INBORN ERRORS OF METABOLISM (BCH545)

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COURSE GENERAL DESCRIPTION

Disorders of :

- **carbohydrate metabolism** (pentosuria, diseases of fructose metabolism and glycogen storage diseases)
- **amino acid metabolism** (urea cycle disorders)
- **lipid and steroid metabolism** (lipoprotein deficiency and hyper-lipoproteinaemia, familial diseases of sterol metabolism)
- **purine, pyrimidine, metals and porphyrin metabolism**

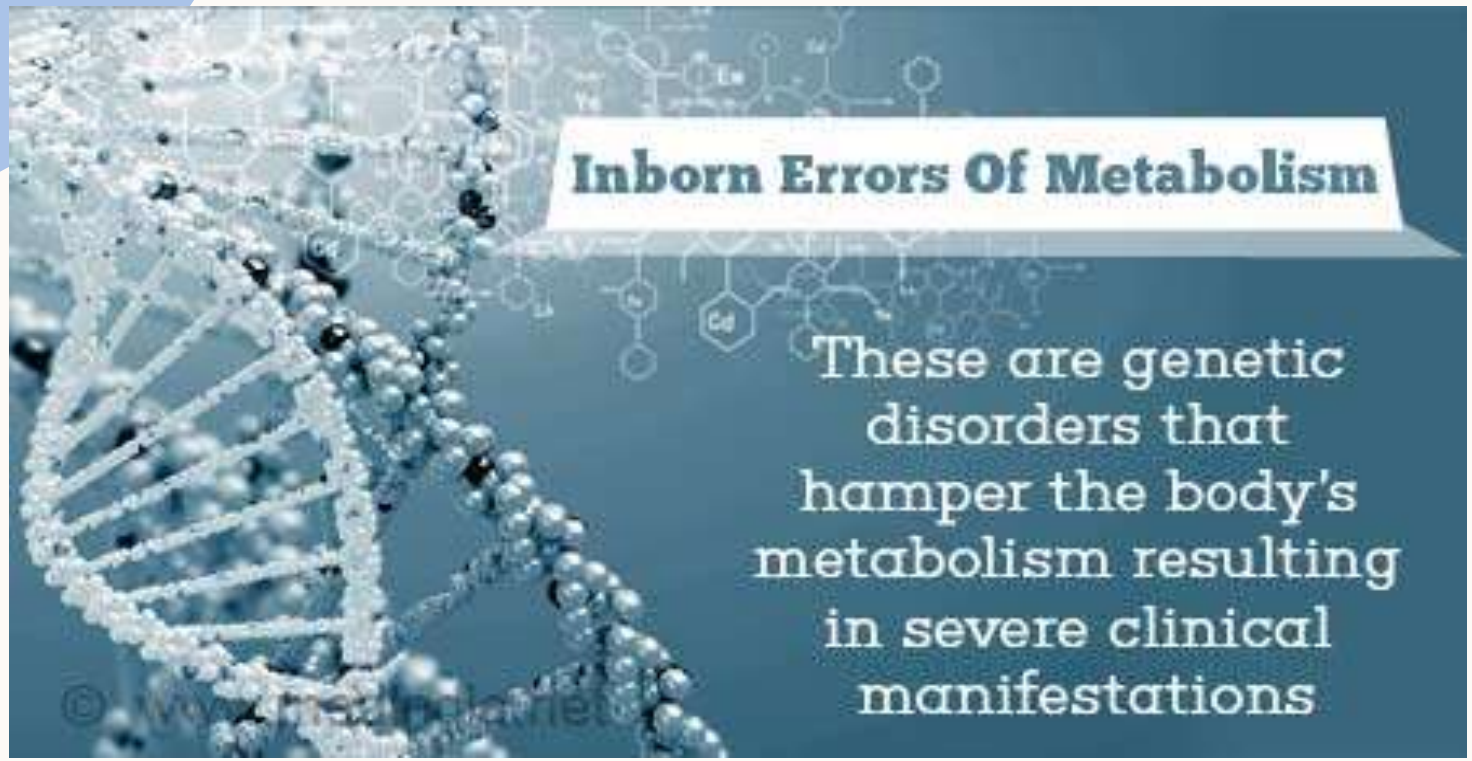
STUDENTS ASSESSMENT ACTIVITIES

No	Assessment Activities *	Assessment timing (in week no)	Percentage of Total Assessment Score
1.	Continuous Assessment Exam I	6	20
2.	Continuous Assessment Exam II	10	20
3.	Two oral presentations	14	20
4.	Final Exam	16	40

REFERENCES AND LEARNING RESOURCES

Essential References	Inborn Metabolic Diseases (By J Fernandes, Saudubray and Van den Berghe), Latest edition
Supportive References	Functional Biochemistry in Health and Disease (2009) (by Newsholme & Leech)
Electronic Materials	Metabolic Regulation (2020) (by Frayn)
Other Learning Materials	Thompson MW, McInnes RR, Willard, HF. Genetics in Medicine. W.B. Saunders Company, London. Latest edition

- The British physician, **Archibald Garrod** (1857-1936) coined the term inborn errors of metabolism in 1902
- He discovered the 1st metabolic disorder “Alkaptonuria”



Examples: phenylketonuria, albinism, lactose intolerance, gaucher disease, fabry disease

inherited congenital disorders: birth defects in newborn infants which passed down from family and affecting metabolism.

INTRODUCTION

Inborn errors of metabolism (IEM) are a group of **inherited congenital disorders** leading to enzymatic defects in the human metabolism in which the body cannot properly break down the nutrients from food.

This results in the accumulation of food substrates in the cells of the body, leading to clinically significant consequences.

If inborn errors of metabolism are not clinically managed, they can lead to developmental delays and other severe health conditions.

RECALL

- What is metabolism and its basic functions?
- What are the metabolic pathways?
- Differentiate between anabolism and catabolism?
- How are anabolism and catabolism interlinked ?

METABOLISM

Definition:

Metabolism is a chemical process to maintain the living state of cell and organism.

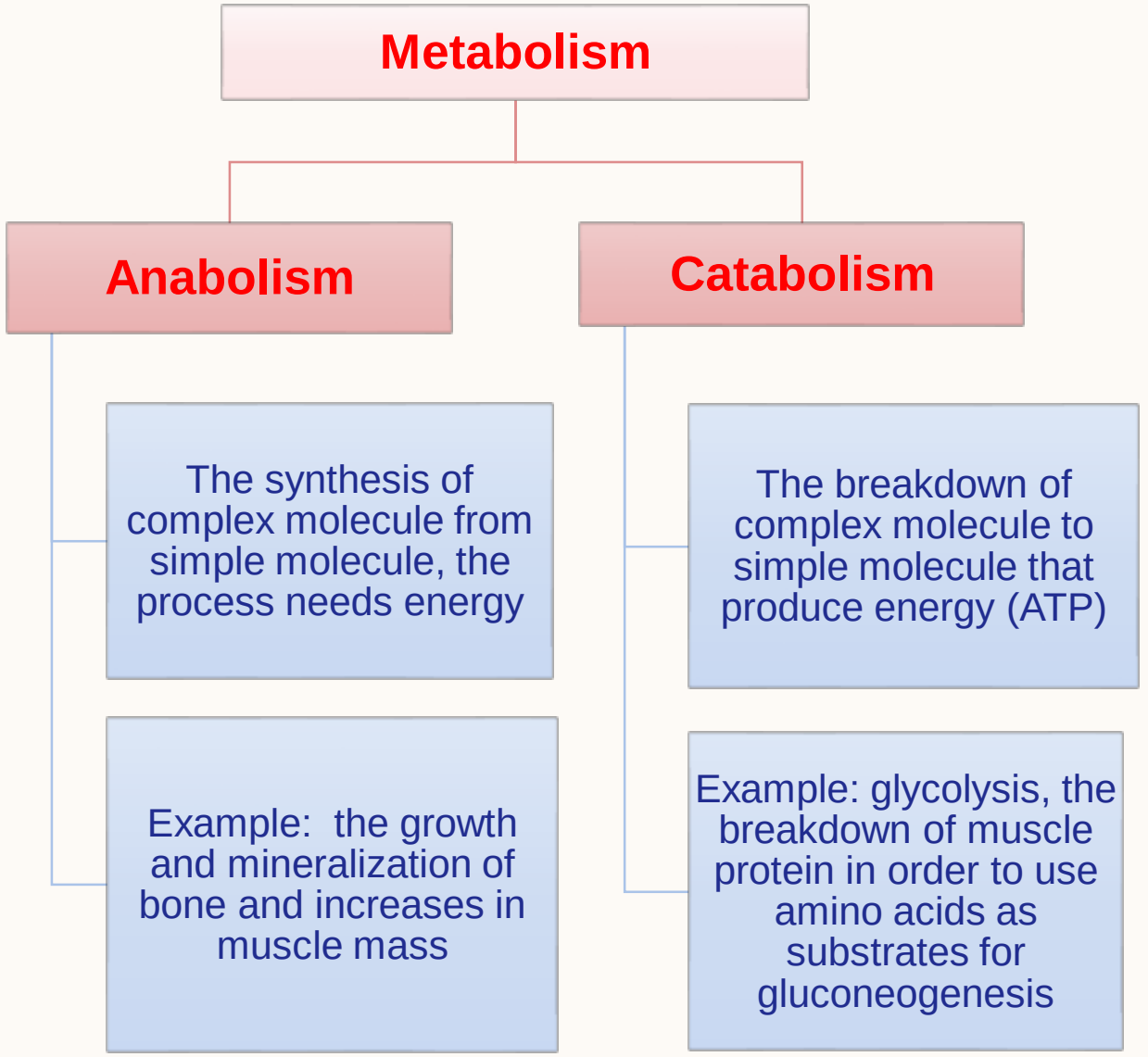
Metabolism can be defined as all biochemical reactions that take place in cell.

Function:

1.The conversion of food/fuel to energy to run cellular processes

2.The conversion of food/fuel to building blocks for proteins, lipids, nucleic acids, and some carbohydrates

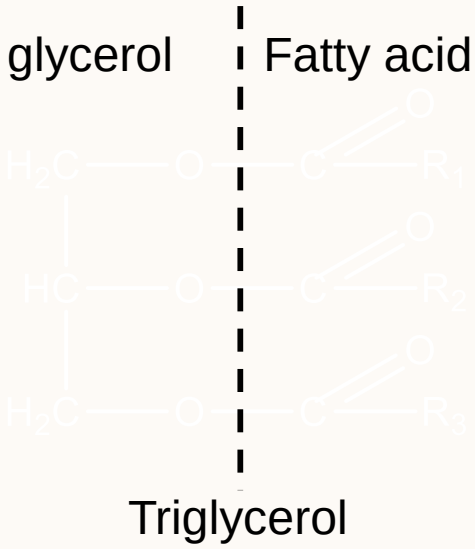
3.The elimination of nitrogenous wastes.

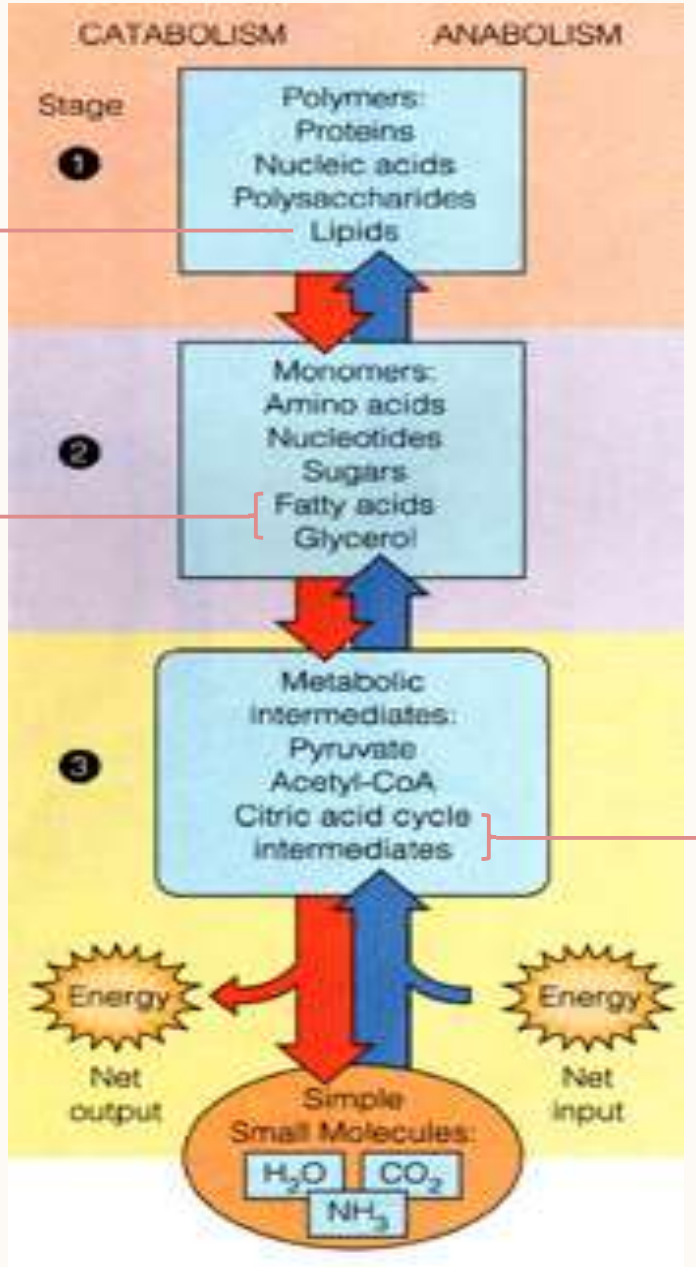


ANABOLISM AND CATABOLISM

Anabolism and catabolism occur in 3 stage.

- **Stage 1**: The conversion of macromolecule (polymer and complex lipid) to monomer intermediates.
- **Stage 2**: The conversion of monomers (amino acids, nucleotides, sugars, fatty acids, and glycerol) to metabolic intermedites (Pyruvate, Acetyl-CoA, and Citric acid cycle intermediates).
- **Stage 3**: Degradation of metabolic intermediates to H_2O, O_2, and NH_3.





Not a polymer

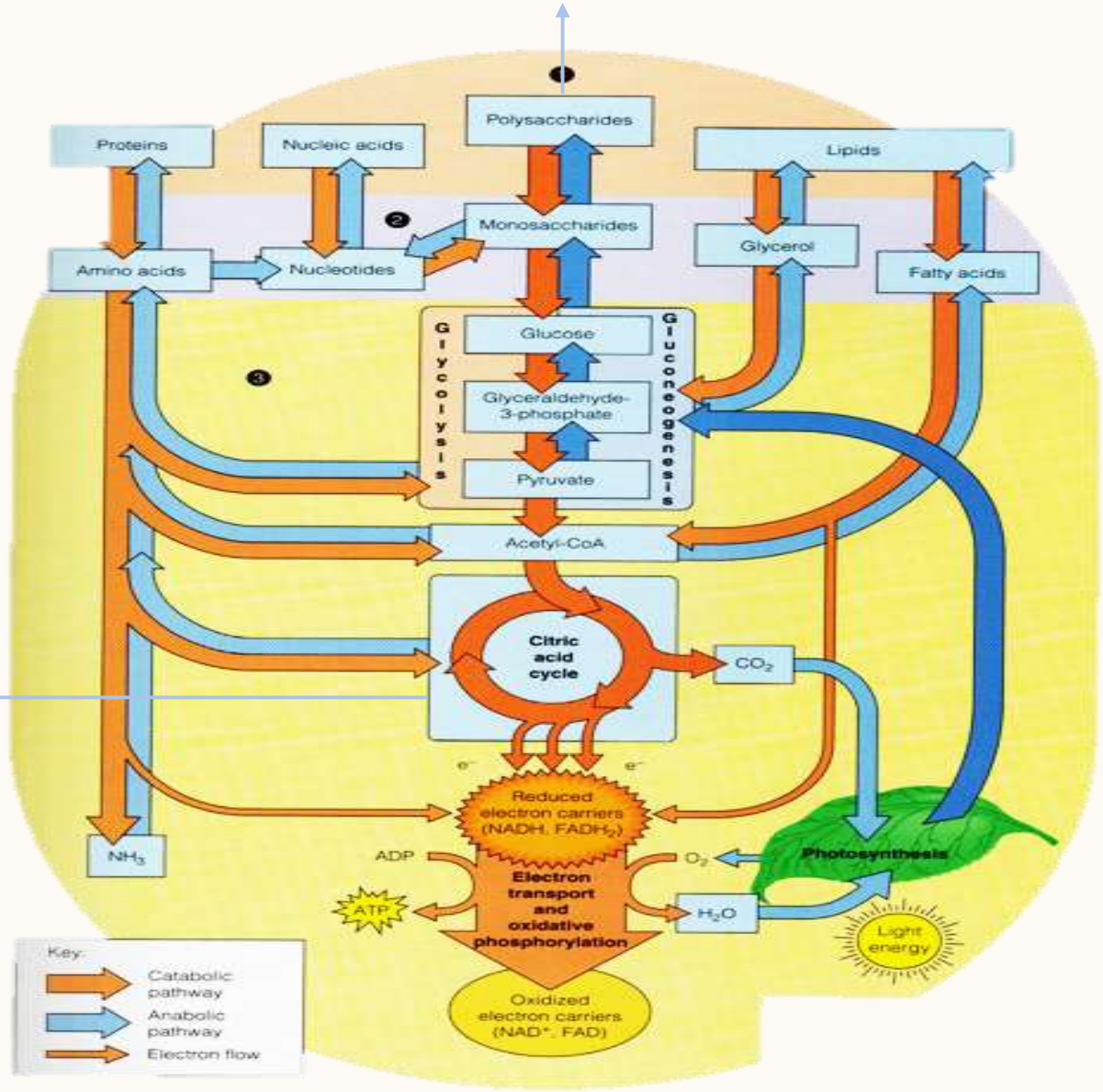
Lipid component

Crab Cycle

METABOLISM

- The whole process of metabolism is really a continuum
- There are electron transport in every process of metabolism

An energy source (act mostly in crab cycle)



polymer

monomer

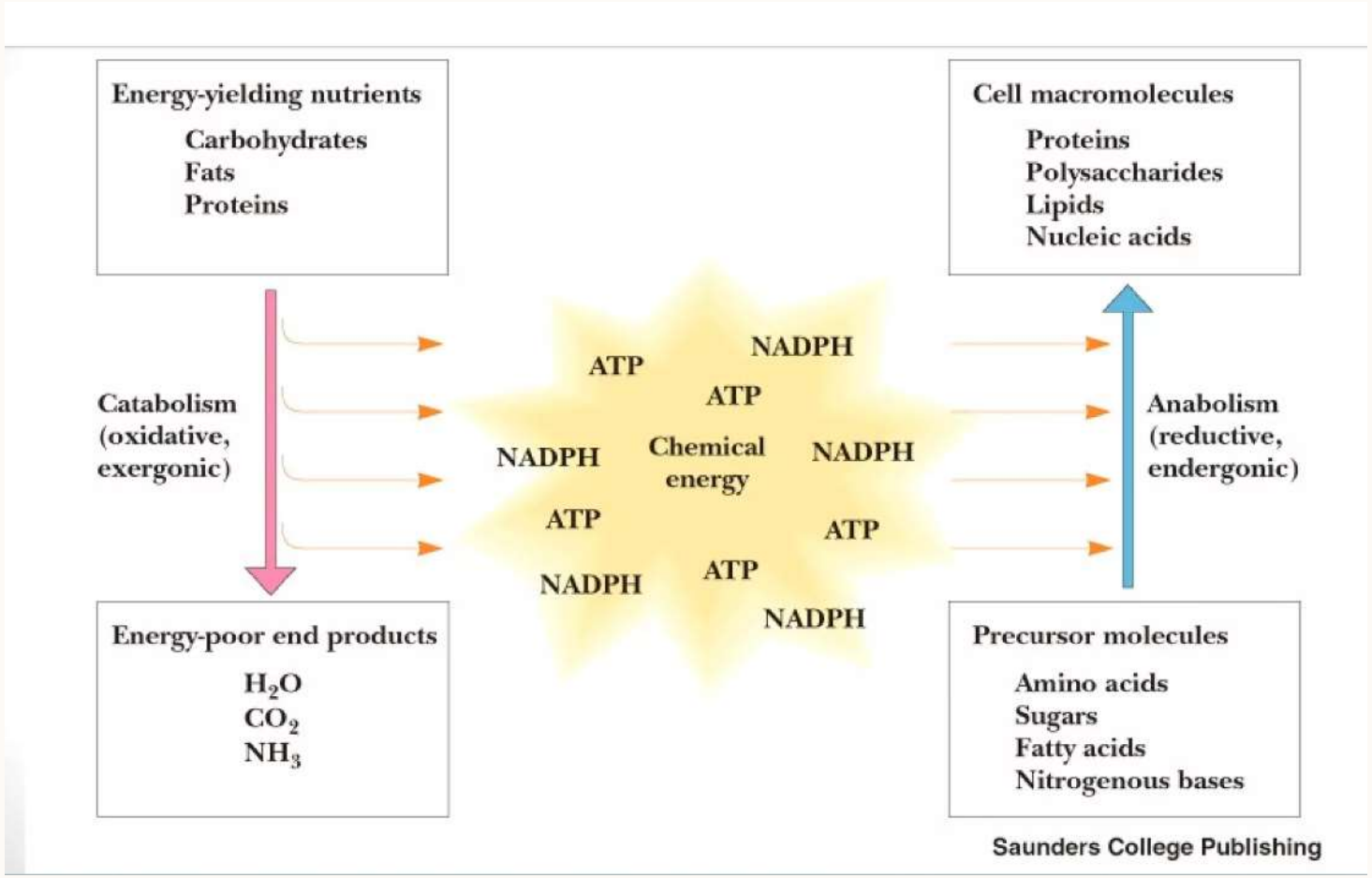
Intermediate result

Produce high energy

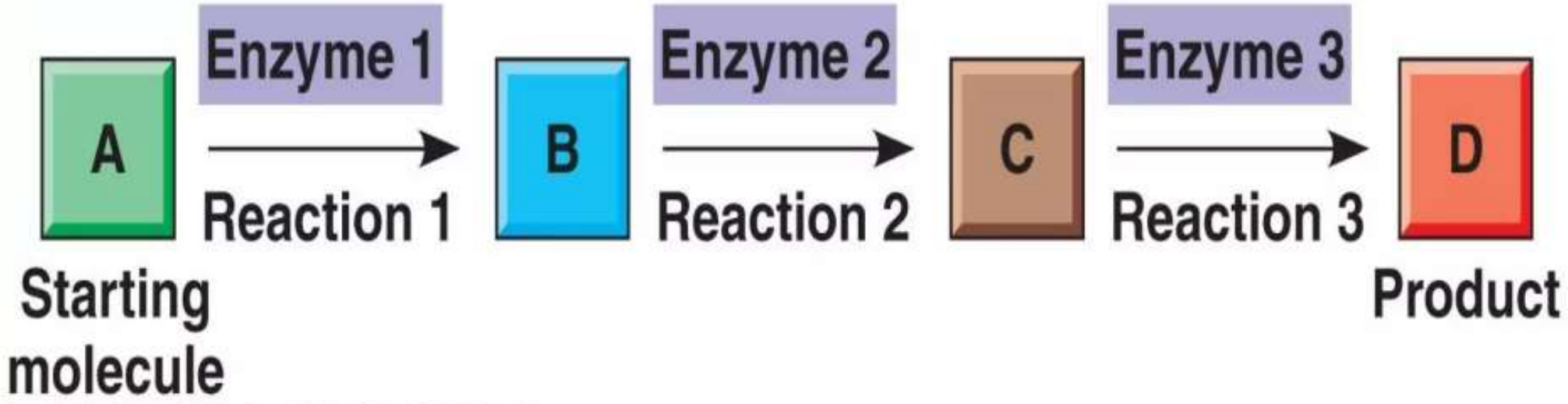
Phosphorylation oxidative

Amphibolic pathways:
Metabolic pathways that occur at crossroad of metabolism and act as a link between anabolism and catabolism (eg. The citric acid cycle)

CATABOLISM AND ANABOLISM ARE RELATED

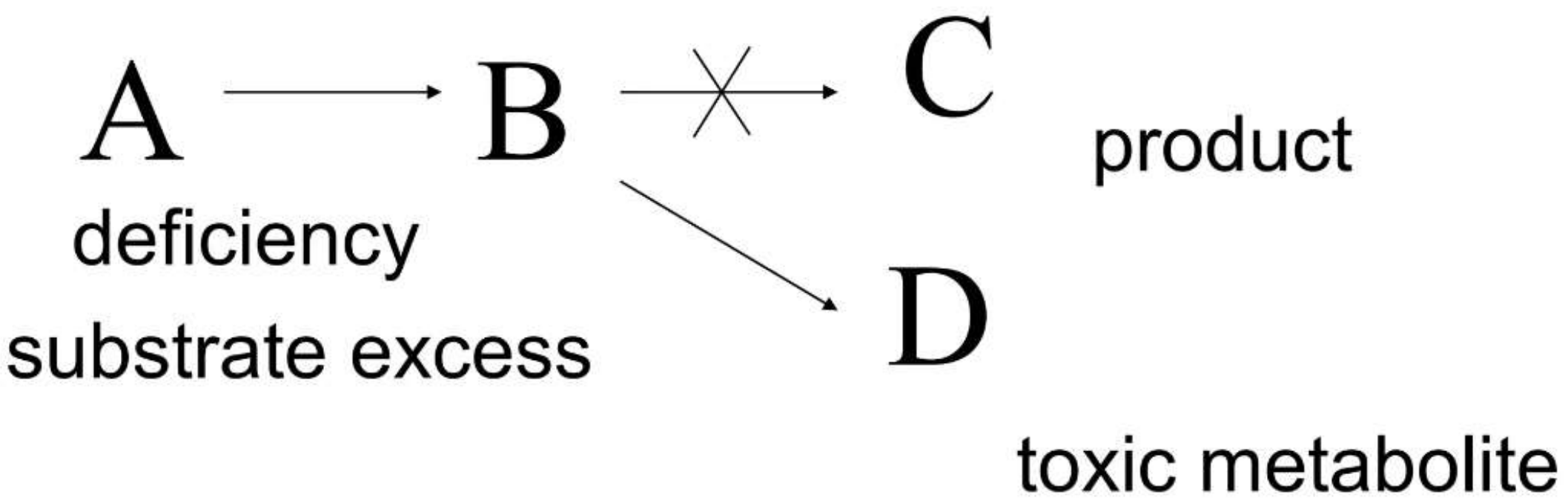


- A metabolic pathway begins with a specific molecule and ends with a product.
- Each step is catalyzed by a specific enzyme



What is a metabolic disease?

- Garrod's hypothesis



IEM can appear at birth or later in life

In IEM , body’s metabolism is affected due to **genetic disorders**.

The cause of IEM is **mutations in a gene that code for an enzyme** leading to synthesis of defective enzyme activity or deficiency of an enzyme that affects the normal function of a metabolic pathway.

The main indication of IEM is an excess storage or accumulation of specific metabolites in tissues, organs and blood which further manifest to health diseases.

Several hundreds of different IEM have been identified.

Most IEM are rare but some are life threatening.

ETIOLOGY

Inborn errors of metabolism are inherited disorders caused by mutations in genes coding for proteins (enzymes, receptors, specific protein , transport proteins, membrane pumps, structural elements) that function in metabolism.

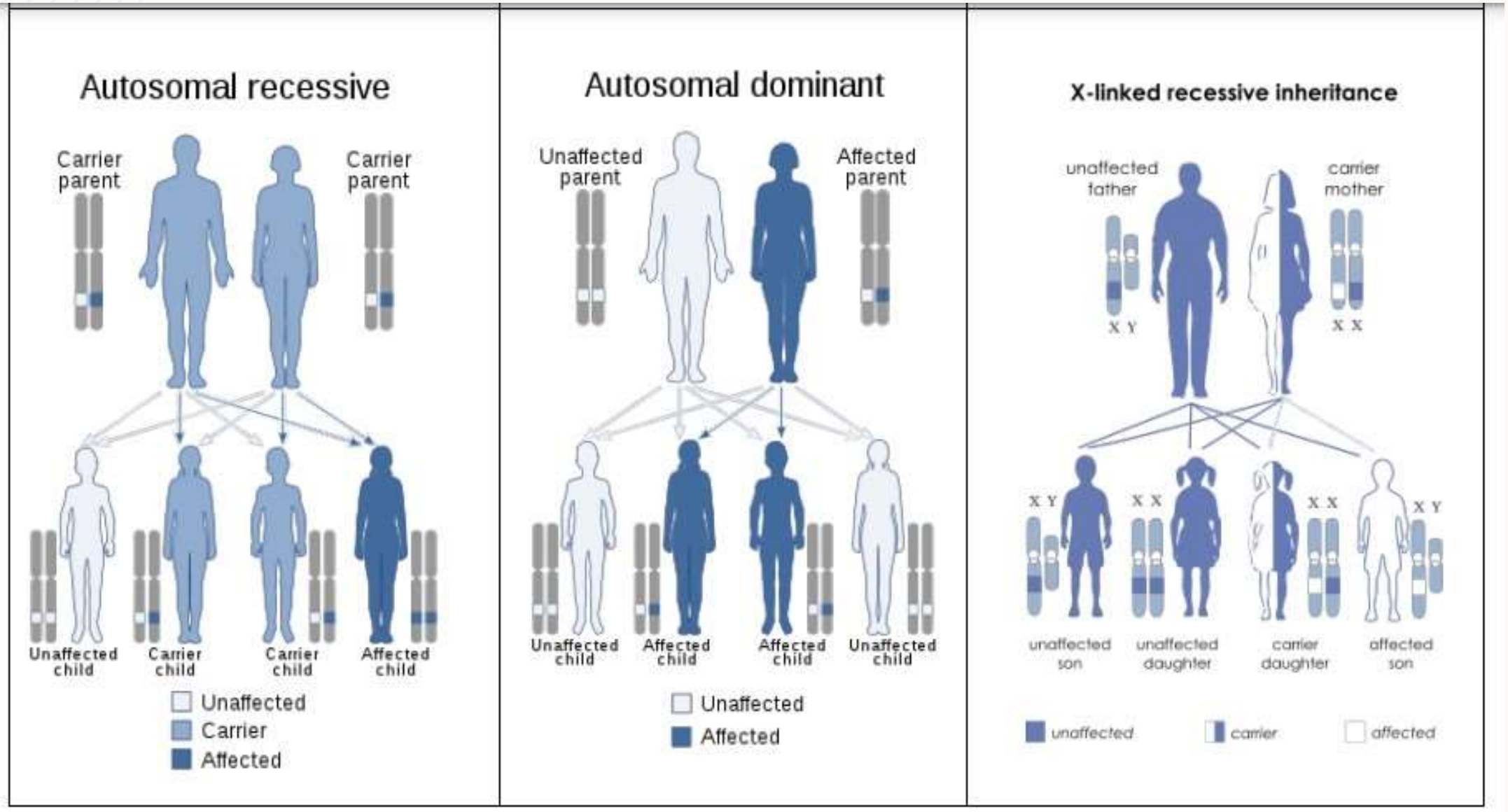
Most are inherited as autosomal recessive.

Rarely, they are autosomal dominant and X-linked.

Environmental, epigenetic, and microbiome factors and additional genes are potential modifying etiologic factors in those with inborn errors of metabolism

✻ Types of Inheritance:

Autosomal Recessive	Autosomal Dominant	X-linked
25% of offspring of unaffected carrier parents	50% of offspring of one affected parent	Normal father, carrier mother > affected male child
✻ Congenital Adrenal Hyperplasia Most important problem is ambiguous genitalia. ✻ Cystic Fibrosis ✻ Friedreich's Ataxia ✻ Galactosemia ✻ Glycogen Storage Disease ✻ Hurler Syndrome (Mucopolysacchridosis I) ✻ Oculocutaneous Albinism ✻ Phenylketonuria ✻ Sickle Cell Disease ✻ Tay-Sach's Disease ✻ Thalassemia ✻ Werdnig Hoffmann disease	✻ Achondroplasia ✻ Ehlers-Danlos Syndrome ✻ Familial Hypercholesterolemia ✻ Huntington's Disease ✻ **Marfan Syndrome** ✻ Myotonic Dystrophy ✻ Neurofibromatosis ✻ Noonan's Syndrome ✻ Osteogenesis Imperfecta ✻ Tuberous Sclerosis	✻ Color-blindness ✻ DMD (Duchenne Muscular Dystrophy) & Becker ✻ Fragile X Syndrome ✻ G6PD urine cola color, low hemoglobin, and jaundice when eating beans ✻ Hemophilia A & B ✻ Hunter's Syndrome (Mucopolysacchridosis II)


Autosomal recessive
Carrier parent
Carrier parent
Unaffected child
Carrier child
Carrier child
Affected child
Unaffected
Carrier
Affected
Autosomal dominant
Unaffected parent
Affected parent
Unaffected child
Affected child
Affected child
Unaffected child
Unaffected
Affected
X-linked recessive inheritance
unaffected father
carrier mother
X Y
X X
X Y
X X
X X
X Y
unaffected son
unaffected daughter
carrier daughter
affected son
unaffected
carrier
affected

What is a metabolic disease?

- Small molecule disease
  - Carbohydrate
  - Protein
  - Lipid
  - Nucleic Acids
- Organelle disease
  - Lysosomes
  - Mitochondria
  - Peroxisomes
  - Cytoplasm

EXAMPLES OF IEM GROUPS

Amino acid metabolism:	phenylketonuria (PKU)
	maple Syrup Urine Disease (MSUD)
	homocystinuria
Urea cycle disorders	arginino succinnic aciduria
	OTC deficiency
Organic Acidaemias	propionic acidaemia
	methyl malonic aciduria
	isovaleric acidaemia
Fat Oxidation Defects:	MCAD deficiency

Carbohydrate Metabolism:	glycogen storage disorders
	galactosaemia
Lysosomal storage disorders:	*gaucher and Fabry diseases*
	mucopolysaccharidoses
Transport protein defects:	cystic Fibrosis
	cystinuria
	cystinosis
Mitochondrial disorders:	Pearson syndrome
	cytochrome oxidase def

Three Types

- Type 1: Silent Disorders
- Type 2: Acute Metabolic Crises
- Type 3: Neurological Deterioration

Type 1: Silent Disorders

- Do not manifest life-threatening crises
- Untreated could lead to brain damage and developmental disabilities
- Example: PKU (Phenylketonuria)

Type 2: Acute Metabolic Crisis

- Life threatening in infancy
- Children are protected in utero by maternal circulation which provide missing product or remove toxic substance
- Example OTC (Urea Cycle Disorders)

Type 3: Progressive Neurological Deterioration

- Examples: Tay Sachs disease
  Gaucher disease
  Metachromatic leukodystrophy
- DNA analysis show: mutations

Treatment

- Dietary Restriction
- Supplement deficient product
- Stimulate alternate pathway
- Supply vitamin co-factor
- Organ transplantation
- Enzyme replacement therapy
- Gene Therapy