The Trusted 'All-in-One' Lifesaver Book for NEET PG (NEXT), INICET and FMGE

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Contents

CHAPTER 4

Biochemistry

1.0 VITAMINS

1.1 Fat Soluble and Water Soluble Vitamins

Fat Soluble Vitamins	Water Soluble Vitamins
▪ Vitamin **A**, **D**, **K**, **E** (**A**ll **D**octors **K**now **E**nglish!") ▪ Vitamin A (Retinol) ▪ Vitamin D (Calciferol) ▪ Vitamin E (Tocopherol) ▪ Vitamin K (Phytomenadione) ▪ ***Absorption*** depends on intact ileum, pancreatic secretions and bile emulsification.	▪ B**1** (**T**hiamine) ▪ B**2** (**R**iboflavin) ▪ B**3** (**N**iacin) (B **1–2-3**....**T**u**RN**!) ▪ B5 (**Pant**othenic Acid, **Pent** = **5**, ***Pent***othenic) ▪ B6 (B si**X** -Pyrido**X**ine) ▪ B7 (biotin) ▪ B**9** (***folate***) (***9 Fol****lows* ***ate/***8") ▪ B12 (Cobalamin) ▪ C (ascorbic acid)

CLINICAL CORRELATION

- Malabsorption syndromes with steatorrhea (celiac sprue, cystic fibrosis) or bile acid deficiency or orlistat, mineral oil intake can cause fat soluble vitamin deficiencies.
- ***Toxicity*** more common with ***fat soluble*** vitamins since (i) these accumulate in the fat (ii) these are not excreted in urine as they are hydrophobic.
- Water soluble vitamins are excreted in urine and hence cannot accumulate to toxic levels. (except ***B12*** - stored in the liver for ***3-4 years***; ***B9*** stored in liver for ***3-4 months***)

1.2 Vitamin B1 (Thiamine)

Sources: ***Whole grain*** cereals (whole wheat, brown rice), yeast, pork, beans/legumes

Functions: Thiamine pyrophosphate (TPP), a.k.a. thiamine diphosphate (TDP) is a cofactor for oxidative decarboxylation/dehydrogenase reactions

- **P**yruvate dehydrogenase (links glycolysis to TCA cycle; pyruvate → AcetylCoA)
- **A**lpha-ketoglutarate dehydrogenase (TCA cycle)
- **T**ransketolase in HMP shunt (B1 deficiency is assessed by *reduced RBC transketolase* activity)
- **B**ranched chain keto acid dehydrogenase (metabolism of *Val,Leu.Ile*)
- (**PAT** your **B**ack)

Deficiency: Seen in alcoholism, malnutrition (***polished rice***). Impaired glucose breakdown → ↓ ATP production; highly aerobic tissues are affected first (brain, heart).

- ***Beri Beri*** (B**1** deficiency = Ber**1** Ber**1**)
  - Dry Beriberi – polyneuritis, symmetrical muscle wasting
  - Wet beriberi – high output cardiac failure (dilated cardiomyopathy), edema
- ***Wernicke's encephalopathy*** (acute reversible condition - **G**lobal confusion, **O**phthalmoplegia - Sixth nerve MC, **A**taxia, **N**ystagmus, - **GOAN**)
- ***Korsakoff's syndrome*** (retro and anterograde amnesia, confabulation, mammillary bodies affected)
- ***Lactic acidosis*** (pyruvate fails to enter TCA cycle; so excess pyruvate is converted to lactate anaerobically)

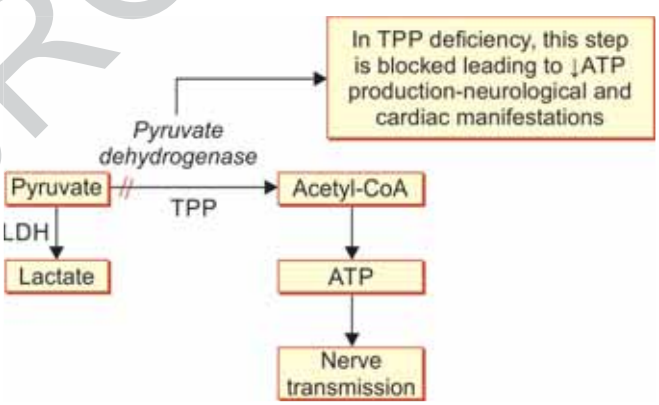

Fig. 4.1: Thiamine deficiency

1.3 Vitamin B2 (Riboflavin)

Sources: Milk, eggs, meat, green vegetables

Functions: ***FMN*** (Flavin Mono Nucleotide) and ***FAD*** (Flavin Adenine Dinucleotide) are derived from riboflavin and used as coenzymes in oxidation-reduction (***redox***) reactions - ex: ***succinate dehydrogenase*** (TCA cycle) and glutathione reductase in RBCs (hence ***B2 deficiency*** can be assessed by ***RBC glutathione reductase*** levels)

Deficiency: ***Angular stomatitis*** (oral mucosa inflammation), ***Cheilosis***, (lips inflammation), ***'magenta'*** tongue, ***Corneal vascularization***, seborrheic dermatitis.

"Ribo**FLAV**in affects **FLAV**our (lips, mouth)!"

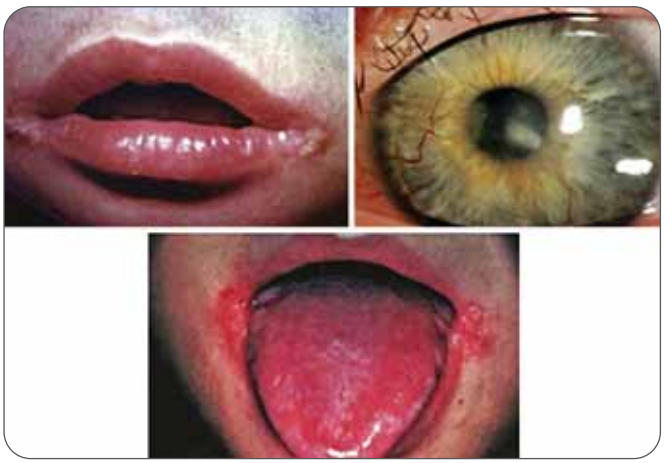

Fig. 4.2: B2 deficiency

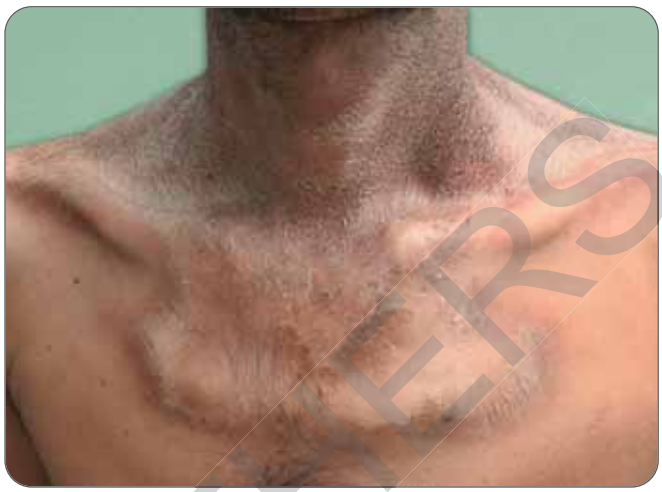

Fig. 4.3: Casal's necklace

1.4 Vitamin B3 (Niacin)

- **Sources**: Meat (liver), fish, plants
- **Formation**: Niacin can be formed in the body from ***tryptophan*** (B**3** from **3**yptophan); 1 mg of niacin is formed from 60 mg of tryptophan
- **Functions**: Active forms are of NAD+, NADP+ (used in oxidation reduction - 'redox' reactions)
- **Deficiency**:
  - Vitamin B3 deficiency can be caused by (i) Hartnup disease (↓ tryptophan absorption) (ii) malignant carcinoid syndrome (↑ Tryptophan metabolism) (iii) INH (↓ vitamin B6) (iv) diet rich in ***maize/corn*** or sorghum/jowar) only - both of these are poor in niacin and tryptophan (BUT rich in leucine and excess leucine inhibits conversion of tryptophan to niacin).
  - ***Pellagra*** = Deficiency of **B3** = **3D**s!: **D**iarrhea, photosensitive **D**ermatitis, **D**ementia, also ***beefy glossitis*** occurs; ***Casal collar***/necklace: erythematous rash in a broad collar like distribution - C3/C4 dermatomes; ***hyperpigmentation*** of sun-exposed areas.
  - ***Hartnup*** disease: AR; ↓ absorption of tryptophan (and neutral AA) from intestine and kidneys) due to SLC6A19 gene defect → neutral aminoaciduria → Niacin deficiency and pellagra like symptoms. Obermeyer test (for indole/indican in urine) is positive.
  - Treat with Niacin and diet rich in tryptophan, high protein diet.
- **Toxicity**: facial ***flushing*** (prostaglandin mediated, NOT histamine, can avoid by taking aspirin with niacin); ***hyperglycemia; hyperuricemia***, fulminant hepatitis; ***macular edema***.
- **Therapeutic use**: Dyslipidemia (Niacin lowers VLDL and increases HDL levels)

1.5 Vitamin B5 (Pantothenic acid)

- **Function**: Constituent of ***Coenzyme A*** (CoA = pantothenic acid + ADP +cysteine) and cofactor for transfer of acyl groups and fatty acid synthase.
- **Deficiency**: Dermatitis, alopecia, enteritis, adrenal insufficiency, 'burning feet' syndrome (parasthesias)
- B**5** = **Pent**othenic acid (*Pent* = *5* - as in *Pentagon*)

1.6 Vitamin B6 (Pyridoxine)

- **Source**: Meat, fish, potato, banana, nuts (B si**X** = Pyrido**X**ine)
- **Function**:
  - Pyridoxal phosphate (***PLP***) is the active form; PLP is a ***coenzyme*** for following reactions
    - Decarboxylation
    - Transamination (ex: AST and ALT)
    - Condensation (delta-ALA synthase)
    - Amino acid metabolism
    - Glycogenolysis (glycogen synthase)
  - PLP is involved in ***synthesis*** of heme, histamine, niacin, glutathione, cystathionine, neurotransmitters (serotonin, dopamine, GABA, norepinephrine, epinephrine)
- **Deficiency**:
  - Irritability, convulsions, ***peripheral neuropathy*** (induced by ***INH*** and ***OCPs***)
  - ***Sideroblastic Anemia*** (impaired transfer of iron to hemoglobin → excess iron accumulates in RBCs)
  - Oxalate kidney stones
  - Deterioration of Parkinsonism
- **Toxicity**: Irreversible sensory neuropathy, photosensitive dermatoses.

- **Therapeutic Use**: Along with TB drugs (to prevent INH peripheral neuropathy); sideroblastic anemia; hyperemesis gravidarum, homocystinuria; oxaluria; cystathionuria, xanthurenic aciduria.
- **Measurement of B6**: RBC aspartate aminotransferase levels; Tryptophan load test (measuring urinary xanthurenic acid following a dose of tryptophan)

1.7 Vitamin B7 (Biotin, Vitamin 'H')

- **Function**: Cofactor for carboxylation reactions which all add a one-carbon group
  - Pyruvate → oxaloacetate (Pyruvate carboxylase, Gluconeogenesis)
  - Acetyl-CoA → Malonyl-CoA (AcetylCoA carboxylase; Fatty acid synthesis)
  - Propionyl-CoA → Methylmalonyl-CoA (Propionyl CoA carboxylase, fatty acid reduction)
- **Deficiency**:
  - Caused by long term *antibiotic use*; excessive ingestion of ***egg whites*** (which contains ***avidin*** - that binds biotin and prevents its absorption)
  - Dermatitis, alopecia, paresthesia, enteritis
  - Deficiency of biotin + carboxylase (holocarboxylase) or biotinidase leads to ***multiple carboxylase deficiency*** (***tomcat urine*** odour)

1.8 Vitamin B9 (Folic Acid, Folate)

- **Sources**: ***Green leafy*** vegetables (**FOL**ate from **FOL**iage), small amounts by intestinal flora.
- Normal blood levels of folic acid = ***2-20 ng/mL***
- Absorbed from ***jejunum***; Small storage depot in liver for ***3-4 months***.
- **Function**
  - Active form = ***THF*** (tetrahydrofolate); Major circulating form = methyl THF
  - Coenzyme for ***1-carbon transfers***; involved in ***methylation*** reactions
  - Required for synthesis of ***bases*** *in DNA* and *RNA*
- **Deficiency**
  - Seen in chronic alcohol overuse, malnutrition, in pregnancy, drug induced (trimethoprim, phenytoin, methotrexate etc)
  - ***Macrocytic megaloblastic*** anemia: due to defective DNA synthesis in RBCs; ***hypersegmented*** neutrophils, glossitis, no neurologic symptoms (v/s vit B12 deficiency), ↑ serum homocysteine, ***Normal*** methylmalonic acid.
  - ***FIGLU*** test: Histidine is normally metabolized to formimino glutamic acid (FIGLU) from which formimino group is removed by THF. Hence in folic acid deficiency, FIGLU is excreted in urine
- **Supplementation**: 0.4 mg (400 mcg/day) of folic acid starting from one month before conception and through full pregnancy and till end of first trimester is recommended to prevent neural tube defects in fetus.

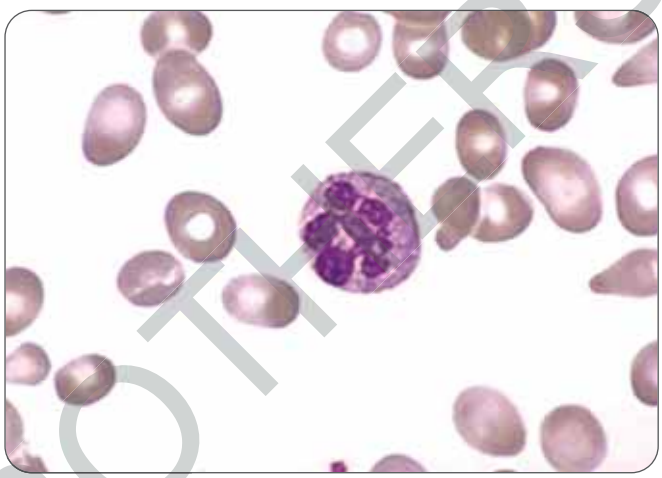

Fig. 4.4: Hypersegmented neutrophils

1.9 Vitamin B12 (Cobalamin)

- **Source**: Found ***ONLY*** in animal products - meat, egg, milk, fish etc; synthesised by colonic flora - BUT cannot be absorbed in humans since site of synthesis (colon) is distal to site of ***absorption (ileum)*** - absorption requires *intrinsic factor (IF) of* ***Castle*** secreted by ***parietal cells*** of stomach.
- **Storage**: Very large reserve pool stored for ***3-4 years*** in the liver
- **Function**: Cofactor for
  - Methionine synthase (in conversion of homocysteine to methionine)
  - Methylmalonyl-CoA isomerase: which catalyses conversion of methylmalonyl- CoA into succinyl- CoA (***methylmalonic aciduria*** occurs in vit B12 deficiency)
- **Deficiency:**
  - Caused by malabsorption (enteritis, sprue, D.latum), lack of intrinsic factor (pernicious anemia, gastric bypass surgery/gastrectomy) or absence of terminal ileum (Crohn's disease) or ***veganism***.
  - Use ***Schilling's test*** to detect etiology of deficiency
  - ***Macrocytic, megaloblastic*** anemia, ***hypersegmented*** neutrophils, Neurological symptoms (***subacute combined degeneration*** - degeneration of dorsal columns, lateral corticospinal and spinocerebellar tracts due to abnormal myelin; optic neuropathy; paresthesia); glossitis

- **Labs:** ↑ serum homocysteine (risk of acute coronary syndrome) and ↑methylmalonic acid with secondary folate deficiency.
- In vit B12 deficiency, the conversion of N5 Methyl Tetra Hydro Folic Acid (THFA) to free THF is blocked. Most of the body folate is irreversibly trapped as N5 Methyl THFA- "***folate trap***" → folate deficiency. THUS a B12 deficiency can lead to folate deficiency.
- ***Imerslund-Grasbeck*** syndrome = Selective vitamin B12 malabsorption with Proteinuria, AR disorder that appears in childhood with failure to thrive and grow and all above features of vit B12 deficiency

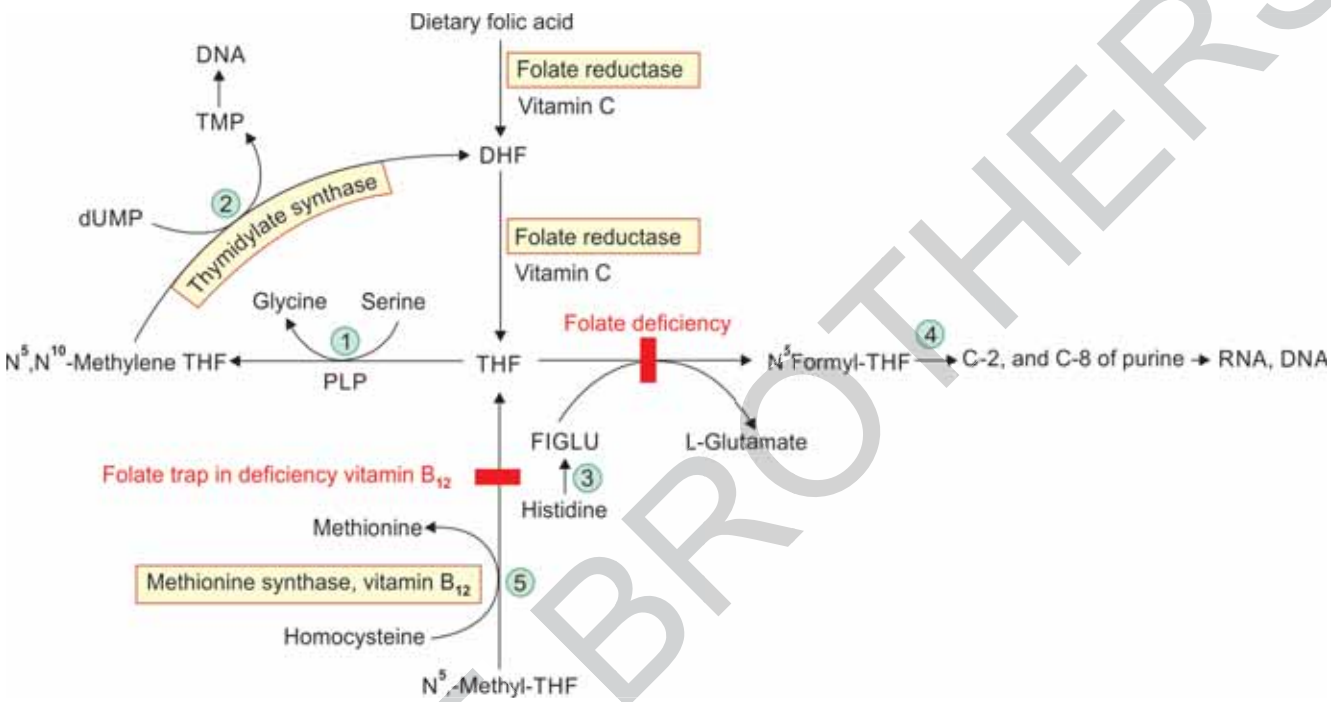

Fig. 4.5: Folate trap

1.10 Vitamin C (Ascorbic Acid)

- **Sources**: *Citrus fruits and vegetables.*
  - Maximum amount of vitamin ***C*** is found in adrenal ***C***ortex and aqeuous humor (20 times that of plasma)
  - Vitamin C cannot be synthesized in humans due to lack of enzyme L-gulonolactone oxidase
- **Function**
  - ***Antioxidant*** (free radical scavenger)
  - Facilitates ***iron absorption*** by keeping iron in Ferrous (Fe^{2+}) state
  - ***Cofactor*** for hydroxylation of proline and lysine in collagen synthesis - important in wound healing
  - ***Cofactor*** for dopamine beta-hydroxylase which converts dopamine to norepinephrine
  - Prophylactic against neurolathyrism
  - Vit C aids cellular respiration by acting as hydrogen transporter ("***respiratory catalyst***").
- **Deficiency**: ***Scurvy*** – easy bruising, swollen gums, poor wound healing, anemia, ***corkscrew*** hairs, ***perifollicular*** and subperiosteal hemorrhages, ***hemarthroses***.
- **Toxicity**: Calcium ***oxalate kidney stones***; can ↑ iron absorption and cause ***iron toxicity***, worsen hemochromatosis and transfusion associated iron overload.

1.11 Vitamin D

- **Sources**:
  - ***Vit D2*** = ***ergocalciferol*** - from ingestion of plants, fungi and yeasts
  - ***Vit D3*** = ***cholecalciferol*** - formed in keratinocytes/ stratum basale in sun exposed skin; ingestion of milk, fish, plants.
  - Both D2 nd D3 are converted to 25-OH D3 (storage form) in the liver and to the active form 1,25 $(OH)_2$D3 (***calcitriol***) in the kidney.
- **Function**: Vit D ↑ ***intestinal absorption*** of ***calcium*** and ***phosphate***; ↑ bone mineralisation at low levels and ↑ bone resorption at toxic levels.
- **Deficiency**: ***Rickets*** in children; ***Osteomalacia*** in adults. Caused by poor sun exposure, poor diet, chronic kidney disease and liver disease (see Page 1039).

- **Toxicity**: *Hypercalcemia, hypercalciuria*, loss of appetite, stupor. Seen in ***sarcoidosis*** where the epithelioid macrophages convert vitamin D to its active form.

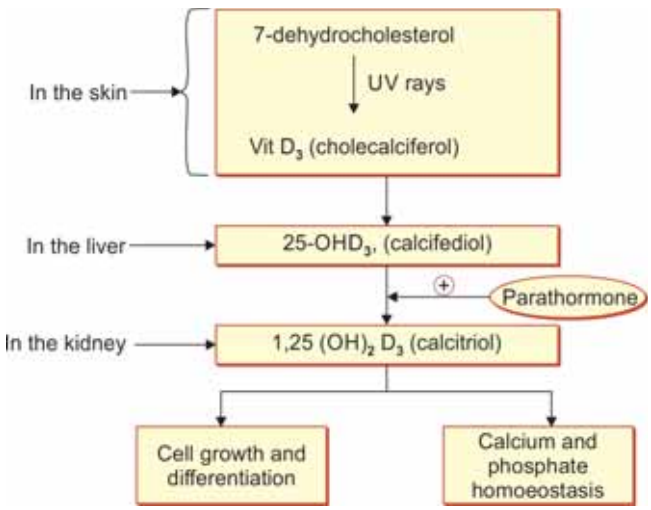

Fig. 4.6: Vitamin D

1.12 Vitamin A

- Source: The major forms of vitamin A are ***retinol, retinal*** and ***retinoic acid***; all are found in animal foods (milk, cheese, butter, eggs, liver and fish oils). ***Beta-carotene*** (Provitamin A) is found in green leafy vegetables (spinach), red, and orange fruits (carrots, tomatoes, mango, papaya) - converted in the small intestine to ***retinol***.
- **Function**: Retinal combines with light sensitive protein 'opsin' to form ***rhodopsin*** (visual purple); ***antioxidant***; helps differentiation of epithelial cells into specialised tissue (mucus secreting cells); ***prevents*** squamous metaplasia
- **Deficiency**: Night blindness (***nyctalopia***), squamous metaplasia of conjunctival epithelium (***Bitot's*** spots); dry eyes (***xerophthalmia***); corneal degeneration (***keratomalacia***); dry skin (xerosis cutis); follicular hyperkeratosis (***phrynoderma***): immunosuppression.

Fig. 4.7: Phrynoderma

Fig. 4.8: Bitot's spot

Fig. 4.9: Keratomalacia

1.13 Vitamin E (Tocopherol)

- **Source**: Vegetable oils and seeds, almonds, nuts, spinach
- **Function**: Antioxidant; Prevents rancidity of fats; Helps body to use vitamin K.
- **Deficiency**: ↑ fragility of erythrocytes - ***hemolytic anemia*** (Vitamin ***E*** affects ***E***rythrocytes!); ***acanthocytosis; myopathy, demyelination*** of posterior columns (↓ proprioception and vibration sensation) and spinocerebellar tract (ataxia).
- **Toxicity**: ***E***nterocolitis in infants; altered metabolism of vitamin K with increased anticoagulant effects of warfarin.

1.14 Vitamin K

- **Forms** of vitamin K : Vitamin ***K1*** - phylloquinone (found in plants); Vitamin ***K2*** - menaquinone (synthesised by intestinal bacteria); synthetic Vitamin ***K3*** - menadione
- **Sources** Green vegetables, dairy products
- **Function**: Activated by ***epoxide reductase*** to the reduced form which catalyzes gamma-carboxylation of glutamic acid residues on various proteins concerned with blood clotting; ***Vitamin K dependent clotting factors*** are 2,7,9,10 and protein C and S; Warfarin and dicoumarin are vitamin K antagonist
- **Deficiency**: ***Neonatal hemorrhage*** with ↑ PT and ↑ aPTT but ***normal*** bleeding time (Because neonates have sterile intestines and are unable to synthesize vitamin K, they are given vitamin K injection at birth to prevent hemorrhagic disease of newborn); vitamin K deficiency can occur after ***prolonged use*** of broad spectrum antibiotics.

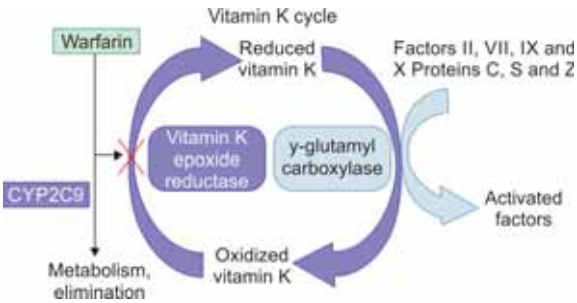

Fig. 4.10: Vitamin K cycle

1.15 One-Liners

- ***Sulfur*** containing vitamins: ***B1***, ***B7***.
- ***Hematopoietic vitamins***: ***B9, B12***
- ***Aneurin***- B1; ***Hormonal*** vitamin - Vitamin D; ***Anti sterility vitamin*** in animals - vitamin E

2.0 TRACE ELEMENTS

2.1 Copper

- **Source:** Shellfish, liver, nuts, legumes, bran, and organ meats
- **Function:** Copper is a constituent of
  - ***Lysyl oxidase*** (collagen cross linking)
  - ***Superoxide dismutase*** (antioxidant - scavenging of superoxide radicals)
  - ***Ferroxidase*** (oxidation of $Fe^{2+} \rightarrow Fe^{3+}$);
  - ***Ceruloplasmin*** (copper transport protein)
  - ***Dopamine hydroxylase*** and ***tyrosinase*** (melanin synthesis)
  - ***Cytochrome oxidase*** (respiratory chain)
- **Deficiency:**
  - *Microcytic anemia, neutropenia* growth retardation, defective keratinization and hypo pigmentation of hair, hypothermia, degenerative changes in aortic elastin, osteopenia, mental deterioration
  - ***Menkes disease***: ***XLR***; connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein (ATP7A). Leads to decreased activity of lysyl oxidase → defective collagen cross linking. Results in brittle 'kinky' hair, growth retardation and hypotonia.

2.2 Zinc

- **Source**: Mainly ***meat***; poor in vegetables
- **Function**: Zinc is a cofactor for enzymes in DNA, RNA and protein synthesis. It is essential for activity of ***>200 enzymes*** (ex: **Al**cohol dehydrogenase, **Al**kaline phosphatase, **AL**A dehydratase, Carbonic anhydrase, Lactate dehydrogenase). Important for formation of ***zinc finger*** motif (transcription factor).
- **Deficiency:** Growth retardation, failure to thrive, gonadal atrophy, congenital malformations, loss of appetite, ↓taste and smell, acrodermatitis enteropathica (alopecia, dermatitis and diarrhea), immune dysfunction, delayed wound healing. Predisposes to alcoholic cirrhosis.
- **Toxicity:** Reduced copper absorption, Occupational exposure → respiratory distress, pulmonary fibrosis

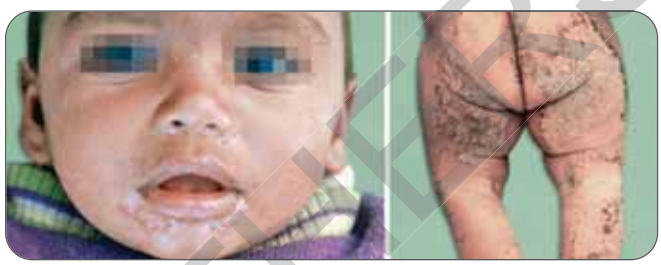

Fig. 4.11: Acrodermatitis enteropathica

2.3 Selenium

- **Function**: Selenium (as selenocysteine) is a component of ***glutathione peroxidase*** (antioxidant), ***deiodinase*** (thyroxine → triiodothyronine) and ***thioredoxin reductase*** (regulates intracellular redox homeostasis).
- **Deficiency**: ***Cardiomyopathy*** (***Keshan disease*** endemic in children, young women in parts of China), heart failure, striated muscle degeneration, ***Kashin Beck disease*** (endemic osteochondropathy in Tibet).
- **Toxicity**: Alopecia, nausea/vomiting, abnormal nails, peripheral neuropathy, ***garlic*** odor to breath, dermatitis; Occupational (lung and nasal carcinomas, liver necrosis, pulmonary inflammation)

2.4 Fluorine

- **Function**: Prevents dental caries; builds strong teeth and bones
- **Deficiency**: Dental ***caries***
- **Toxicity**: ***Dental fluorosis*** (discoloration, cracking, pitting and chipping of teeth) and ***skeletal fluorosis*** (renal tubular damage, paresthesias, interosseous membrane calcification), osteosclerosis

Fig. 4.12: Dental fluorosis

2.5 Iron

- **Source**: Meat, eggs, green leafy vegetables, jaggery, nuts
- **Function**: Component of hemoglobin, myoglobin, cyctochrome C and many enzymes.
- **Deficiency**: ***koilonychia***, ***pica, microcytic hypochromic anemia***, ↓ work performance, impaired cognitive development, premature labor, ↑ perinatal maternal mortality
- **Toxicity**: Gastrointestinal effects (nausea, vomiting, diarrhea, constipation), iron overload with organ damage, acute systemic toxicity.

2.6 Metals as Prosthetic Groups for Enzymes

- ***Manganese***: Enolase, Arginase
- ***Molybdenum***: Xanthine oxidase, sulfite oxidase
- ***Magnesium***: Enolase, Glucose 6 phosphatase; also Mg is a cofactor in enzymes of DNA, RNA synthesis and ATP metabolism.

3.0 ENZYMES

- ***Enzymes*** are proteins that acts as catalyst in biochemical reactions.
- ***Simple*** enzyme = Proteins; ***Complex*** enzyme = Proteins part (apoenzyme) + Non-protein part (Coenzyme or Cofactor/Prosthetic group).
- ***Coenzymes*** are organic molecules whereas ***Cofactors/Prosthetic*** groups are inorganic metals.

Examples of Common Coenzymes

Enzyme	Coenzyme
Transaminase, Decarboxylase	PyridoxaL Phosphate, PLP (Vit B6)
Transketolase	Thiamine PyroPhosphate, TPP (Vit B1)
Carboxylase	Biotin (Vit B7)
Kinases	ATP/GTP
Dehydrogenases	NAD+/FAD

3.1 Enzyme Terminology

Enzyme Class	Description
Dehydrogenases	Oxido-reductases; Catalyses oxidation-reduction reactions (ex: pyruvate dehydrogenase)
Carboxylase	Transfers CO_2 groups with the help of biotin (ex: pyruvate carboxylase)

Contd…

Contd…

Enzyme Class	Description
Kinase	Catalyses transfer of phosphate group from a high energy molecule (ATP) to a substrate - ***substrate level phosphorylation*** (ex: glucokinase, hexokinase, phosphofructokinase)
Mutase	Relocates a functional group within a molecule (ex: Methyl malonyl CoA mutase - vitamin B12 dependent)
Hydroxylase	Adds hydroxyl group (-OH) onto substrate (ex: tyrosine hydroxylase)
Phosphorylase	Adds inorganic phosphate onto substrate without using ATP (ex: glycogen phosphorylases)
Phosphatases	Removes phosphate group from a substrate (Fructose 1-6 bisphosphatase)

Enzyme Kinetics

- Increasing ***temperature increases*** velocity of reaction; ***Bell-shaped*** curve is obtained by plotting temperature against velocity of reaction; Highest activity of enzyme is at the ***optimum temperature*** (between 35-40 = 37 deg C)
- Temperature coefficient, ***(Q10)*** is the factor by which the velocity of a reaction increases for a 10 deg C rise in temperature. Most biological processes typically double for a 10 degrees rise in temperature - i.e, ***Q10 = 2***.
- Optimal activity of most intracellular enzymes occurs at ***pH 5-9***. ***Bell***-shaped curve is obtained by plotting enzyme activity and pH (hydrogen ion concentration).

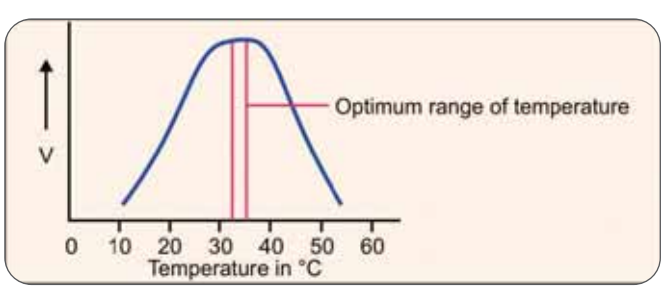

Fig. 4.13: Effect of temperature on velocity

3.2 Michaelis-Menten Equation

- For a fixed enzyme concentration, ***velocity of reaction (V)*** is directly proportional to the ***substrate concentration (S)*** up to certain concentration of substrate - '***saturation point***'; after this further increase in substrate concentration does NOT increase the enzyme activity. The velocity of reaction at this stage is called maximum velocity (V_{max}).

- ***Michaelis constant (K_m)*** is defined as the substrate concentration required to produce half maximum velocity of reaction (***1/2 V_{max}***) .
- Characteristics of ***K_m*** are:
  - K_m is ***independent*** of enzyme concentration;
  - K_m is ***unique*** for each enzyme substrate pair - hence called signature of enzyme K_m is ***constant*** for an enzyme
  - K_m is ***inversely proportional*** to ***affinity*** of enzyme for the substrate - lower the K_m, higher will be the affinity for the substrate and vice versa.
- Most enzymatic reaction follow Michelis Menten kinetics (***hyperbolic*** curve); BUT enzymatic reactions that exhibit a sigmoid curve show cooperative kinetics (hemoglobin).

3.3 Lineweaver-Burk-Plot

- A graphical plot of 1/S on X-axis and 1/V on Y-axis; hence a.k.a '***double reciprocal*** plot'.
- In the graph - the closer to 0 on the X axis, the higher the Km; the closer to 0 on the Y axis, the higher the V_{max}

3.4 Enzyme Inhibition

Competitive Inhibition	Non-Competitive Inhibition
Inhibitor will resemble substrate (structural analog)	Inhibitor is an unrelated molecule
Reversible	Irreversible
Excess substrate abolishes inhibition	Excess substrate DO NOT abolish inhibition
K_m increases (***"Kom***petitive ***in***hibitors ***in***crease ***K_m***")	K_m remains the same
V_{max} remains the ***same***	V_{max} decreases
↓ ***efficacy***	↓ potency
Ex: Mostly ***drugs*** (Statins - HMG CoA reductase; Warfarin - Vit K Epoxide reductase; Digoxin - Na-K ATPase etc.)	Ex: Mostly ***poisons*** (cyanide - cytochrome xidase, fluoride - enolase etc.)

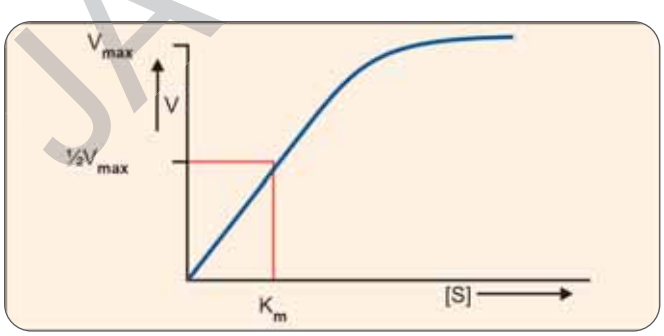

Fig. 4.14: Effect of substrate concentration (substrate saturation curve)

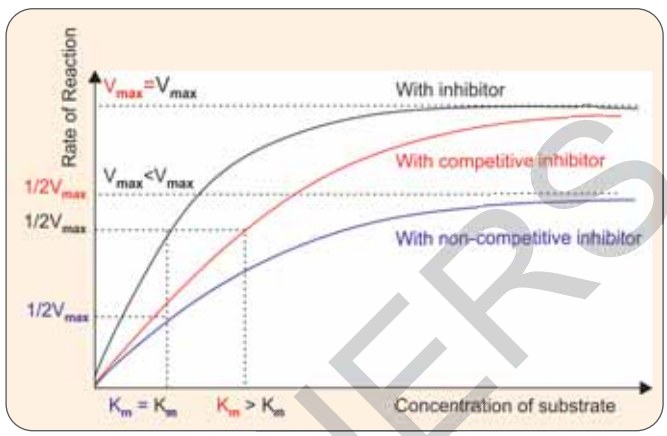

Fig. 4.15: Competitive Vs non-competitive inhibition

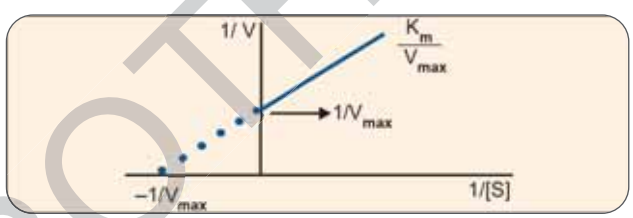

Fig. 4.16: Lineweaver-Burk plot

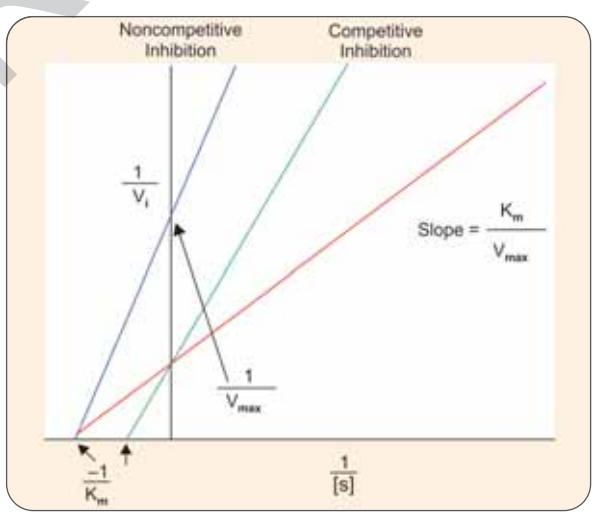

Fig. 4.17: Competitive Vs non-competitive inhibition

- **Suicide inhibition**: Special type of ***irreversible*** inhibition wherein the inhibitor makes use of the enzymes own reaction mechanism to inactivate it (***mechanism based*** inactivation); examples: Allopurinol inhibits xanthine oxidase; Aspirin inhibits cyclooxygenase.
- **Feedback Inhibition:** Activity of the enzyme is inhibited by the final product of the biosynthetic pathway (***feedback/end-product inhibition***); examples: Inhibition of delta-ALA synthetase by the end product heme, Inhibition of aspartate transcarbamoylase by CTP.

CLINICAL CORRELATION

- Enzymes used for ***diagnosis***: Reverse transcriptase for polymerase chain reaction; alkaline phosphatase/horseradish peroxidase in ELISA; hexokinase for glucose estimation etc.
- Enzymes used for ***therapy***: Streptokinase/urokinase for intravascular clot lysis; Alpha-1-Antitrypsin for emphysema; Asparaginase for ALL etc.

4.0 AMINO ACIDS

4.1 Basics of Amino Acids

20 amino acids (AAs) are involved in the formation of human proteins.

Each AA has an ***amino*** group (-NH2) and a ***carboxyl*** group (-COOH) attached to the ***alpha carbon*** atom (αCH - "CHiral" carbon atom) and a variable ***side chain*** (R).

Chirality means that AA (*except* ***glycine***) can exist as two stereo-isomers (enantiomers) named D and L. - All AAs found in proteins are of ***L***-configuration.

Amino acids are dipolar ions with a positive charge at one end and a negative charge at other end of the molecule. The pH at which amino acid becomes ***zwitter ion***, i.e bears no net charge and thus does not migrate to anode or cathode is called ***isoelectric pH***.

CLINICAL CORRELATION

- ***Polar AA*** (being hydrophilic - form hydrogen bonds with water) are distributed on the ***surface*** of the protein whereas non-polar AA being hydrophobic (lipophilic) are distributed within the protein. Thus in transmembrane proteins, nonpolar AA are embedded in the lipid bilayer while polar AA are present outside or inside the membrane.

4.2 Classification of Amino Acids

Semi Essential AA's : ***A***rginine (Arg); ***H***istidine (His)

Essential AA's: ***I***soleucine (Ile); ***L***eucine (Leu); ***T***ryptophan (Try); ***L***ysine (Lys); ***M***ethionine (Met); ***P***henylalanine (Phe); ***T***hreonine (Thr); ***V***aline (Val). Mnemonic: (***A***ny ***H***elp ***I***n ***L***earning ***T***hese ***L***ittle ***M***olecules ***P***roves ***T***ruly ***V***aluable!)

Ketogenic AA's: ***Leu*** (purely ketogenic), Lys

Glucogenic AA's: Met, Val, Ala, Arg, Asparagine Aspartate, Cysteine, Glutathione, glutamic acid, Gly, His, Proline, Serine, Thr,

Glucogenic/Ketogenic Aa's: Phe, Ile, Tyr, Thr

Acidic AA's: Aspartic *acid* (*lowest* isoelectric point); Glutamic *acid*

Basic AA's: ***His, Lys, Ar***g (most basic, *highest* isoelectric point) - (***His*** Lies/***Lys Ar***e **Basic**")

Sulfur containing AA's: ***Me***thionine, ***Cy***steine, ***Cy***stine ("**Sulfur** is ***MeCCy***")

Aromatic AA's: ***His***tidine, ***Phe***nylalanine, ***T***yrosine, ***T***ryptophan (***His PheTT*** (feet!) have ***aroma***); aromatic AAs absorb high wavelength (280 nm, 250-290 nm) UV light. Tryptophan has the highest absorption maximum.

Imino acid: ***Pro***line - here nitrogen of amino group is not free, has NH instead of NH2 (***I'm Pro***)

21st AA - Selenocysteine; coded by ***UGA*** ("***U G***o ***A***way at **21**")

22nd AA - Pyrrlolysine; coded by ***UAG*** - stop codon ("***U A***re ***G***one at **22**")

4.3 Amino Acid Derivatives

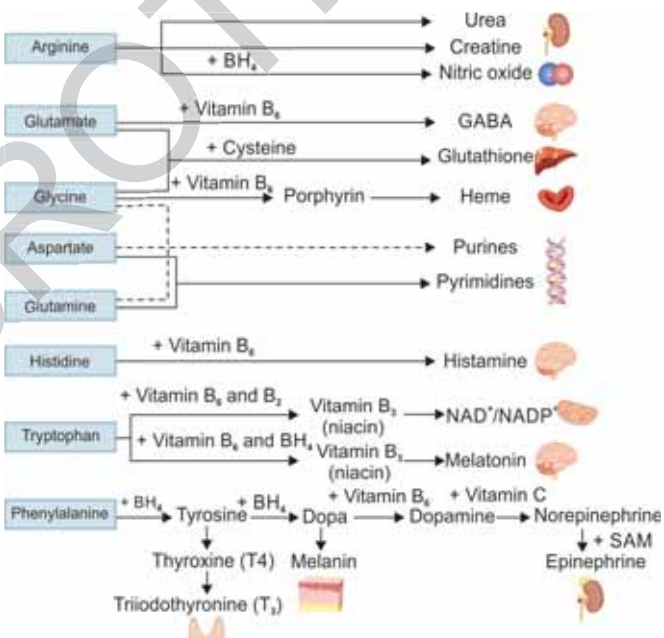

Fig. 4.18: Amino acid derivatives

4.4 Important AA One Liners

Glycine + **A**rginine + **ME**thionine = Creatinine (**GAME**).

Arg and His are required during periods of ***growth***.

Glutamic acid is ***most abundant AA*** in the body

Cysteine, taurine ↓ aging; Homocysteine ↑ aging.

Enzymes with ***tetrahydrobiopterin (BH4) as coenzyme*** are: phenylalanine hydroxylase ; tyrosine hydroxylase; tryptophan hydroxylase ; Nitric Oxide synthase

Major end product of epinephrine, norepinephrine = ***vanillyl mandelic acid***.

Major end product of dopamine = ***Homovanillic*** acid.

- ***Xanthoproteic*** Test: Concentrated nitric acid + aromatic AA = yellow color (picric acid).
- **3**yp**TO**phan- B**3** (Niacin), sero**TO**nin, mela**TO**nin.

4.5 Urea Cycle

- Amino acid catabolism results in release of excess nitrogen in the form of ***ammonia*** → detoxified in the ***liver*** to form ***urea*** (urea cycle) → excreted by the ***kidneys*** via urine.
- ***Transamination*** occurs in ***all tissues***; ***PLP*** is coenzyme; NO free ammonia is liberated.
- ***Oxidative deamination*** occurs in the ***liver*** liberating ***free ammonia***.
- Free ammonia generated all over the body has to be detoxified (since it is toxic to brain) in the liver via the urea cycle. ***Transport of ammonia*** from most of the tissues including brain is in the form of ***glutamine*** (except from skeletal muscle is in the form of ***alanine***)
- Urea cycle - ***first 2*** reactions occur in ***mitochondria*** and the ***next 3*** reactions in ***cytoplasm*** of ***liver*** cells. Carbamoyl phosphate synthetase -1 (***CPS-1***) is the ***rate limiting step***.
- ***Urea bicycle***: Urea is linked to TCA cycle through fumarate and aspartate - hence called urea bicycle

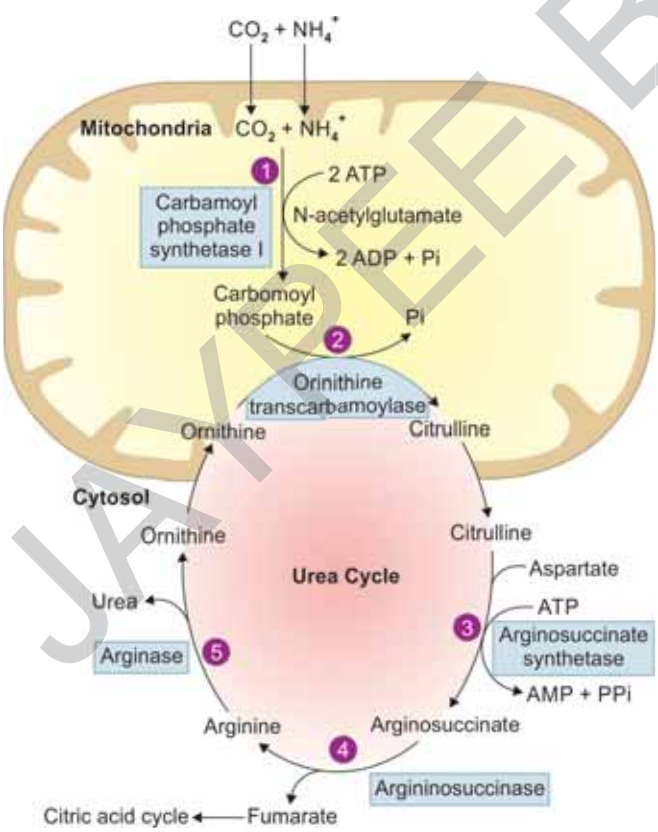

Fig. 4.19: Urea cycle

CLINICAL CORRELATION

- ***Urea Cycle Disorders***: All urea cycle disorders are characterized by: ***Hyperammonemia***; ***Encephalopathy*** (flapping tremor/ asterixis, slurred speech, drowsiness, vomiting, cerebral edema, blurred vision), ***respiratory alkalosis***, ↑ ***glutamine*** and ↓ ***BUN***.
- Treatment:
  - ***Low protein*** diet
  - ***Arginine*** supplementation (provides ornithine)
  - Measures to ↓ ammonia levels
    - ***Lactulose*** to acidify GI tract and trap NH_4^+ for excretion
    - ***Antibiotics*** (rifamixin, neomycin) to ↓ ammoniagenic bacteria
    - ***Nitrogen scavengers***: benzoate, phenylacetate, phenylbutyrate divert nitrogen away from the urea cycle by promoting the synthesis of nitrogen-rich metabolites which are excreted at high rates in the urine
- Individual enzyme deficiencies and diseases are mentioned in table below:

Disease	Enzyme/Transporter affected	Features
Hyperammonemia type 1	Carbamoyl phosphate synthetase -1 (CPS-1)	*Mental retardation*
Hyperammonemia type 2	Ornithine transcarbamoylase (OTC)	***MC*** and ***only X linked*** urea cycle disorder (all others are ***AR***); ***Orotic aciduria*** - ***pink*** *urine stones* (due to channeling of carbamoyl phosphate into pyrimidine synthesis)
Citrullinemia type 1 (classic)	Argininosuccinate synthetase	
Citrullinemia type 2	Citrin (aspartate glutamate ***carrier protein***) defect	Chromosome ***7q***
Argininosuccinic aciduria	Argininosuccinate lyase	***Trichorrhexis nodosa*** (dry and brittle hair)
Hyper - argininemia	Arginase	Causes ***least*** hyperammonemia; progressive ***spastic diplegia*** may occur
Hyper-ornithenemia	Ornithine Permease; Ornithine Transporter protein - ***ORNT***-1 gene defect	Failure to import ornithine from cytoplasm to mitochondria; ***H***yperornithinemia-***H***yperammonemia-***H***omocitrullinuria (***HHH*** *syndrome*)

4.6 Disorders of Phenylalanine Metabolism

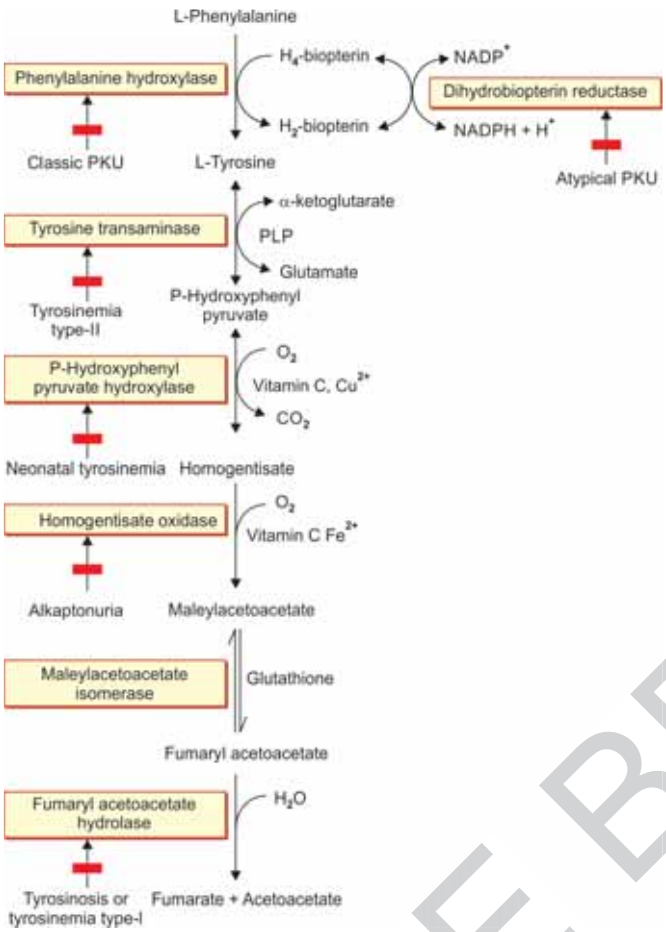

Fig. 4.20: Phenylalanine/tyrosine metabolism

4.7 Phenylketonuria (PKU)

- ***MC*** disorder of AA metabolism; ***AR***, Chromosome ***12q***.
  - ***Classic*** PKU: ***Phenylalanine hydroxylase*** (***PAH***) deficiency
  - ***Atypical*** PKU: ***Dihydrobiopterin reductase*** or tetrahydropterin , ***BH4*** (cofactor for PAH) deficiency
- **Mechanism**: In PKU there is inability of oxidation of Phe into Tyr → ↑ ***Phe*** and ↑ ***Tyr*** in blood (hyperphenylalaninemia) → metabolized to ***phenylketones*** (*phenylacetate, phenylpyruvate, phenyllactate*) → excreted in urine.
- **Clinically**:
  - Infant is ***normal at birth***. If untreated symptoms appear within first 10 days of life; Profound ***mental retardation***; ***Growth retardation***; ***Fair hair and fair skin*** (Phe is a competitive inhibitor of tyrosinase - so no melanin in skin!!), ***Eczema***, ***Microcephaly***, *hyperactivity, seizures , intractable vomiting.*
  - ***Musty or Mousy odor*** of skin, hair and urine (due to phenylacetic acid)
  - ***Phenylalanine embryopathy*** - ↑ ***Phe*** in pregnant patients with untreated PKU - fetal IUGR, microcephaly, mental retardation, congenital heart defects in the baby.
- **Screening Tests**
  - ***Tandem mass spectrometry*** - IOC now (detects Phe in serum)
  - Earlier tests: ***Guthrie's*** test (detects Phe in serum using Bacillus subtilis) and ***Ferric chloride*** test (Phe in urine gives green color with FeCl3)
- **Treatment:**
  - ***Low Phe*** (cassava based) and ***high Tyr*** diet (soy products, chicken, fish, milk)
  - Supplementation of ***large neutral amino acids*** including Tyr
  - Synthetic form of ***BH4 - Sapropterin*** dihydrochloride.
  - ***Pegvaliase*** (Peglated phenylalanine ammonia lyase)- substitute for PAH enzyme.
  - ***Avoid aspartame*** (artificial sweetener) - contains Phe

4.8 Disorders of Tyrosine Metabolism

Disease	Enzyme-deficient	Comments
Type 1 Tyrosinemia (Hepatorenal)	Fumaryl acetoacetate	▪ "Boiled Cabbage" odour; liver failure, cirrhosis, peripheral neuropathy, Fanconi syndrome ▪ Treatment: Nitisinone; Tyr and Phe restricted diet
Type 2 (Two) Tyrosinemia (Oculo-cutaneous)	Tyrosine Transaminase	▪ Palmoplantar keratosis, painful corneal erosions with photophobia, mental retardation. Dietary protein restriction advised
Type 3 (neonatal) Tyrosinemia	Para hydroxy phenyl pyruvic acid (p-HPPA)	▪ Normal skin and liver, ataxia rarely ▪ Dietary protein restriction + ascorbic acid advised
Hawkinsinuria	P-HPPA	▪ "Swimming Pool odor"; ▪ Transient failure to thrive, metabolic acidosis in infancy
Alkaptonuria	Homogentisic acid oxidase	▪ Discussed separately below
Albinism (oculocutaneous)	Tyrosinase	▪ Hypopigmentation of hair, skin and retina; photophobia; visual loss

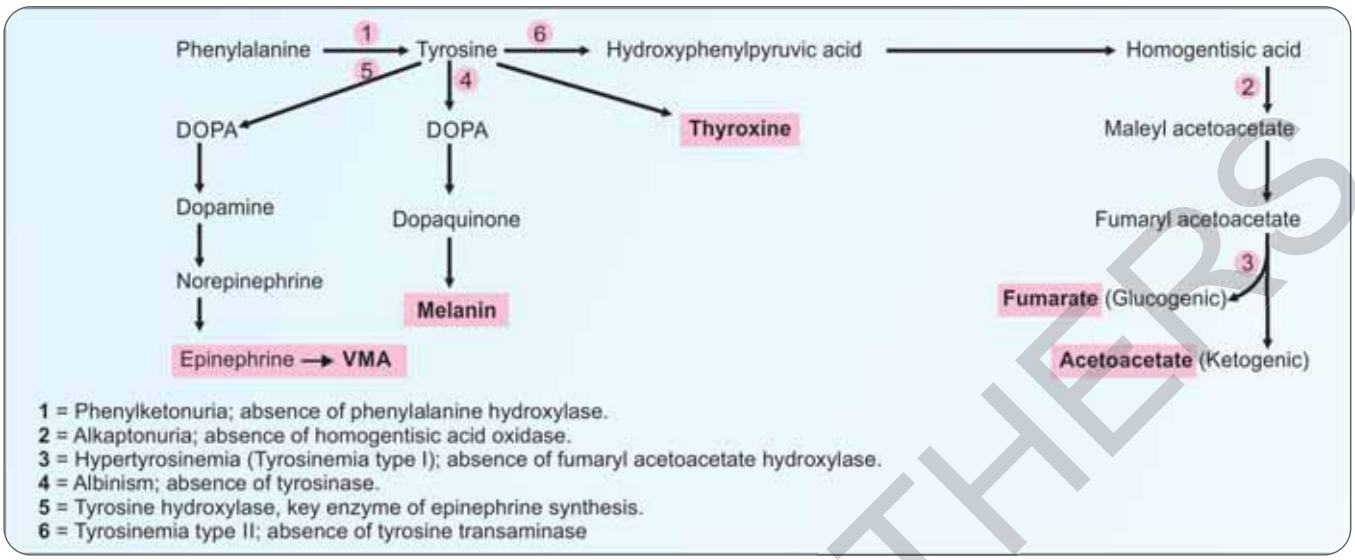

Fig. 4.21: Summary of tyrosine metabolism

4.9 Alkaptonuria

- ***AR***; Deficiency of ***homogentisic acid oxidase*** (homogentisate dioxygenase) in the degradative pathway of tyrosine to fumarate → pigment forming homogentisic acid builds up in tissues → ***bluish black cartilage*** of nose and pinna, sclera and connective tissues (***Ochronosis***)
- Alkapton bodies cause ***urine to turn black*** on standing
- May have debilitating arthralgias; ***intervertebral disc calcification*** in lumbar area (X-ray spine - Parrot beak appearance).

Fig. 4.22: Sclera, pinna and hands affected in Alkpatonuri

4.10 Homocystinuria

- ***AR*** disorder of ***methionine metabolism***
- Etiology: ***Cystathionine beta synthase*** deficiency; Methionine synthase deficiency; MTHFR deficiency.
- ***Tall*** stature (Marfanoid), Kyphosis, Mental retardation; Osteoporosis, InferoNasal lens subluxation (HomocystINuria); Atherosclerosis and ***thrombosis*** (stroke and MI, caution with Gen. Anesthesia); ***Hypopigmented*** skin
- ***Cyanide nitroprusside test*** detects ↑ homocysteine in urine
- Treatment: ***Pyridoxine (Vit B6)*** is the drug of choice (along with Vit B12 and folate in diet); supplement cysteine in diet.

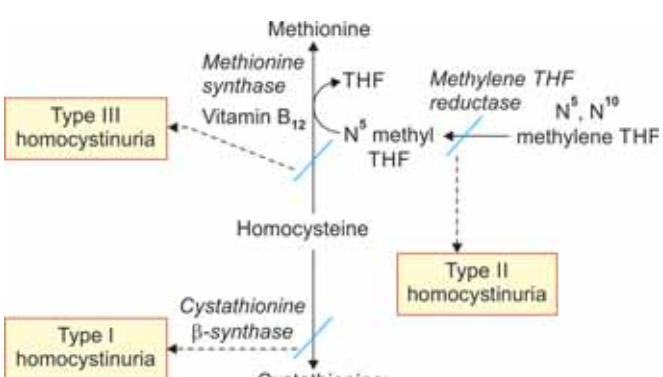

Fig. 4.23: Homocystinuria enzymes affected

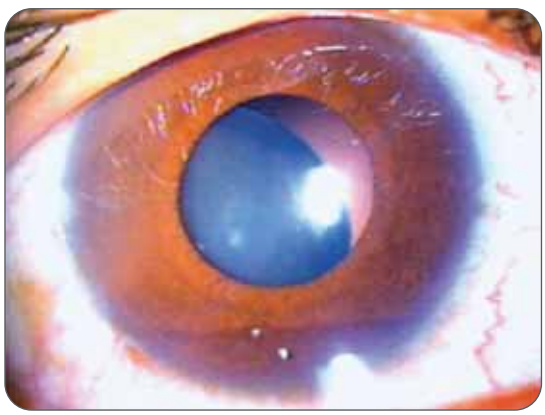

Fig. 4.24: Lens Subluxation in Homocystinuria

4.11 Cystinuria

- ***AR***, defect of dibasic amino acid ***transporter*** for ***C***ystine, ***O***rnithine, ***L***ysine and ***A***rginine (***COLA***) in the ***PCT*** of the kidneys.
- Excess cystine in urine causes ***hexagonal*** cystine kidney stones (radiopaque, relatively resistant to lithotripsy)
- ***Cyanide nitroprusside test*** also detects ↑ cystine in urine
- Treatment: ***Alkalinize urine*** (acetazolamide, potassium citrate); chelating agents (penicillamine).
- ***Garrod's tetrad***: ***Cys***tinuria; ***Al***binism; ***Al***kaptonuria; ***Pen***tosuria (***Garrod Cys*** (sees) ***All Pens***).
- Note: Cystinosis is ***NOT*** the same as Cystinuria.

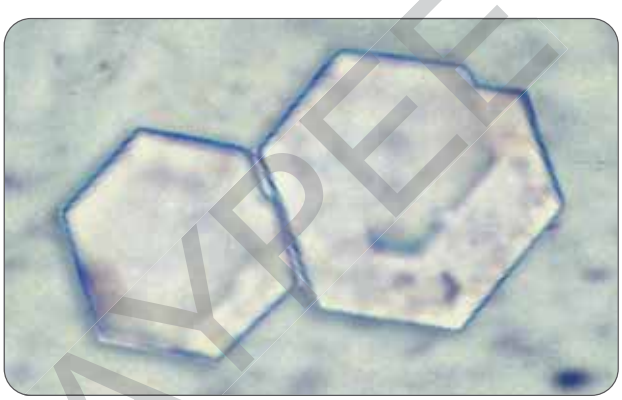

Fig. 4.25: Cystine hexagonal crystals in urine (**Six**tine)

4.12 Maple Syrup Urine Disease

- AR; deficiency of branched chain α-keto acid dehydrogenase (***BCKAD***) → defective oxidative decarboxylation of *branched chain amino acids* (***Leu, Ile*** and ***Val***) → their levels are ↑ in plasma and urine - Branched chain ketonuria.
- Clinically: Poor feeding, severe CNS defects, mental retardation and death.
- ***Burnt sugar/Maple syrup*** odor of urine
- Treatment: Restrict branched chain AA's; give high doses of ***thiamine (B1)***.

4.13 Isovaleric Acidemia

- Defect of metabolism of branched chain amino acids (Leu, Ile, Val)
- Due to Isovaleryl-CoA dehydrogenase deficiency
- Cheesy odor of breath and body fluids; "Sweaty feet" odor of urine
- Treat by administering ***glycine***.

4.14 Organic Acidemias

- ***Organic acidemias***, (a.k.a organic acidurias), are characterized by accumulation of abnormal (and usually toxic) organic acid metabolites and increased excretion of organic acids in urine.
- Presents in infancy with *poor feeding, vomiting, hypotonia, high anion gap metabolic acidosis (HAGMA), hepatomegaly, seizures, hyperammonemia.*
  1. **Propionic acidemia**: Deficiency of ***propionyl CoA carboxylase*** - ↑ propionyl CoA, ↓ methylmalonic acid.
  2. **Methylmalonic acidemia**: Deficiency of ***methylmalonyl -CoA mutase*** or ***Vit B12***.
- Treat by low protein diet limiting substances that can be metabolised to propionyl CoA (-***VOMIT*** - ***V***aline, ***O***dd chain fatty acids, ***M***ethionine, ***I***soleucine, ***T***hreonine).

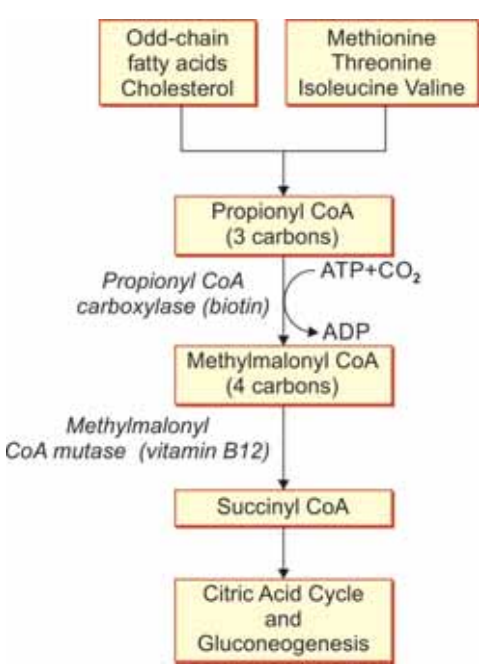

Fig. 4.26: Fate of propionyl CoA

4.15 Urine Odours in Diseases

Urine Odour	Disease
Phenylketonuria	Musty/Mousy
Maple syrup/Burnt sugar	Maple Syrup Urine Disease
Isovaleric acidemia, glutaric acidemia	Sweaty (Sveaty)feet
Tyrosinemia; Hypermethioninemia	Boiled Cabbage (rancid butter) Cab Tyres
Multiple CArboxylase deficiency	ToMCAt urine
Trimethylaminuria	Rotting fish
Hawkinsinuria	Swimming pool
Sulfurous	Cystinuria

4.16 Canavan Disease

- ***AR***; MC in Ashkenazi Jews.
- Deficiency of ***aspartoacylase*** leading to accumulation of of N-Acetyl Aspartic acid in brain and it's increased excretion in urine (CaNAAvan).
- MRI is diagnostic - white matter in ***subcortical U fibres*** mainly affected - leukodystrophy.
- Clinically, there is progression from lethargy and hypotonia, to megalencephaly and spasticity, blindness and death within 5 years.
- ***No*** treatment exists.

5.0 GLYCOGEN AND GLYCOGEN METABOLISM

- Glycogen is a α-***1,4*** glucose polymer with α-***1,6*** branches. It is the ***storage form of glucose***, and is found in abundance in the ***liver*** and ***muscle***.
- ***Liver glycogen*** can be ***released*** to maintain blood glucose levels, BUT muscle glycogen can only support muscle glycolysis to produce ATP for muscle contraction (because ***glucose 6-phosphatase*** is ***absent in muscles***).
- In an average 70 kg man: ***Liver*** glycogen = ***70 g***; ***Muscle*** glycogen = ***245 g***
- Enzyme common to glycogenesis and glycogenolysis is ***phosphoglucomutase.***

Glycogenesis	Glycogenolysis
Conversion of excess glucose to glycogen for storage	Degradation of stored glycogen
Promoted by glycogen synthase	Promoted by glycogen phosphorylase
Activated by insulin	Activated by glucagon (in liver), epinephrine (in liver and muscle), protein kinase A, cyclic AMP, Calcium
Inhibited by epinephrine (in liver and muscle), glucagon (in liver)	Inhibited by insulin

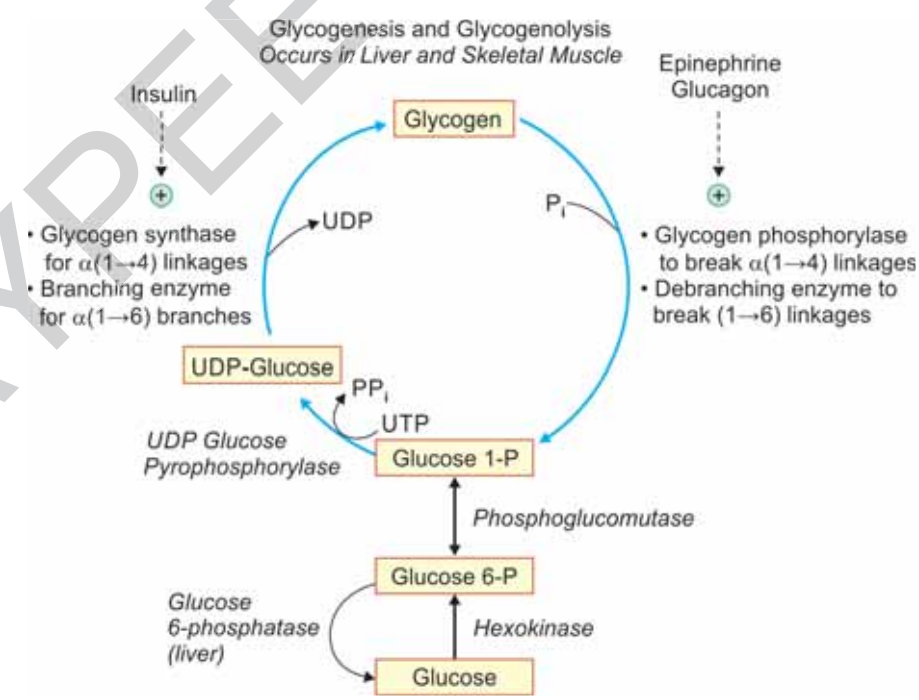

Fig. 4.27: Glycogenesis and glycogenolysis

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