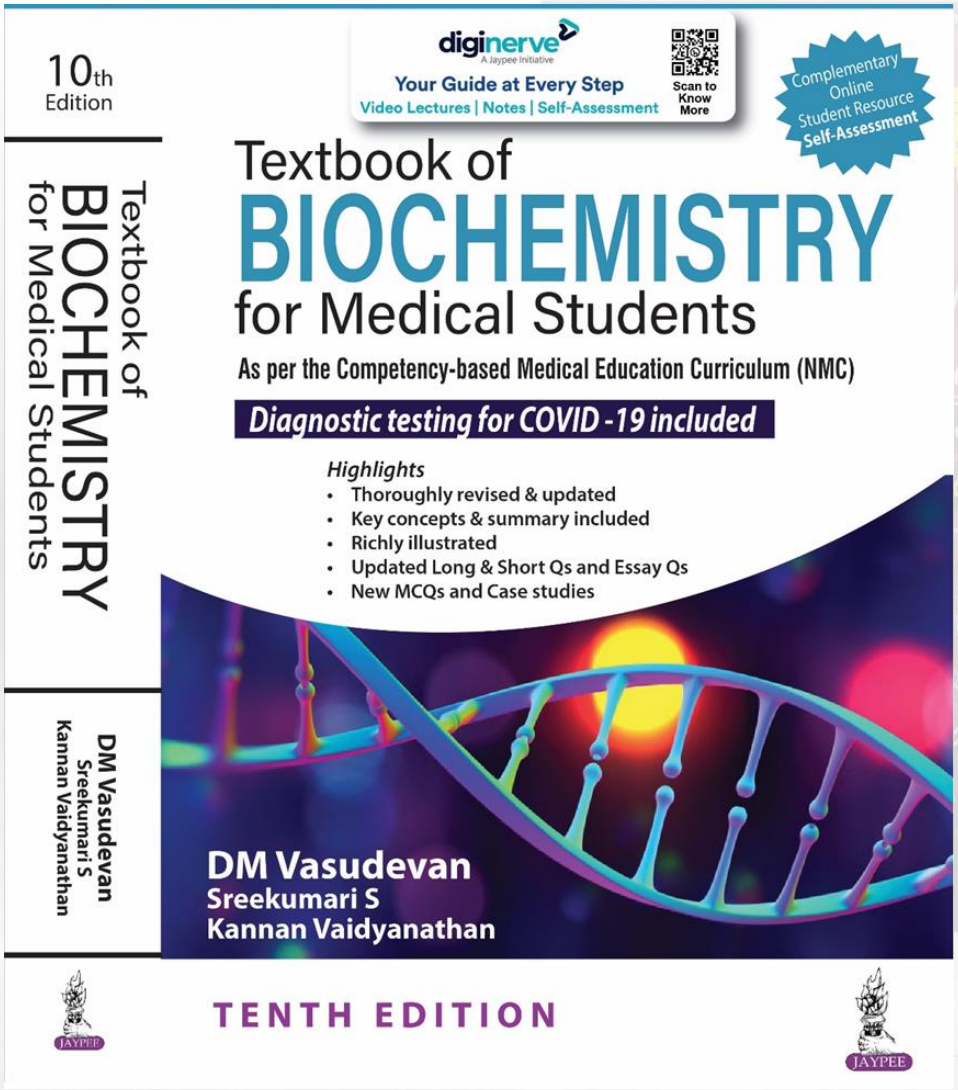
Chapter 19:

Overview of Metabolism



Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

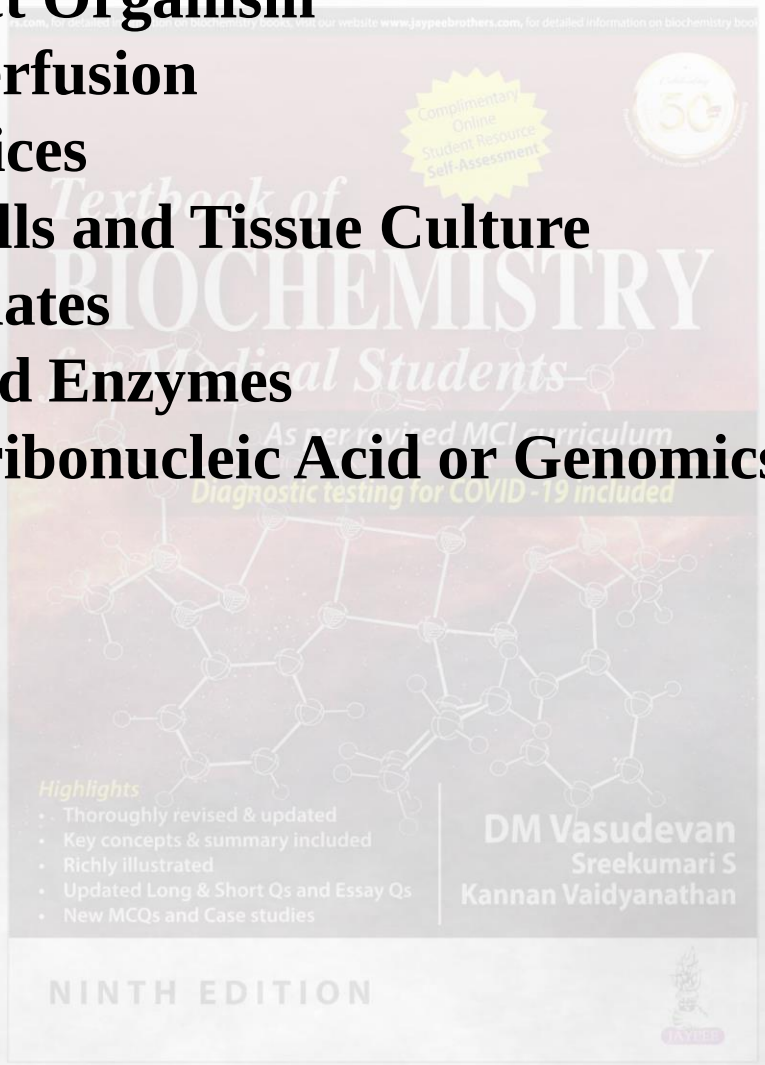
Experimental Study of Metabolism

The study of metabolic sequences may be conducted at **six levels of organizations,** each at deeper levels of cellular architecture, and each giving different perspectives to the same phenomenon.

Level 1: The Intact Organism

The essential nature of amino acids and vitamins, etc. could be understood by feeding animals with diets lacking in one of the ingredients of food. Radiolabelled iron (59Fe) is given, and incorporation of the radioactivity in bone marrow and erythrocyte precursors are studied, which provides information regarding the life span of **red blood cells (RBCs)** and rate at which heme is degraded.

Level 1: The Intact Organism
Level 2: Organ Perfusion
Level 3: Organ Slices
Level 4: Intact Cells and Tissue Culture
Level 5: Homogenates
Level 6-A: Purified Enzymes
Level 6-B: Deoxyribonucleic Acid or Genomics



Studies on Metabolism

Four aspects of metabolic pathways are studied:

1. Sequence of reactions
2. Precursor-product relationship
3. Mechanism of reaction
4. Control mechanisms.

Metabolic pathways may also be studied by creating perturbances to the system, such as:

- By causing metabolic blocks
- By studying organisms or human beings with metabolic defects
- Genetic manipulation, e.g. gene knockout.

Metabolism

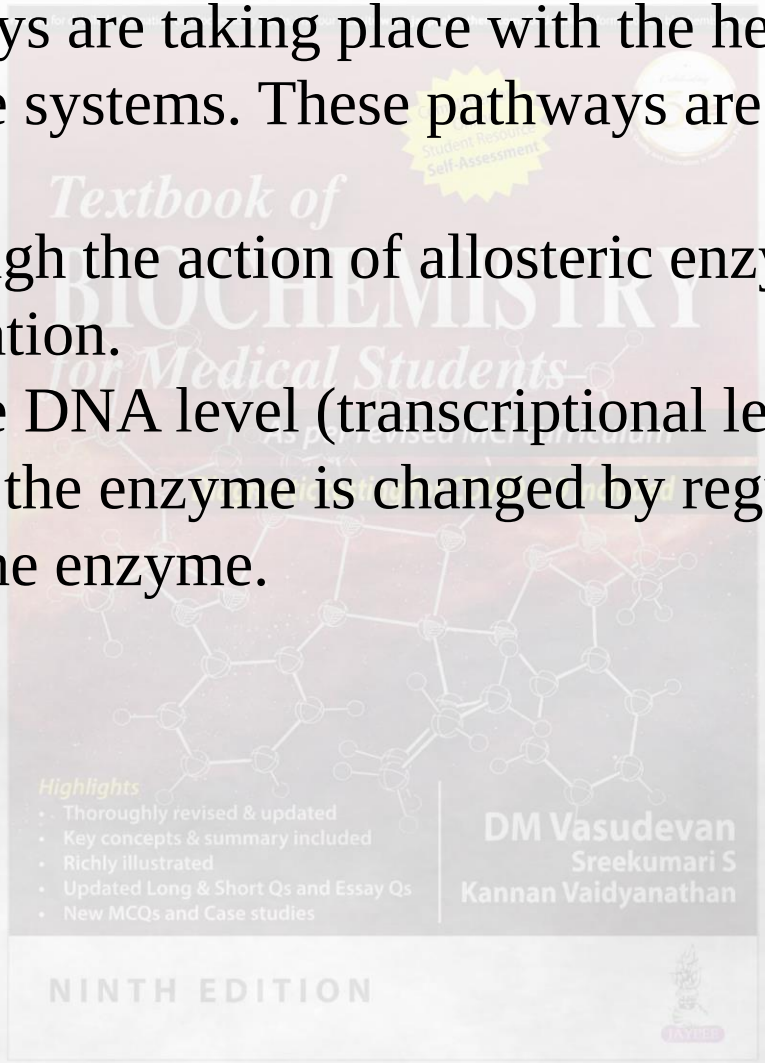
Human beings derive energy by oxidation of nutrients. A constant supply of energy (ATP) is required for all cells to survive and function normally. Balance between need and mobilization of stored energy is called metabolic **homeostasis or calorie homeostasis**.

Thousands of chemical reactions are taking place inside a cell in an organized, well coordinated, and purposeful manner; all these reactions are collectively called as **metabolism**. The metabolism serves the following purposes:

- Chemical energy is obtained from the degradation of energy-rich nutrients.
- Food materials are converted into macromolecules, such as proteins, nucleic acids, polysaccharides.

- Metabolic pathways are taking place with the help of sequential enzyme systems. These pathways are regulated at three levels:

1. Regulation through the action of allosteric enzymes.
2. Hormonal regulation.
3. Regulation at the DNA level (transcriptional level); the concentration of the enzyme is changed by regulation at the level of synthesis of the enzyme.

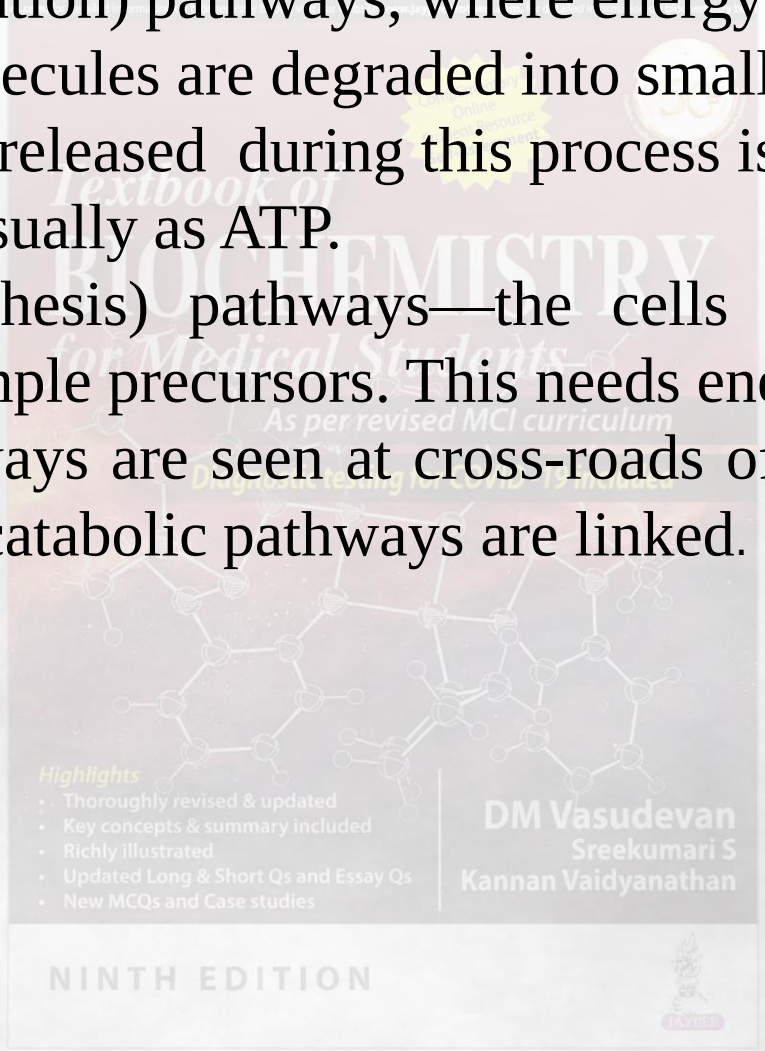


Types of Metabolic Pathways

Catabolic (degradation) pathways, where energy rich complex macromolecules are degraded into smaller molecules. Energy released during this process is trapped as chemical energy, usually as ATP.

Anabolic (biosynthesis) pathways—the cells synthesize complex molecules from simple precursors. This needs energy.

Amphibolic pathways are seen at cross-roads of metabolism, where both anabolic and catabolic pathways are linked.



Stages or Phases of Metabolism

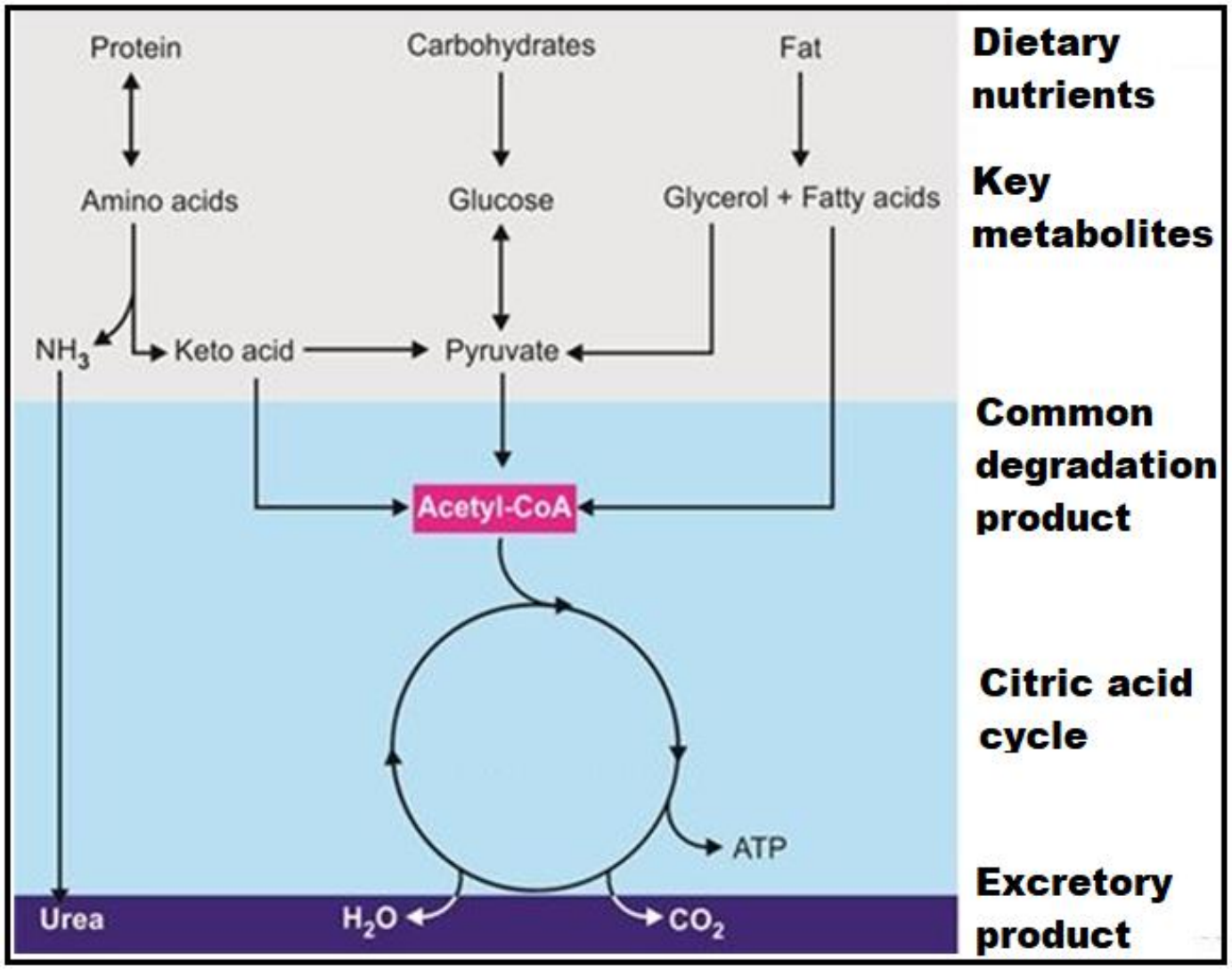
The degradation of foodstuffs occurs in 3 stages.

1. In the first stage, digestion in the gastrointestinal tract converts the macromolecules into small units. For example, proteins are digested to amino acids. This is called **primary metabolism.**
2. Then these products are absorbed, catabolized to smaller components, and ultimately oxidized to CO2. In this process, NADH or FADH2 is generated. This is called **secondary or intermediary metabolism**.
3. Then these reduced equivalents enter into the **electron transport** chain (respiratory chain), where energy is released. This is the **tertiary metabolism** or internal respiration or cellular respiration

Major Fuels

- Glucose
- Fatty acids
- Amino acids
- Ketone bodies

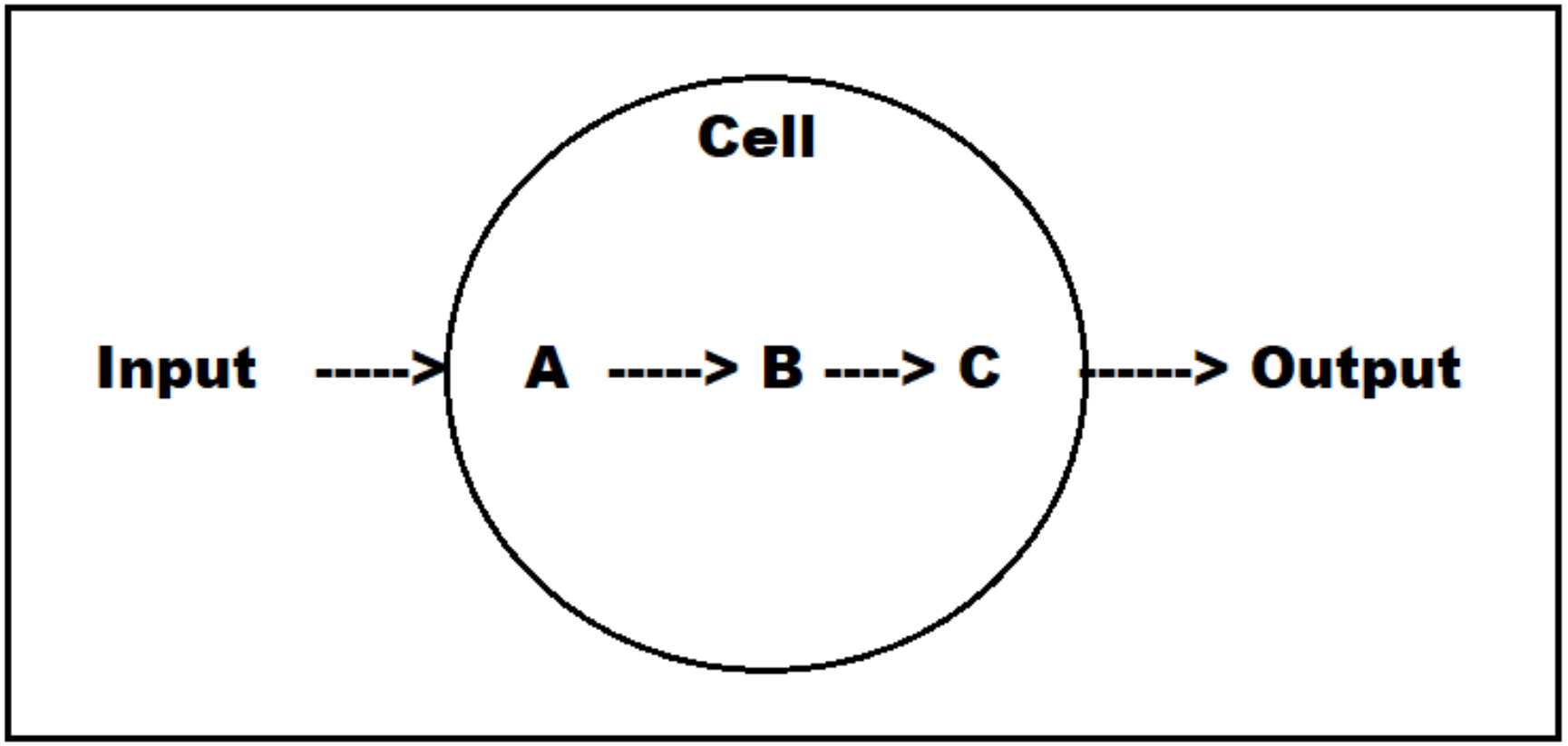
Integration of Metabolism



Homeostasis

Homeostasis means keeping constant conditions in an organism's internal environment, even when the external environment is changed. For example, the body keeps a constant temperature of 37°C, even though the external temperature varies. Biological systems operate under a relatively narrow and controlled set of conditions. Molecules are entering the cell, and going out of the cell all the time. But, the cell maintains the total number of a particular molecule constant at all the times. Homeostasis within a cell or organism is regulated in many ways, for example by alterations in gene expression and activation or inactivation of enzymatic catalysts. Homeostasis in the cell is maintained by regulation, and by the more or less steady state exchange of materials and energy with its surroundings.

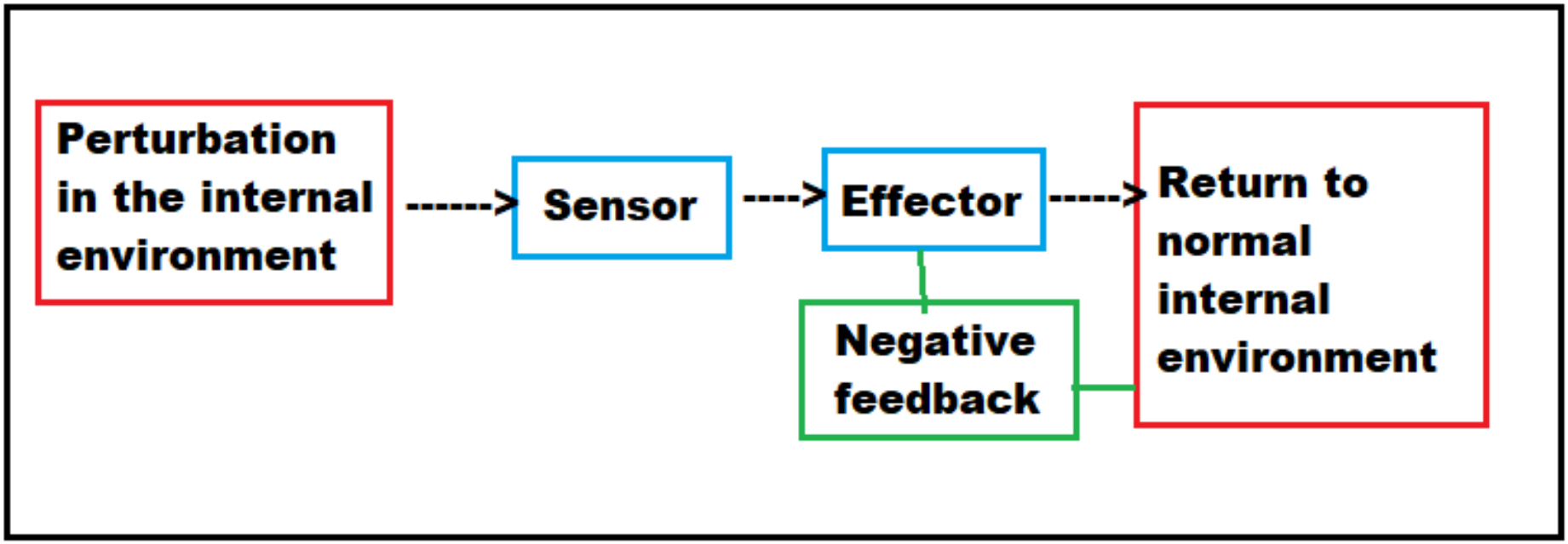
Homeostasis



Steady State Equilibrium

In metabolic reactions, molecule A is converted to B and then C molecule. But if we analyze, the total number of "A" molecules in a cell at different time intervals, the quantity will be seen as more or less constant. That means the number of molecules entering the cell will be roughly the same that are metabolized. This is called steady state equilibrium, meaning the molecules are always going out, but the same number is pulled in. Such homeostasis is taking place at the level of the cell, organism, or the whole body. For the maintenance of homeostasis, the organism needs a sensor and effector mechanisms.

Steady State Equilibrium



Energy Reserves of Man (70 kg)

Stored fuel	Weight (in gram)	Energy equivalent (in kilo calories)
Glycogen in liver	70	280
Glycogen in muscle	120	480
Glucose in body fluids	20	80
Fat in adipose tissue	15,000	135,000
Protein in muscle	6,000	24,000

Energy Stores in Man

Tissue Fuel	Reserve (grams)	Starvation	Walking	Marathon
Fat	15,000	34 days	11 days	3 days
Muscle Glycogen	350	14 hours	5 hours	70 minutes
Liver Glycogen	80	3.5 hours	70 minutes	18 minutes
Blood Glucose	20	40 minutes	15 minutes	4 minutes
Body Protein	6000	15 days	5 days	1.3 days

Major Metabolic Pathways

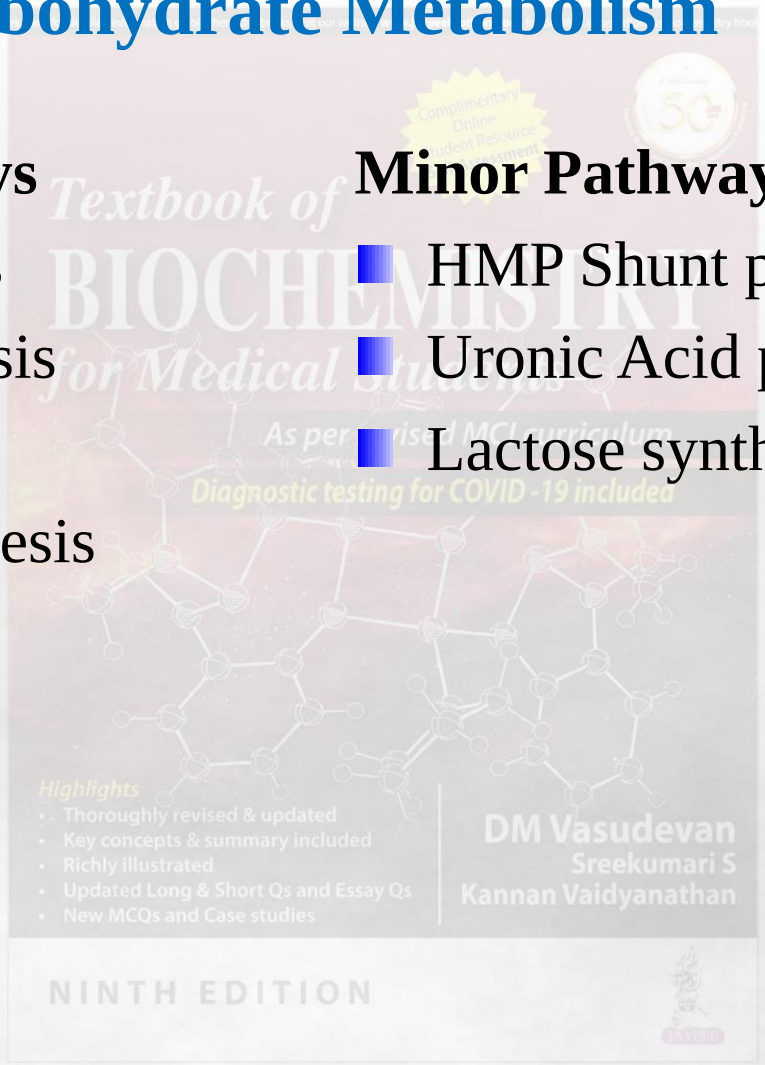
Carbohydrate Metabolism

Major Pathways

- Glycogenesis
- Glycogenolysis
- Glycolysis
- Gluconeogenesis

Minor Pathways

- HMP Shunt pathway
- Uronic Acid pathway
- Lactose synthesis



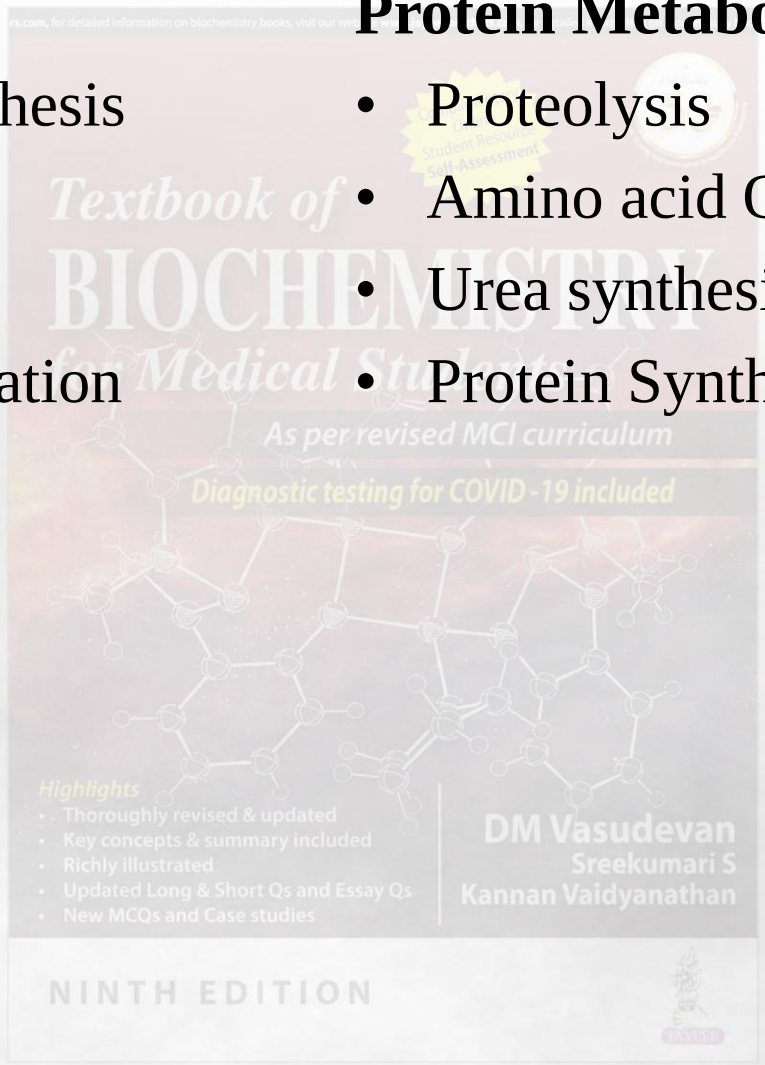
Major Metabolic Pathways

Fat Metabolism

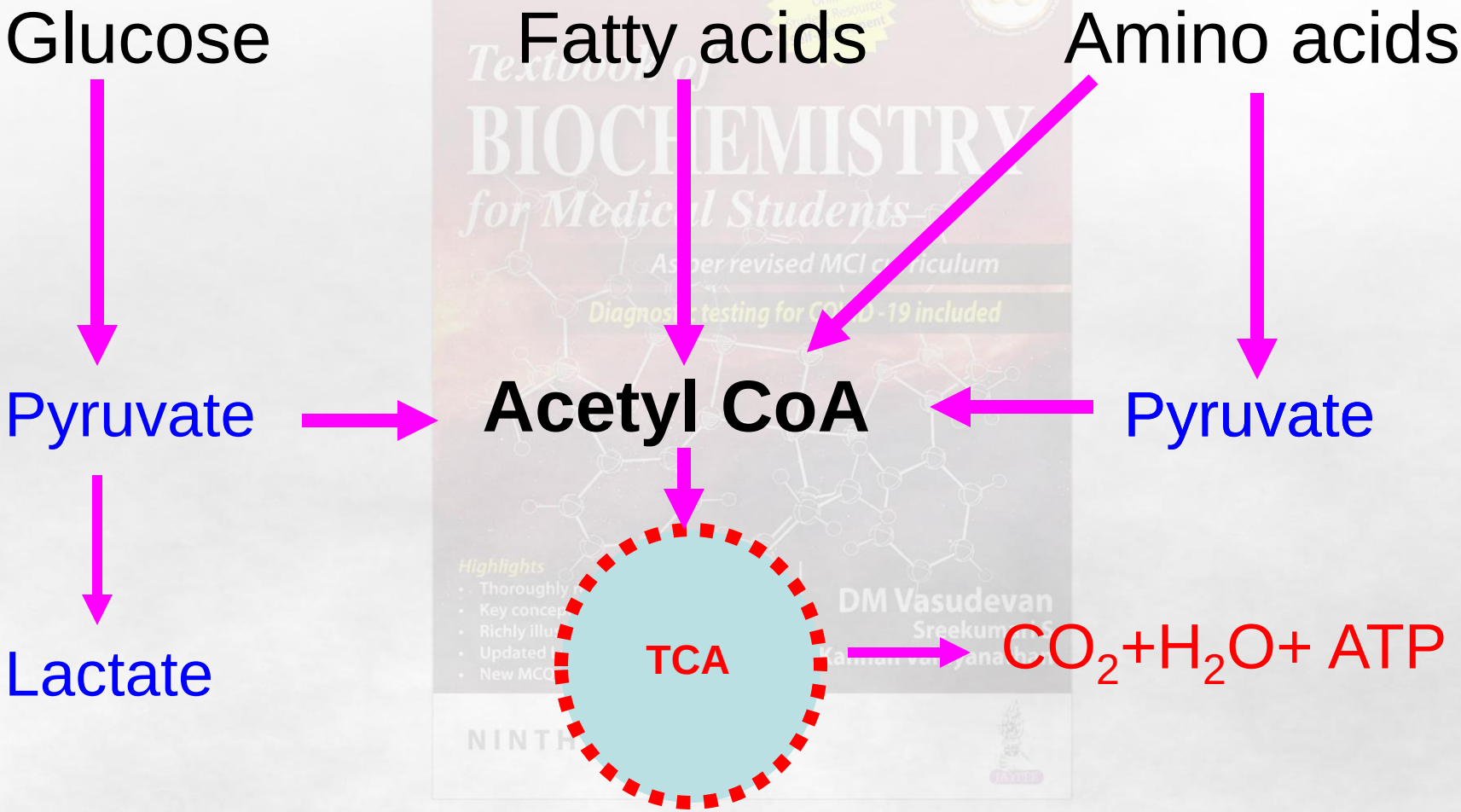
- Fatty acid Synthesis
- Lipogenesis
- Lipolysis
- Fatty acid oxidation
- Ketogenesis
- Ketolysis

Protein Metabolism

- Proteolysis
- Amino acid Oxidation
- Urea synthesis
- Protein Synthesis



Major Metabolic Pathways

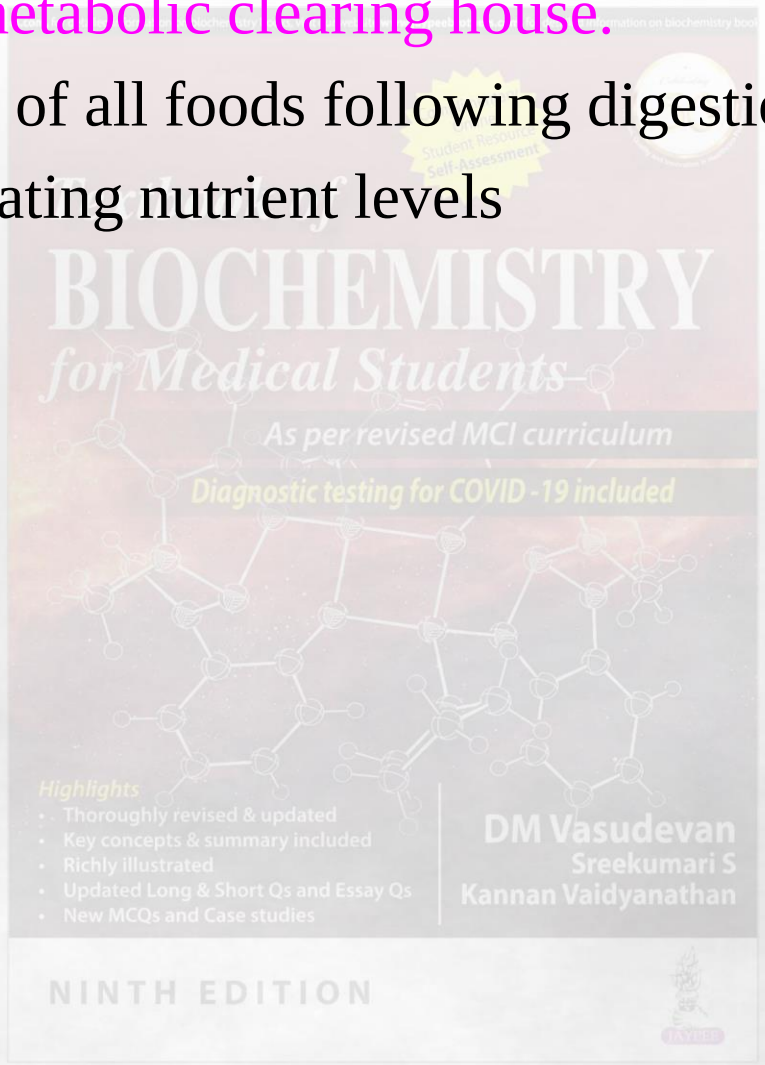


Organs Concerned with Metabolic Integration

- Liver
- Skeletal Muscle
- Adipose tissue
- Gut
- Kidney

Liver

- Body's central metabolic clearing house.
- The site of entry of all foods following digestion.
- Maintains circulating nutrient levels

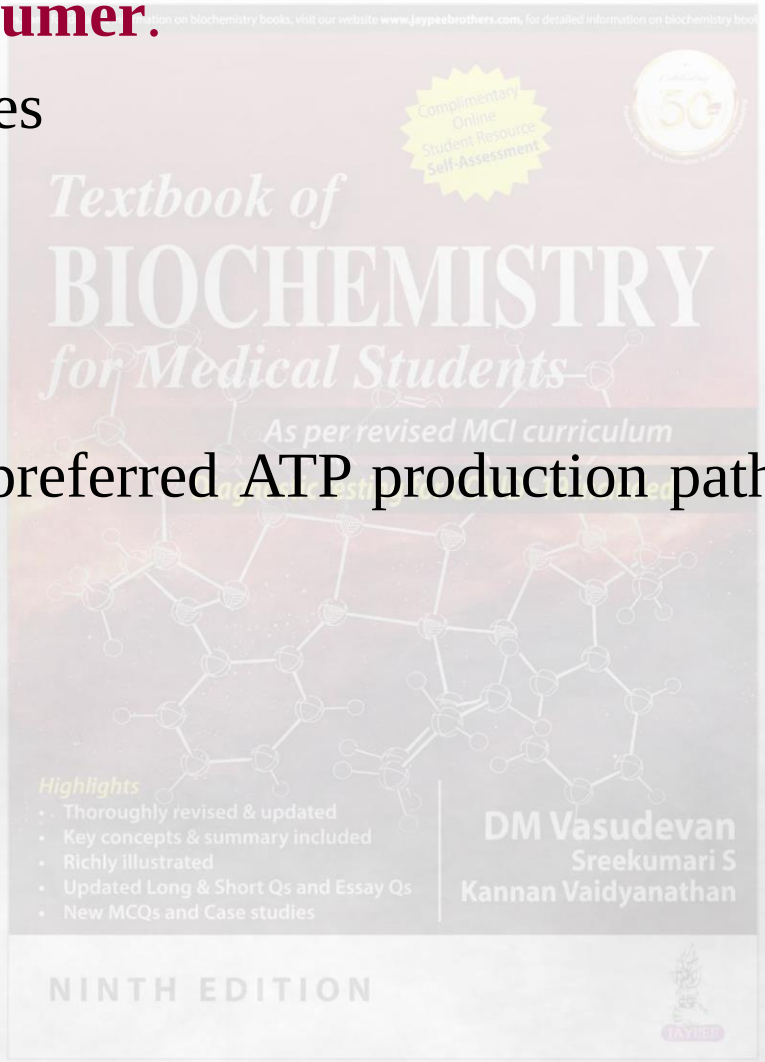


Skeletal Muscles

Major **energy consumer**.

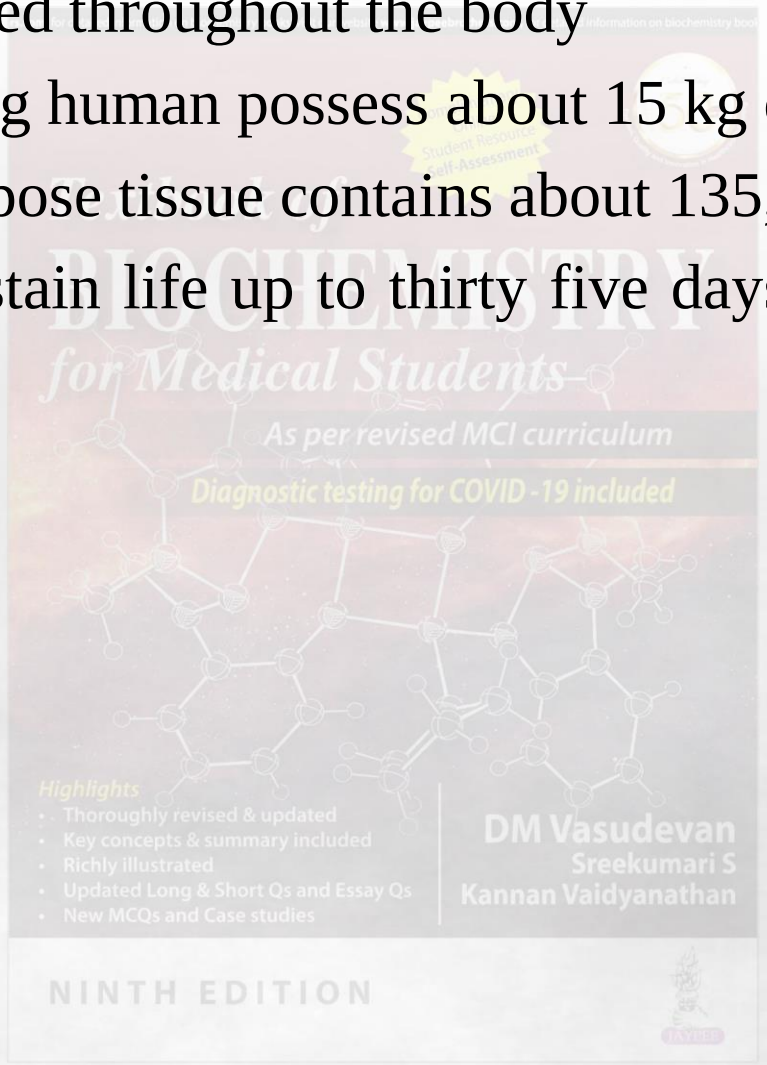
Takes up and utilizes

- Glucose
- Ketone bodies
- Fatty acids
- Glycolysis is a preferred ATP production pathway in exercising muscle.



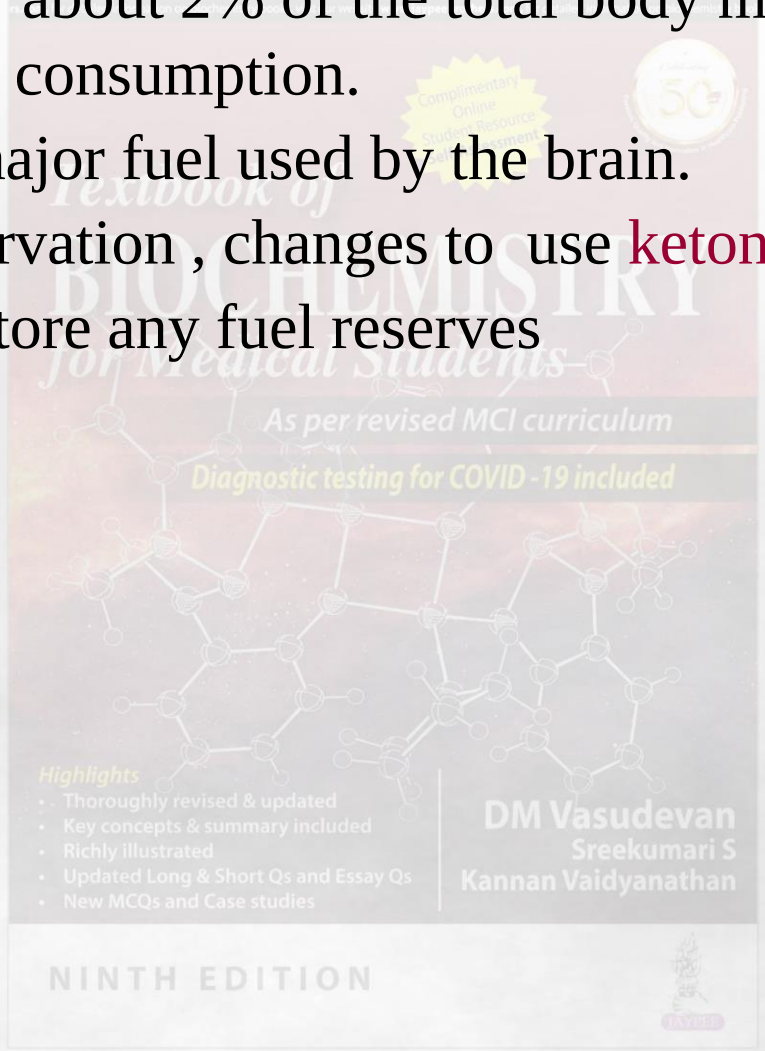
Adipose Tissue

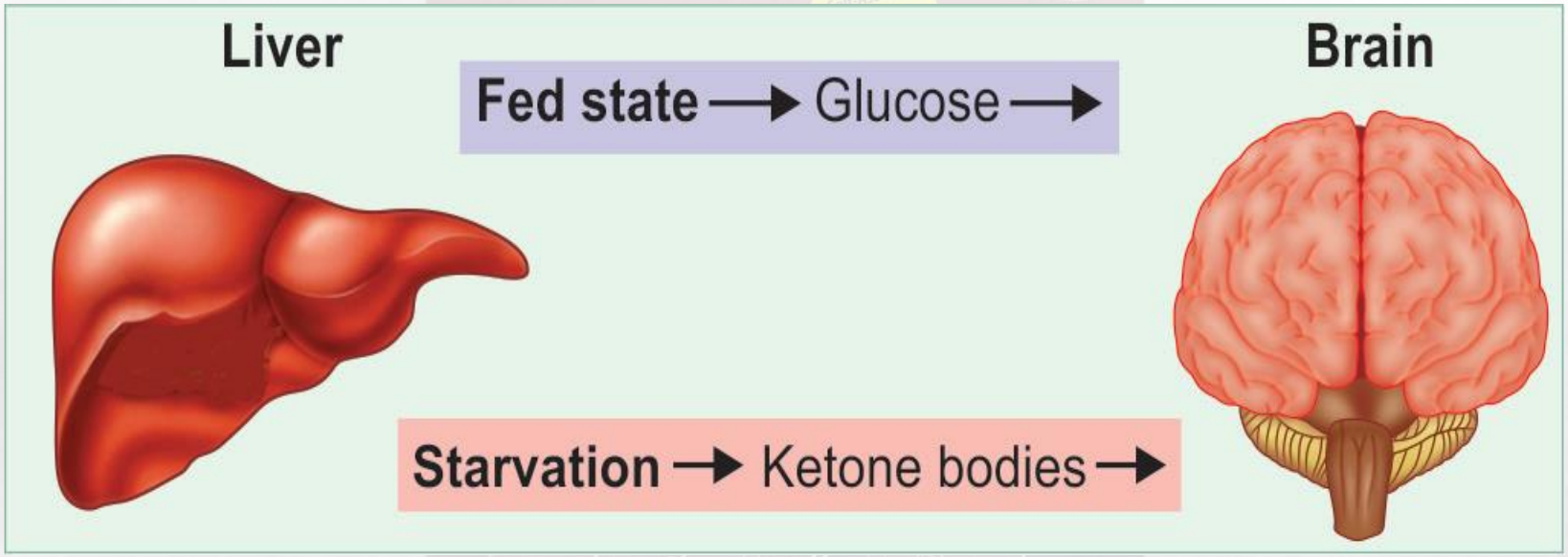
- Widely distributed throughout the body
- An average 70 kg human possess about 15 kg of fat tissue.
- The mass of adipose tissue contains about 135,000 kcal of energy
- Sufficient to sustain life up to thirty five days without any food intake.



Brain

- It makes up only about 2% of the total body mass but uses 20% of the total body consumption.
- Glucose is the major fuel used by the brain.
- In prolonged starvation , changes to use ketone bodies as a fuel.
- Brain does not store any fuel reserves

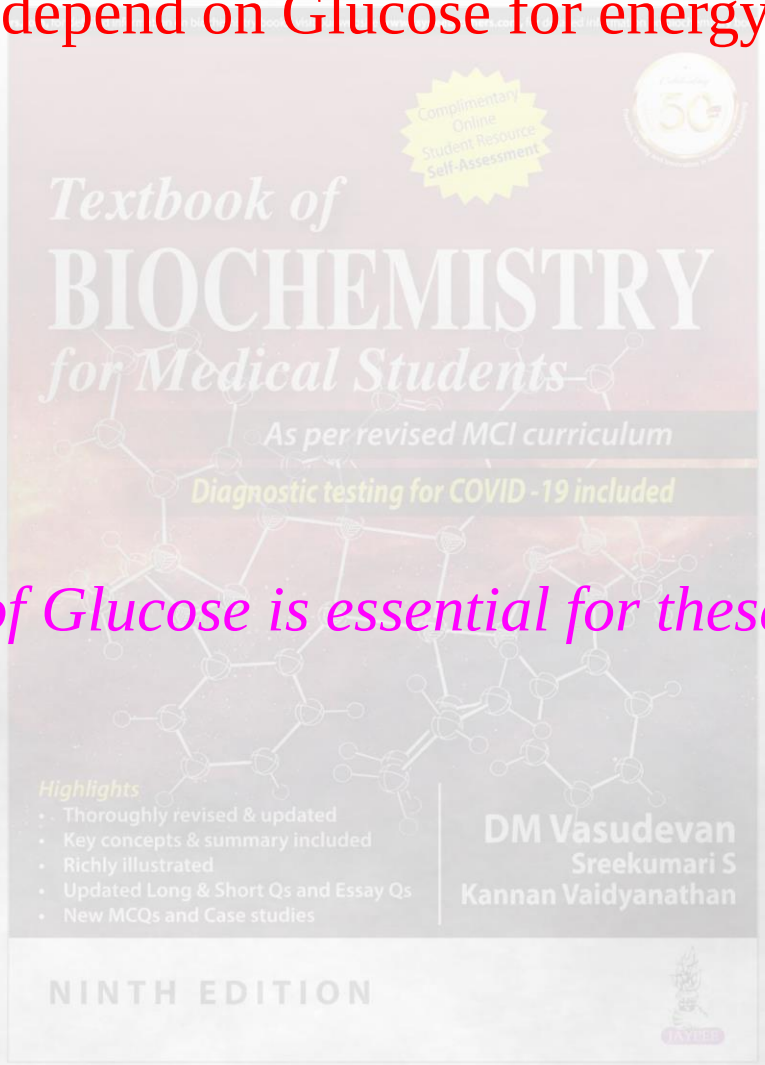




Metabolic alterations in brain.

Major organs solely depend on Glucose for energy are

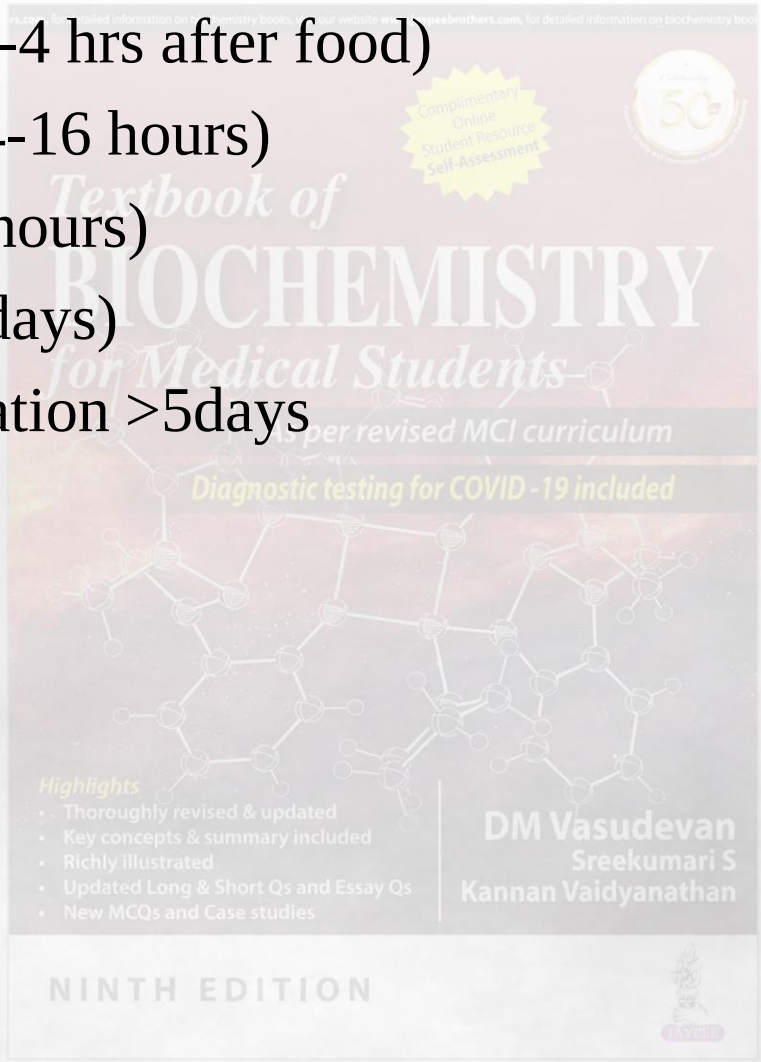
- Brain
- RBCs
- Retina
- Renal medulla
- Testis



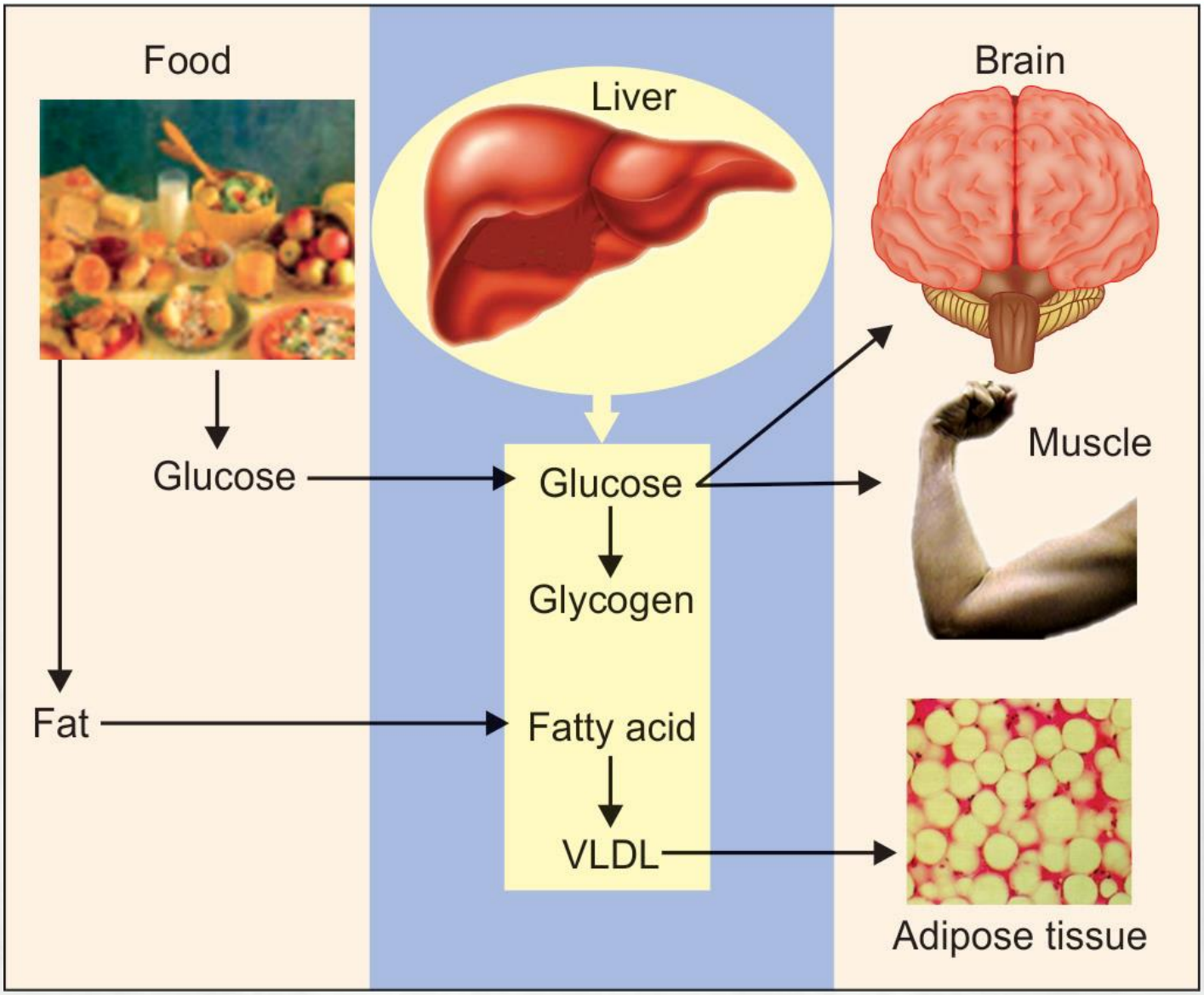
A constant supply of Glucose is essential for these organs

Starve- Feed Cycles

- Well fed state (1-4 hrs after food)
- Early Fasting (4-16 hours)
- Fasting (16-48 hours)
- Starvation (2-3 days)
- Prolonged starvation >5days



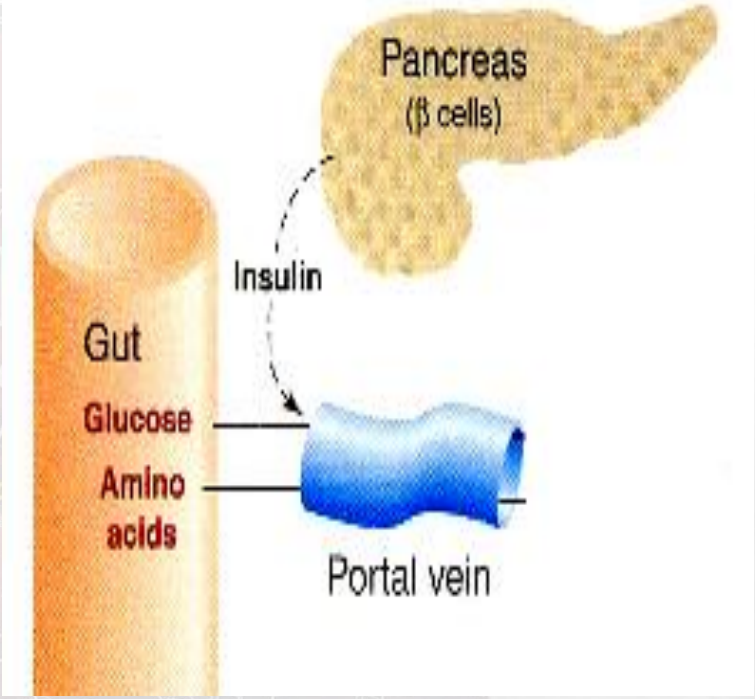
Metabolism of well fed state



Well fed state

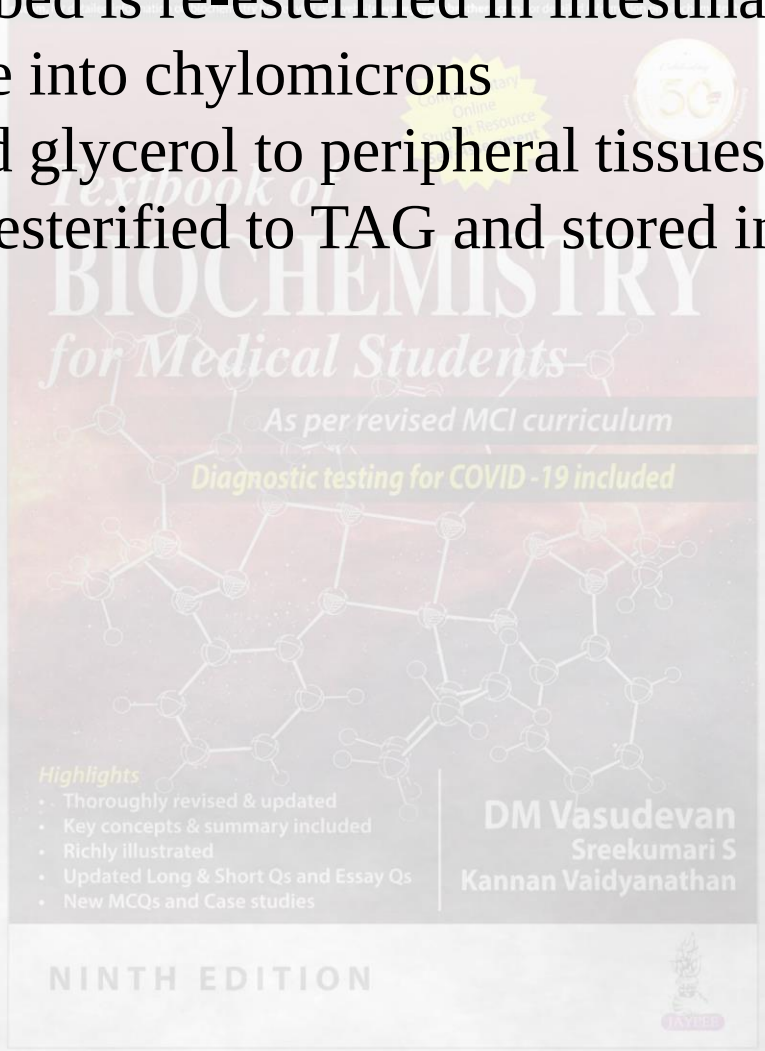
- Absorption of Glucose from gut
- ↑ Blood Glucose

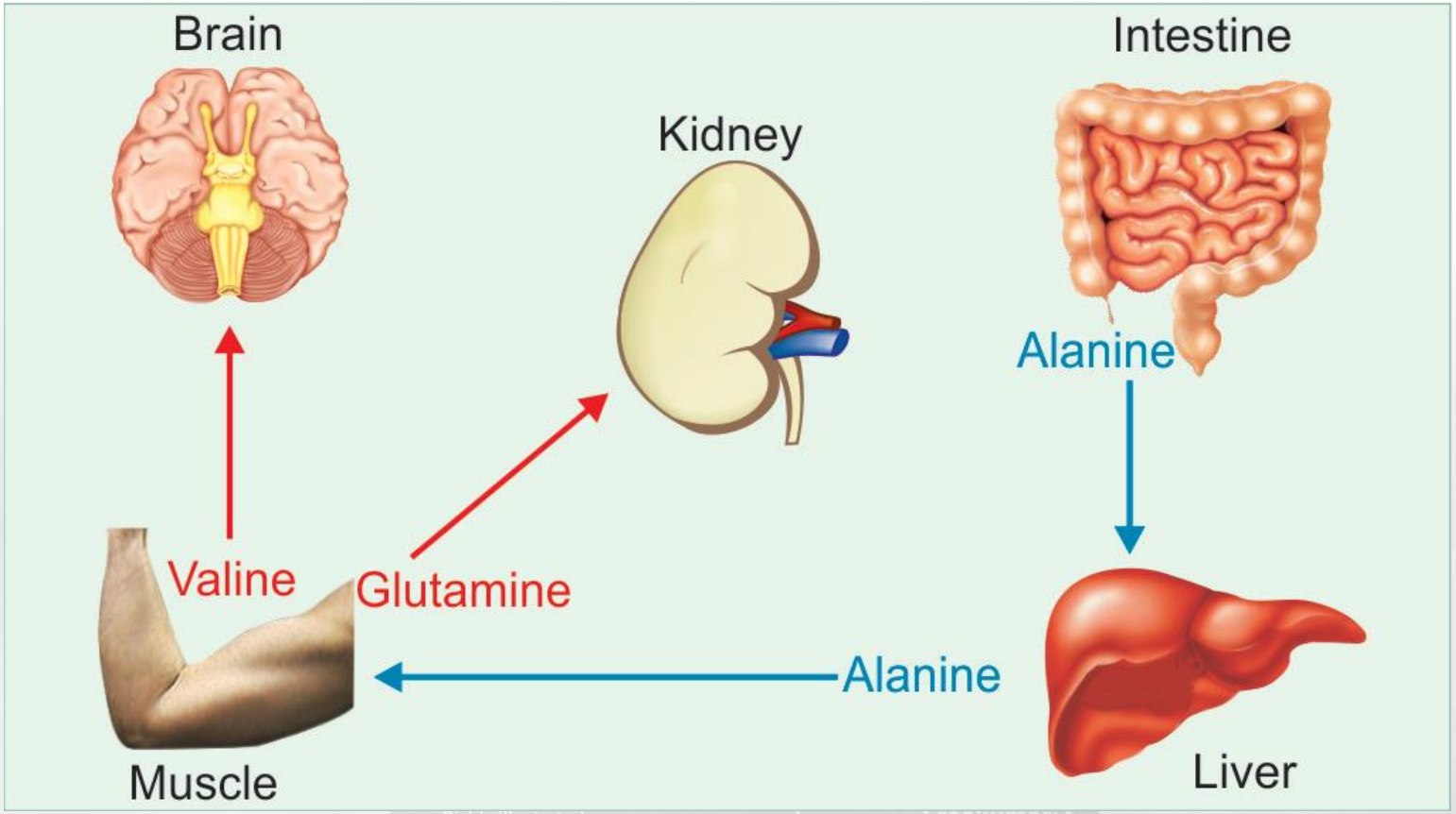
- Secretion of Insulin from βcells of Islets of Langerhans



Fate of Fat in Fed State

- Dietary fat absorbed is re-esterified in intestinal mucosal cells and package into chylomicrons
- Delivers FFA and glycerol to peripheral tissues
- In adipocytes re-esterified to TAG and stored in adipose tissue

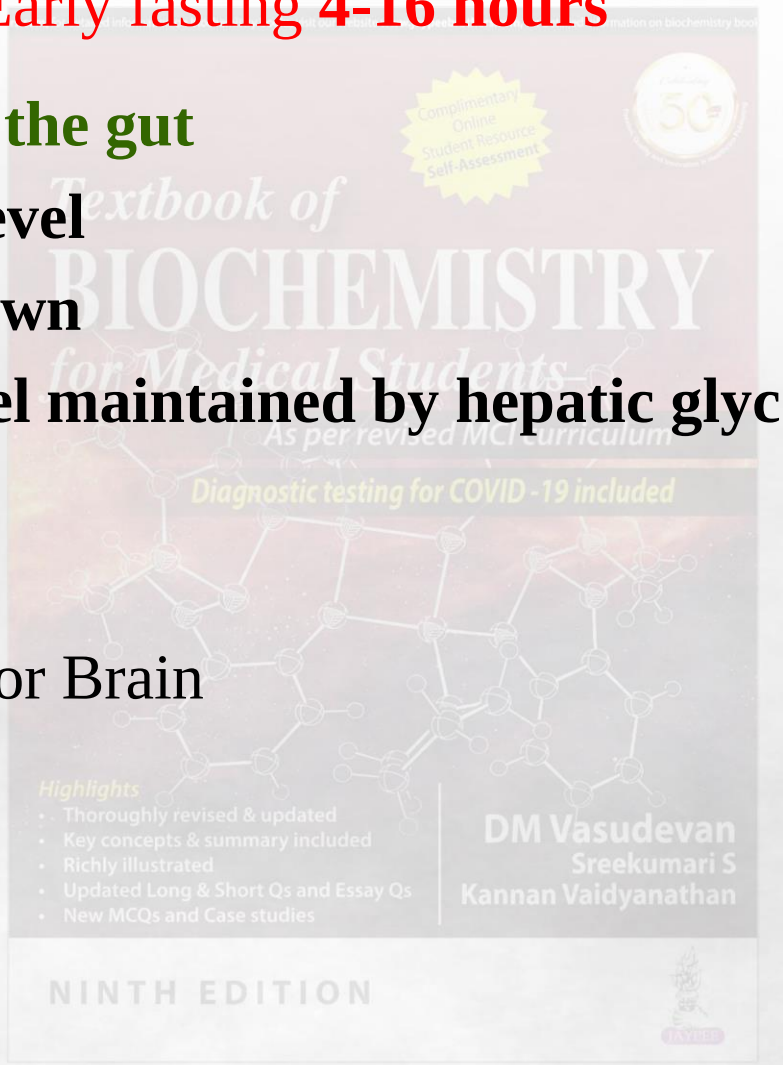




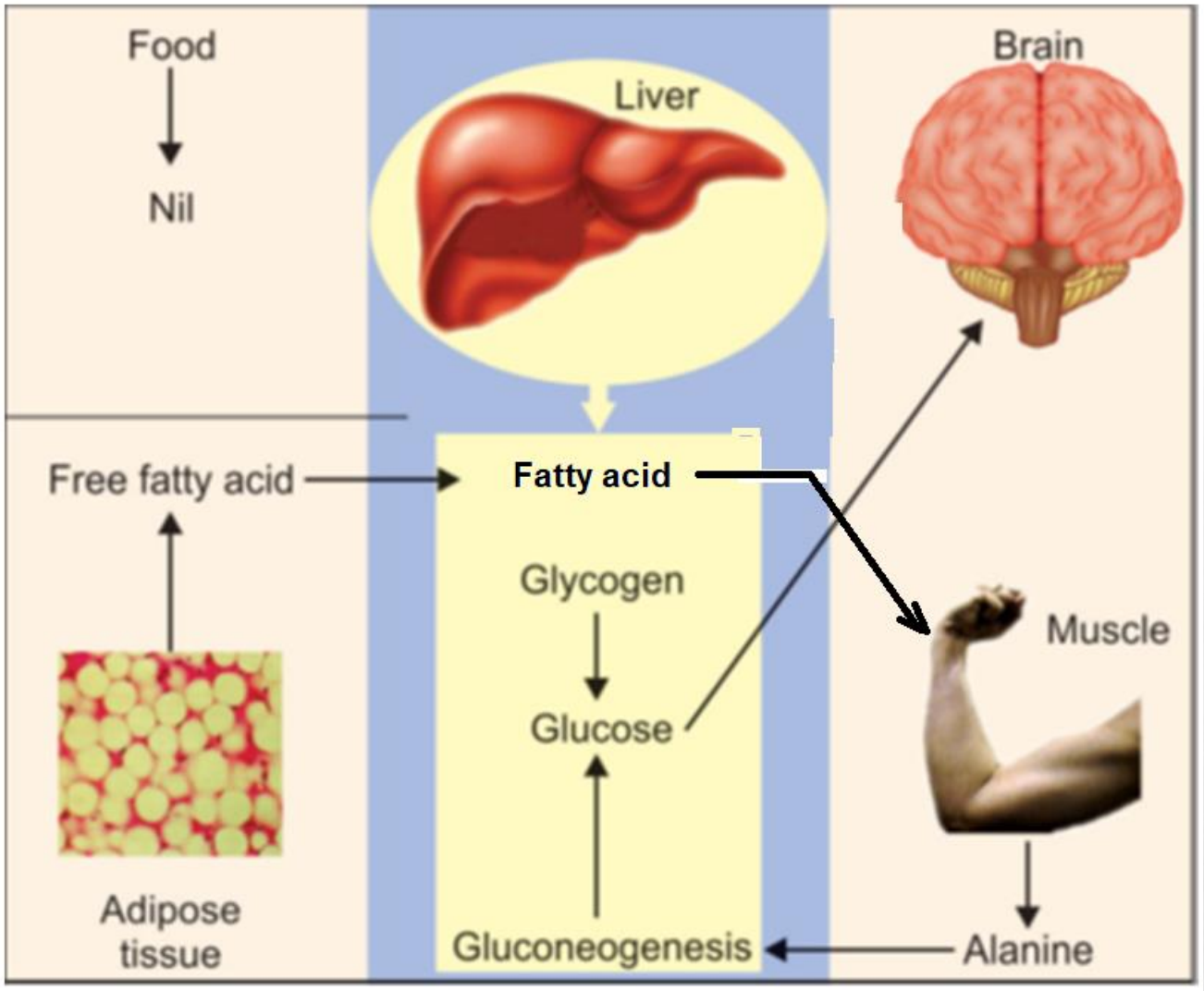
Interorgan transport of amino acids after taking food (postprandial condition).

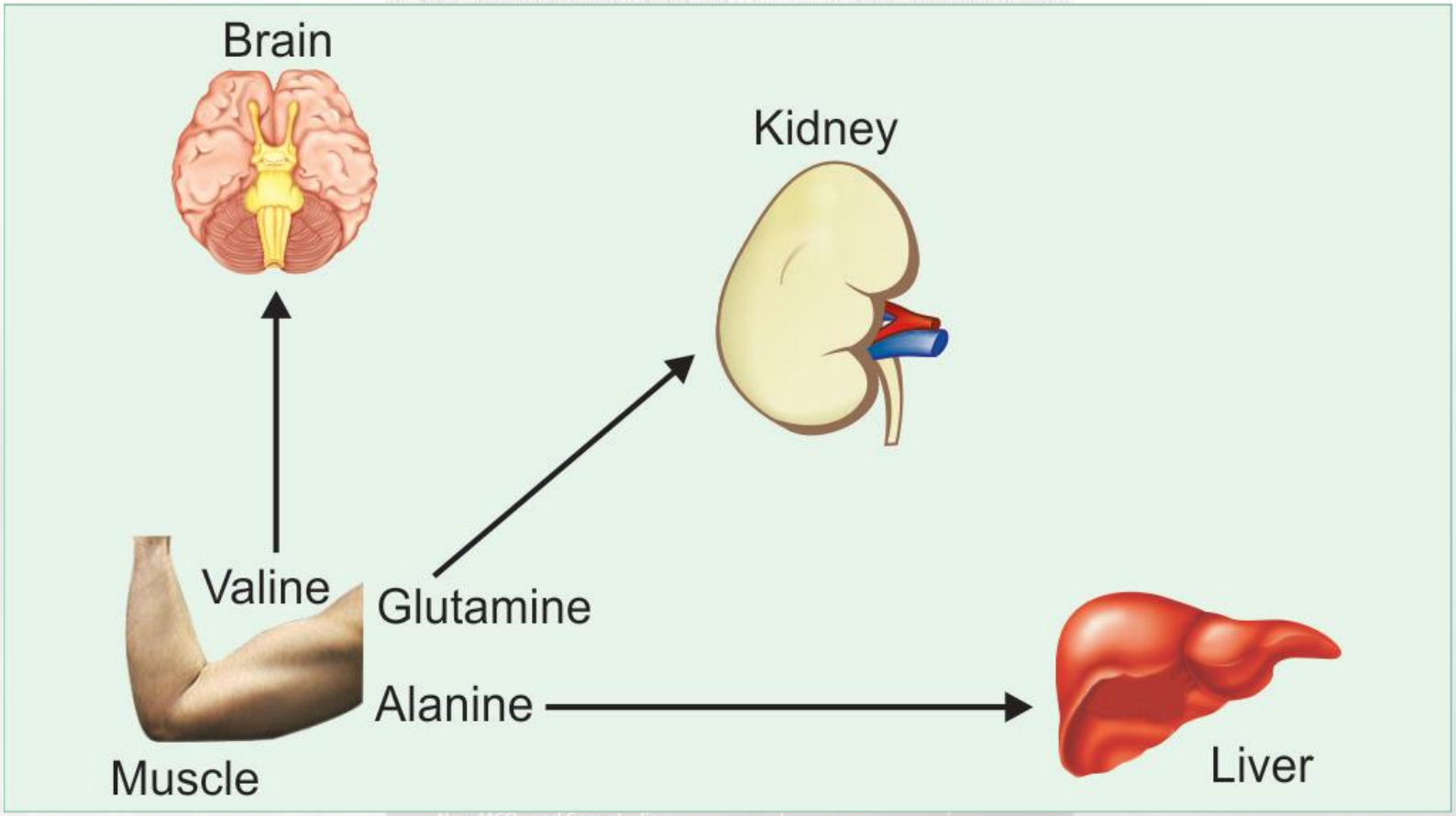
Metabolic events - Early fasting **4-16 hours**

- **Fuel stops from the gut**
- **⇓ Blood sugar level**
- **Insulin slows down**
- **Blood sugar level maintained by hepatic glycogenolysis**
- **⇓ Glycogenesis**
- **⇓ Lipogenesis**
- Glucose spared for Brain

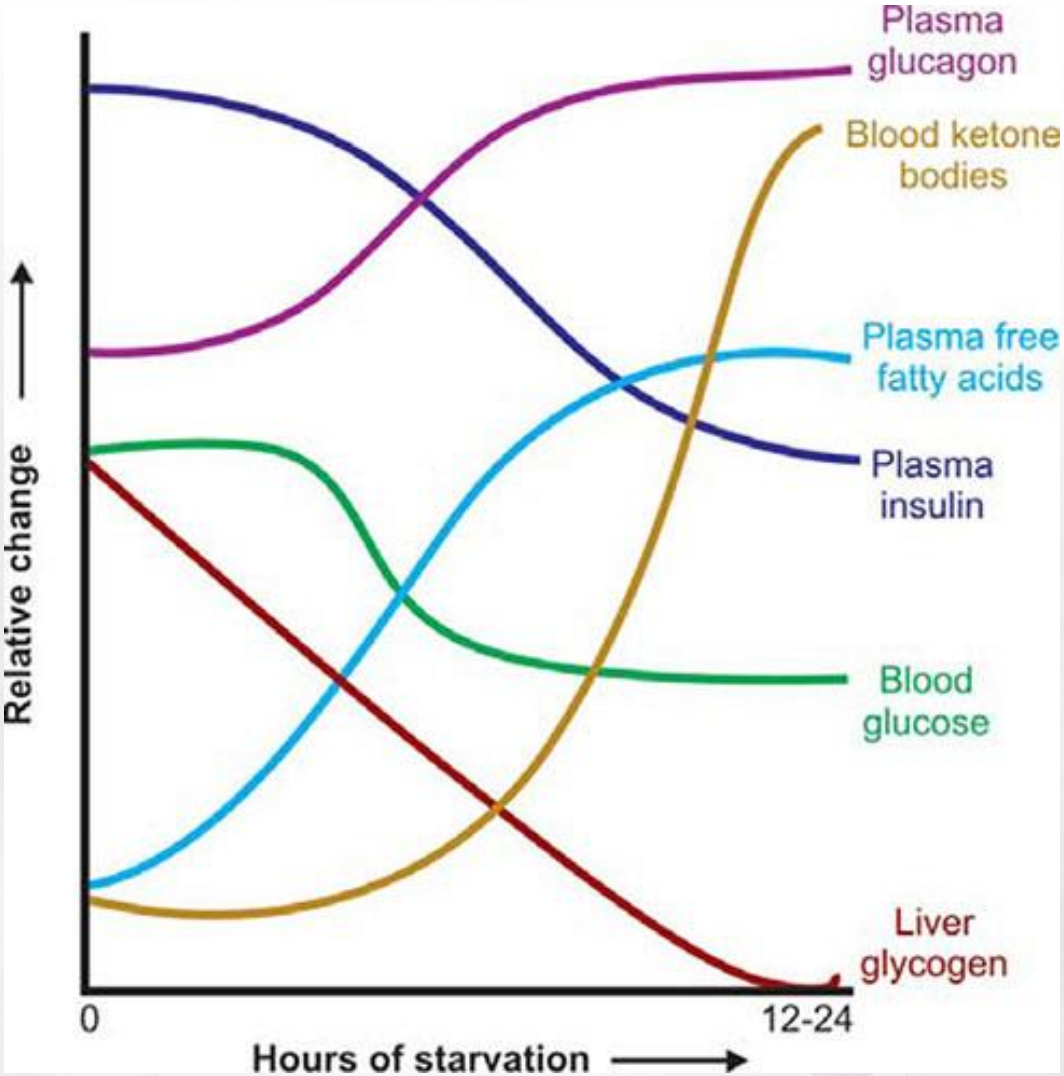


Metabolism during overnight fasting





Interorgan transport of amino acids during fasting conditions.



Relative changes of important parameters during starvation.

Metabolic Adaptations During Starvation

First Stage: Glycogenolysis

During fasting, for first 18 hours, blood glucose level is maintained by hepatic glycogenolysis.

Second Stage: Gluconeogenesis

Even before the glycogen stores are depleted, gluconeogenesis is accelerated. The amino acids released from muscle form the major substrate for gluconeogenesis. The **glucose alanine cycle** serves to transport the amino nitrogen of other amino acids to liver in a harmless form. The **branched chain amino acids** liberated by protein catabolism are utilised by the muscle to give energy. Brain can preferentially take up the glucogenic valine from the blood stream.

Third Stage: Lipolysis

Then skeletal muscle, heart and kidney will shut down their glucose utilisation; and will depend mainly on fatty acids for energy needs. K**etone bodies** provide fuel for tissues like heart muscle, skeletal muscle and to some extent the brain. **Fourth Stage: Acidosis**

Production of ketone bodies leads to metabolic acidosis. The pH falls and hyperventilation occurs as a compensatory mechanism.

Fifth Stage: Death from Starvation

Metabolic acidosis and dehydration, unless corrected efficiently, will lead to death. A normal person has fuel reserves to live up to 45–60 days.

Major fuels in different organs during fasting and starvation

	Brain	Skeletal muscle	Cardiac muscle	Adipose tissue
After a meal	Glucose	Glucose, Fatty acids	Glucose, pyruvate	Fatty acids; Glucose
Fasting (short term)	Glucose	Fatty acids	Fatty acids	Fatty acids
Fasting (long term)	Glucose; Ketone bodies	Ketone bodies; Bran-ched chain aa	Ketone bodies	Fatty acids; Ketone bodies

Key enzymes under well fed conditions and starvation

Enzyme	Fed state	Fasting	Starvation	Activator	Inhibitor
Glucokinase	In-crease	De-crease	De-crease	Insulin, Glucose	F-6-P
Phospho-fructokinase1	In-crease	De-crease	De-crease	F-2,6-bisP, AMP	ATP, Citrate
Fructose 1,6 bisphosphatase	De-crease	In-crease	Increase	ATP, Citrate	F-2,6-bisP, AMP
Pyruvate carboxylase	De-crease	In-crease	Increase	Acetyl CoA	
PEPCK	De-crease	In-crease	Increase	Glucocorticoids	Insulin

Key enzymes under well fed conditions, fasting and starvation

Enzyme	Fed state	Fasting	Starvation	Activator	Inhibitor
Glycogen phosphorylase	Decrease	Increase		Glucagon, AMP	Insulin
Glycogen synthase	Increase	Decrease	Decrease	Insulin, G-6-P	Glucagon
Carnitine acyl transferase		Increase	Increase	Glucagon	Malonyl CoA
Acetyl CoA carboxylase	Increase	Decrease	Decrease	Insulin, Citrate	Fatty acyl CoA
Hormone sensitive lipase	Decrease	Increase	Increase	Glucagon	Insulin

PEPCK = phospho enol pyruvate carboxy kinase;
F-6-P = fructose-6-phosphate; F-2,6-bisP = fructose-2,6-bisphosphate; G-6-P = glucose-6-phosphate

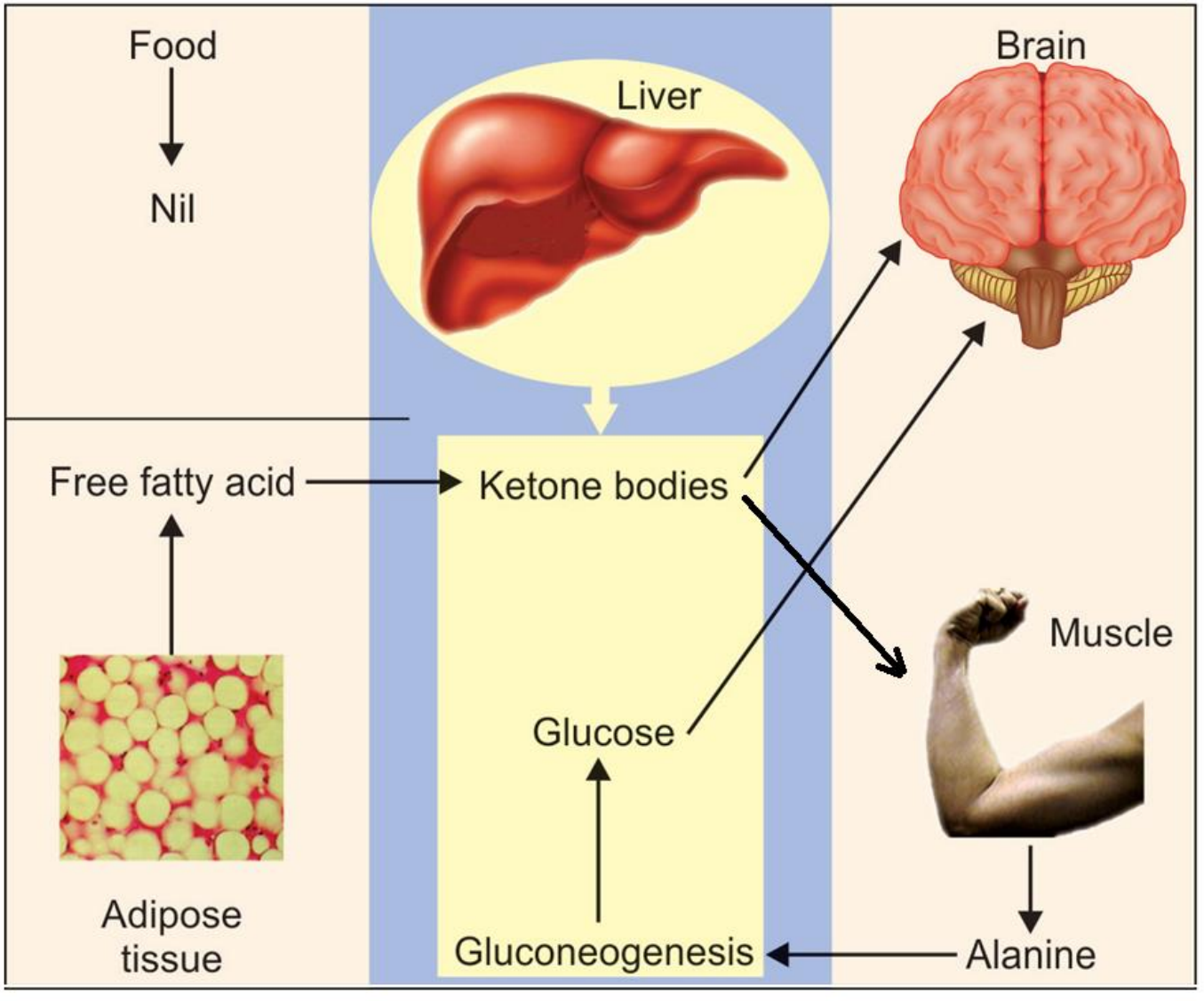
Adaptations During Starvation

Fed State	Skeletal Muscle	Cardiac Muscle
Preferred fuel at rest	Fatty acids	FFA, ketone bodies, lactate
Exercise	Glycogen to lactate	Fatty acids
Starvation Adaptations	Protein breakdown; release of amino acids; FFA, ketone bodies and branched chain amino acids utilised	Fatty acids, branched chain amino acids and ketone bodies utilised

Metabolic Profiles of Organs

Organ	Primary fuel	Other fuels
Brain	Glucose Requires a steady supply	
Skeletal muscle	Glucose from glycogen	Fatty acids in resting state.
Cardiac muscle	Glucose –Aerobic metabolism	Fatty acids and ketone bodies
Adipose tissue	Fatty acids and glucose	Mainly storage function
Liver	Glucose and fatty acids	Storage of glucose, gluconeogenesis, ketogenesis

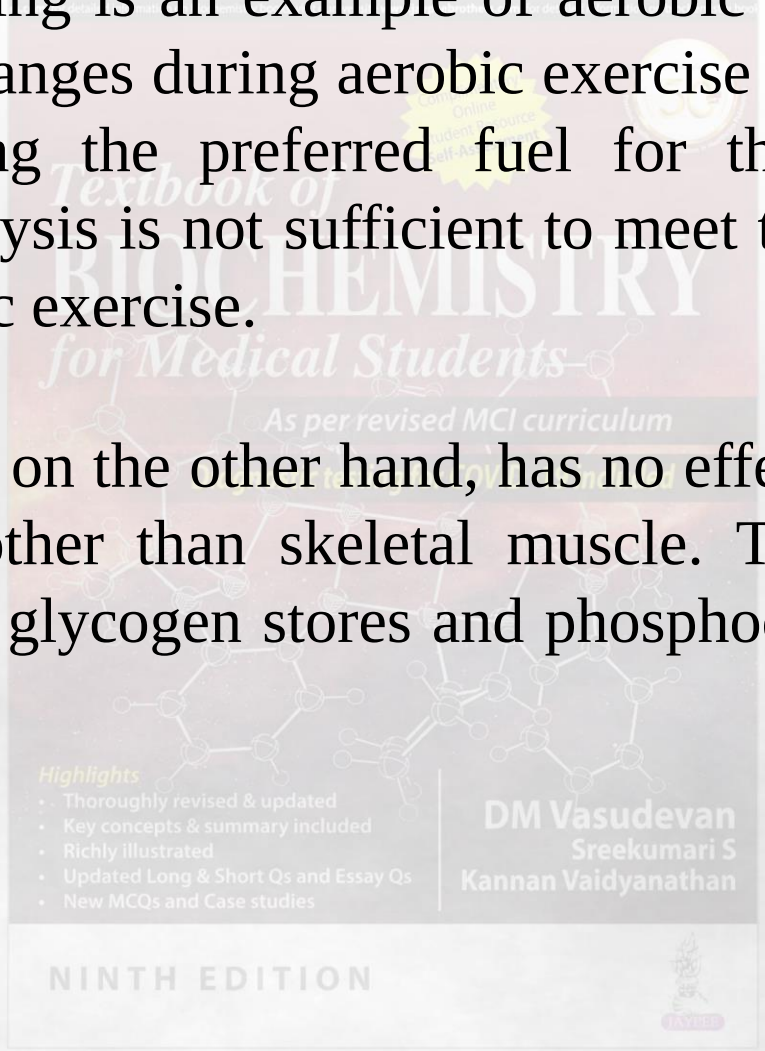
Metabolism during prolonged starvation



Long Distance Runners do not compete with Sprinters!!

Long distance running is an example of aerobic exercise. Metabolic profile of organs changes during aerobic exercise with fatty acids and ketone bodies being the preferred fuel for the skeletal muscle. Because glycogenolysis is not sufficient to meet the energy demands of prolonged aerobic exercise.

Anaerobic exercise, on the other hand, has no effect on the metabolic profile of organs other than skeletal muscle. The skeletal muscle depends on its own glycogen stores and phosphocreatine to meet the demand for ATP.



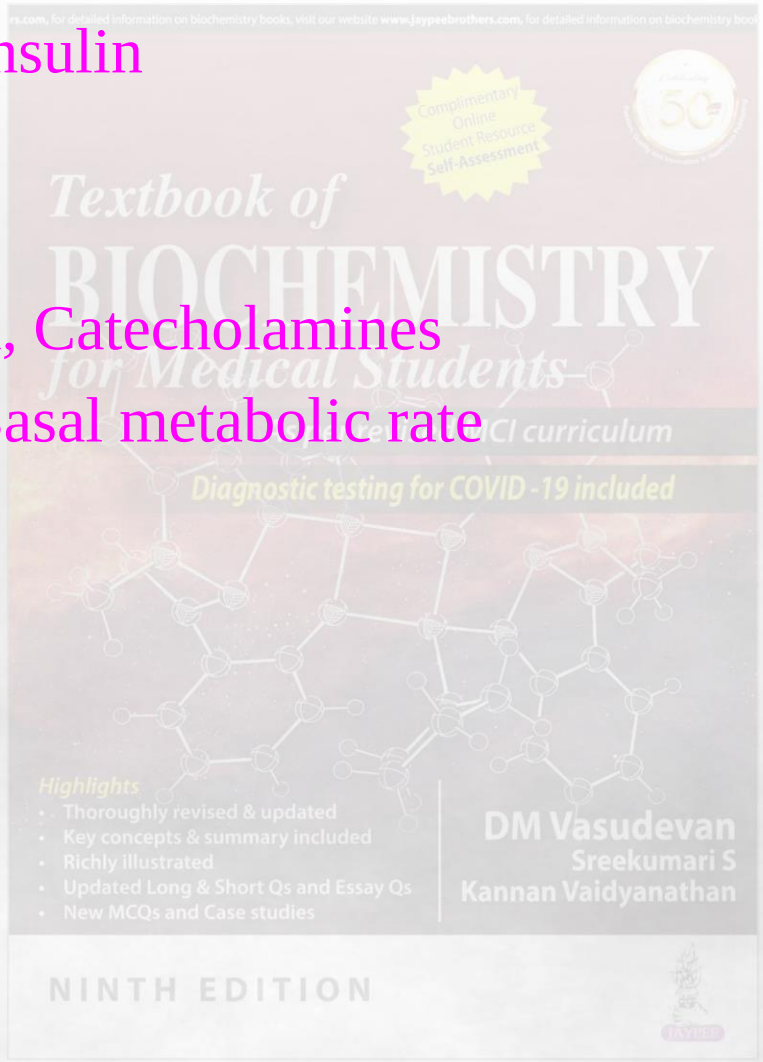
Hormonal regulation

- Well fed state- Insulin

- Starvation

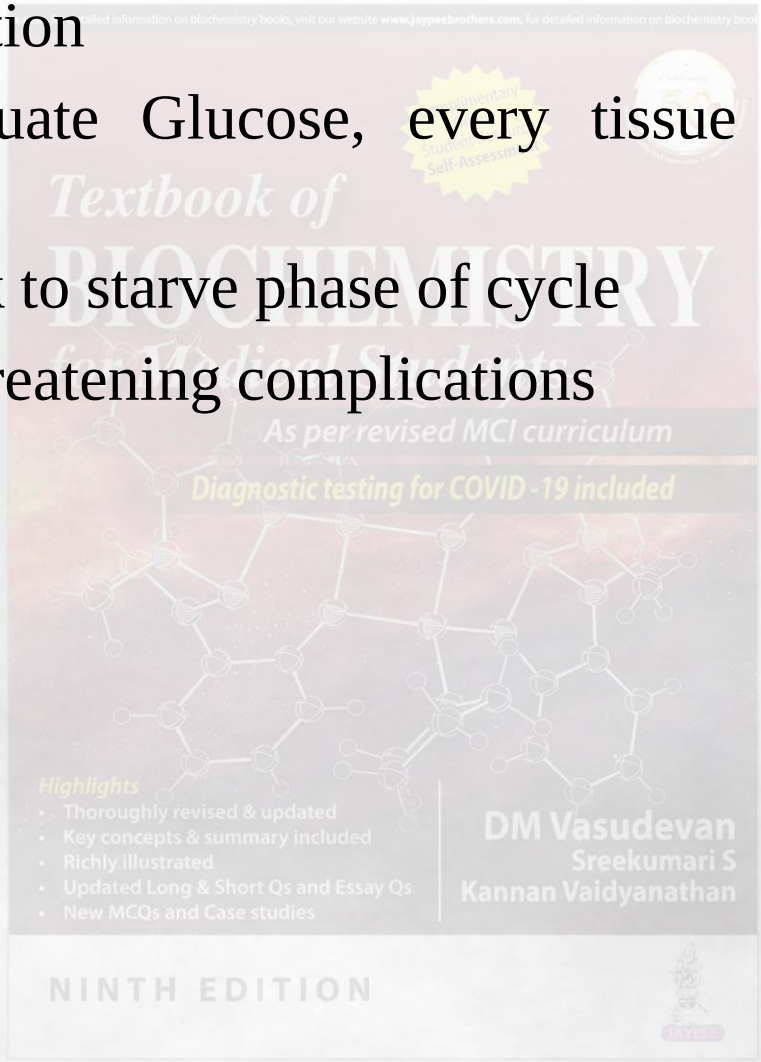
  ↑ Glucagon, Catecholamines

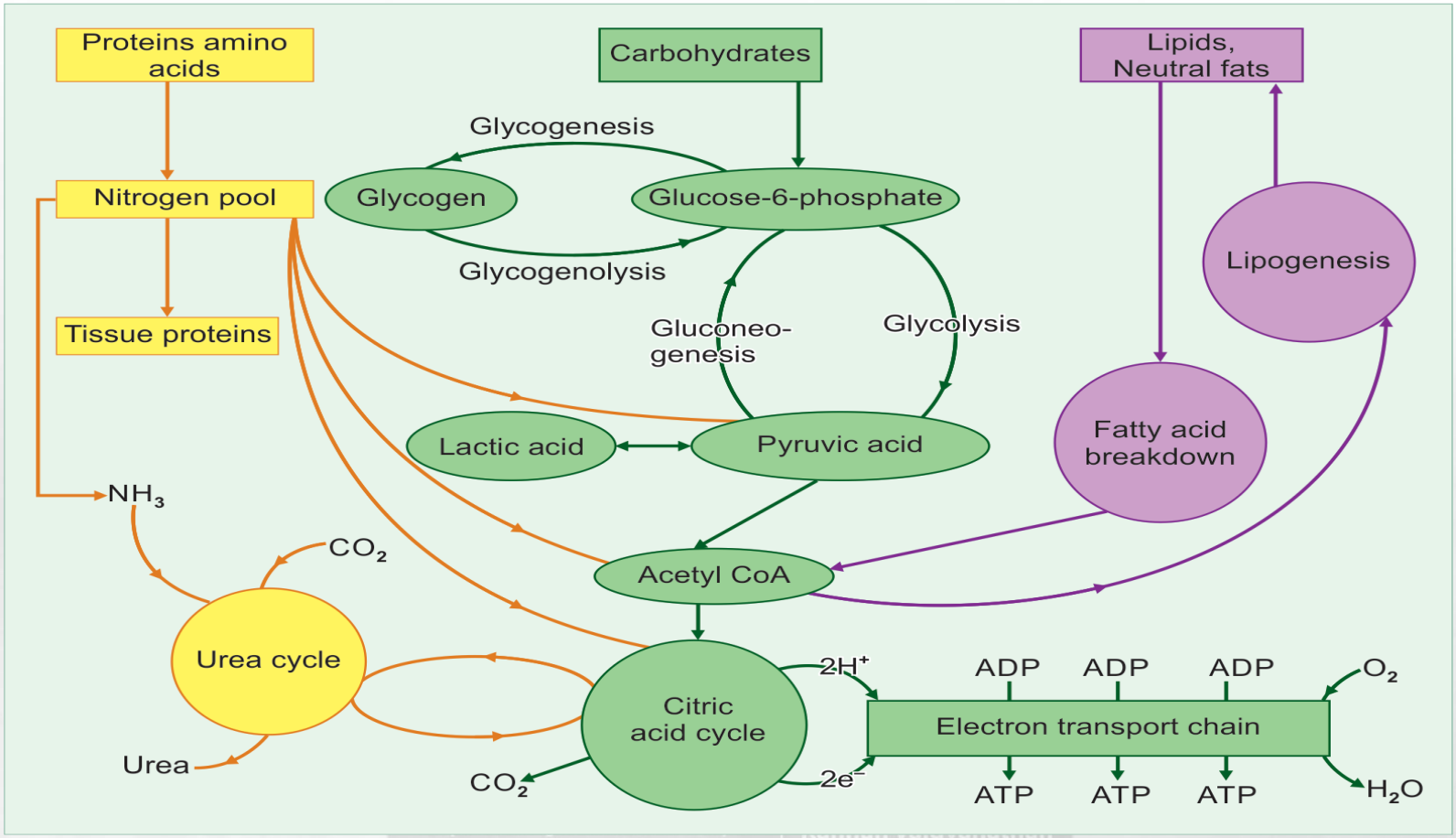
  ↓ T_3 → ↓ Basal metabolic rate



Metabolic Changes in Diabetes Mellitus

- Similar to starvation
- Inspite of adequate Glucose, every tissue switches over to catabolic roles
- Metabolism stick to starve phase of cycle
- Results in life threatening complications





Interrelationship of metabolic pathways and end products of secondary metabolism.

Metabolic Changes During Pregnancy

Hormonal Changes

Levels of **progesterone and estrogens** rise continually throughout pregnancy, suppressing the hypothalamic axis and subsequently the menstrual cycle. Estrogen is mainly produced by the placenta and is associated with fetal well–being.

Placenta also produces **human chorionic gonadotropin** (β-hCG).

Prolactin levels increase due to an enlargement of maternal pituitary gland.

Parathyroid hormone (PTH) is increased.

Adrenal hormones such as cortisol and aldosterone are also increased.

Cardiovascular Changes

During the course of pregnancy, blood volume slowly increases by 40–50%. Cardiac output rises from 4 to 7 liters in the 2nd trimester.

Hematological Changes

During pregnancy, the plasma volume increases by 50% and the RBC volume increases only by 20–30%. There is production of coagulation factors, mainly fibrinogen and factor VIII.

Metabolic Alterations

During pregnancy, One kilogram of extra protein is deposited, with half going to the fetus and another half going to uterus.

Nutrition

Pregnant women require an increase of 300 kcal/ day of energy and an increase of 70 or 75 g/day of proteins. There is also an increased folate requirement from 0.4 mg/day to 0.8 mg/day.

Renal Function

During pregnancy, the glomerular filtration rate (GFR) increases by 50% and then returns to normal around 20 weeks postpartum. There is decreased blood urea and creatinine. Persistent glucosuria may suggest gestational diabetes mellitus.

Pregnancy-related Conditions

Pregnancy may be related with prediabetic stage or gestational diabetes mellitus. Pregnancy may be related with gestational hypertension.

Metabolic Changes in Trauma and Critical Illness

Critical illness related stress is characterized by the activation of hormonal response in the hypothalamic-pituitary-adrenal axis. Thus cortisol is released from the adrenal gland. In addition, epinephrine, norepinephrine, glucagon, and GH are also increased.

The oxygen and energy requirement increases in proportion to the severity of trauma. FFAs are primary sources of energy after trauma. Triglycerides meet 50–80% of the consumed energy after trauma and in critical illness. There is increased protein degradation.

The metabolic response to trauma in humans has been defined in three phases:

The **first phase** develops within the 24–48 hours after injury. There is a decrease in total body energy and urinary nitrogen excretion. Catecholamines and cortisol are increased.

The **second phase** is for 2–7 days. There is increased oxygen consumption and metabolic rate. The utilization of glucose is reduced, with an increase in triglyceride and FFA break down.

The **third phase** of anabolic state is reached by 3–8 days after uncomplicated elective surgery. The positive nitrogen balance ensures increase in protein synthesis, and a rapid and progressive increase of weight and muscle force.

Metabolic Changes after Trauma

Changes in lipid metabolism: FFAs are primary sources of energy after trauma. Triglycerides provide 50–80% of the energy consumed in critical illness. Lipolysis is accelerated in the early period because of increased ACTH, cortisol, catecholamine, glucagon, GH, and insulin levels.

Changes in protein metabolism: There is an increase in protein catabolism, negative nitrogen balance, and increased protein turnover. The action is mediated by glucocorticoids.

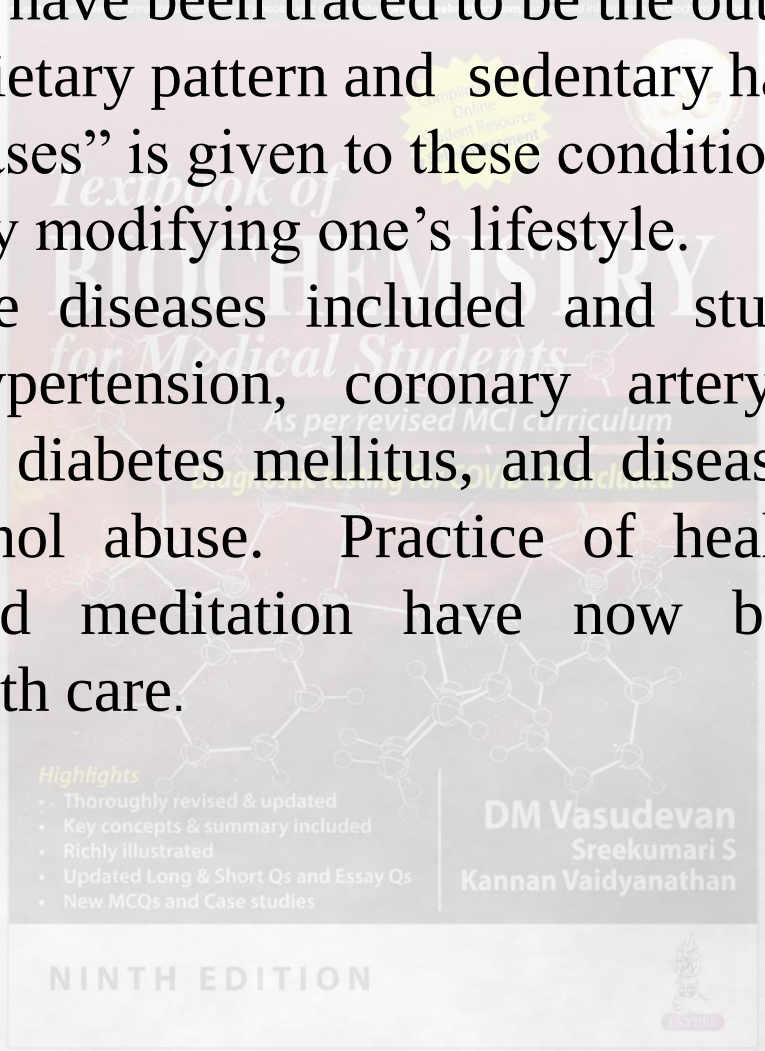
Changes in carbohydrate metabolism: Administration of glucose during fasting reduces protein breakdown. Daily infusion of 50 g of glucose increases fat oxidation and suppresses ketogenesis. In the first phase, hepatic glycogen stores are used for a period of 12–24 hours. Gluconeogenesis is driven by stress hormones and cytokines.

Insulin resistance and stress: Amino acids, FFAs, and glucose are released into the blood stream from various tissues in stress response. These reactions can be corrected with exogenous insulin therapy. Insulin infusion sufficient enough to normalize glucose levels can be used as the final aim to achieve these reactions.

Lifestyle Diseases

A group of diseases have been traced to be the outcome of our changed lifestyle, dietary pattern and sedentary habits. The term "lifestyle diseases" is given to these conditions. These diseases can be prevented, by modifying one's lifestyle.

The major lifestyle diseases included and studied in detail are atherosclerosis, hypertension, coronary artery disease, stroke, obesity and type 2 diabetes mellitus, and diseases associated with smoking and alcohol abuse. Practice of healthy eating habits, exercise, yoga and meditation have now become a part of comprehensive health care.



As per the ICMR study entitled, “India: Health of Nation’s states”, the estimated proportion of all deaths from noncommunicable diseases (NCD) has increased from 37.09% in 1990 to 61.80% in 2016. Life style diseases form a major fraction of NCD. The National Health Policy 2017 has its focus from “Sick Care to Wellness”. The major thrust under this policy is prevention and health promotion to reduce the incidence of cardiovascular diseases, cancer, diabetes and chronic respiratory diseases. The national program for the prevention of these diseases has been launched. These programs target the population at risk by screening and early detection of cancer (Cervix, Breast, Oral). As a part of comprehensive primary health care, screening and control of common NCDs like diabetes, hypertension, and cancer are included. Hence it is only natural that the primary level physician should have a clear idea of the etiopathogenesis, metabolic and genetic basis of these diseases and their prevention and control.

Modifiable risk factors are those the effect of which can be either reduced or those which can be totally avoided—diet, exercise, abstinence from alcohol, smoking and drug abuse, changing posture, working hours, etc.

The **nonmodifiable risk** factors which cannot be changed or avoided are age, gender, hereditary factors, family history, ethnicity and race.

In addition to these, certain metabolic risk factors like hyperglycemia, dyslipidemia, overweight or obesity can contribute the onset of many of the NCDs without any symptoms or signs. Early screening and detection of these alterations is of paramount importance in these cases.

Life style diseases and associated risk factors.

Disease	Modifiable risk factors	Nonmodifiable risk factors	Features
Coronary vascular disease	Hypertension, abnormal lipid profile, sedentary life style, obesity/ overweight, smoking, heavy alcohol use, energy rich diet, metabolic syndrome, type 2 diabetes	Age Family history Heredity Gender Ehnicity	Number one cause of death globally. More than 17 million deaths per year.

Life style diseases and associated risk factors.

Disease	Modifiable risk factors	Nonmodifiable risk factors	Features
Type 2 Dia-betes mellitus	High carbohydrate food, food with low fiber content, physical inactivity, obesity/overweight, hypertension, dyslipidemia, stress at work place, heavy consumption of alcohol	Advanced age Family history Genetics Race Abdominal obesity	

Life style diseases and associated risk factors.

Disease	Modifiable risk factors	Nonmodifiable risk factors	Features
Cancer	Cervix: Low socio economic status, HPV infection. Lung: Smoking, active or passive air pollution, exposure to asbestos, soot, pollution of air.	Mutation of Oncogenes/ tumour suppressor genes) Eg: BRCA gene in breast cancer.	Cancer of different parts of the body has different risk factors that may be modifiable or not

Life style diseases and associated risk factors.

Disease	Modifiable risk factors	Nonmodifiable risk factors	Features
Cancer	Breast: Hormone treatment in post menopausal women, weight gain, sedentary life style. Colorectal: Diet with less fiber and untimely eating habits.	Eg: BRCA gene in breast cancer, HNPCC in DNA repair defect	Cancer of different parts of the body has different risk factors that may be modifiable or not
COPD and Asthma	Smoking, air pollution, recurrent infections		

Key Concepts