NATIONAL UNIVERSITY OF PHARMACY

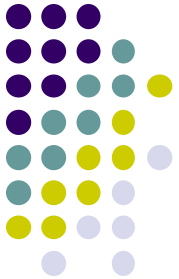
DEPARTMENT OF PATHOLOGICAL PHYSIOLOGY

Disturbances of protein metabolism

PLAN OF LECTURE

1. The concept of nitrogen balance, its violation.
2. Disturbance of digestion and absorption of proteins in the gastrointestinal tract.
3. Disturbance of synthesis and protein transformation.
4. Gout, definition, etiology, pathogenesis, clinical signs.

Questions of Independent work



1. Disturbance of acid-base equilibrium. The concept of acidosis and alkalosis: the causes, types, principles of correction.
2. Violation of phosphorus-calcium metabolism. Disturbance of microelement exchange.
3. The concept of basic and energy exchanges. Infringement of power supply of a cell: the reasons, consequences.
4. Hereditary disorders of protein and amino acid metabolism. Gout. Principles of correction.
5. Starvation: causes, types, consequences. The concept of curative starvation.

Suggested Reading

Basic

1. General and clinical pathophysioilogy/ Editer by Anatoliy V. Kubyshkin. – Vinnytsa : Nova Knyha Publishers, 2016. – 656 p.
2. Lecture notebook pathological physiology. Manual for working in lectures / N.M. Kononenko, S.I. Kryzhna, V.A. Volkovoy at al.; Kh.: NPhaU, 2013. – 99 p.
3. Pathological Physiology: The textbook for the students of higher pharmaceutical educational institutions and pharmaceutical faculties og higher medical educational institutions III-IV levels of accreditation / S/I/ Kryzhna, N.M. Kononenko, I.Yu. Tishenko et al.: under edition of the professor A.I. Bereznyakova. – Kharkiv: NphaU, 2006. – 416 p.

Auxiliary

1. Professional guide to Pathophysiology / M.H. Birney, C. L. Brady, K.T. Bruchak et al. – Lippincott Williams and Wilkins. – 2002. – 696 p.
2. Crowley L.V. An introduction to human disease: pathology and pathophysiology correlations / L.V. Crowley . – London : Lones and Bartlett Publishers International Bard House. 2001. – 790 p.

What is Protein➔

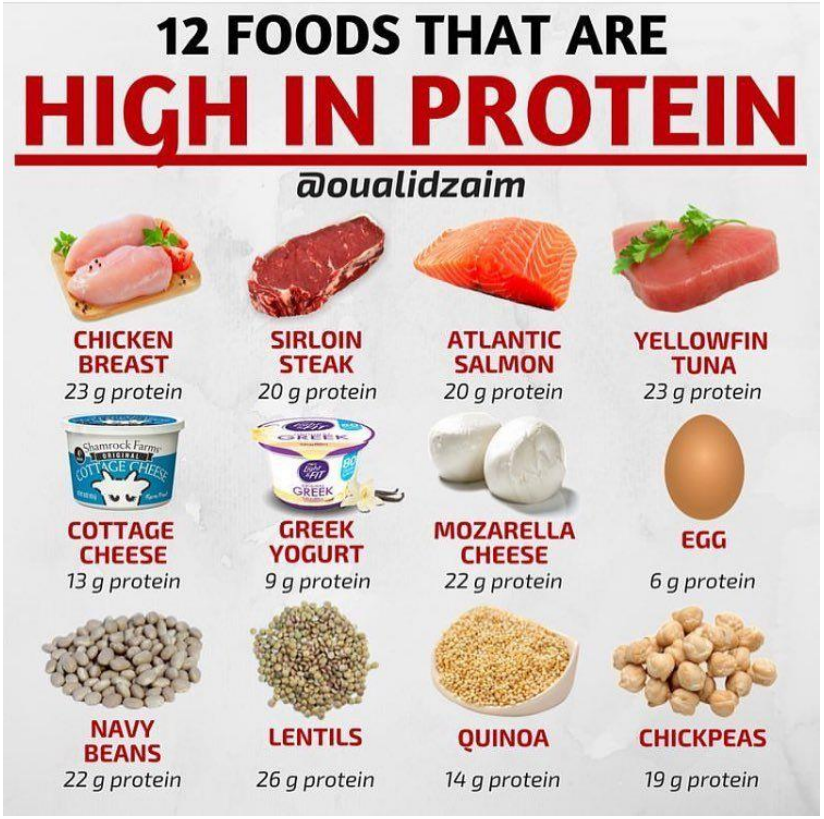
➔**Proteins** are large molecules consisting of amino acids which our bodies and the cells in our bodies need to function properly.

➔Our body structures, functions, the regulation of the body's cells, tissues and organs cannot exist without proteins.

➔Our muscles, skin, bones and many other parts of the body contain significant amounts of protein. Protein accounts for 20% of total body Weight.

- Proteins are organic compounds that are also known as polyamides. Poly means many and amides mean amino acids. In total, there are about 20 amino acids that undergo various combinations to make different proteins. Out of these 20, there are 9 essential amino acids that we require in our diet.

Essential	Conditionally Non-Essential	Non-Essential
Histidine	Arginine	Alanine
Isoleucine	Cystine	Asparagine
Leucine	Glutamine	Aspartate
Lysine	Glycine	Glutamate
Methionine	Proline	Serine
Phenylalanine	Tyrosine	
Threonine		
Tryptophan		
Valine		



PROTEINS: Types and Functions

actin & myosin

contractile

insulin

hormonal

immunoglobulin (antibody)

protection

rhodopsin

receptor

hemoglobin

transport

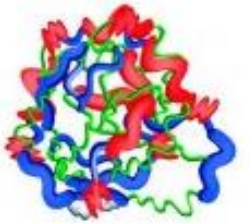
spider silk

structural

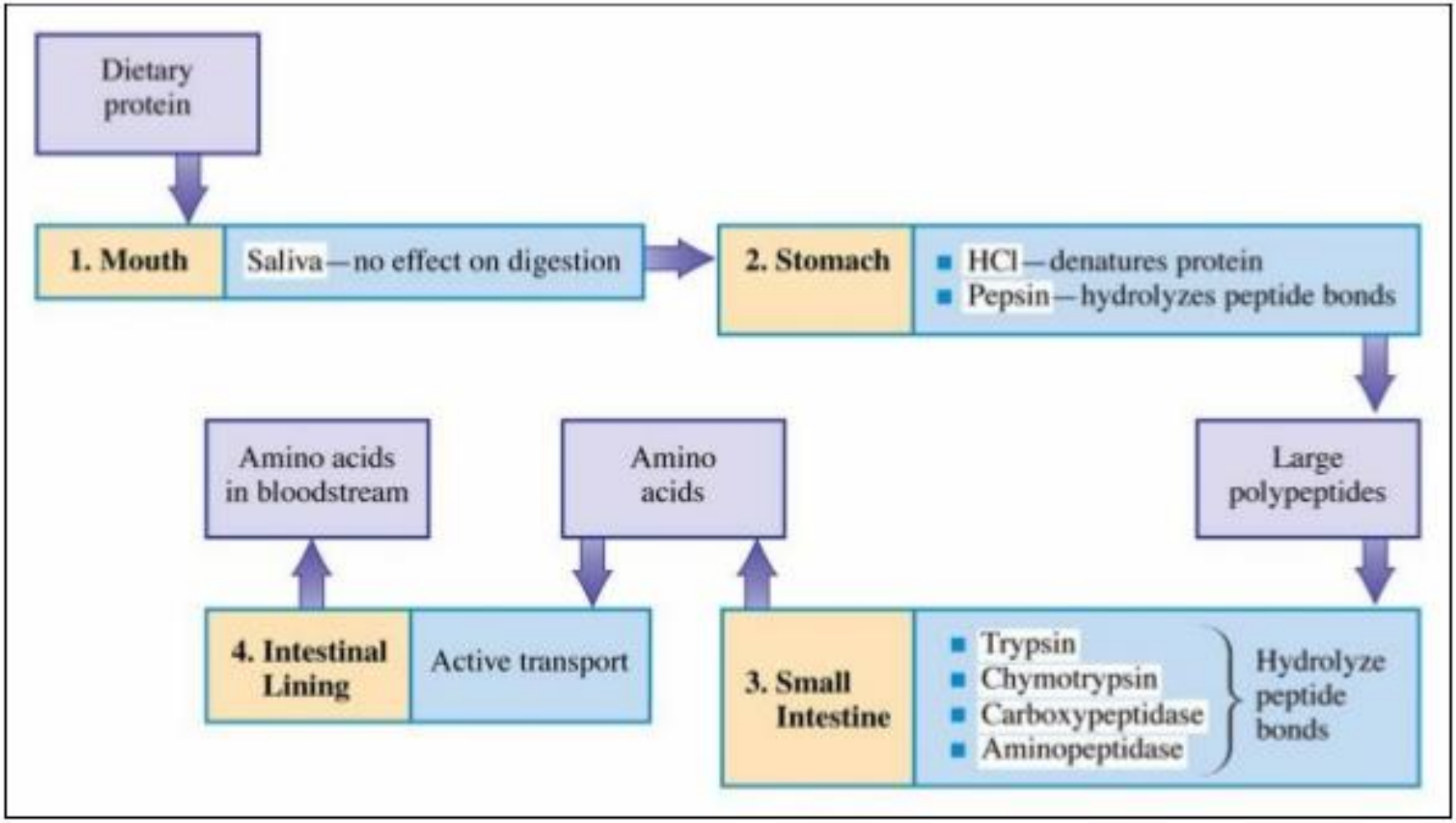
storage

ferritin

enzyme



Pepsin


Dietary protein
1. Mouth
Saliva—no effect on digestion
2. Stomach
HCl—denatures protein
Pepsin—hydrolyzes peptide bonds
Large polypeptides
3. Small Intestine
Trypsin
Chymotrypsin
Carboxypeptidase
Aminopeptidase
Hydrolyze peptide bonds
Amino acids
4. Intestinal Lining
Active transport
Amino acids in bloodstream

Protein metabolism

Protein digestion:

A) In stomach:

passage of food into stomach stimulates gastric mucosa to secret a polypeptide hormone called: Gastrin which has the following actions:

1- stimulate the chief cells of gastric mucosa to secret the inactive zymogen "pepsinogen"

2- stimulates the parietal cells of gastric mucosa to secret HCl which activates pepsinogen into pepsin which activates more pepsinogen"autoactivation"

Pepsin is an endopeptidase, partially hydrolyse the ingested proteins into polypeptides.

$$\text{Pepsinogen} \xrightarrow{\text{HCl}} \text{Pepsin}$$

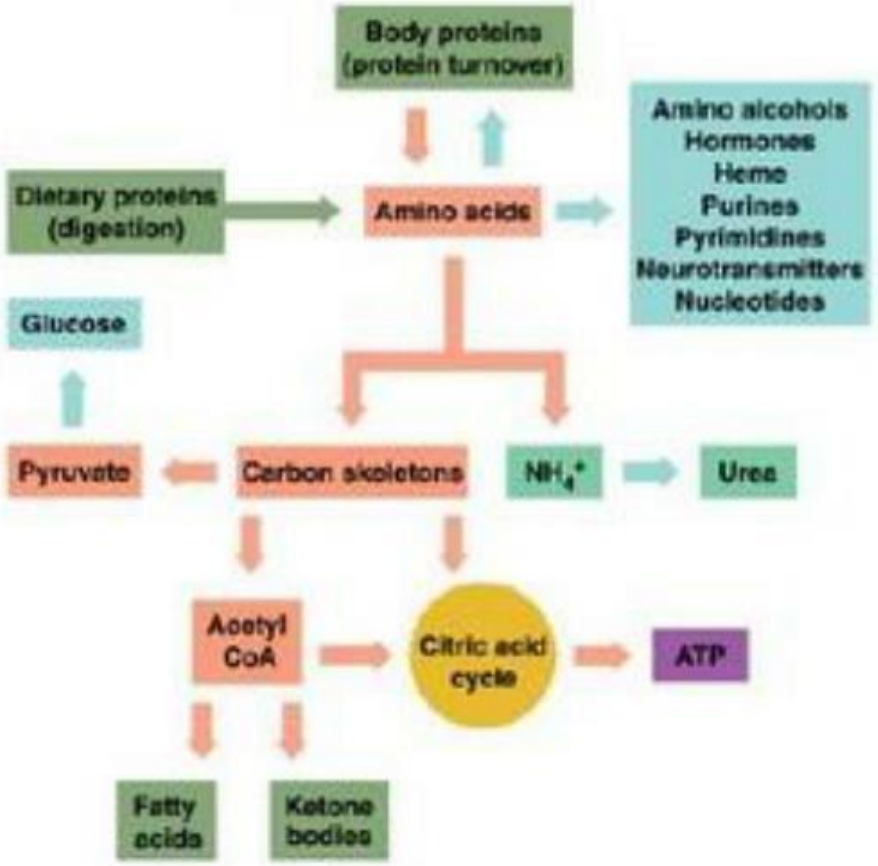
Auto activation

$$\text{Pepsinogen} \xrightarrow{\text{pepsin}} \text{Pepsin}$$

Proteins in the Body

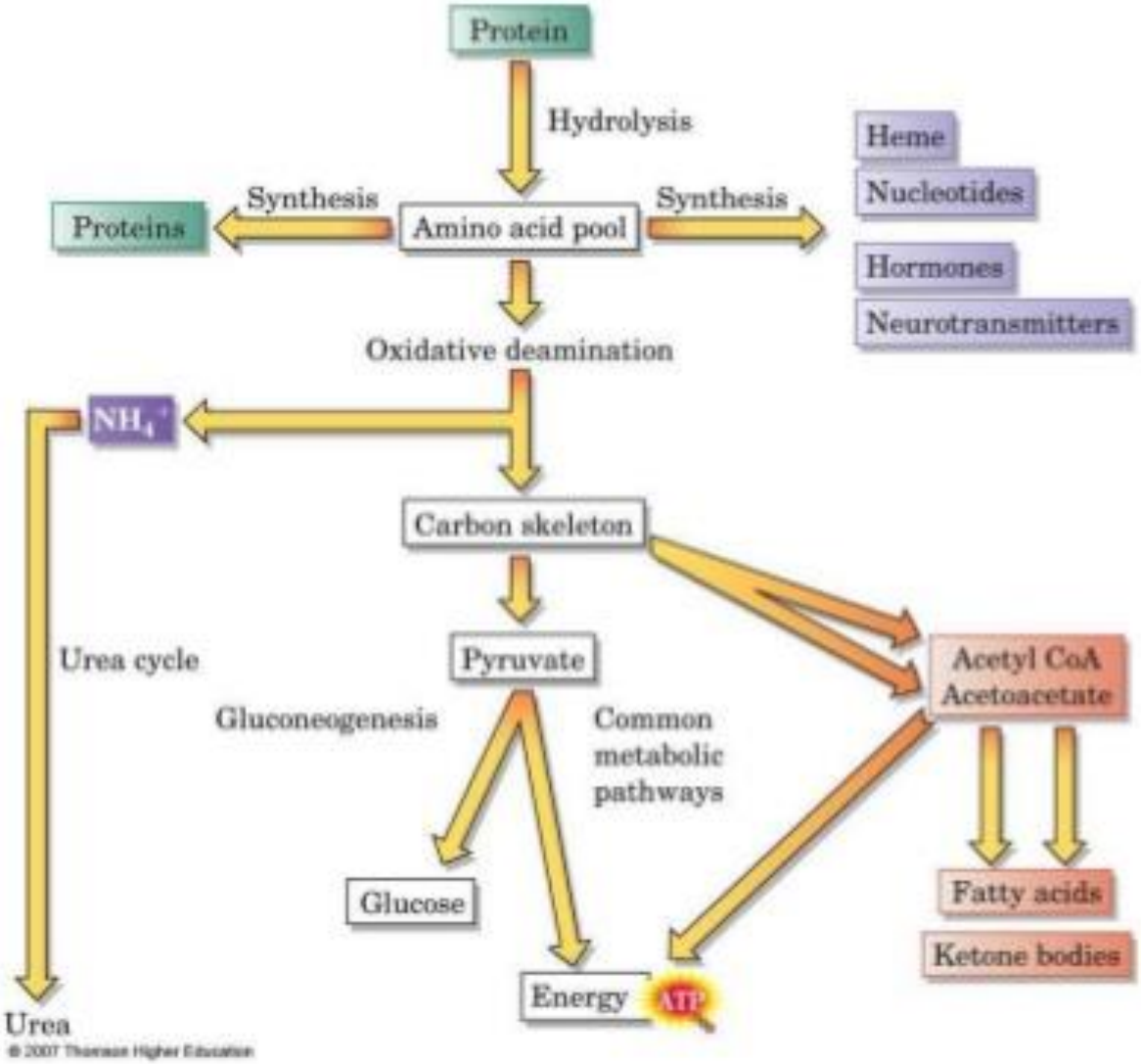
Proteins provide:

- Amino acids for protein synthesis.
- Nitrogen atoms for nitrogen-containing compounds.
- Energy when carbohydrate and lipid resources are not available.



Protein Catabolism

Overview of Protein catabolism.



Protein is a complex of amino acids, which include nitrogen. Nitrogen does not accumulate in the body.

What is Nitrogen balance?

- Is a specific term, describes status of nitrogen metabolism in Human body.
- Defined as a balance between amount of Nitrogen intake in the form of dietary protein
- and
- amount of Nitrogen lost or excreted in the form of Urea, Uric acid, Creatinine and small amount of amino acids by an individual.

- In adults, the **nitrogen balance** is generally in **equilibrium** (Quantities of protein nitrogen **taken-in** and **excreted** per day are approximately **equal**.

- **Positive** or **Negative** nitrogen balance indicate the conditions of **nutrition**, **metabolism** and **diseases**.

Nitrogen balance

Positive

intake is greater than loss

- growth of the organism
- pregnancy
- intake of anabolic hormones
- after starvation

Negative

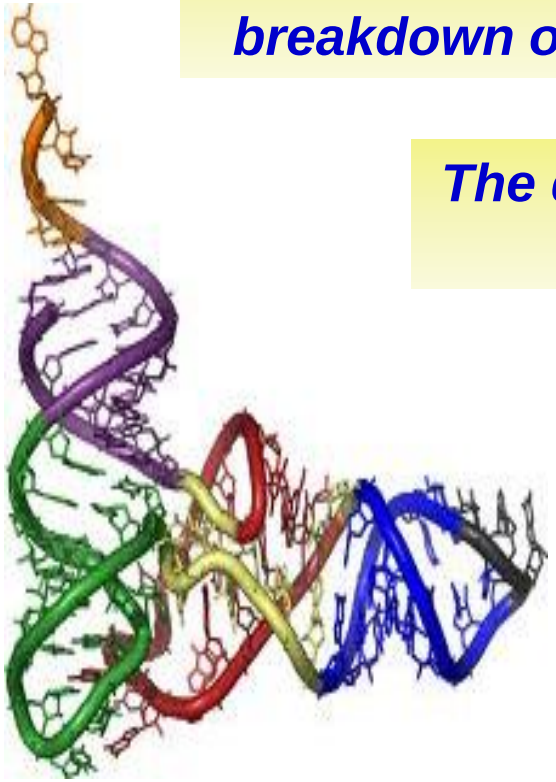
intake is less than loss

- starvation
- proteinuria
- infectious diseases
- burns
- operations
- intake catabolic hormones

Disturbances of protein metabolism

The disturbance of protein intake, digestion and amino acid absorption in the gastrointestinal tract

The disturbance of the synthesis and breakdown of proteins in cells and tissues

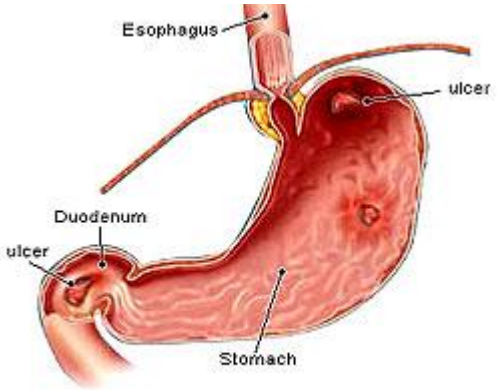


The disturbance of intermediate metabolism of amino acids

The disturbance of the final stages of protein metabolism

Disorders of the intake, digestion and absorption of proteins in the gastrointestinal tract

- Insufficient of protein and amino acids in food (starvation (complete and incomplete), nutritional deficiency)
- Diseases of the stomach and intestines (gastritis, peptic ulcer); lack of pancreatic juice
- Accelerated passage of food masses through the intestines

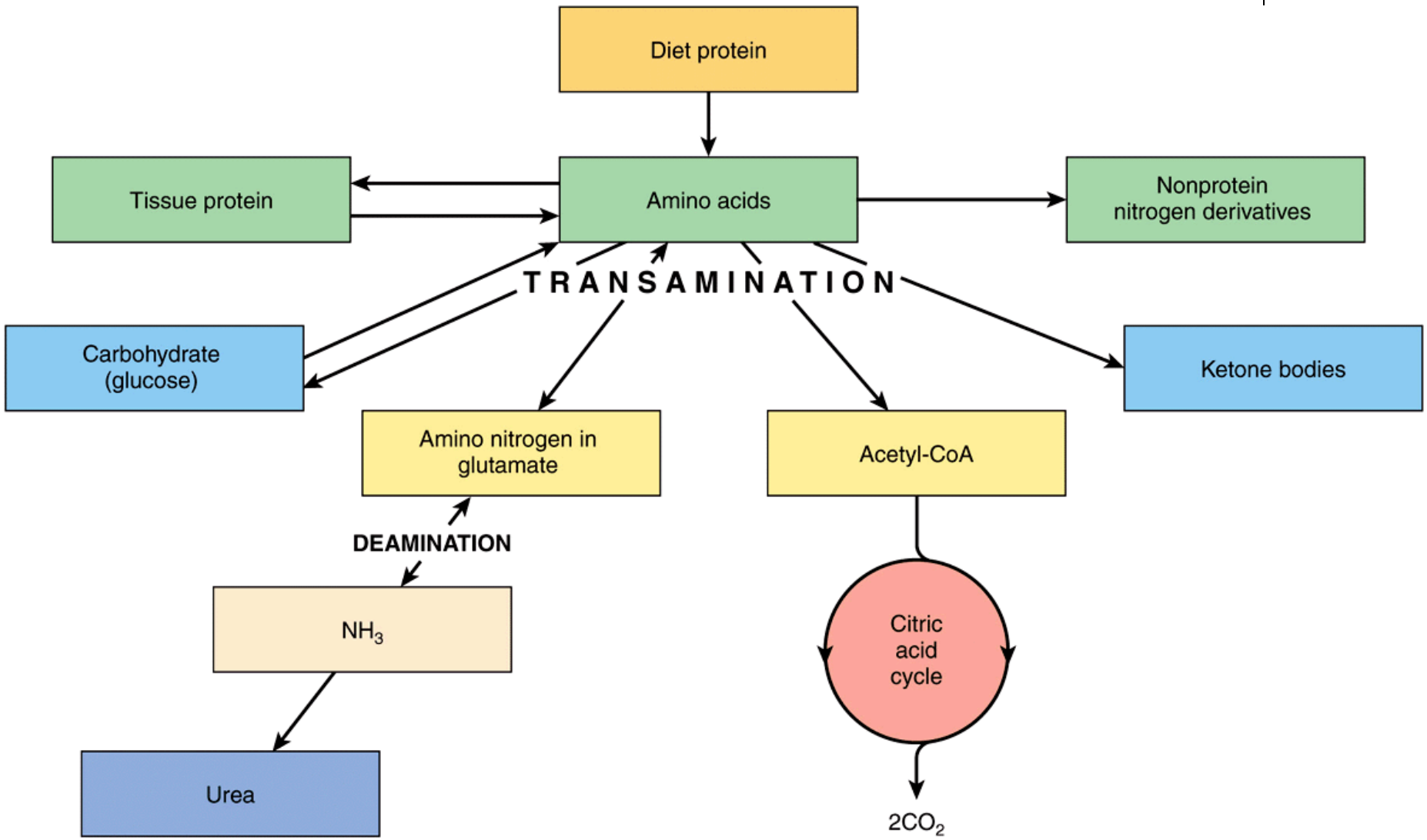


Gastritis

The disturbance of the synthesis and breakdown of proteins in cells and tissues

- violation of genetic structures under the influence of ultraviolet rays, ionizing radiation;
- disorders of neuro-endocrine regulation;
- toxic effect of drugs (antibiotics)

The disturbance of intermediate metabolism of amino acids



The disturbance of intermediate metabolism of amino acids

- **1. The disturbances of deamination**

• deficiency of pyridoxine (B_6), riboflavin (B_2), nicotinic acid

• hypoxia;

• protein deficiency during starvation

- **2. The disturbances of decarboxylation**

• hypoxia;

• ischemia;

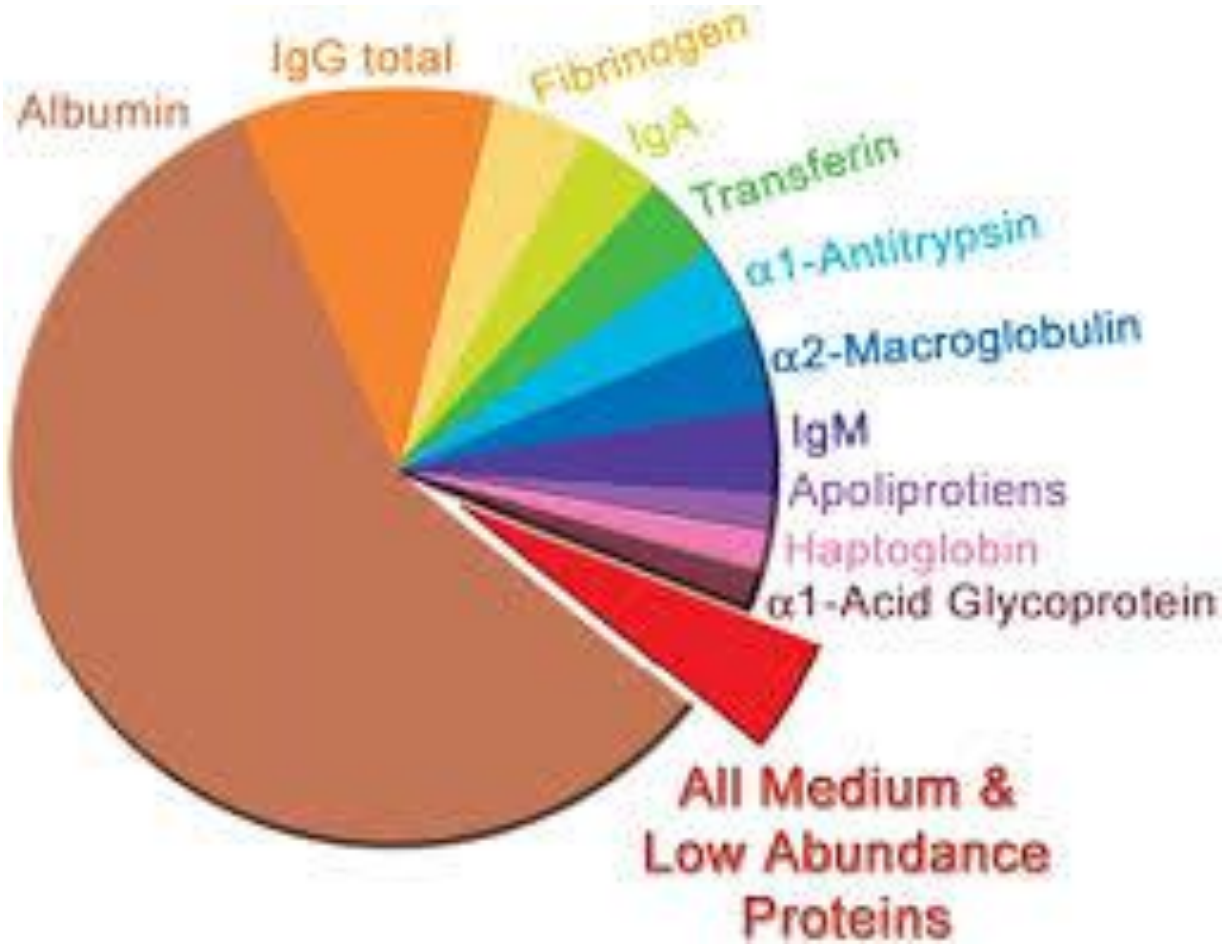
• tissue destruction (injury, radiation).

Disorders of plasma protein composition.

- hypoproteinemia
- hyperproteinemia
- dysproteinemia
- paraprotyeinemia

Types of plasma proteins

Blood protein	Normal level	%	Function
Albumins	3.5-5.0 g/dl	60%	create oncotic pressure and transports other molecules
immunoglobulins	1.0-1.5 g/dl	18%	in immune system
Fibrinogens	0.2-0.45 g/dl	4%	blood coagulation
alpha 1-antitrypsin			neutralize trypsin that has leaked from the digestive system
Regulatory proteins		<1%	Regulation of few gene expression


Albumin
IgG total
Fibrinogen
IgA
Transferin
α1-Antitrypsin
α2-Macroglobulin
IgM
Apoliprotiens
Haptoglobin
α1-Acid Glycoprotein
All Medium &
Low Abundance
Proteins

Hyperproteinemia

- Total protein level > 8.3 g/dL
- Causes
  - Dehydration
    - Excess water loss leads to the increased concentration of proteins
    - Examples: vomiting, diarrhea, diabetic acidosis, hypoaldosteronism
  - Excessive production of gamma globulins
    - Examples: Multiple myeloma, Waldenstrom's macroglobulinemia

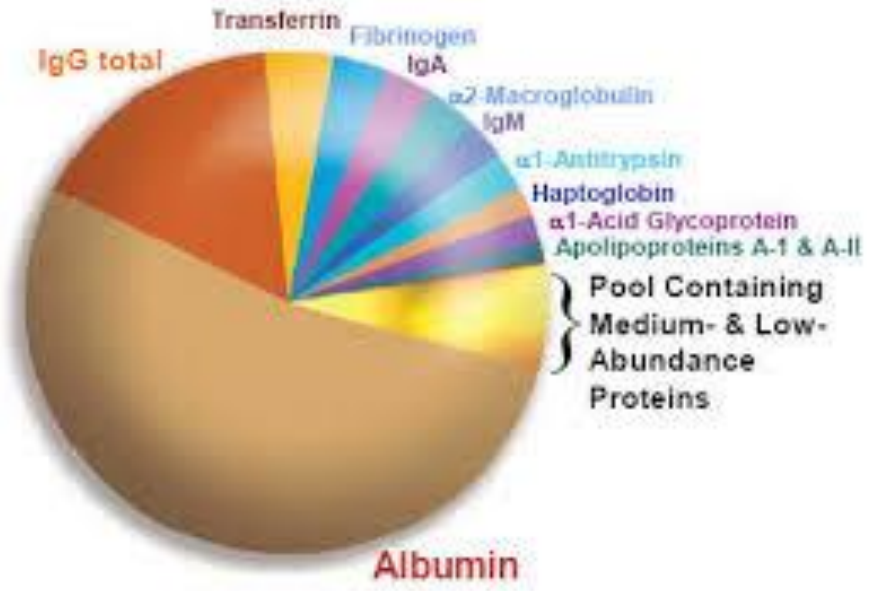
Hypoproteinemia

- Total protein level <6.4 g/dL
- Due to a negative nitrogen balance
- **Causes**
  - Excessive loss
    - renal disease, blood loss, burns
  - Decreased intake
    - Malnutrition, intestinal malabsorption
  - Decreased synthesis
    - Liver disease, inherited immunodeficiency
  - Acceleration of catabolism of proteins
    - Burns, trauma

Dysproteinemia

Is the change in the ratio of different plasma proteins

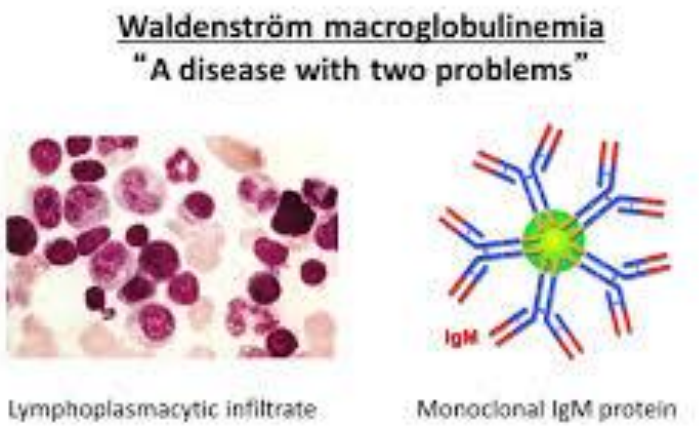
- **Inflammation**
- **Allergy**
- **Coagulopathy**
- **Diseases of liver**

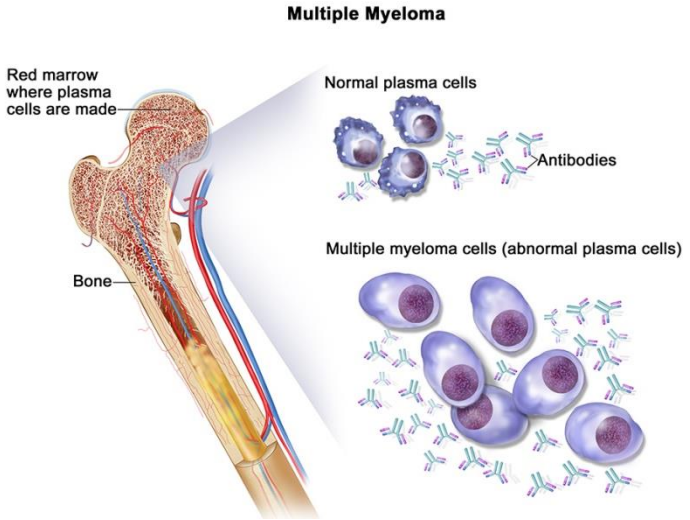


Paraproteinemia

is the appearance of abnormal forms of proteins

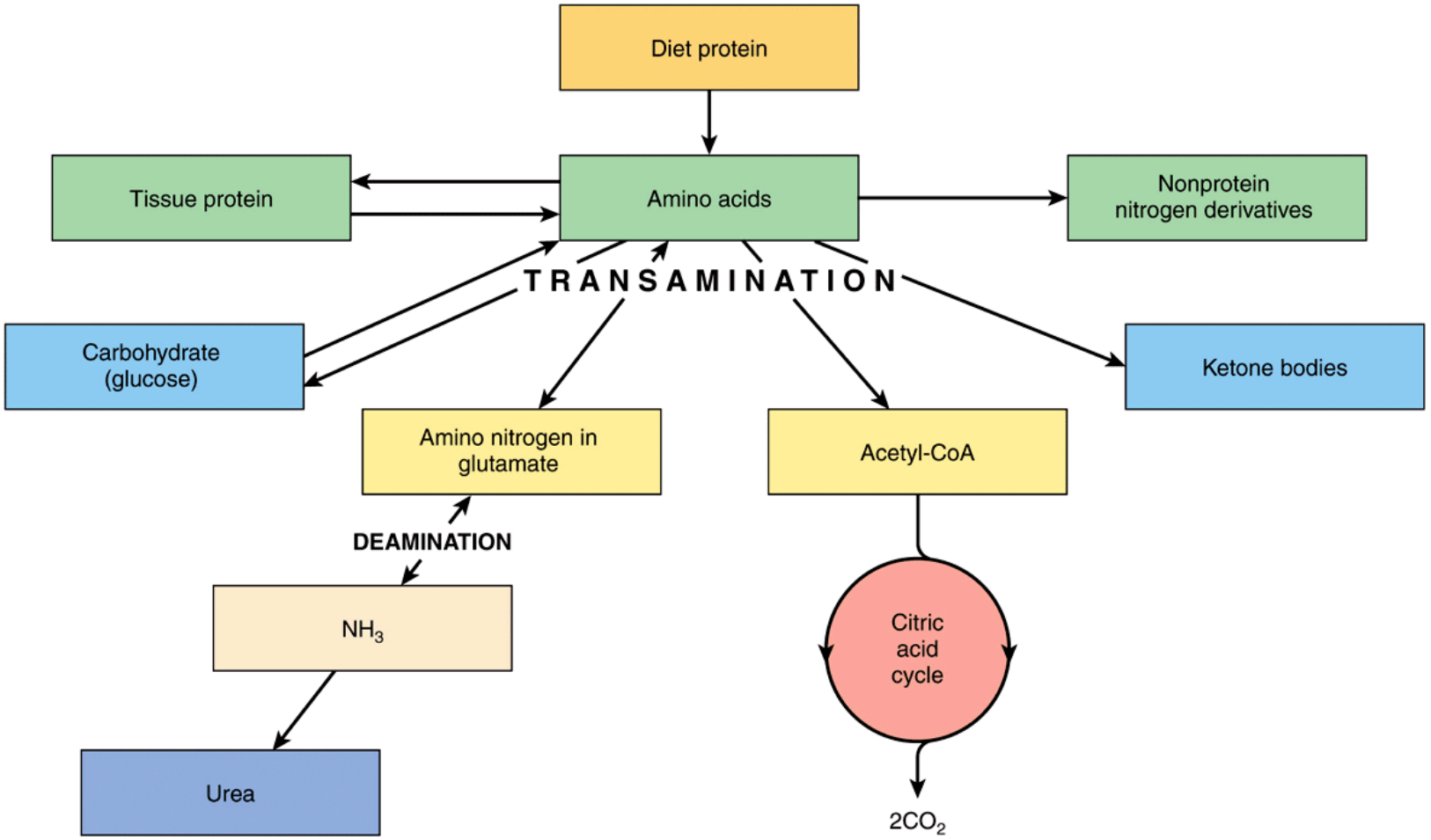
- **Multiple Myeloma**
- **Waldenstrom macroglobulinemia**
- **Lymphoma**
- **Chronic lymphatic leukemia**



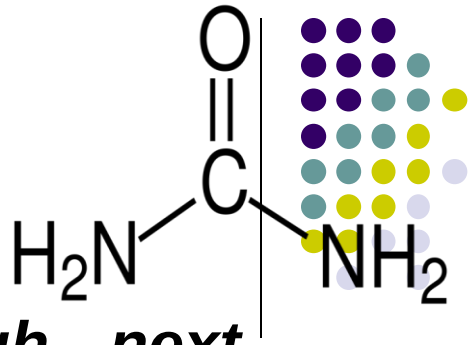


The disturbance of the final stages of protein metabolism

The final products of the desintegration of amino acids are: ammonia, urea, uric acid and water.

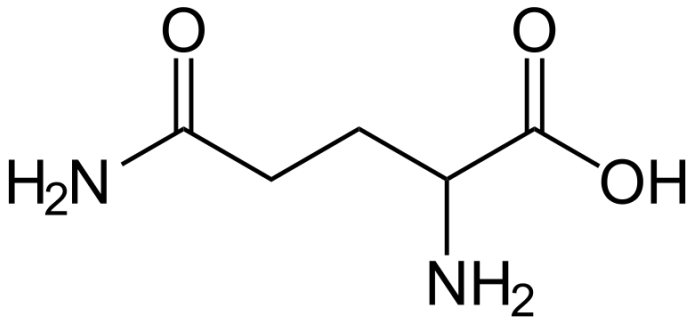


Ammonia - a toxic substance



Disposal of ammonia develops through next mechanisms:

1. ***In the liver - by the formation of urea***
2. ***In most peripheral tissues - by adding ammonia to glutamic acid (by amidation) to form glutamine.***
3. ***In skeletal muscles – by formation alanine***



Disposal of Ammonia

1- Urea

in the liver

- is quantitatively the **most important** disposal route for ammonia
- Urea is formed in the **liver** from ammonia (urea cycle)
- **Urea** travels in the blood from the liver to the **kidneys** where it is filtered to appear in **urine**

Disposal of Ammonia

2- Glutamine

in most peripheral tissues especially brain, Skeletal Muscles & liver

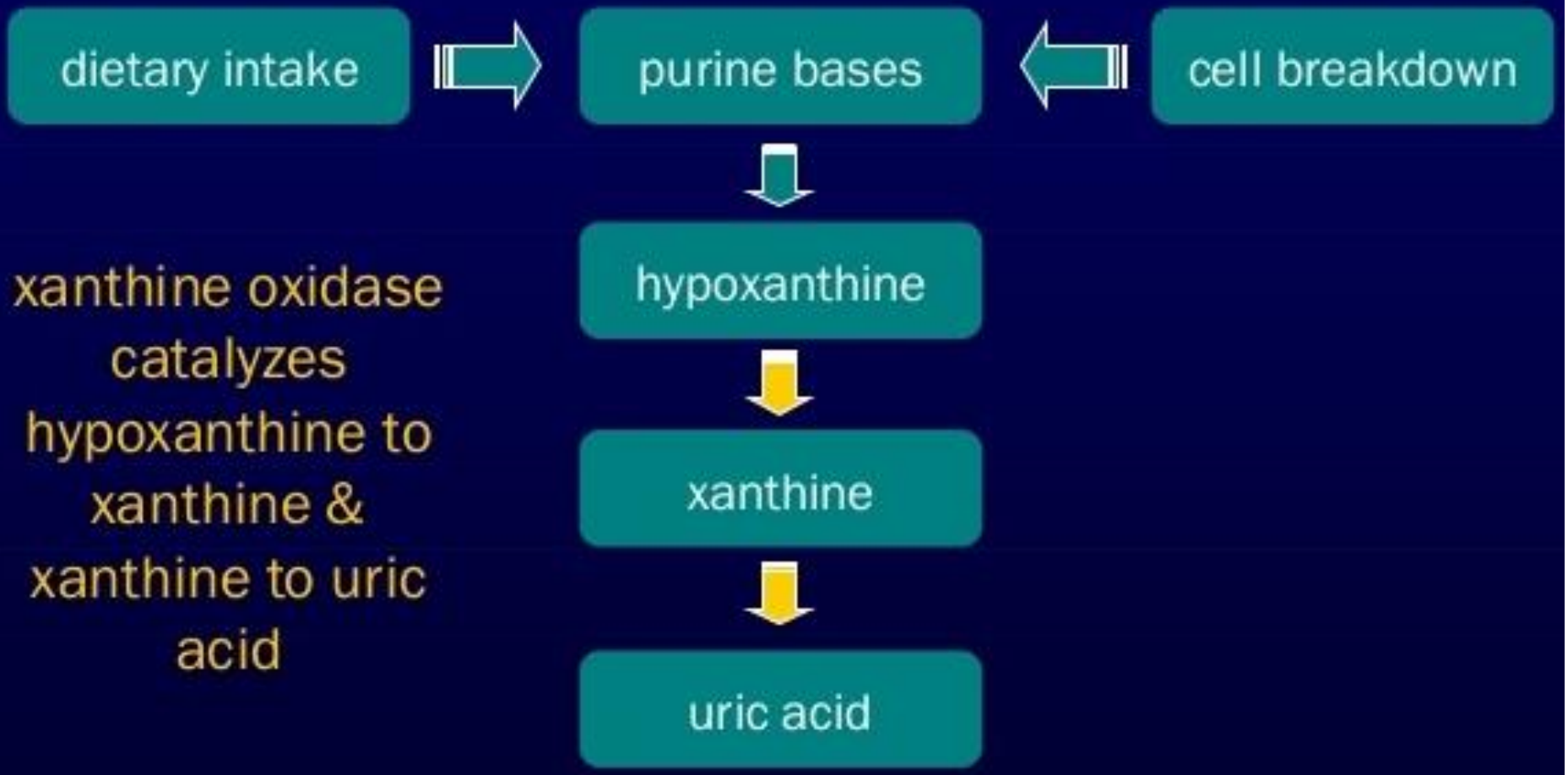
- In most peripheral tissues, glutamate binds with **ammonia** by action of **glutamine synthase**
- in the **brain**, it is the major mechanism of removal of ammonia from the brain
- This structure provides a **nontoxic storage & transport form of ammonia**
- Glutamine is transported to blood to other organs esp. liver & kidneys
- In the liver & Kidney, glutamine is converted to ammonia & glutamate by the enzyme **glutaminase**.

Disposal of Ammonia cont.

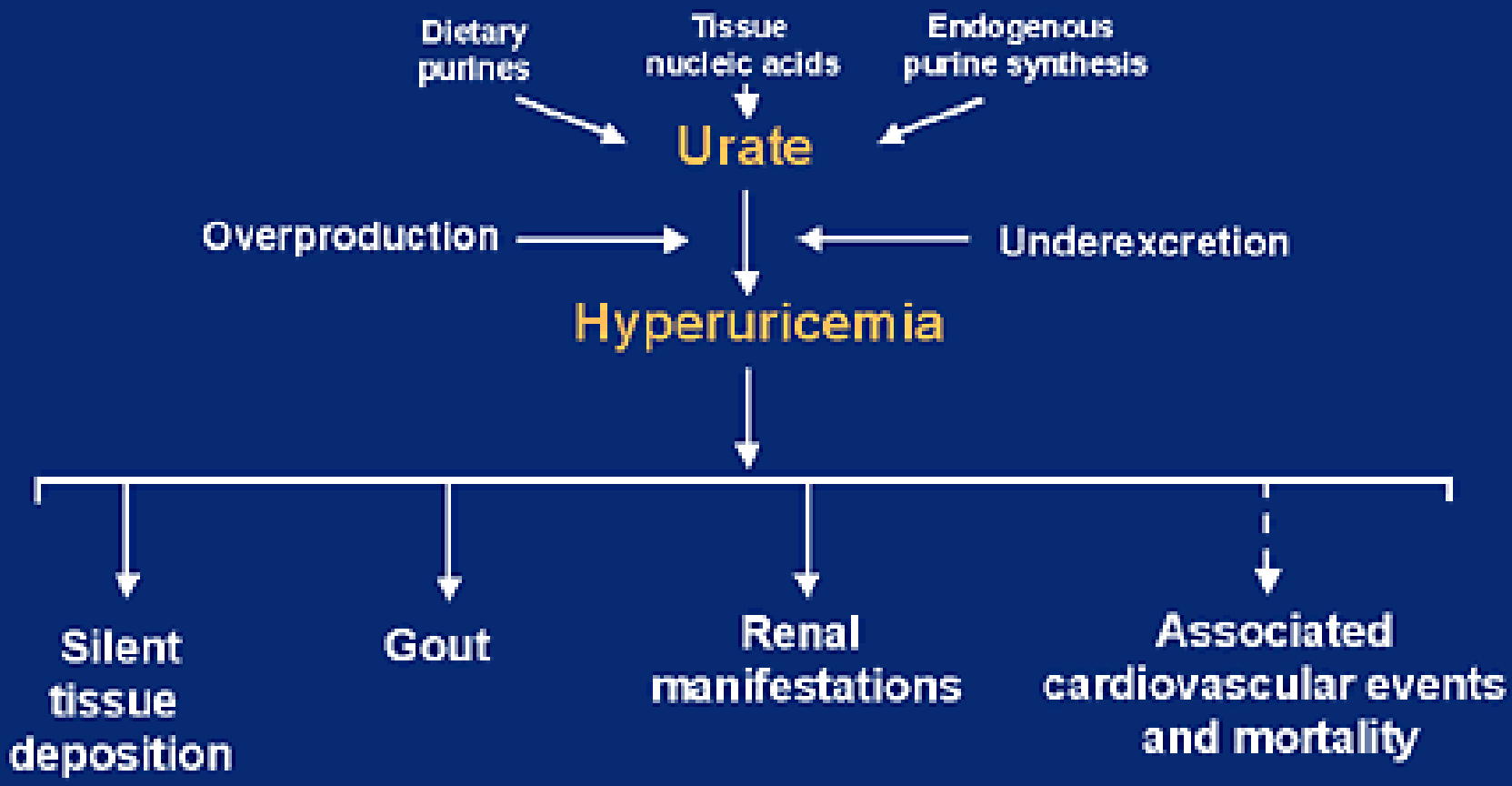
3- Alanine in skeletal muscles

- **Ammonia** + Pyruvate form **alanine** in skeletal muscles
- Alanine is transported in blood to liver
- In liver, alanine is converted to pyruvate & **ammonia**
- Pyruvate can be converted to **glucose** (by gluconeogenesis)
- **Glucose** can enter the blood to be used by skeletal muscles **(GLUCOSE - ALANINE PATHWAY)**

Uric acid metabolism



The Hyperuricemia Cascade



DISEASES ASSOCIATED WITH DEFECTS IN PURINE METABOLISM

- HYPERURICEMIA
- GOUT
- LESCH-NYHAN SYNDROME
- KIDNEY STONES
- SEVERE COMBINED IMMUNODEFECIENCY (SCID)

GOUT

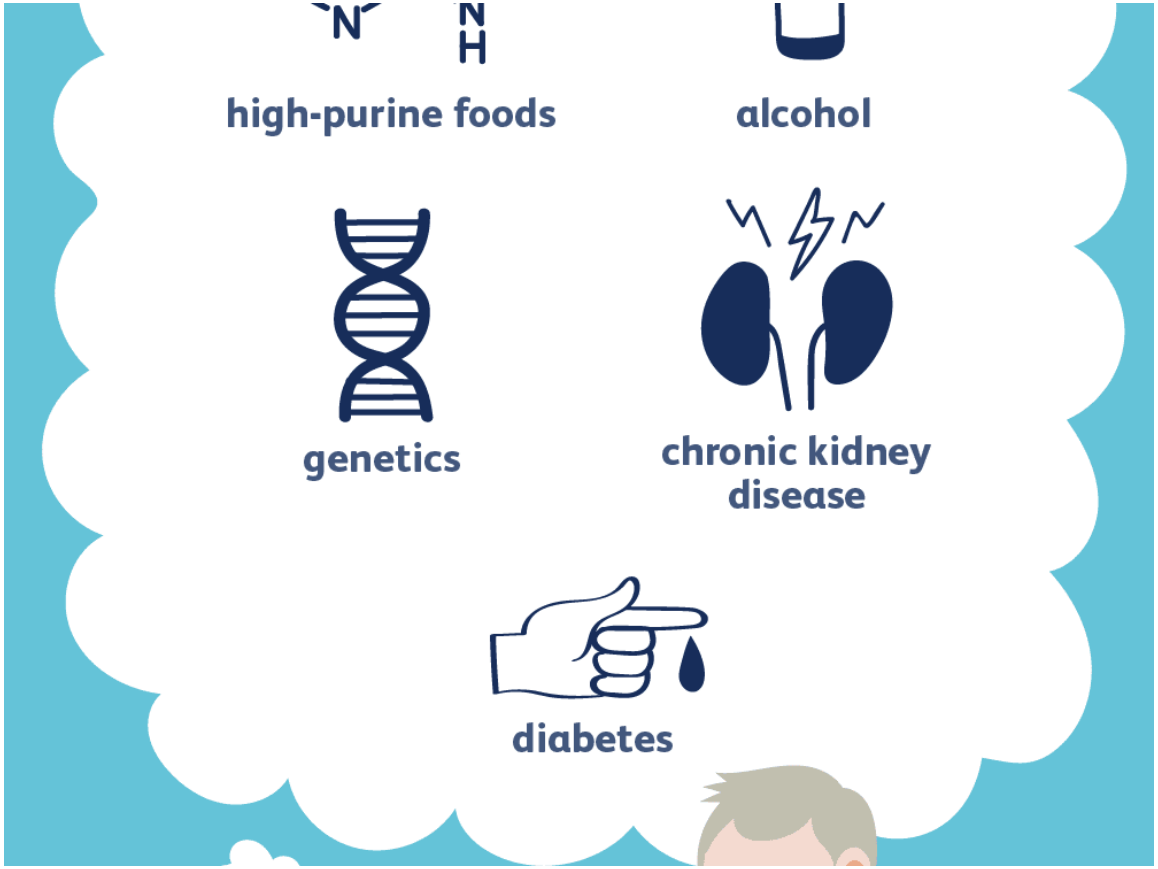
Gout is a metabolic disorder which results in an excess of uric acid in the bloodstream and the deposit of its salts (urates) in joint and tissues.

GOUT

ETIOLOGY:

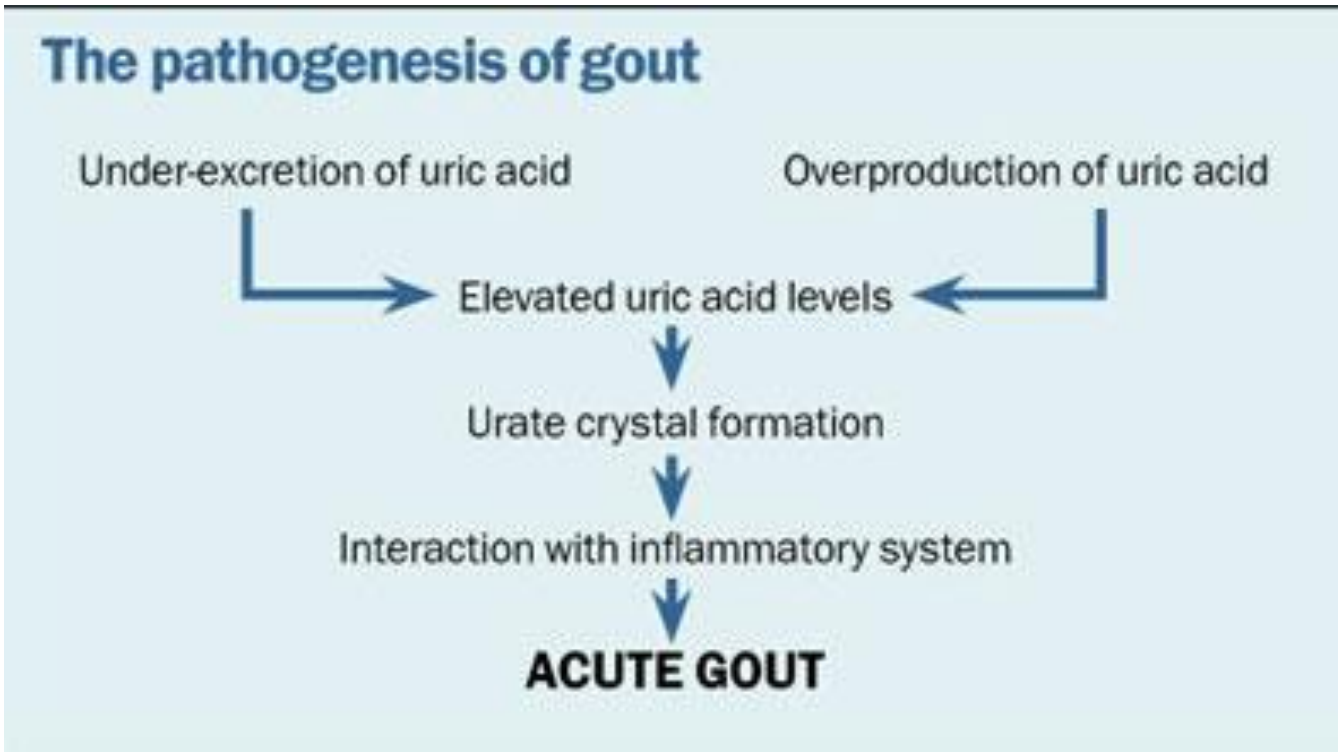
primary gout **– inherited increase of level the uric acid in blood;**

secondary gout **– changes of metabolism by another diseases**



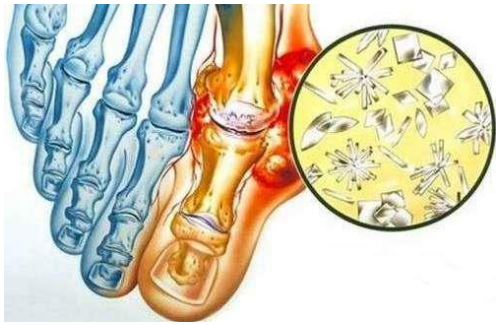
GOUT

Risk factors – surplus entering of purines into the organism with food



PATHOGENESIS:

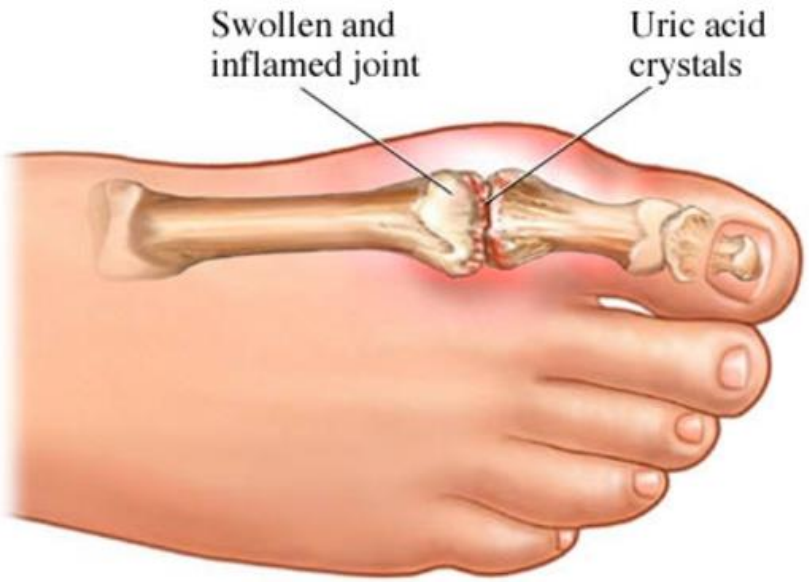
- **hyperuricemia and accumulation of urates in the body;**
- **urates deposition in tissues of joints, cartilages, tendons;**
- **acute gouty inflammation.**



CLINICAL SIGNS

- acute arthritis,
- swelling of the joints and soft tissues of the foot,
- redness,
- pyrexia (skin over the affected area is hot).

Pain intensity is very high: light touch causes excruciating pain.



The Stages of Gout Progression

STAGE 1:
High Uric Acid Levels

Uric acid is building up in the blood and starting to form crystals around joints

STAGE 2:
Acute Gout

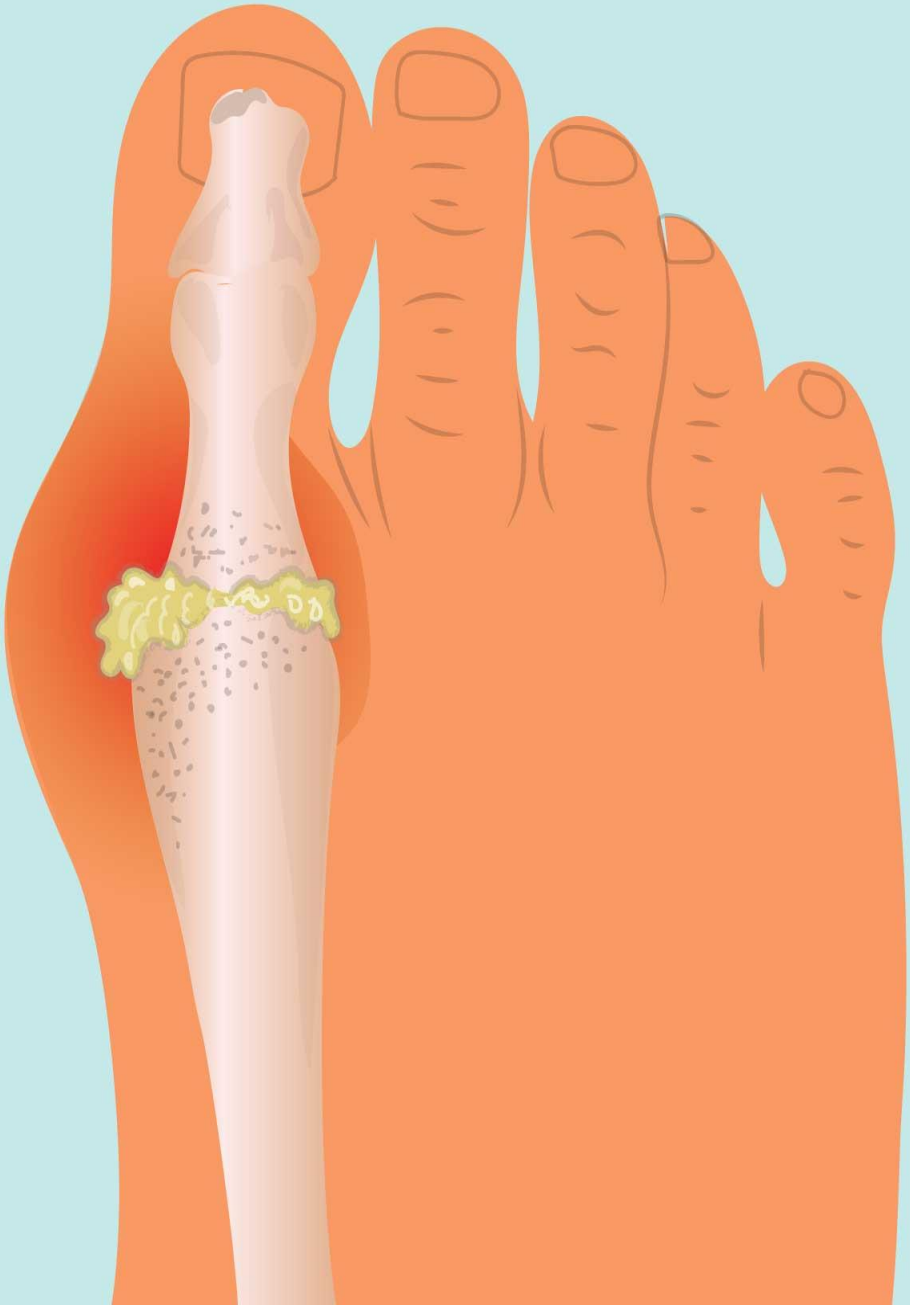
Symptoms start to occur, causing a painful gout attack

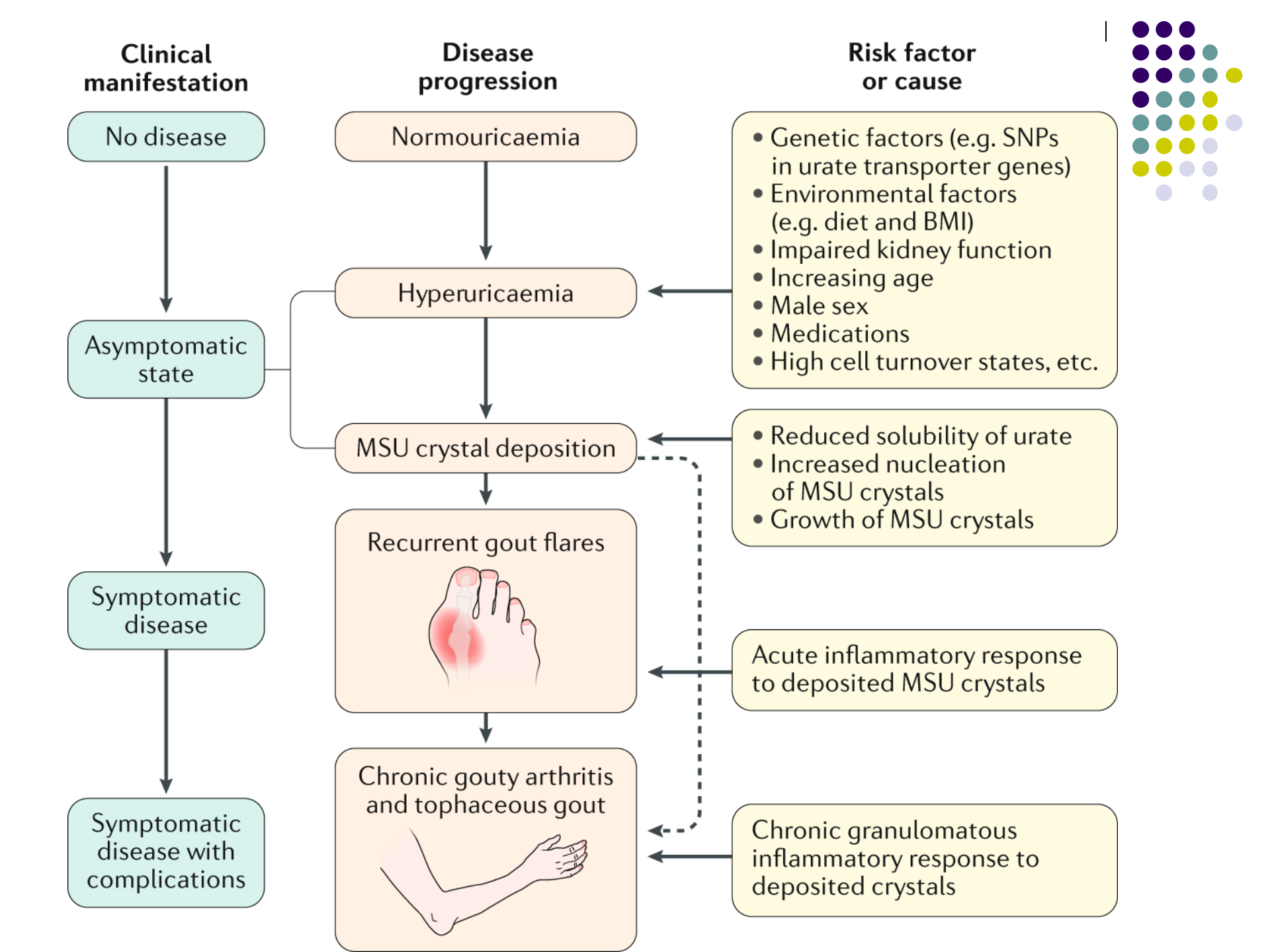
STAGE 3:
Intercritical Gout

Periods of remission between gout attacks

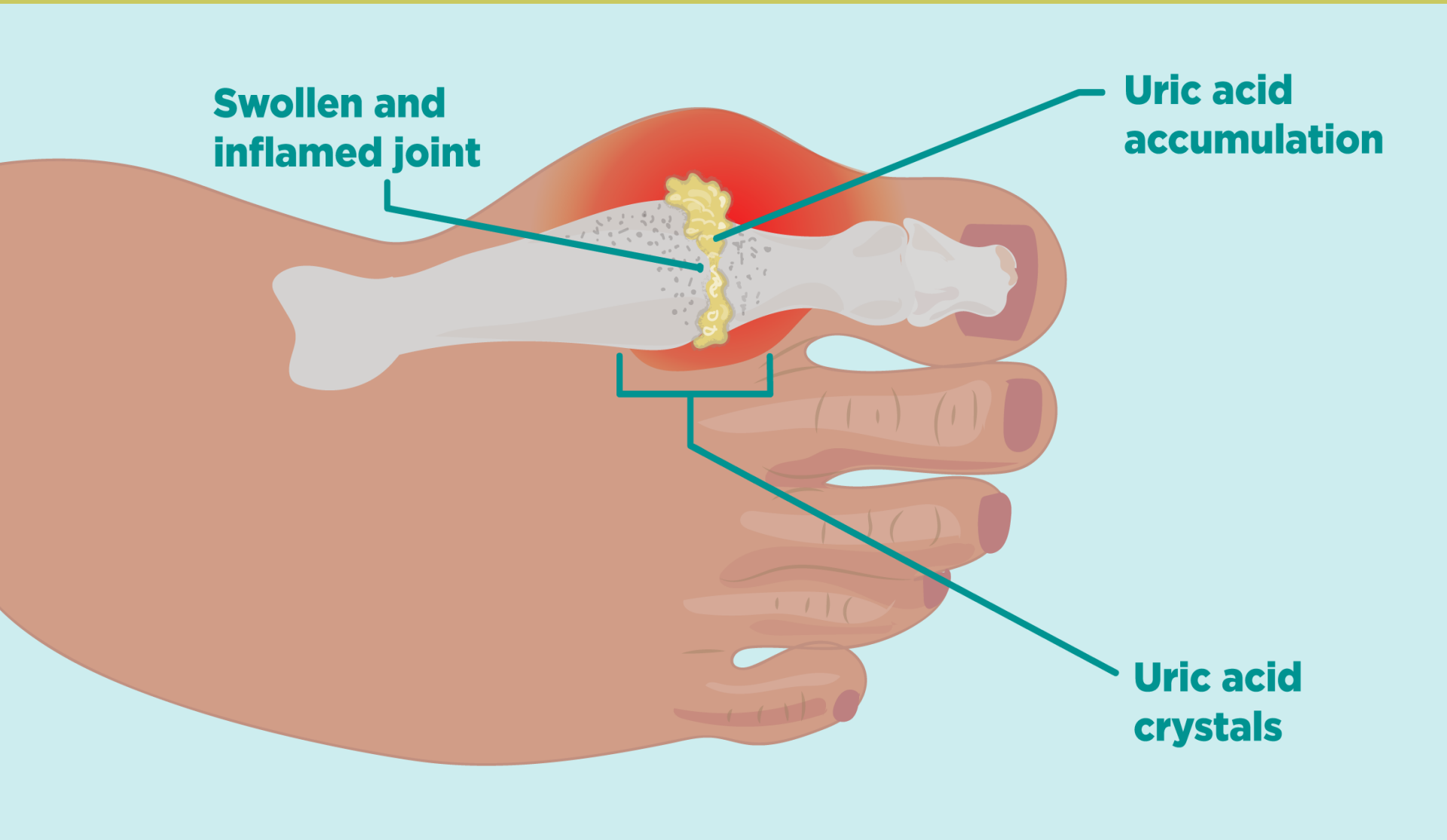
STAGE 4:
Chronic Gout

Gout pain is frequent and tophi form in joints

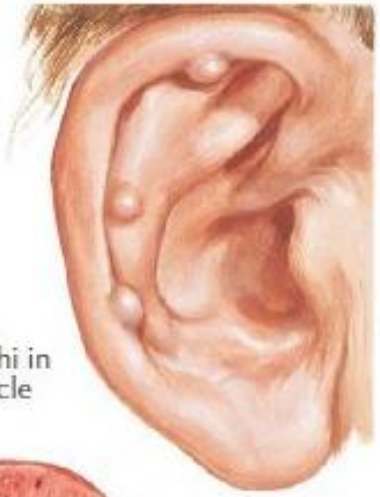



Clinical manifestation
Disease progression
Risk factor or cause
No disease
Asymptomatic state
Symptomatic disease
Symptomatic disease with complications
Normouricaemia
Hyperuricaemia
MSU crystal deposition
Recurrent gout flares
Chronic gouty arthritis and tophaceous gout
• Genetic factors (e.g. SNPs in urate transporter genes)
• Environmental factors (e.g. diet and BMI)
• Impaired kidney function
• Increasing age
• Male sex
• Medications
• High cell turnover states, etc.
• Reduced solubility of urate
• Increased nucleation of MSU crystals
• Growth of MSU crystals
Acute inflammatory response to deposited MSU crystals
Chronic granulomatous inflammatory response to deposited crystals

A tophus (Latin: "stone", plural tophi) is a deposit of monosodium urate crystals, in people with longstanding high levels of uric acid in the blood, a condition known as hyperuricemia



Tophaceous deposits in olecranon bursae, wrists, and hands



Tophi in auricle

Hand grossly distorted by multiple tophi (some ulcerated)

Resolution of tophus after 27 months of treatment with uricosuric agents

Treatment of Gout

Acute Treatment

- NSAIDs
  - Caution in renal insufficiency and peptic ulcer dz
- Colchicine
  - Diarrhea, bone marrow suppression
- Steroids
  - Oral, IV or intraarticular injection

Prevention of Recurrence

- Modify risk factors
  - Obesity, alcohol, red meat, thiazides
- Uricosuric agents
  - Probenecid, sulfinpyrazone
  - Contribute to kidney stones
- Xanthine oxidase inhibitors
  - Allopurinol, febuxostat
  - Can precipitate acute attack

Thank you for your attention