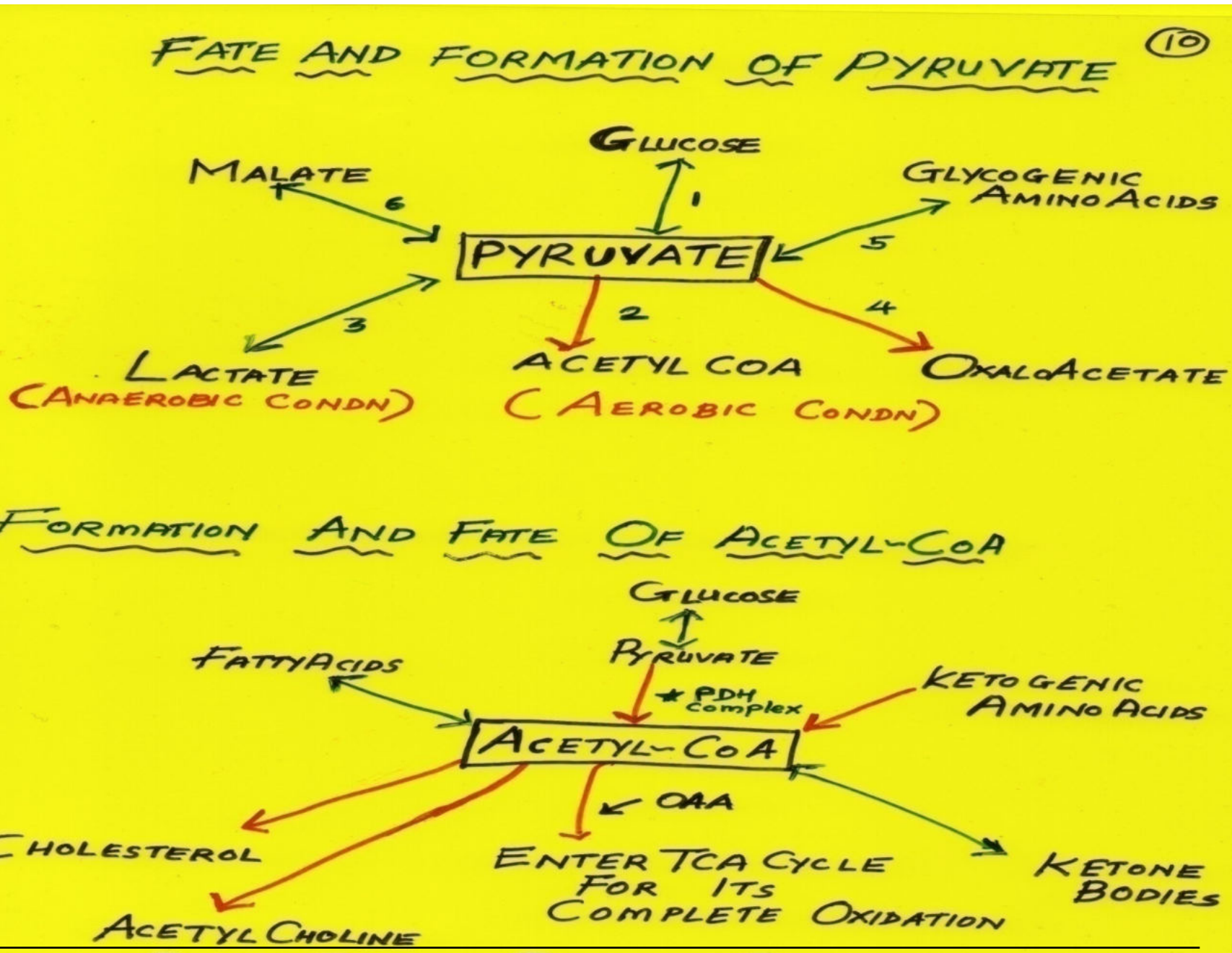
Crossroads Of Metabolism

- **Important Metabolites** in human body who function as **crossroads of metabolism** :

1. **Pyruvate**
2. **Acetyl-CoA**
3. **OAA**
4. **Succinyl-CoA**

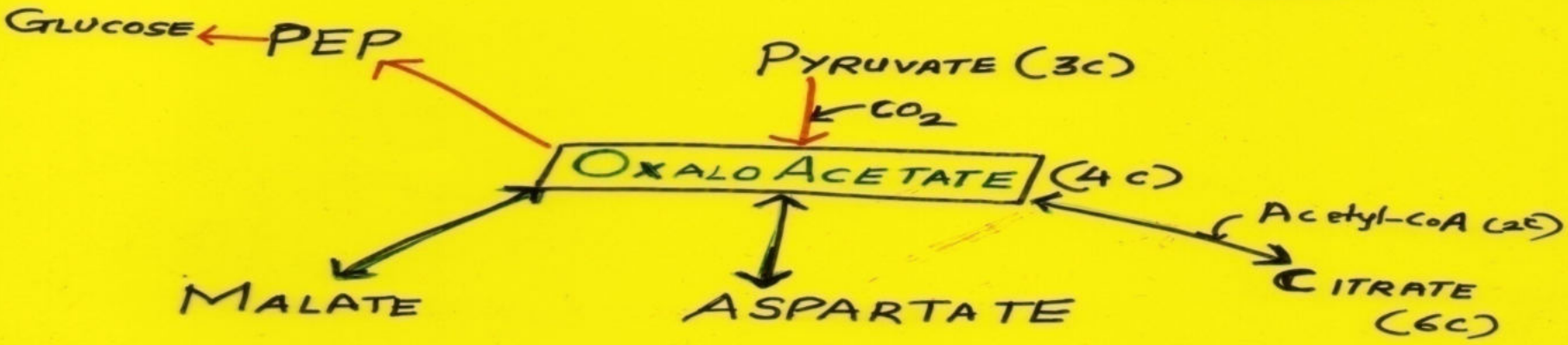
Formation And Fates Of Pyruvate

Formation And Fates Of Acetyl CoA

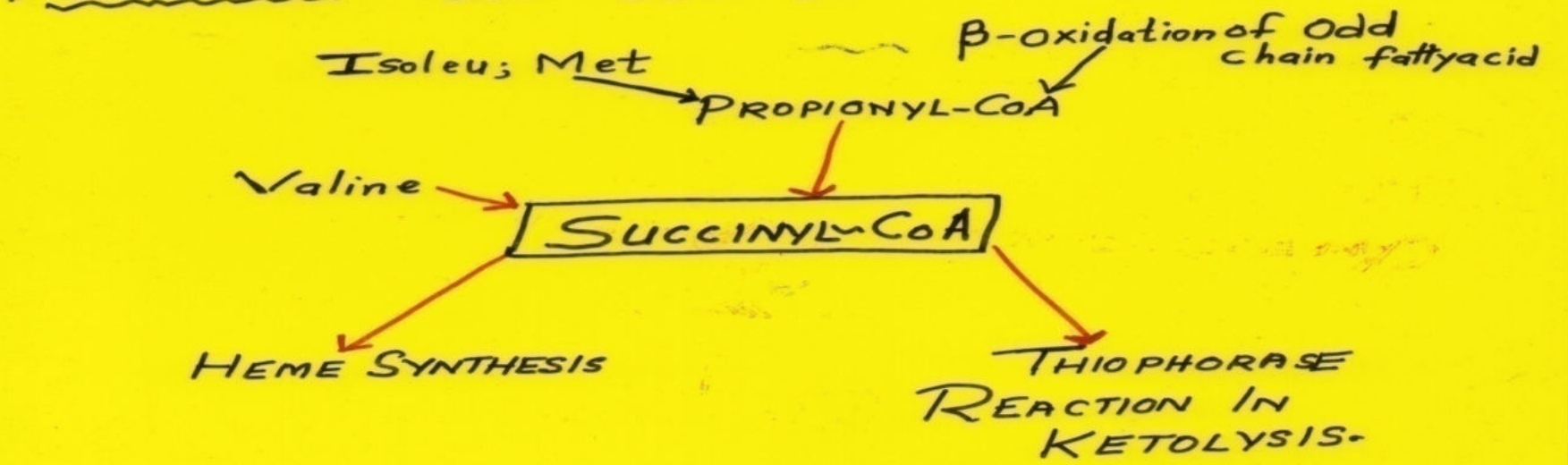


Formation And Fates Of Oxaloacetate
OR
Formation And Fates Of Succinyl-CoA

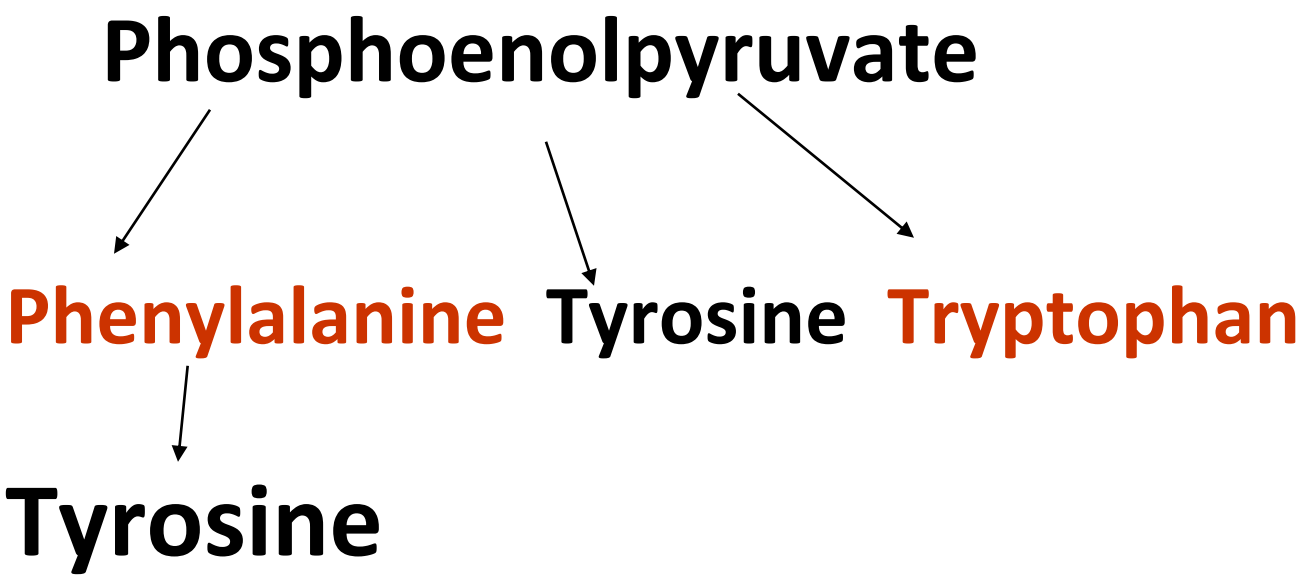
FORMATION AND FATE OF OXALOACETATE:



FORMATION AND FATE OF SUCCINYL-CoA

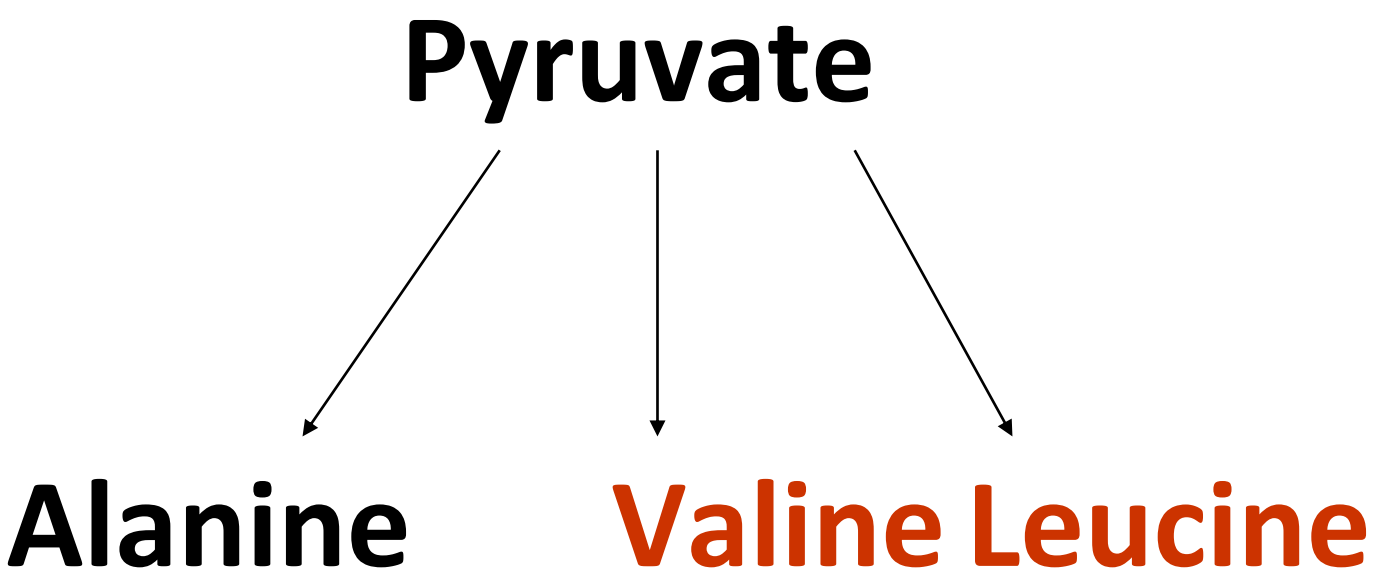


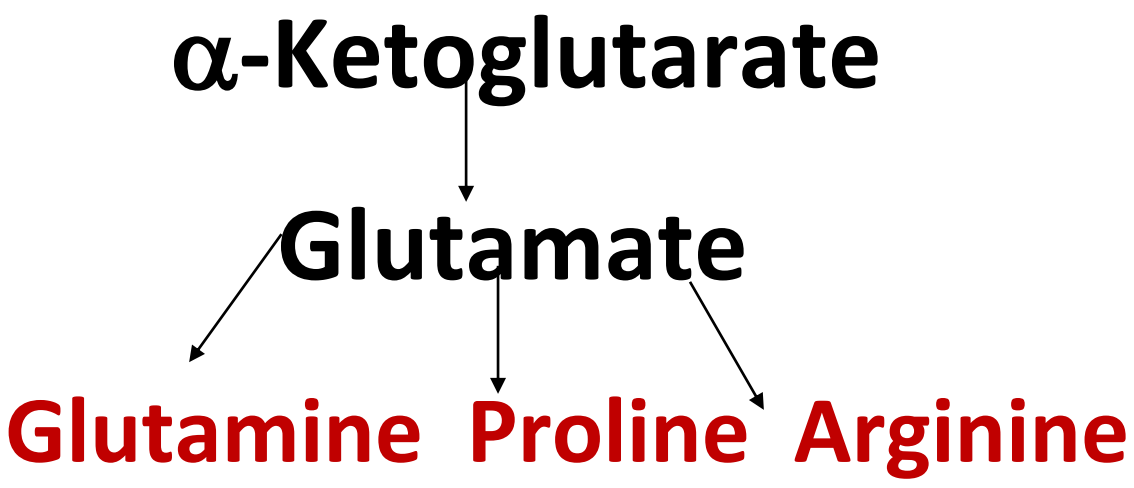
Metabolites Forming Non essential Amino acids In Human Body

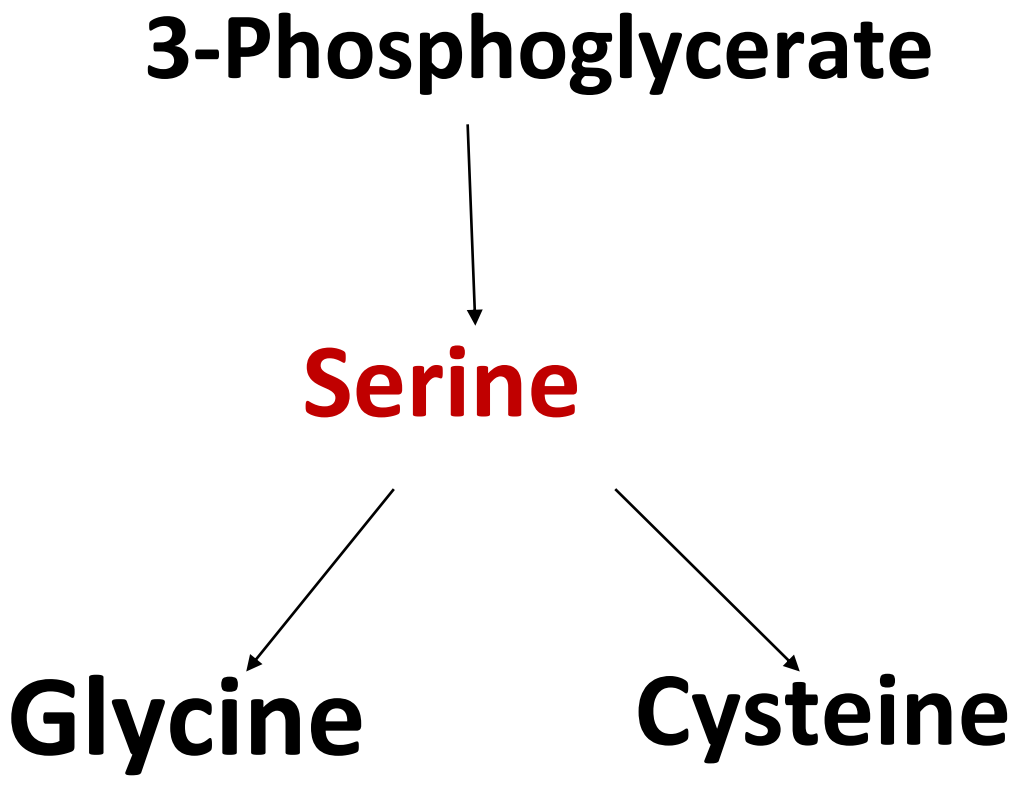


Ribose 5-phosphate

Histidine



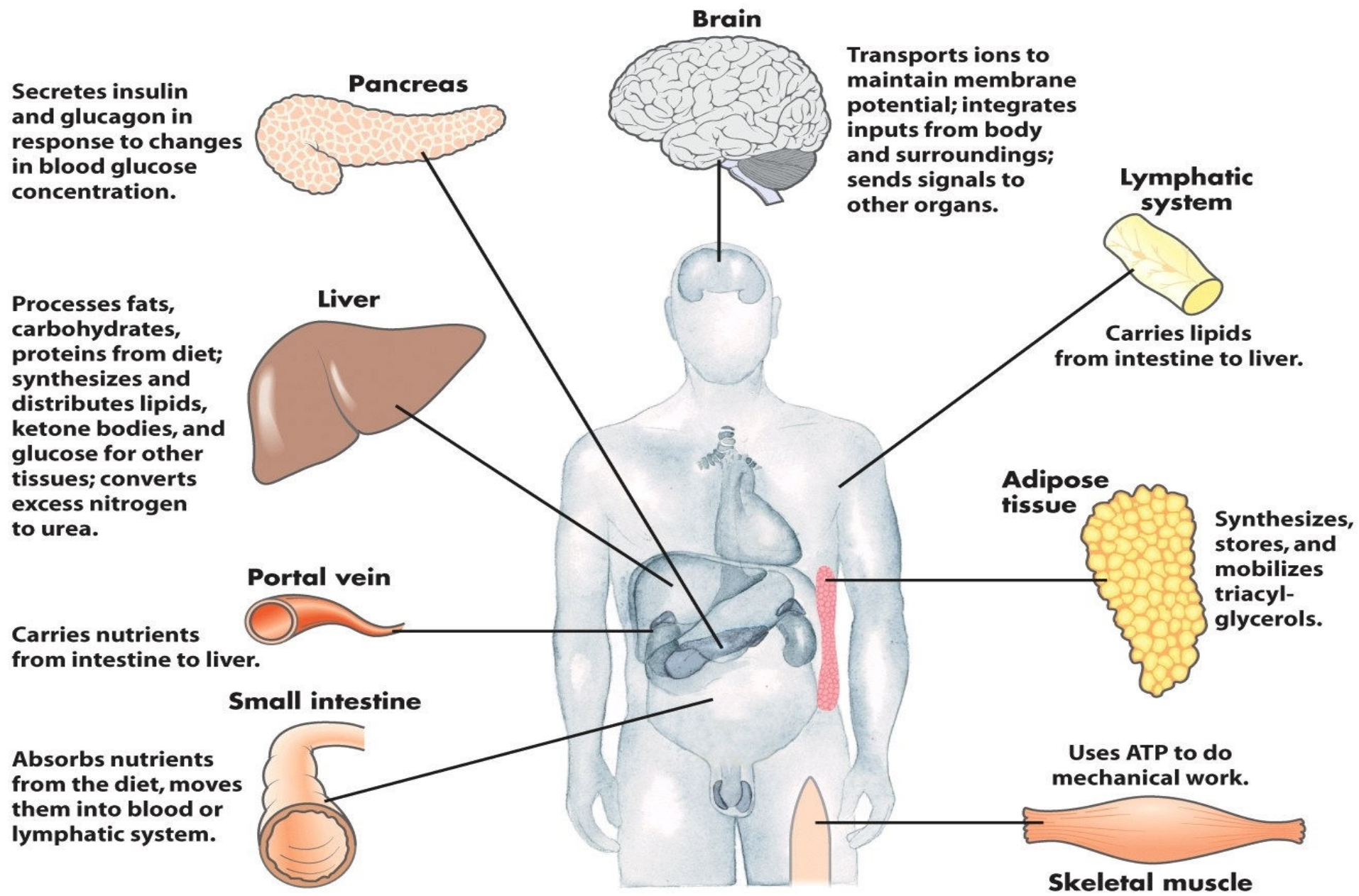




Metabolic Profile
And
Interrelationship Among Organs

Important Metabolic Organs And Their Interrelationships

Metabolic Profile of Organs



Liver

- **Biochemical Factory** of Human body
- **Metabolically very active** in all states (well fed and fasting).
- Has **good coordination with** other body organs.

- **Liver** is a **Glucostatic organ regulates blood Glucose in all conditions.**
  - In a **well fed** condition Liver **stores excess free Glucose as Glycogen.**
  - **In emergency condition In Liver Glycogen is degraded via Glycogenolysis and biosynthesizes Glucose via Gluconeogenesis.**

- Liver biosynthesizes **endogenous Lipids and mobilize out it as VLDL** for extra hepatic use.

Muscles

- In a normal metabolic state muscle uses **Glucose and Fatty acids as main sources of energy**.

- In a well fed state muscles has large **stores of Glycogen** (3/4th)

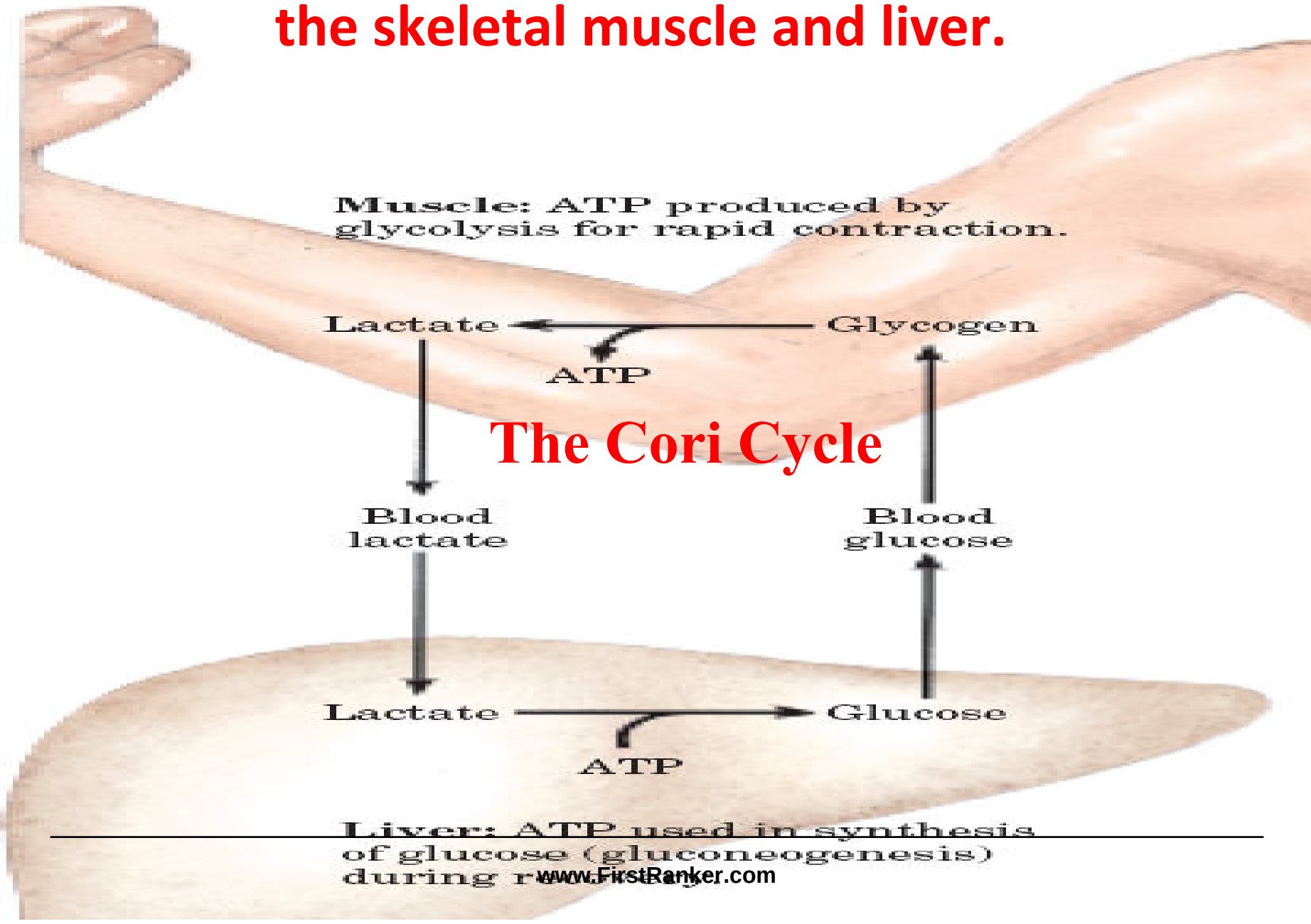
- In **contracting muscles** during **severe exercise** in **anaerobic condition** **Glycolysis ends as Lactate**.

- Later **Lactate** is metabolized by converting it **into Glucose** after carried through blood **in Liver** via **Gluconeogenesis(Cori cycle).**

- In **resting Muscle fatty acids** are the **major source of energy**

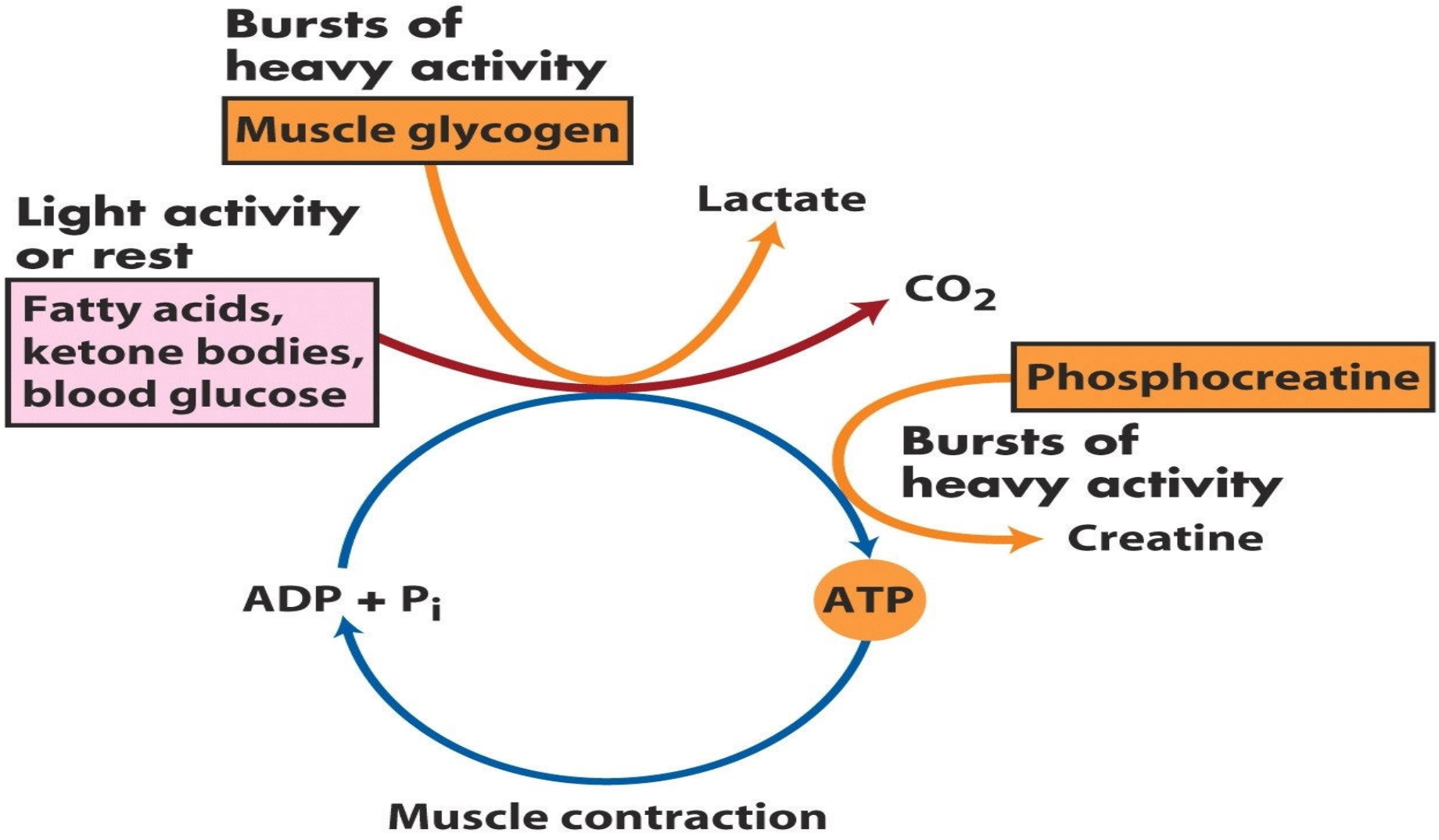
- **This use spare Glucose to be used by Brain and Erythrocytes.**

Metabolic cooperation between the skeletal muscle and liver.



The Cori Cycle

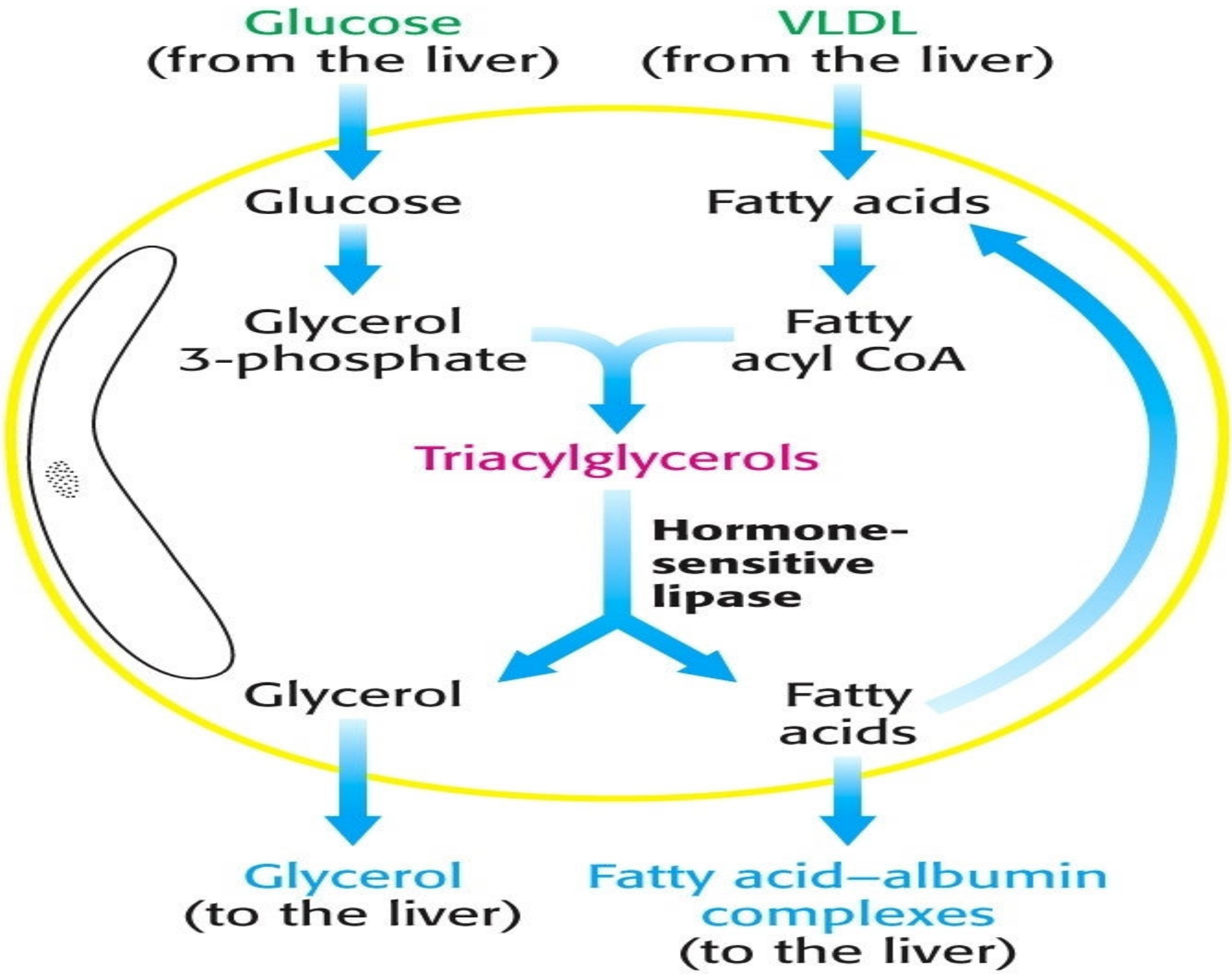
Metabolic Profile of Muscles



Adipose Tissue

- **TAG** can be abundantly and **unlimitedly stored** in adipocytes
- TAG serve as a **reserve store** of energy during well fed condition.

- TAG is the major fuel for this tissue.



Metabolic Profile of Adipose Tissue

- **Needs Glucose for biosynthesis of TAG**
- **Glucose level determines to release Fatty acids into blood**
- **Hormone sensitive Lipase is activated when Insulin/Glucagon ratio is low**

Brain

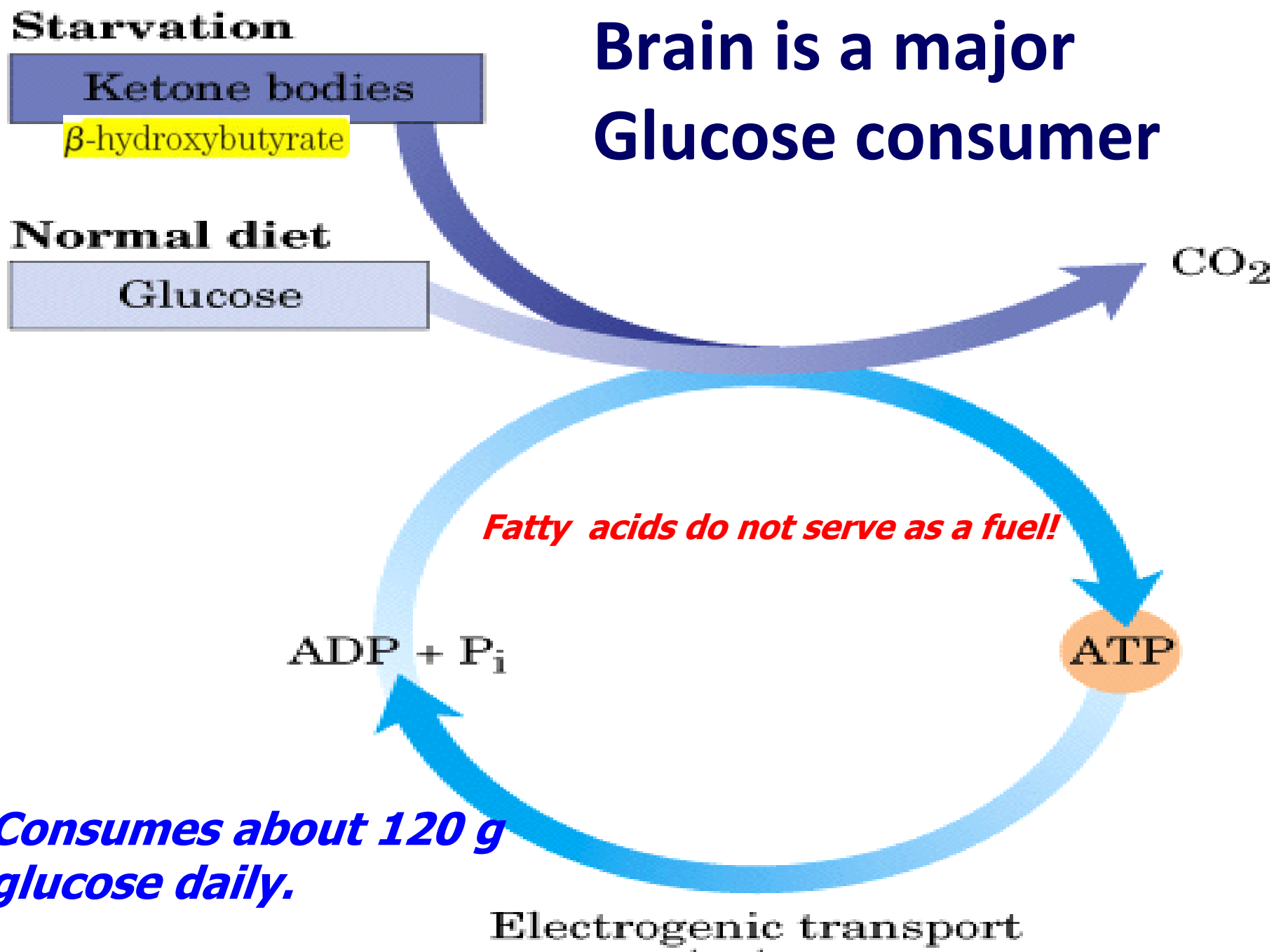
- **Glucose** is the **main fuel of Brain (120 gm/day)**
- **Fatty acids** cannot be utilized by brain as they are bound to Albumin and **cannot cross blood brain barrier.**

Metabolic Profile of Brain

60-70 % **of bodies utilization of Glucose is by Brain.**

In starvation -> Ketone bodies can replace Glucose

Brain is a major Glucose consumer



Consumes about 120 g glucose daily.

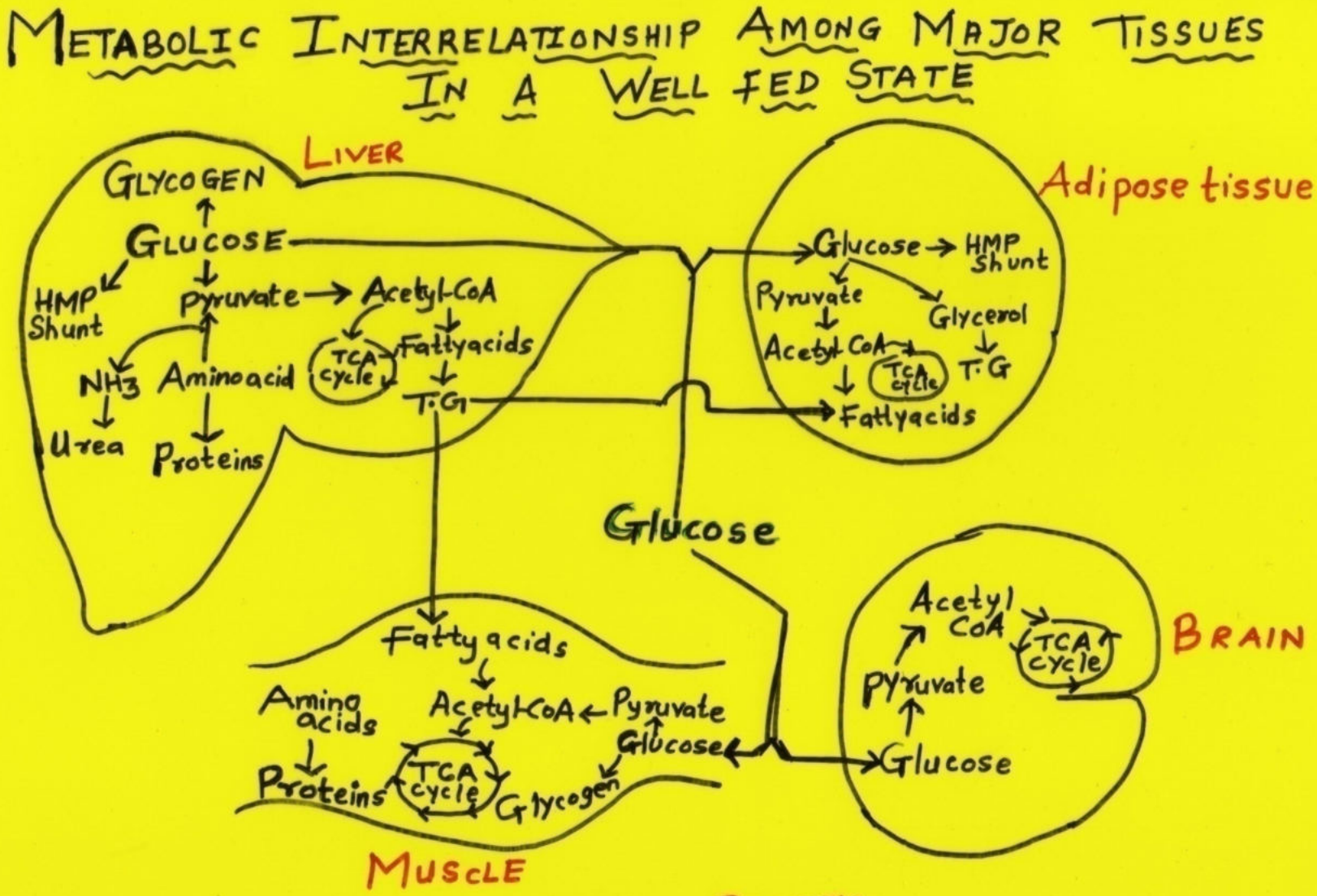
Erythrocytes

- Erythrocytes uses **obligatorily Glucose** for its activity.

- It **lacks Mitochondria** hence the **Glycolysis ends in Lactate.**

Metabolic Profile of Kidney

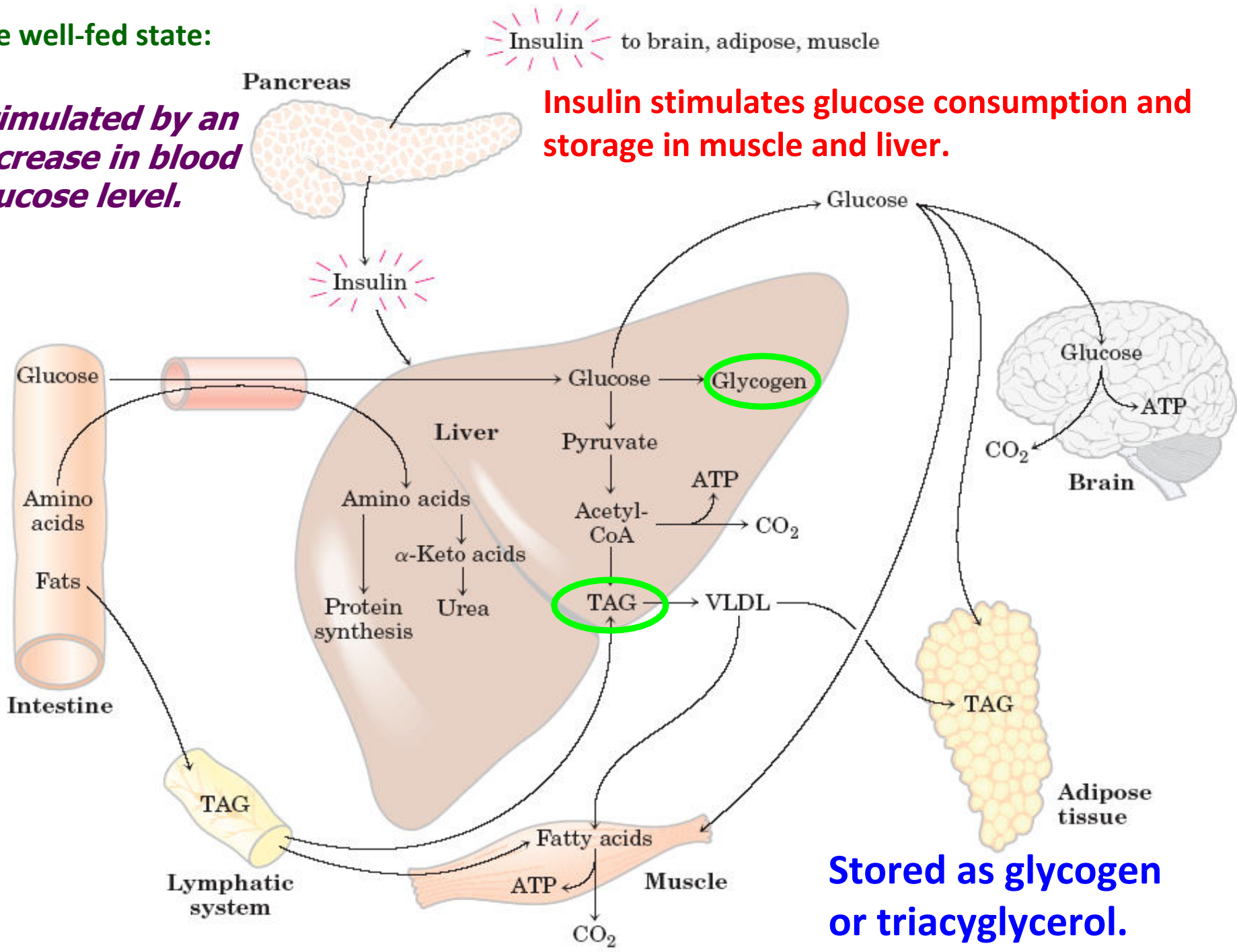
- **Filtration of Blood-** Plasma Ultra Filtrate
- Reabsorption ,Secretion of Substances
- From Plasma Ultra filtrate -> Water , Glucose important absorbable metabolites reabsorbed as per the threshold values.
- Production of Urine -> Secretion of waste products
- During Starvation -> Important site of Gluconeogenesis (1/2 of blood Glucose)

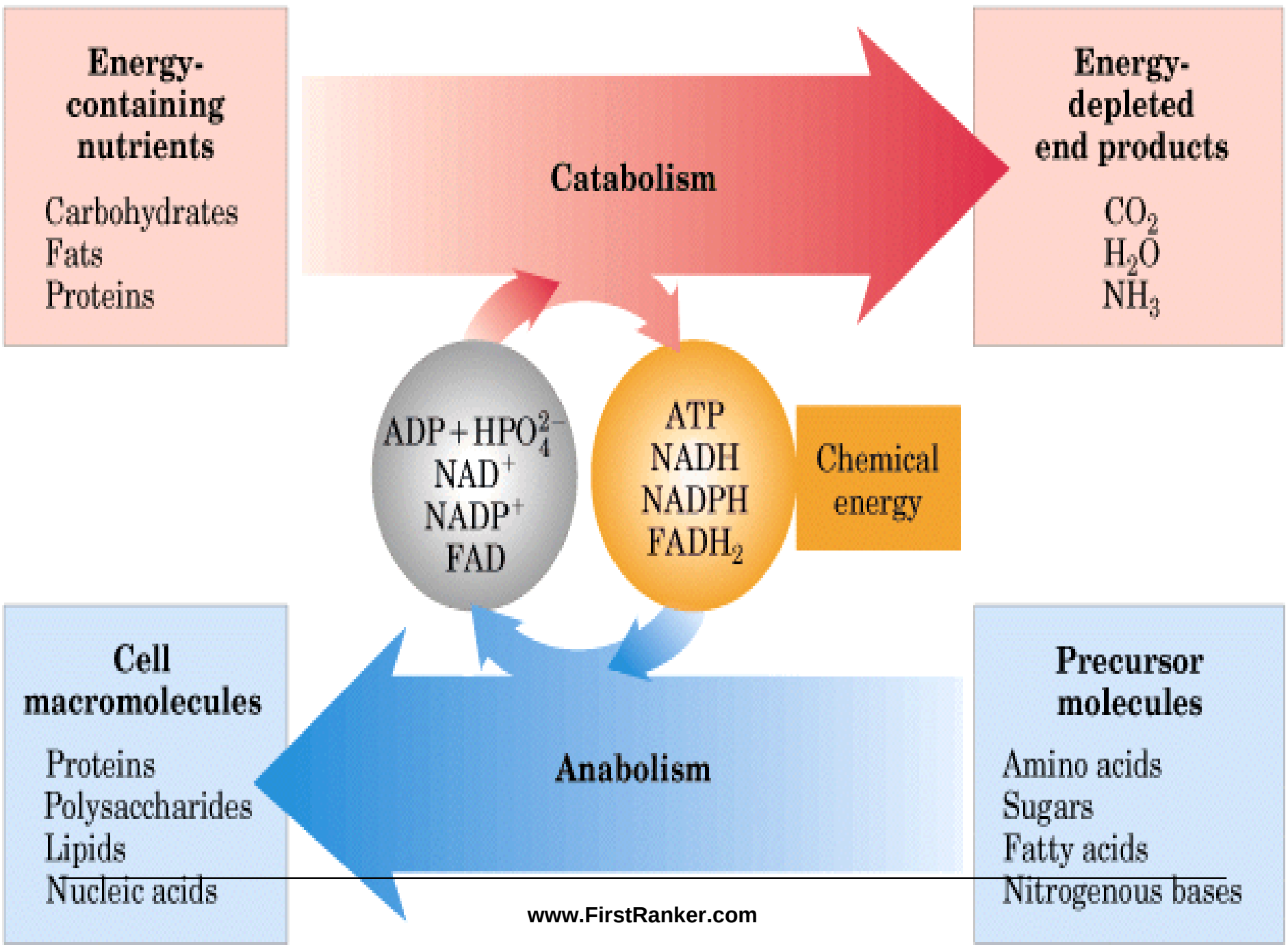


The well-fed state:

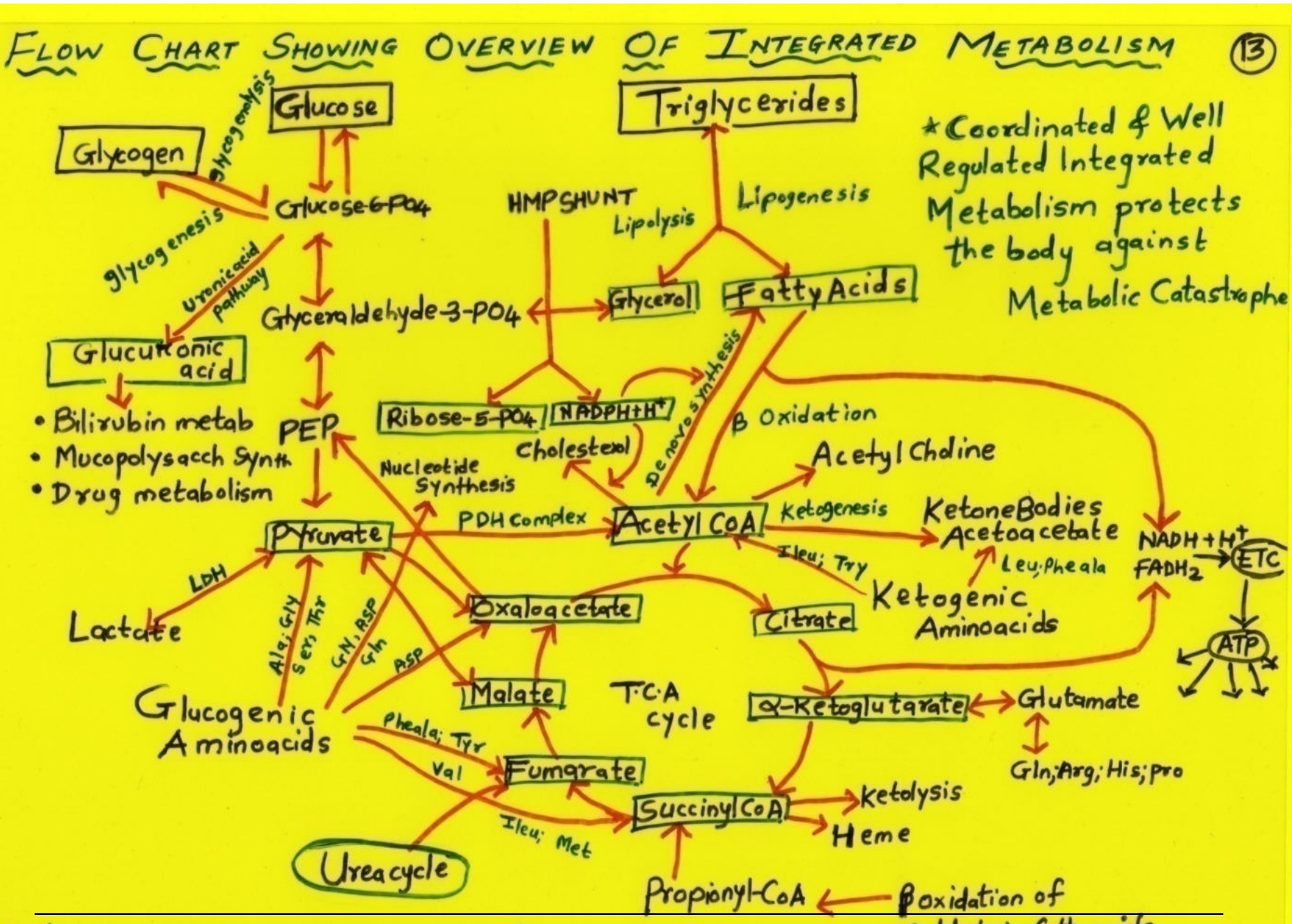
Stimulated by an increase in blood glucose level.

Insulin stimulates glucose consumption and storage in muscle and liver.



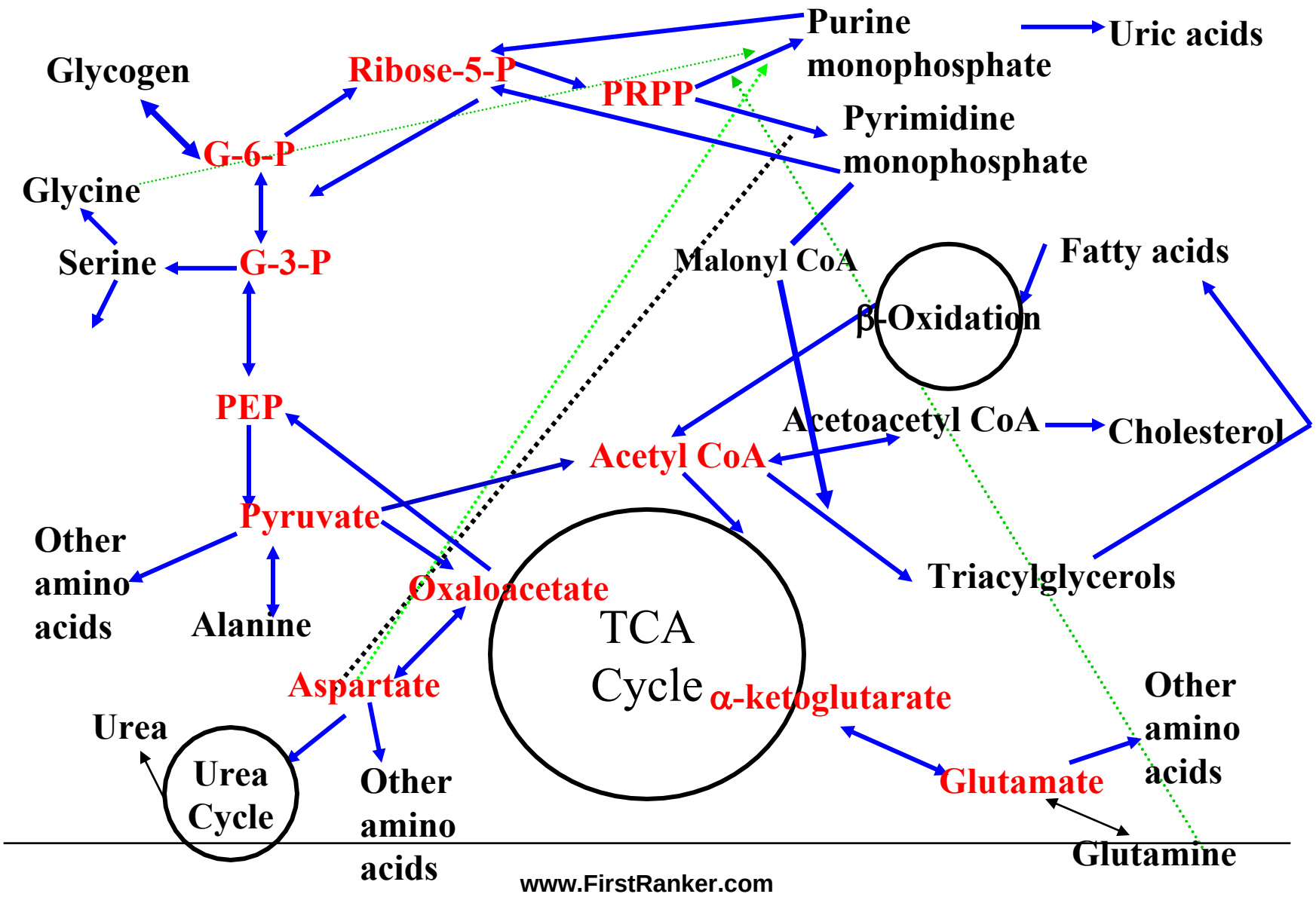


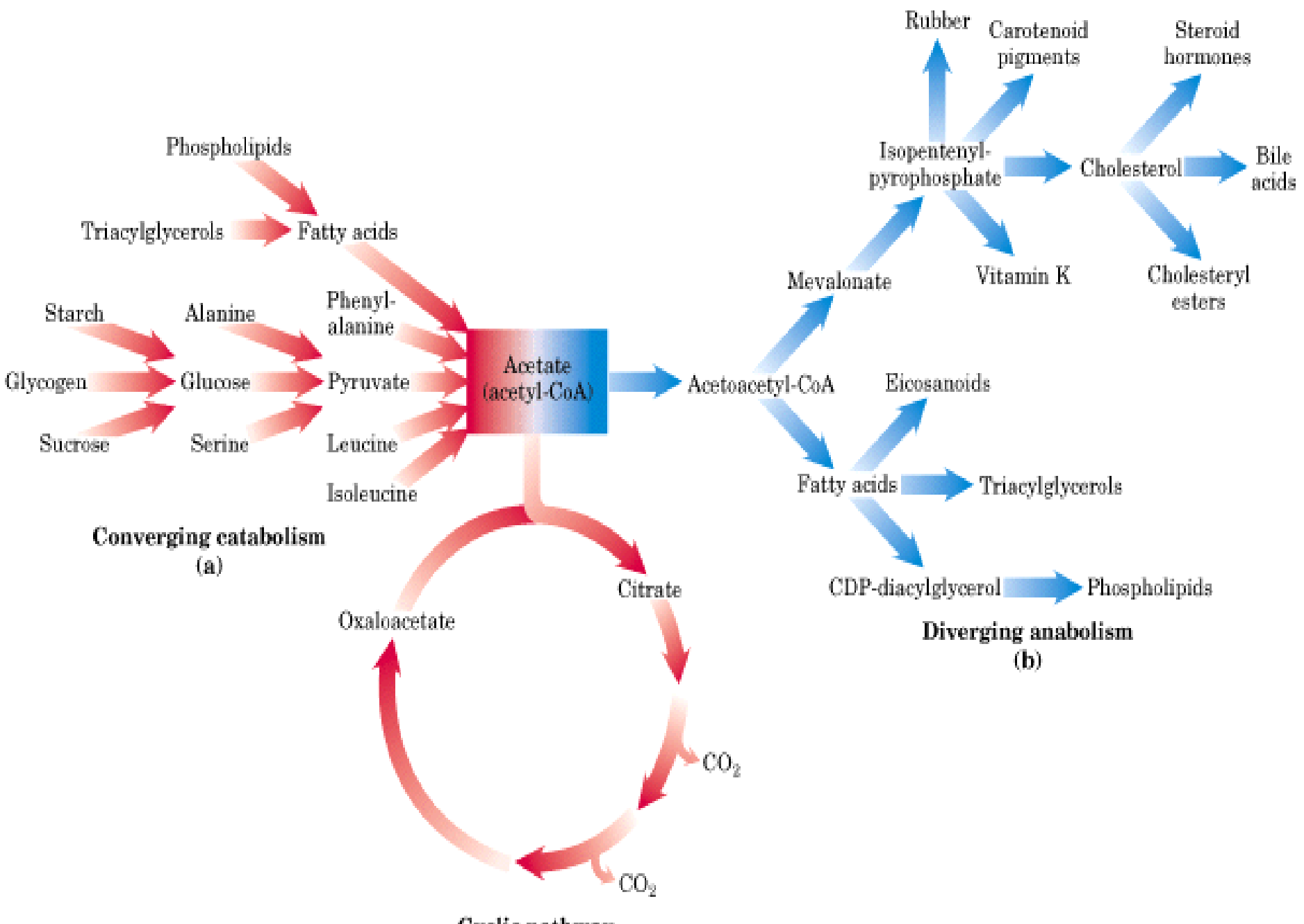
In Human Body
There Prevails
Chemical Unity In Diversity



"WORKING TOGETHER IS ESSENTIAL"

- **Intermediates/End Products** of one metabolic pathway may be connected to another metabolic pathway of **same or another metabolite.**
- An **end product** of **one metabolic pathway** of **Carbohydrate** is **connected to another metabolic pathway of Carbohydrate**.
- **Intermediate of Carbohydrate metabolic pathway** is **interrelated to a metabolic pathway of Lipid or Nucleic acid.**





Why Metabolic Pathways are Integrated?

OR

What Is the Significance Of Integrated Metabolism To Human Body?

Integrated Metabolism Occurs To

1. To **Interconvert biochemical metabolites as per the cellular need.**
2. To **meet the bodies fuel demand.**
3. To **regulate the levels of intermediary metabolites** and **maintain their equilibrium.**
4. To **coordinate with the various cells, tissues and organs for existence.**
5. To **impart normal biochemical environment and maintain health.**

- A well **coordinated** and **regulated integrated metabolism** of human body
- **Protects from metabolic catastrophes.**

Significance Of Knowledge Of Integrated Metabolism To Doctors

- **Doctors are responsible for confirm diagnosis and treatment of biochemical alterations of a disordered patients.**
- **Study of integrated metabolism with their interrelationships in a normal healthy conditions helps a doctor :**
  - To **better understand** **various deranged metabolic conditions and the related complexities.**
  - **Rule out the right biochemical underlying cause of metabolic disorders and pathogenesis.**
  - ~~**Try correct the altered metabolism in treatment.**~~

- **Prerequisite to Become A Good Doctor Is to**
  - –Acquire **Profound Knowledge of Integrated Metabolism**
  - –With **Good Concepts And its Understanding.**

A good Doctor is one

Who has An

Understanding Knowledge of Biochemistry

Questions

- **Long Essays.**

- Q.1.Describe the **common metabolic pathway**.
  OR
- Why TCA cycle is called as common metabolic pathway? Explain with reactions.

- Q.2.Explain **"Fat burns under the flame of Carbohydrates"**.

- Which metabolic pathway is an excellent example of integrated metabolism? Justify it.

- Q.3.How Carbohydrate, Lipid & Protein metabolic pathways are integrated & interrelated with each other. Explain with the help of flow diagram.

- Q.4.Explain the **three stages** in the **intermediary metabolism** of Carbohydrate, Lipid & Protein.

- Influx & Efflux of TCA intermediates.

- Integration of TCA with Urea cycle.

- **Formation and Fates of**
  - Pyruvate
  - Acetyl-CoA
  - Succinyl-CoA
  - Oxaloacetate
  - α-Ketoglutarate

- **Q.5.Describe the role of following organs during wellfed condition.**
  - **–Liver**
  - **–Brain**
  - **–Muscles**
  - **–Adipose tissues**

THANK YOU

Biochemistry Department