BHARATHIDASAN UNIVERSITY
Tiruchirappalli- 620024,
Tamil Nadu, India

Programme : M.Sc., Biochemistry
Course Title : CLINICAL BIOCHEMISTRY
Course Code: BC303CR

UNIT – III

DISORDERS OF PROTEIN & INBORN ERRORS OF METABOLISM

Dr. KALAIARASI A
Dept. of Biochemistry
BDU. Trichy

Agammaglobulinemia
alpha fetoprotein
AmyLoidosis

Agammaglobulinemia:

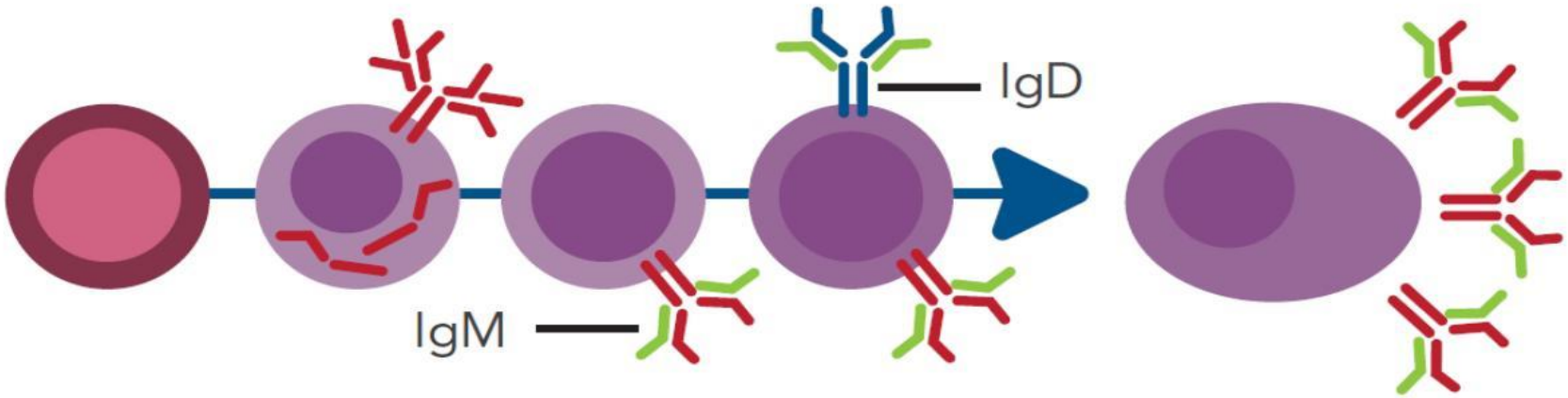
- Agammaglobulinemia is an inherited disorder in which a person has very low levels of protective immune system proteins called immunoglobulins. Immunoglobulins are a type of antibody. Low levels of these antibodies make you more likely to get infections.

Causes: This is a rare disorder that mainly affects males. It is caused by a gene defect that blocks the growth of normal, mature immune cells called B lymphocytes.

- Immunoglobulins play a major role in the immune response which protects against illness and infection.

- Common infections include ones that are due to bacteria such as Haemophilus influenzae, pneumococci (Streptococcus pneumoniae), and staphylococci.
- Common sites of infection include:
- Gastrointestinal tract , Joint,Lung,Skin,Upper respirator tract.
- Agammaglobulinemia is inherited, which means other people in your family may have the condition.
- Agammaglobulinemia in two types :
- X linked Agammaglobulinemia , Autosomal recessive Agammaglobulinemia.
- X linked Agammaglobulinemia is caused by a mutation in the Bruton tyrosine kinase (BTK) gene, located on the long arm of the X-chromosome.
- BTK is encodes for cytoplasmic non-receptor tyrosine kinases, which are signal transduction molecules.

- BTK plays a major role in promoting the maturation of pro B cells to pre-B cells.
- The mutation in the BTK gene results in the failure of B cell development, leading to significantly low levels of mature B lymphocytes in peripheral blood circulation.
- Autosomal recessive agammaglobulinemia has been reported to be caused by genes that affect B cell development,Up to 15% are presumed to be autosomal recessive.
- The genetic cause of ARAG is much more complex as it involves other genes mapped to loci on different chromosomes.



Alpha fetoprotein:

- Alpha-fetoprotein is a glycoprotein that is normally produced during gestation by the fetal liver and yolk sac, the serum concentration of which is often elevated in patients with HCC.
- Serum levels of AFP do not correlate well with other clinical features of HCC such as size, stage or prognosis.
- Elevated serum AFP occurs in pregnancy with tumors of gonadal origin (both germ cell and non-germ cell) and in a variety of other malignancies, of which gastric cancer is the most common.
- Elevated serum AFP may also be seen in patients with chronic liver disease without HCC such as acute or chronic viral hepatitis.

A rise in serum AFP in a patient with cirrhosis or hepatitis B should raise concern that HCC has developed.

- It is generally accepted that serum levels greater than 500 mg/L (normal in most laboratories is between 10 and 20 mg/L) in a high-risk patient is diagnostic of HCC

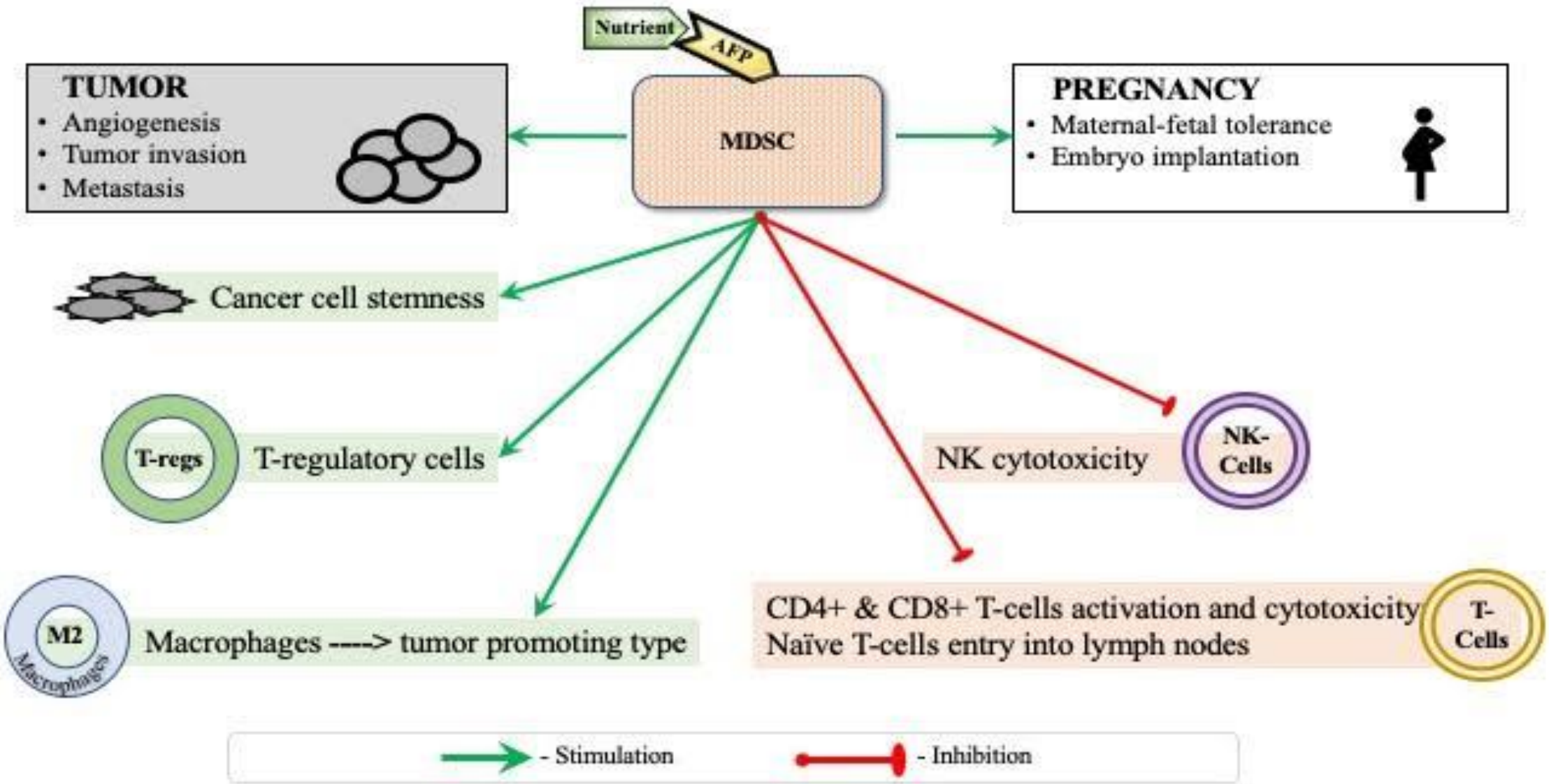
Blood levels of Alpha fetoprotein:

- **Normal levels** of AFP are usually less than 10 ng/Ml (nanograms per milliliter).
- At birth, normal infants have AFP levels 4 or more times normal range, decreasing during the first 1-2 years of life.
- **Pysiological increase :** The majority of pregnant women having a high concentration of serum alpha fetoprotein.
- **Pathological increase:**

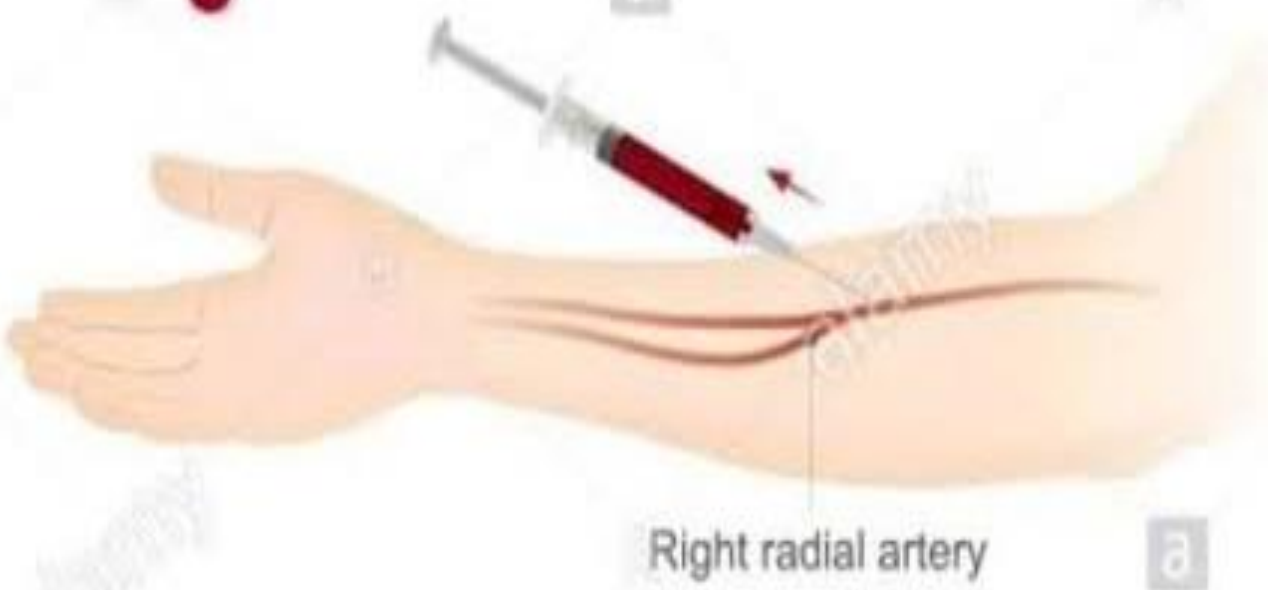
  1- Liver diseases

  2- Testicular cancer

  3- Ovarian cancer


Nutrient
AFP
MDSC
TUMOR
• Angiogenesis
• Tumor invasion
• Metastasis
PREGNANCY
• Maternal-fetal tolerance
• Embryo implantation
Cancer cell stemness
T-regs
T-regulatory cells
NK cytotoxicity
NK-Cells
M2
Macrophages
Macrophages ----> tumor promoting type
CD4+ & CD8+ T-cells activation and cytotoxicity
Naïve T-cells entry into lymph nodes
T-Cells
- Stimulation
- Inhibition

Blood is withdrawn from vein between the 16-18 weeks of pregnancy



AFP : ☐ –

☐ +

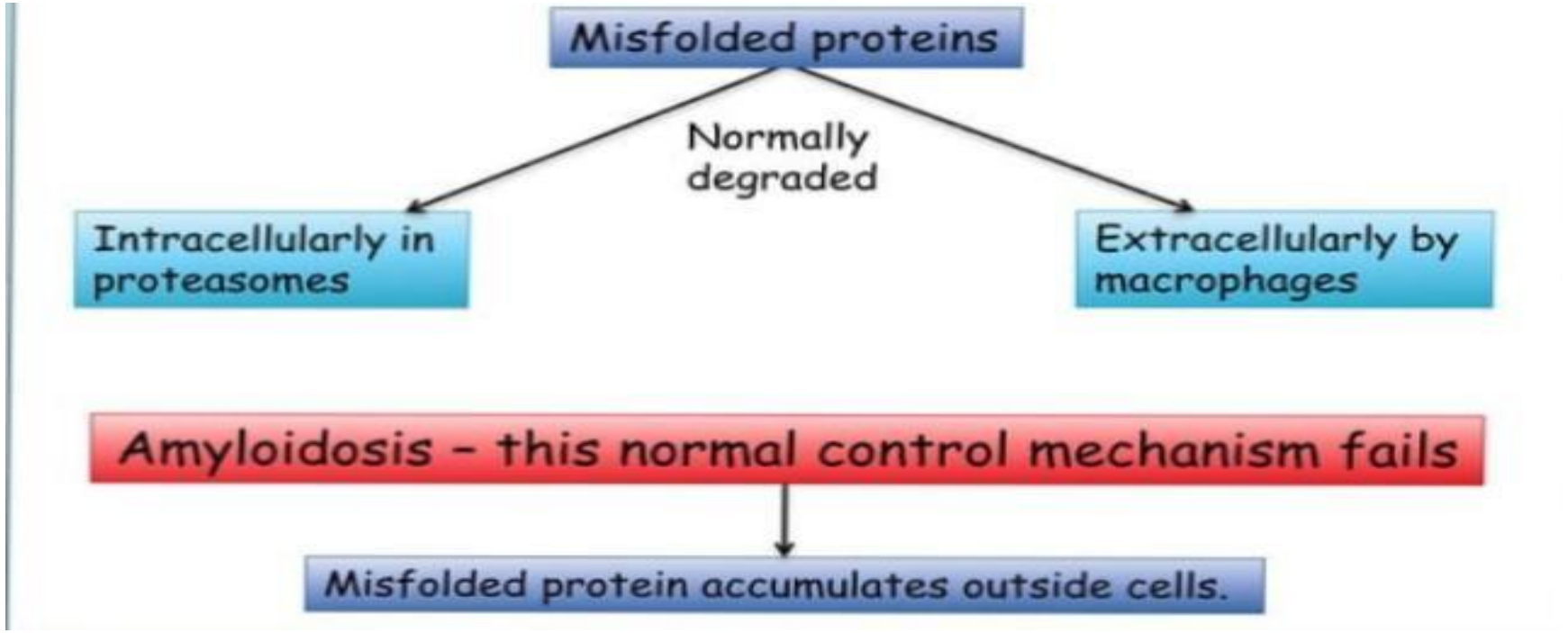
- To detect liver cancer
- Other chromosomal abnormalities
- Defects in the abdominal wall of the fetus
- To screen for neural tube defect (high level AFP)
- To screen for Down's syndrome (low level AFP)

Amyloidosis:

- **DEFINITION:**

Amyloidosis is a disorder characterized by the extracellular deposits of misfolded proteins that aggregate to form insoluble fibrils leads to tissue damage and functional compromise.

-



Two categories of proteins that form Amyloid

Normal proteins that have inherent tendency to misfold (excessive production)

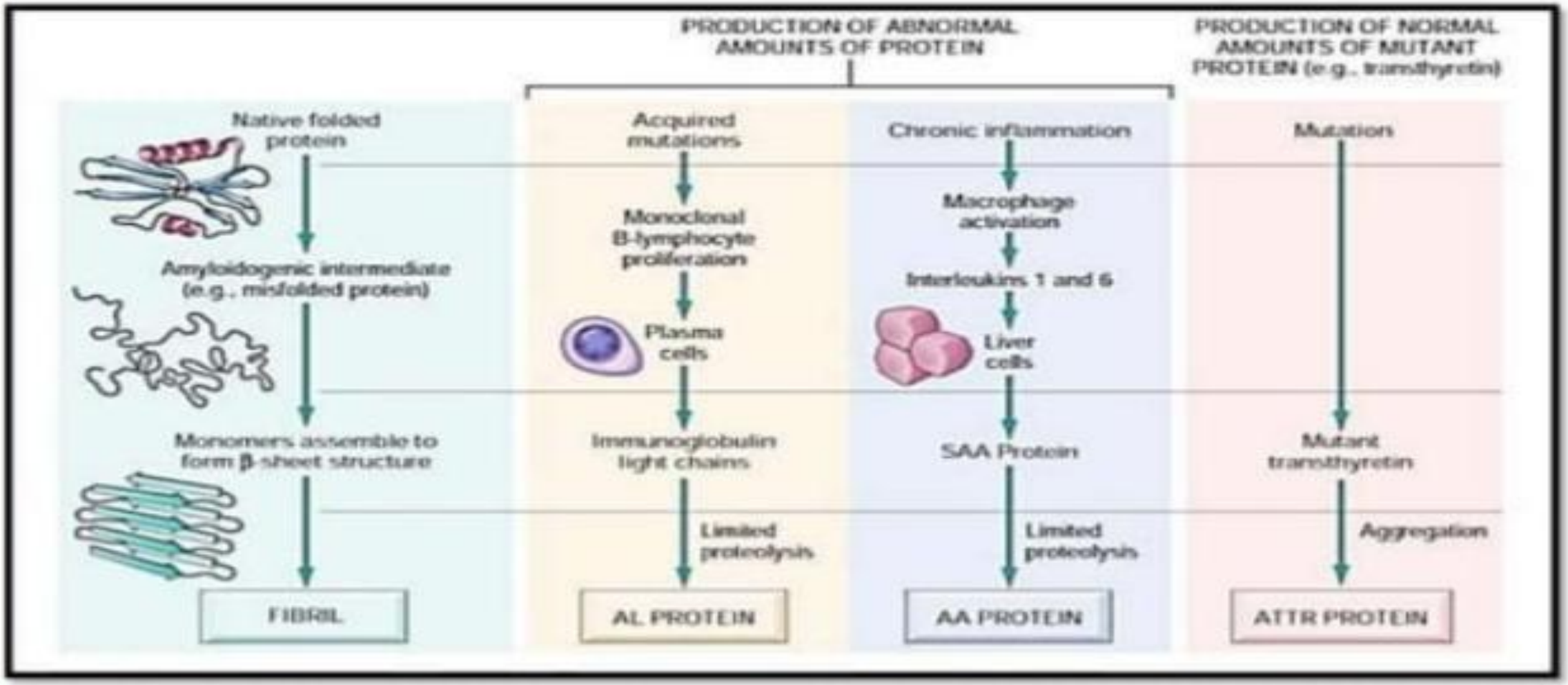
Mutant proteins that are prone to misfolding

Amyloidosis:

1. Localized: involves single organ
2. Systemic: involves multiple organs or tissues

Effect: tissue damage and compromised function

Major forms of Amyloid fibrils



Classification:

Primary amyloidosis:

- Plasma cell disorder associatedAL type amyloid proteinIg secreted by clonal plasma cell prone to form Amyloid (due to its intrinsic physio-chemical properties)5 - 15% multiple myeloma cases develop amyloidosis.
- Amyloidogenic potential of particular chain depends upon its specific amino acid sequence.
- Most of AL amyloid do not have overt multiple myeloma or clonal B cell neoplasm.
- But they are classified as primaryamyloidosis (their presentation is due to amyloiddeposition without any associated disease)Modest increase in plasma cell noted in marrow without any tumor effect (monoclonal gummopathy).

- Reactive systemic amyloidosis: Associated with inflammatory condition-AA type amyloid proteinCommon associationRheumatoid arthritis (MC) - 3%, half of them clinically significant Ankylosing spondylitis.
- Inflammatoryy bowel disease(previously common association - TB, bronchiectasis, chronicosteomyelitis).
- **Heredofamilial Amyloidosis:** Rare & occur in limited geographic area> Familial Mediterranean fever (AR inheritence) MC AA type amyloid protein, Related to the recurrent bouts of inflammation. Familial amyloidotic polyneuropathy –mTTR
- **Hemodialysis associated amyloidosis:**Patients on long-term hemodialysisdeposition of ß2-microglobulin cannot be filtered through dialysis membranes.
- Localized Amyloidosis:Involves single organ Macroscopically normal or nodular depositsLung, larynx skin, urinary bladder, tongue
- In some cases surrounded by lymphocytes and plasma cell & AL type amyloid.

Endocrine amyloidosis:

- Microscopic deposits of localized amyloid o found in certain endocrine tumors, such as medullary carcinoma of the thyroid gland, islet tumors of the pancreas, pheochromocytomas, andundifferentiated carcinomas of the stomach, andin the islets of Langerhans in individuals with type IIdiabetes mellitus.
- Amyloidogenic proteins seem to be derived either frompolypeptide hormones (e.g., medullary carcinoma) or unique proteins (e.g., islet amyloid polypeptide).
- **Amyloid of aging Senile systemic amyloidosis:** systemic deposition of amyloid in elderly patients (usually in their 70s and 80s).
- previously called senile cardiac amyloidosis. (Because of the dominant involvement and related dysfunction of the heart)The amyloid in this form is composed of the normal TTR molecule.

Clinical Biochemistry

TOPIC- Abnormalities in Nitrogen metabolism Uremia, hyperuricemia, porphyria and factors affecting nitrogen balance and its clinical investigation

Content

- Uremia
- Hyperuricemia
- Porphyria
- Factors affecting nitrogen balance
- Clinical investigation
- References

Uremia

- Uremia is a dangerous condition that occurs when kidney stop filtering toxins out through your urine (decreased function) so that waste products or toxins that your kidneys normally send out in your urine end up in your bloodstream instead.
- Waste products or toxins are build up in your blood.
- Uremia means “urine in the blood” .
- It affects the entire body, if untreated, can be life-threatening.
- Uremia most often occurs due to **chronic kidney disease (CKD)** that may lead to end-stage renal (kidney) disease (ESKD), but can also occur quickly leading to acute **kidney injury** and failure (AKI).

Causes of Azotemia (Uremia)

Prerenal

1. Congestive heart failure
2. Burns
3. Haemorrhage in GIT
4. Shock and stress
5. Dehydration

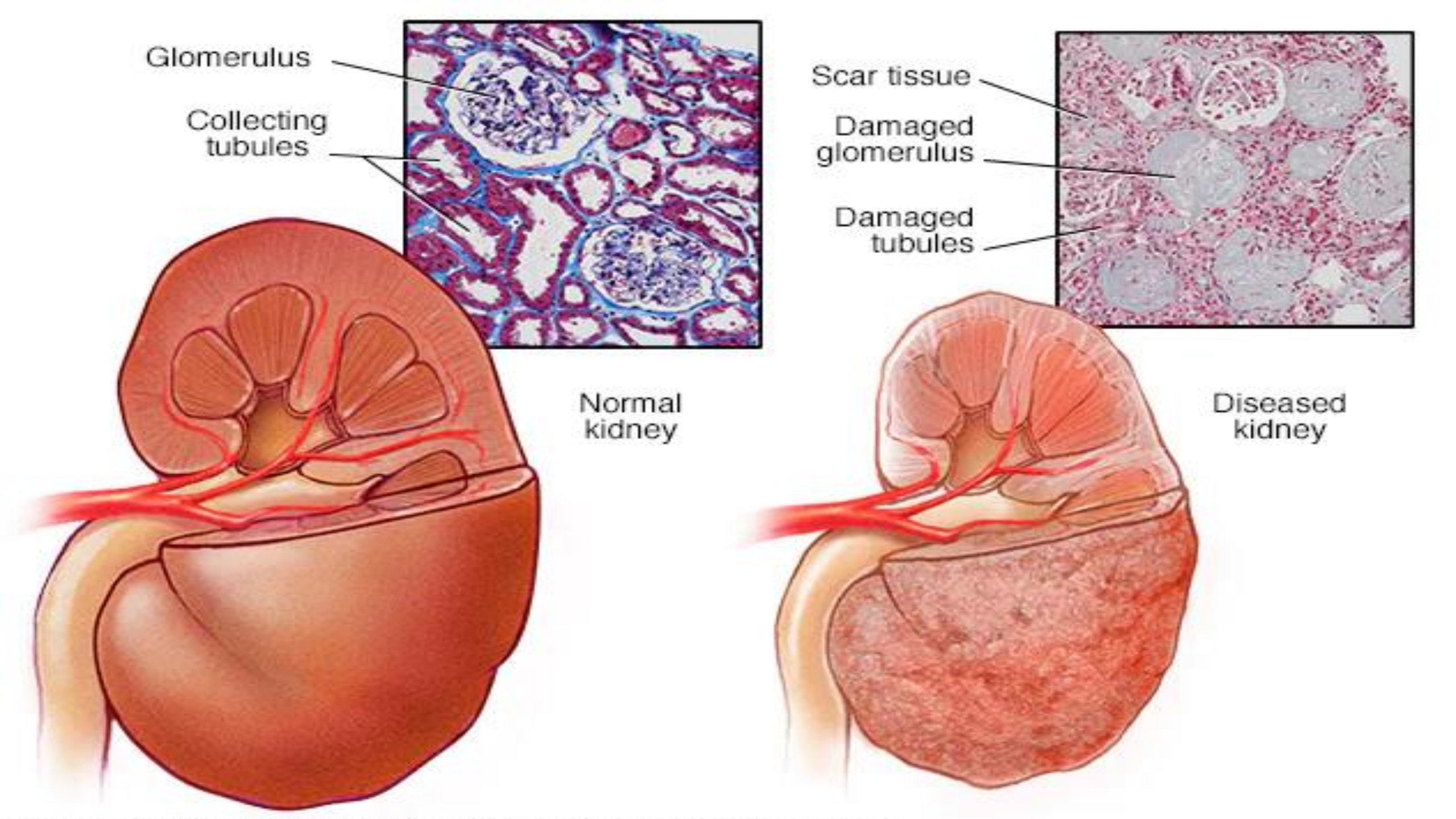
Renal

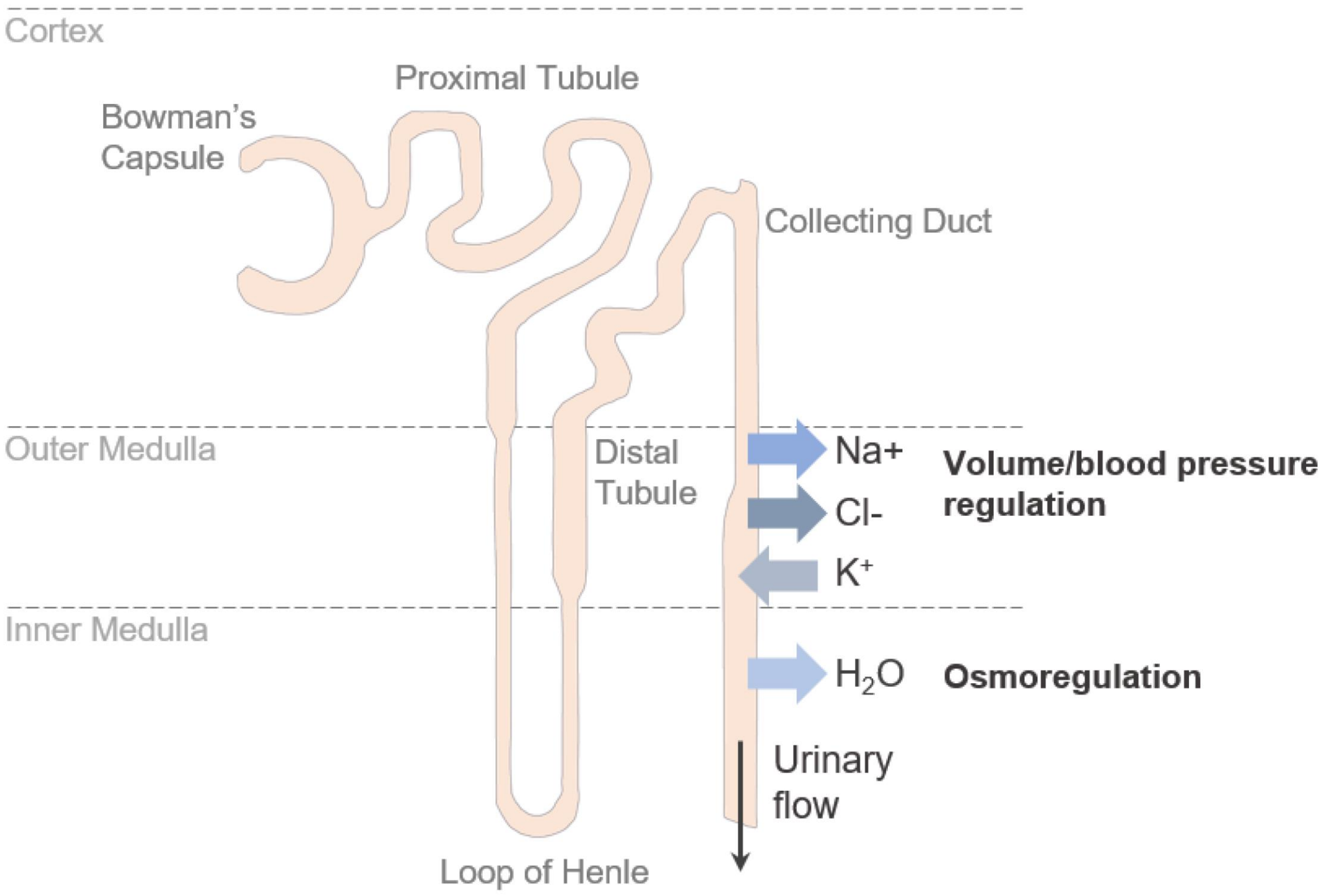
1. Glomerulonephritis
2. Pyelonephritis
3. Diabetes mellitus
5. Nephrotoxic drugs
6. Renal failure
7. Anabolic steroids use

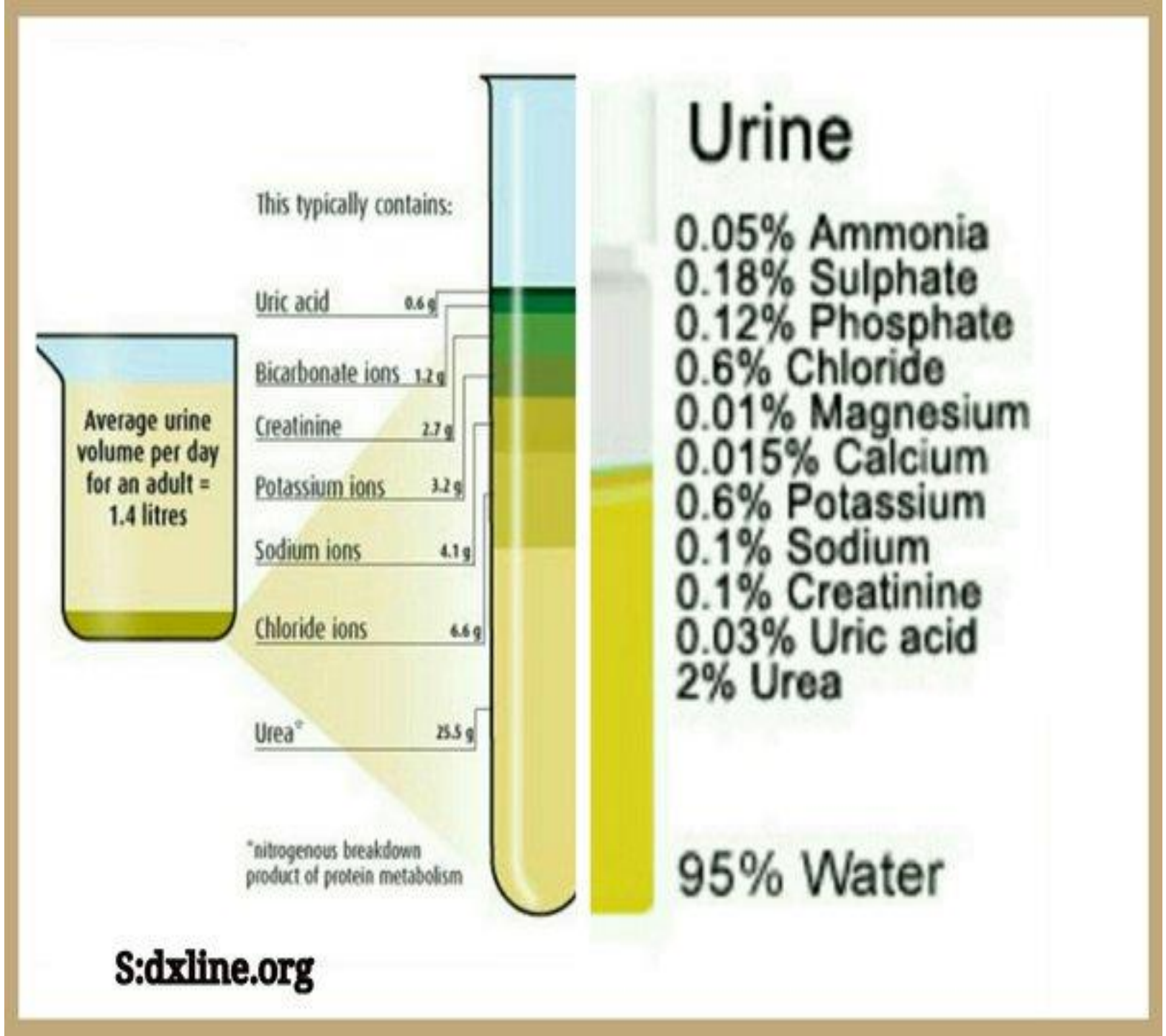
Post renal

Urinary tract obstruction

1. Stones/neoplasm
2. Bladder/Urethral abnormality
3. Bladder outlet obstruction

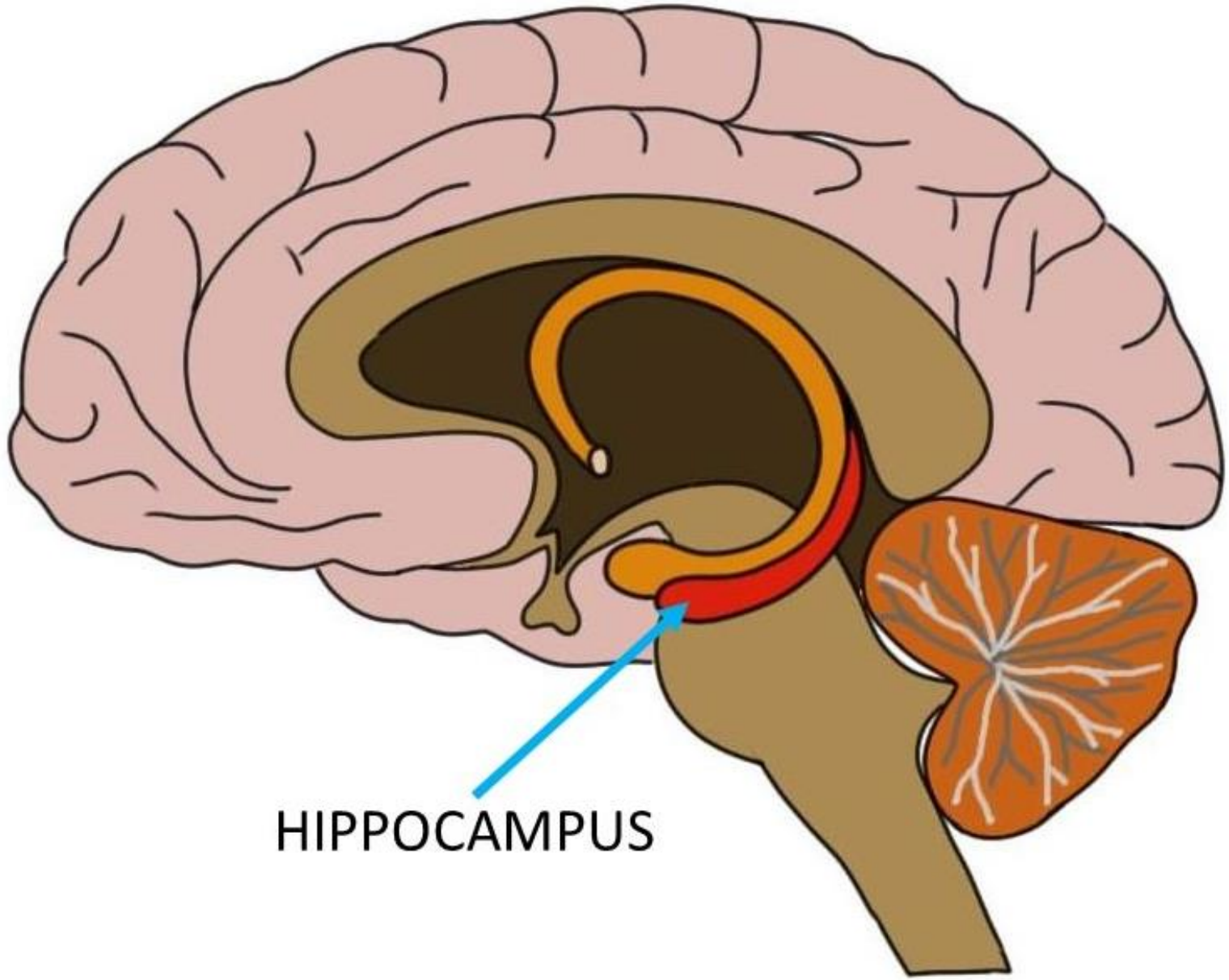

Glomerulus
Collecting tubules
Normal kidney
Scar tissue
Damaged glomerulus
Damaged tubules
Diseased kidney


Cortex
Proximal Tubule
Bowman's Capsule
Collecting Duct
Outer Medulla
Distal Tubule
Na+
Cl-
K+
Volume/blood pressure regulation
Inner Medulla
H2O
Osmoregulation
Urinary flow
Loop of Henle


Urine
This typically contains:
Uric acid 0.6 g
Bicarbonate ions 1.2 g
Creatinine 2.7 g
Potassium ions 3.2 g
Sodium ions 4.1 g
Chloride ions 6.6 g
Urea* 25.5 g
Average urine volume per day for an adult = 1.4 litres
*nitrogenous breakdown product of protein metabolism
0.05% Ammonia
0.18% Sulphate
0.12% Phosphate
0.6% Chloride
0.01% Magnesium
0.015% Calcium
0.6% Potassium
0.1% Sodium
0.1% Creatinine
0.03% Uric acid
2% Urea
95% Water
S:dxline.org

Symptoms of uremia?

- Cognitive dysfunction (problems with thinking and remembering).
- Fatigue.
- Shortness of breath from fluid accumulation.
- Loss of appetite.
- Muscle cramps.
- Nausea and vomiting.
- Itching.
- Unexplained weight loss.


HIPPOCAMPUS

Causes of uremia

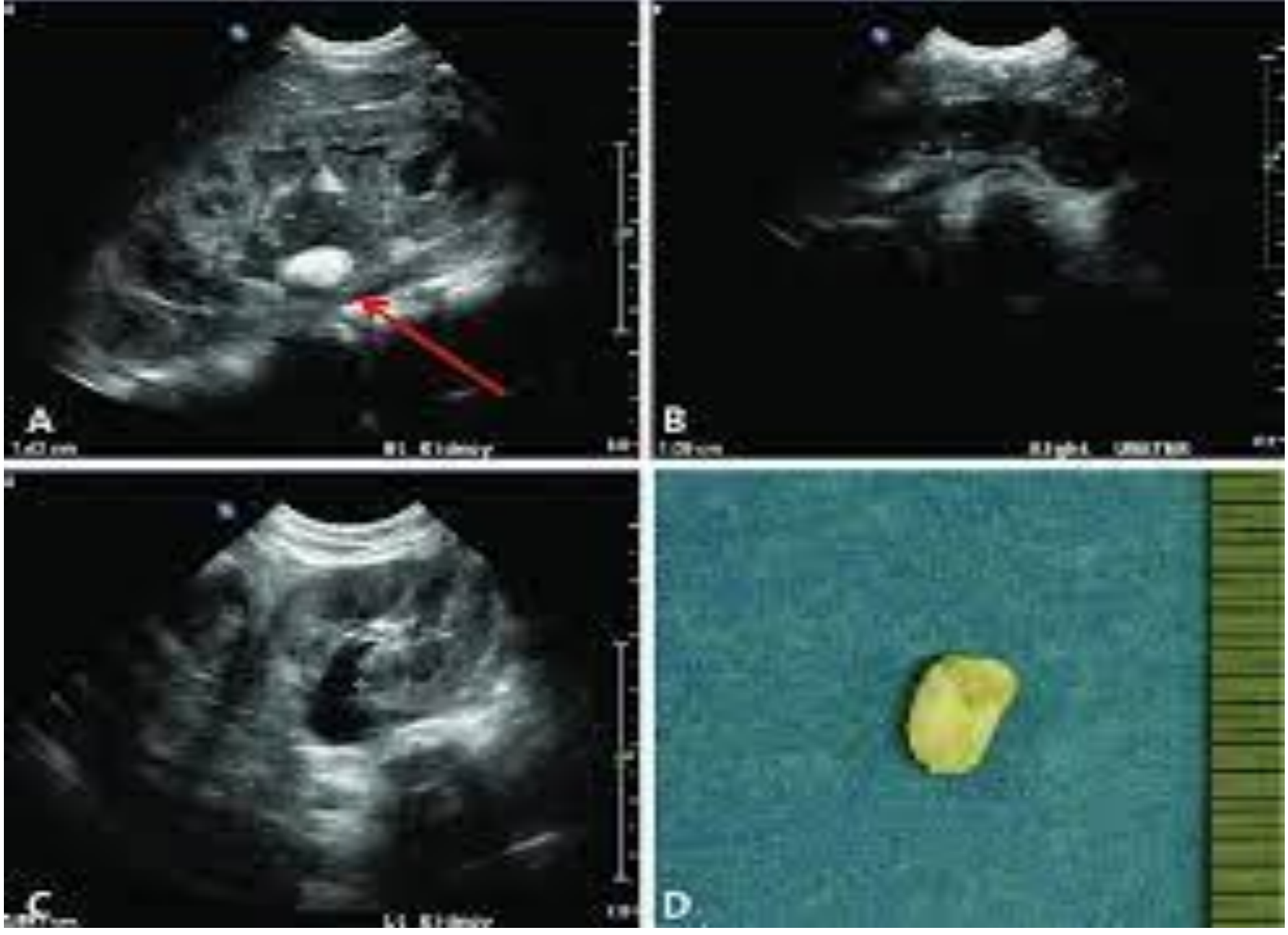
- Uremia is caused by extreme and usually irreversible damage to your kidneys.
- This is usually from **chronic kidney disease**. The kidneys are no longer able to filter the waste from your body and send it out through your urine.
- Instead, that waste gets into your bloodstream, causing a potentially life-threatening condition.

Causes of chronic kidney disease may include:

- High blood pressure
- Polycystic kidney disease
- Diabetes (both type 1 and 2)
- Inflammation of the filtering units in the kidneys called glomeruli
- Inflammation of the kidney's tubules and the structures around them
- Some types of cancer
- kidney stones that block the urinary tract for a prolonged period of time
- kidney infections

Uremia diagnosed?

- Evaluates your symptoms.
- Performs a physical exam.
- Reviews the lab tests mentioned above. Creatinine (measure of how well your kidneys are performing their job of filtering waste from your blood) and Blood Urea Nitrogen (BUN) test (measure urea level in the blood)
- They also used to estimate your glomerular filtration rate (eGFR). This rate measures your kidney function.
- A kidney ultrasound checks the shape and size of your kidneys and looks for scarring. An ultrasound can also detect kidney blockages, such as kidney stones, or injuries.


A
B
C
D

Treatment options

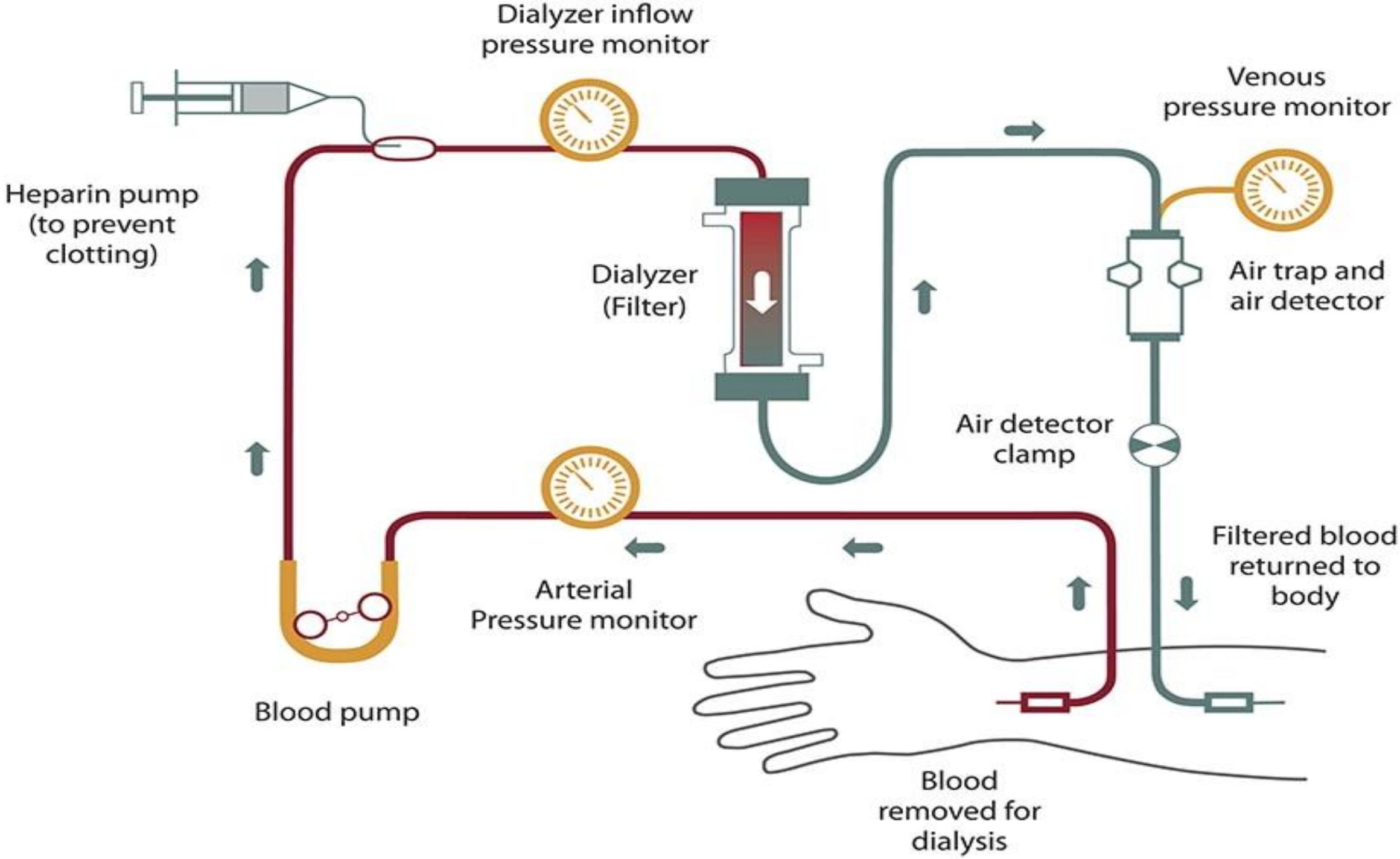
I. Dialysis is the main treatment option for uremia.

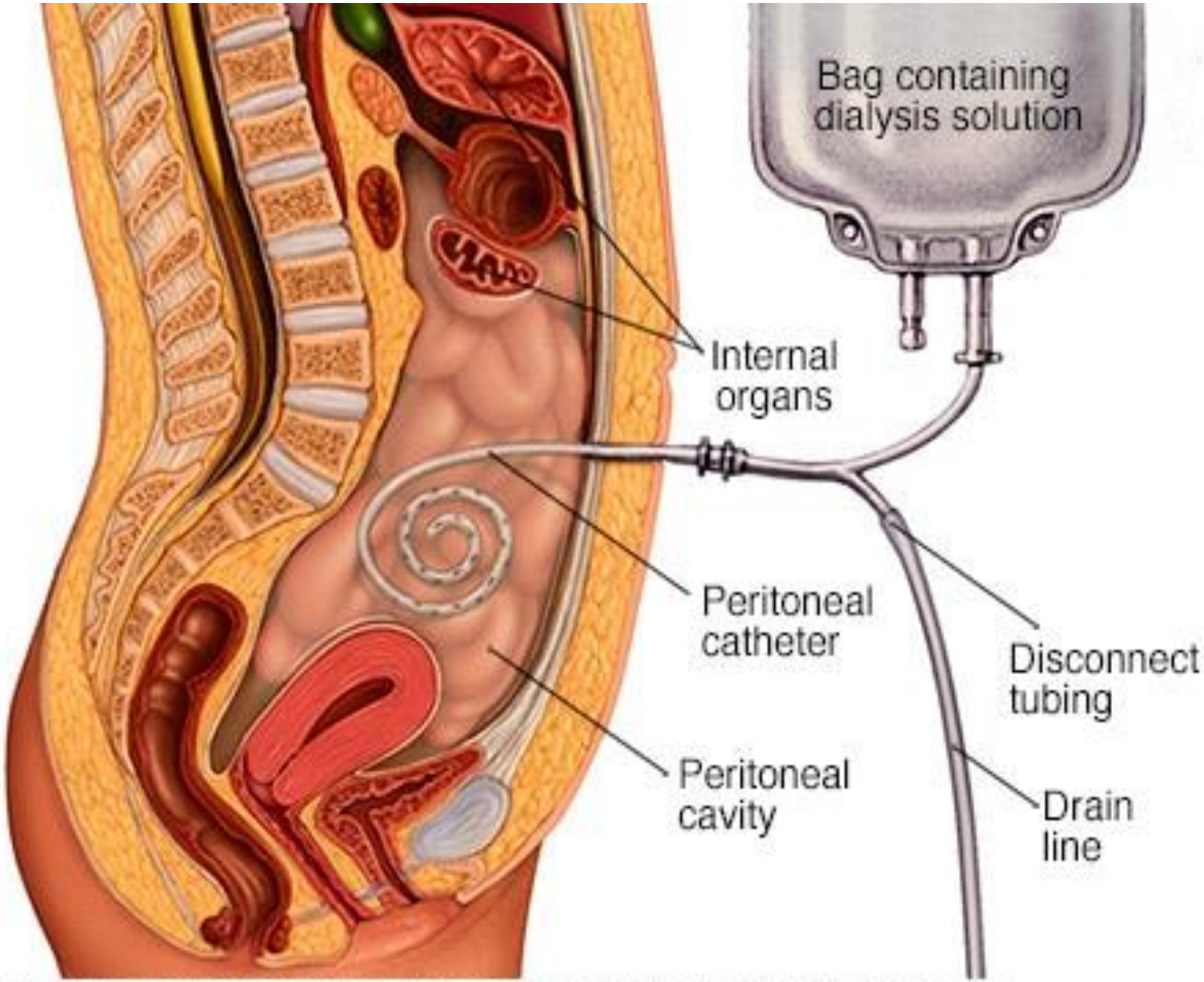
- Dialysis is when the removal of wastes, extra fluids, and toxins from your bloodstream is handled artificially instead of by your kidneys. There are two types of dialysis. These types are:

1. **Hemodialysis:** A machine is used to remove the waste from your blood.
2. **Peritoneal dialysis:** A catheter (small tube) is inserted into your abdomen. A dialysis fluid fills your abdomen. This fluid absorbs the waste and extra fluid. Eventually, the fluid will remove the wastes from your body when it drains out.

II. A kidney transplant is another treatment option if you reach end-stage renal failure.

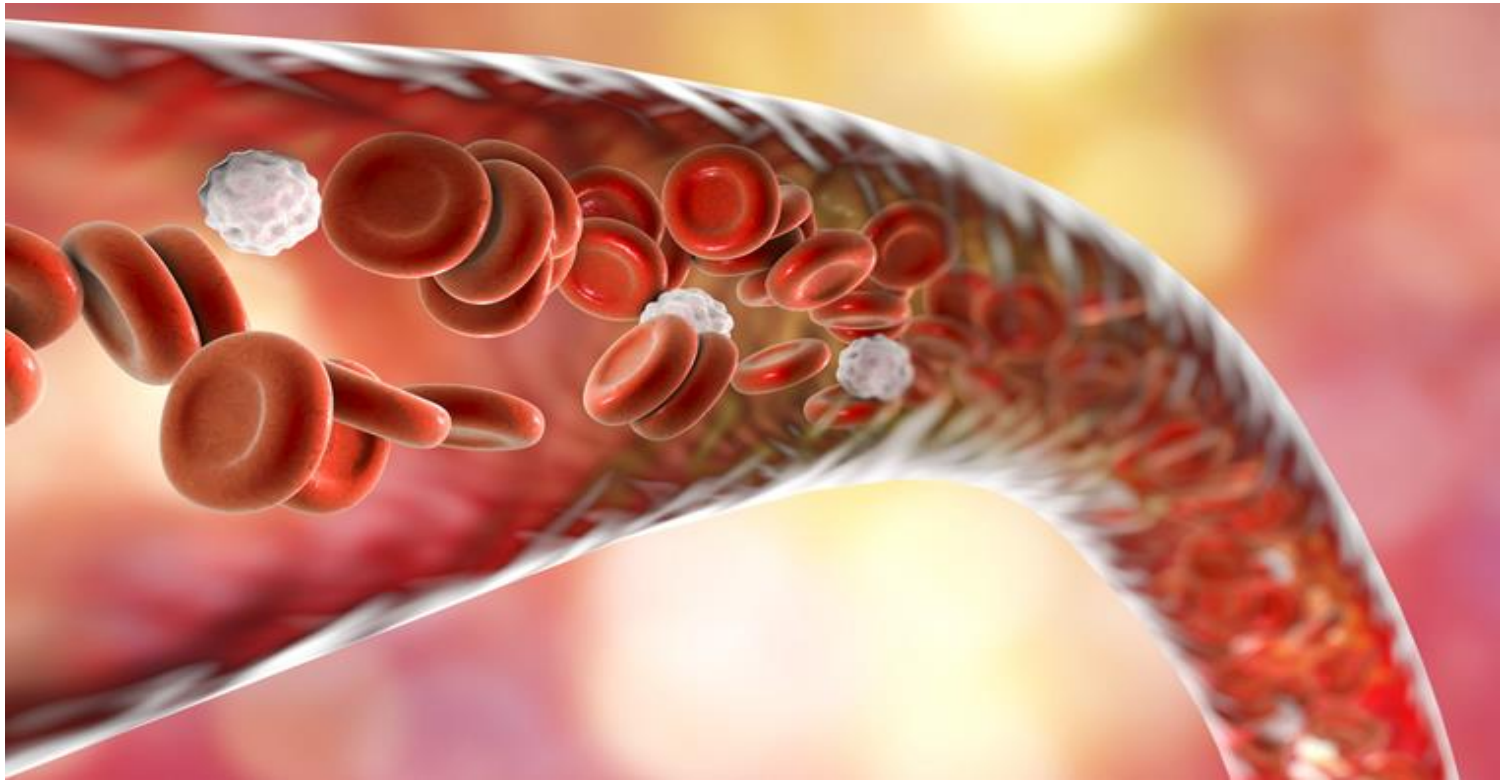
- Antirejection medication long-term to prevent your body from rejecting the donor kidney.


Dialyzer inflow
pressure monitor
Venous
pressure monitor
Heparin pump
(to prevent
clotting)
Dialyzer
(Filter)
Air trap and
air detector
Air detector
clamp
Filtered blood
returned to
body
Arterial
Pressure monitor
Blood pump
Blood
removed for
dialysis



Hyperuricemia

- Hyperuricemia is when you have too much uric acid in your blood.
- (Hyper- high) (Uricemia- uric acid)
- This condition can lead to health problems such as gout and kidney stones.



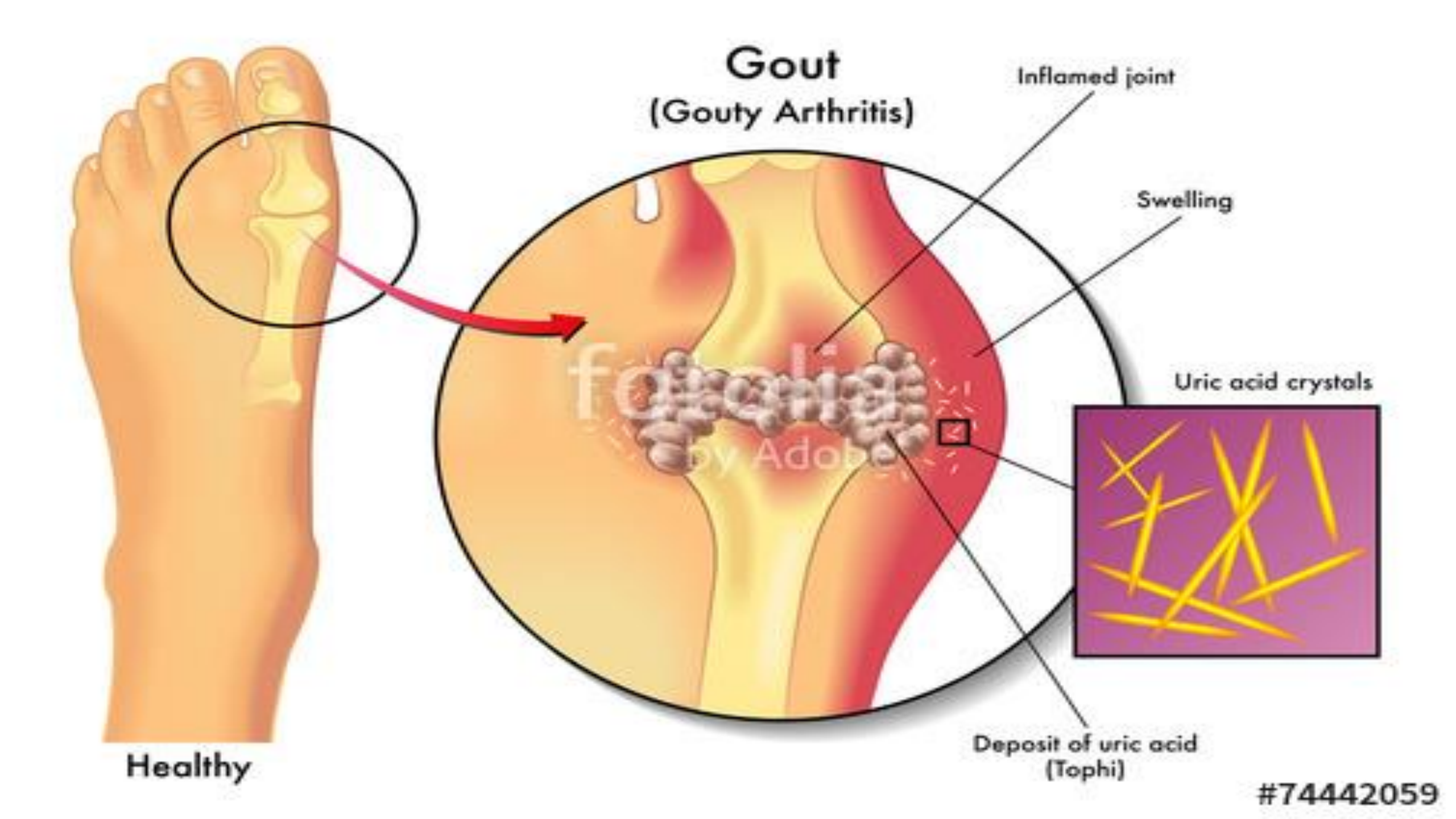
Causes of Hyperuricemia

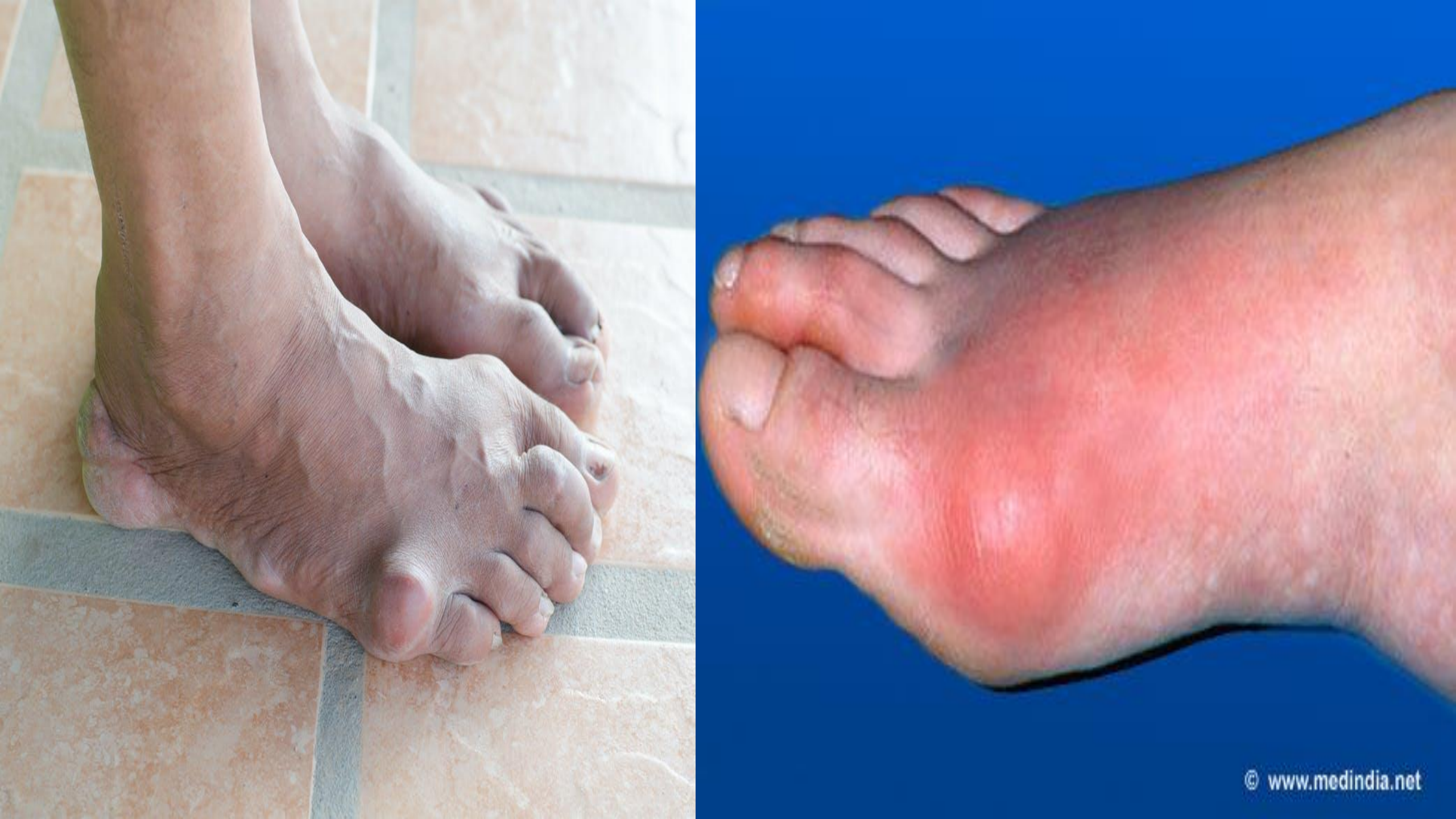
You may be producing too much uric acid if:

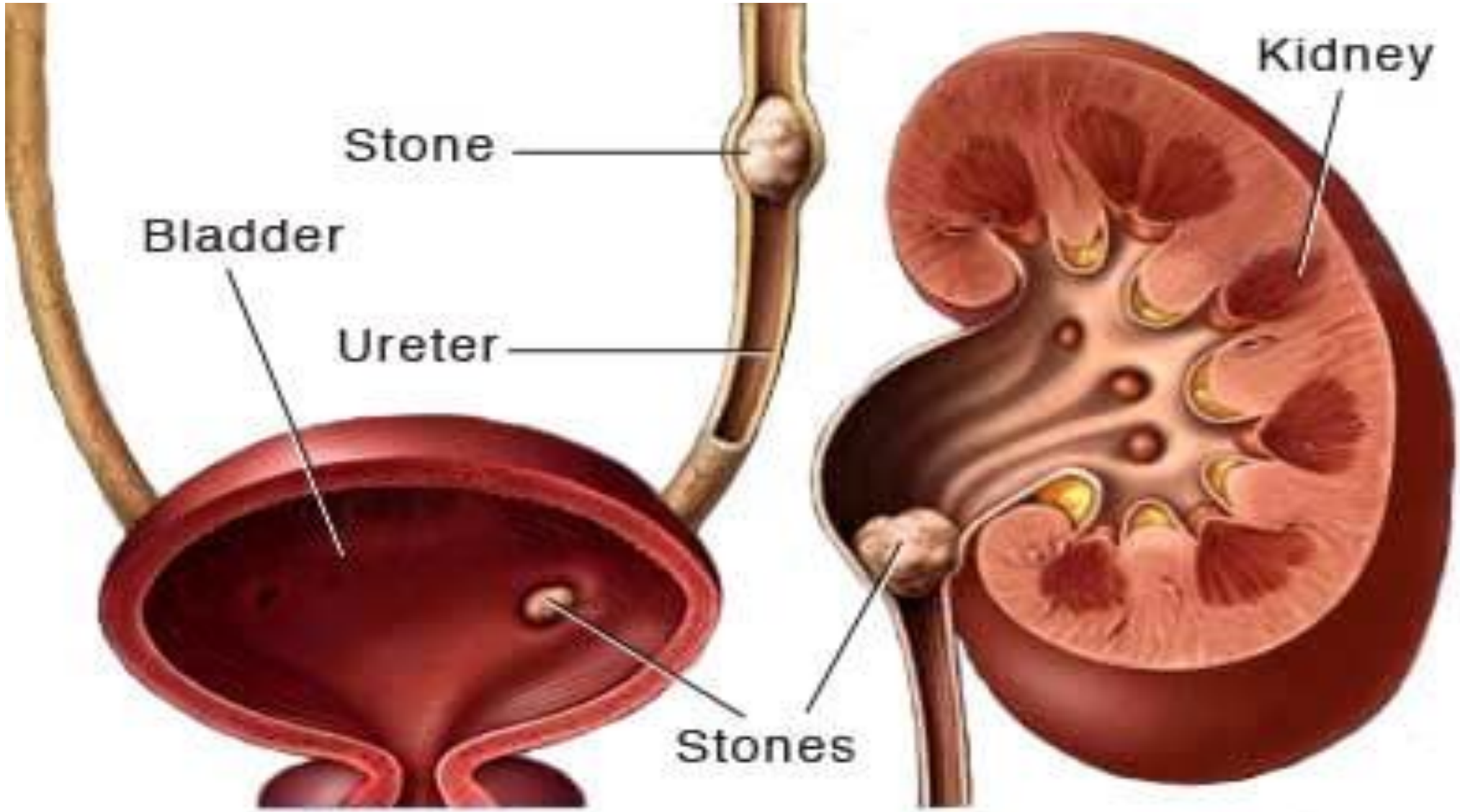
- You have a **purine-rich diet**. Foods high in purine include some organ meats, game, herrings and a few other types of seafood, and beer.
- Your **body's cells break down** due to exercise and certain other conditions.
- Your **body naturally makes too many purines**.

Symptoms of Hyperuricemia

- Most people with hyperuricemia have no symptoms
- According to research, around 21 percent of the general population don’t have symptoms.
- General U.S. population, 3.9 percent have **gout**, the most common complication of hyperuricemia. This is a disorder where uric acid builds up in the tissues and blood and leads to painful joints, particularly in your big toe.
- Another common symptom of hyperuricemia is the formation of **kidney stones**, which can lead to sharp pain in the abdomen or side, nausea, and vomiting.


Gout
(Gouty Arthritis)
Inflamed joint
Swelling
Uric acid crystals
Deposit of uric acid
(Tophi)
Healthy
#74442059


© www.medindia.net



Diagnosing Hyperuricemia

- **Physical examination.** If you have gout, you'll have a swollen and warm joint. Gout usually affects the big toe, but it can also affect any joint in your body.
- If you have kidney stones, a particular area of your lower back will be tender to the touch.
- **Lab studies.** Your doctor may order bloodwork to test for your level of uric acid. Your doctor may ask you to collect your urine over a 24-hour period to test for its quantity of uric acid.
- **Renal ultrasound.** Your doctor may suggest that you get a renal or kidney ultrasound if you have kidney stones.

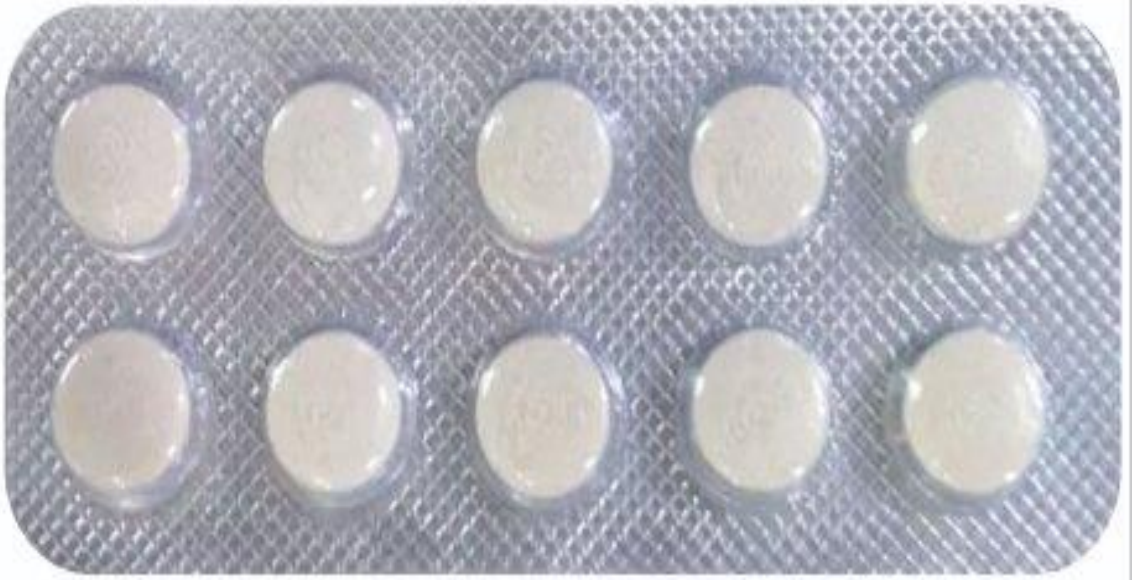
Treatment

Gout

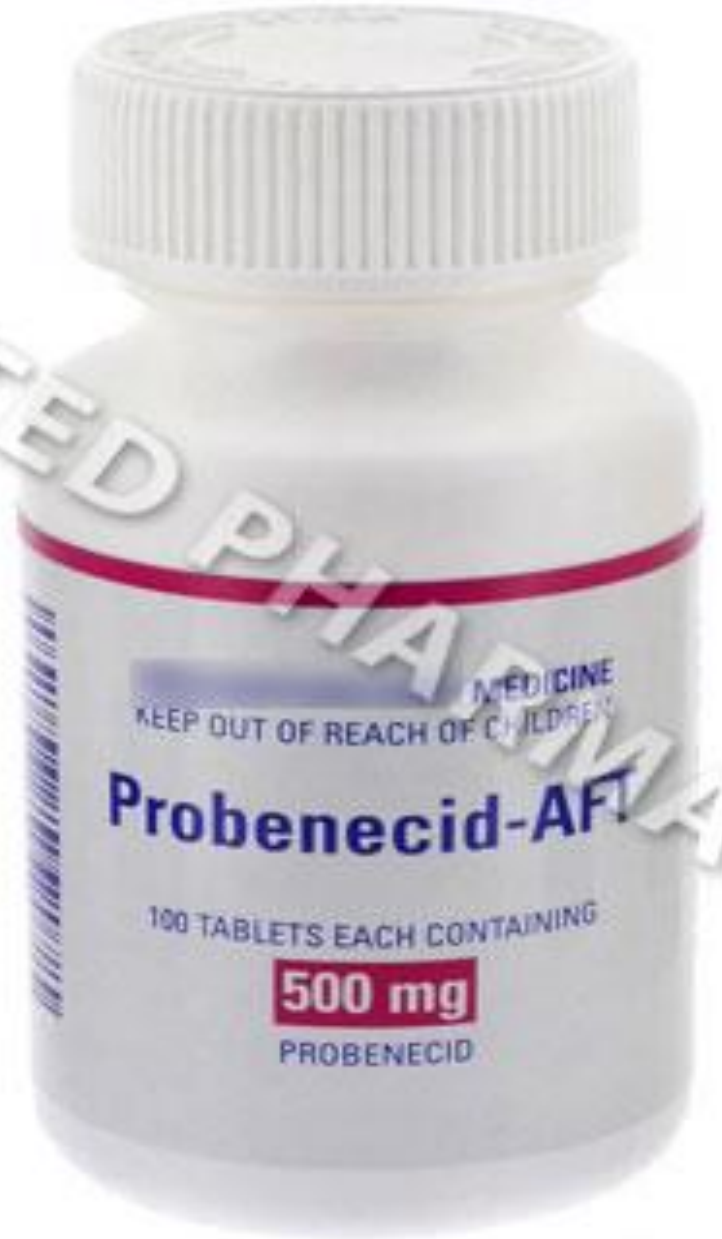
1. **Nonsteroidal anti-inflammatory drugs** (NSAIDs) can help prevent or reduce the severity of gout. These include ibuprofen (Advil, Motrin IB), naproxen (Aleve, Naprosyn), and celecoxib (Celebrex),
2. **Colchicine** is often used to prevent or treat gout, particularly for people who don’t tolerate NSAIDs well.
3. **Probenecid** helps lower uric acid levels by increasing urination and is used to help prevent gout attacks. Probenecid does not cure gout, but after you have been taking it for a few months it will help prevent gout attacks. This medicine will help prevent gout attacks only as long as you continue to take it.
4. **Allopurinol** and **febuxostat** help prevent gout by reducing the amount of uric acid in your bloodstream.


Bell's Healthcare
Ibuprofen
200mg Coated Tablets
For Fast
Effective
Pain Relief


Naproxen Tablets 250mg.
Naproxen-250
नेप्रोक्सेन–250
10x10 Tablets
Blister pack
Ausmed




colchicine

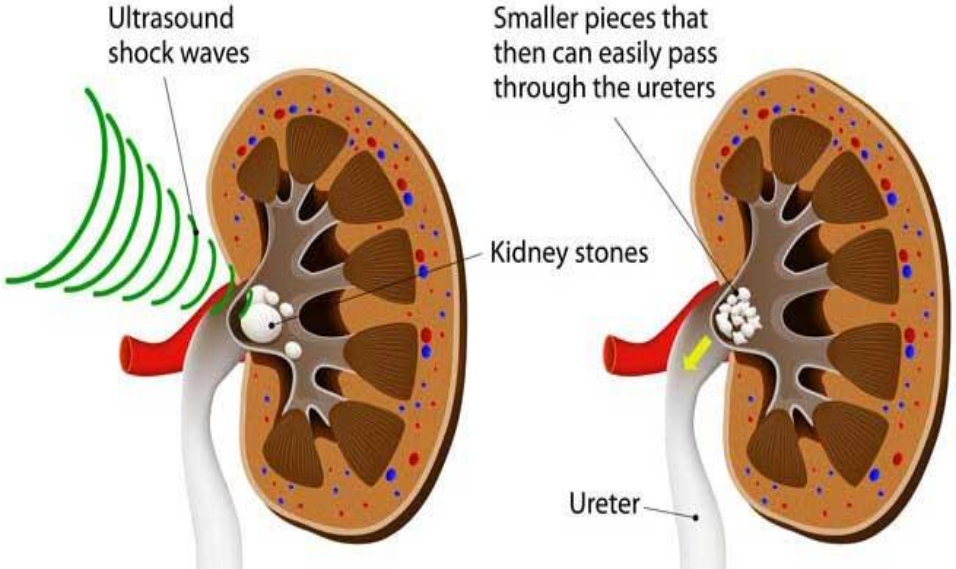



NDC 0591-5543-10
Allopurinol
Tablets USP
100 mg
Watson
1000 Tablets Rx only

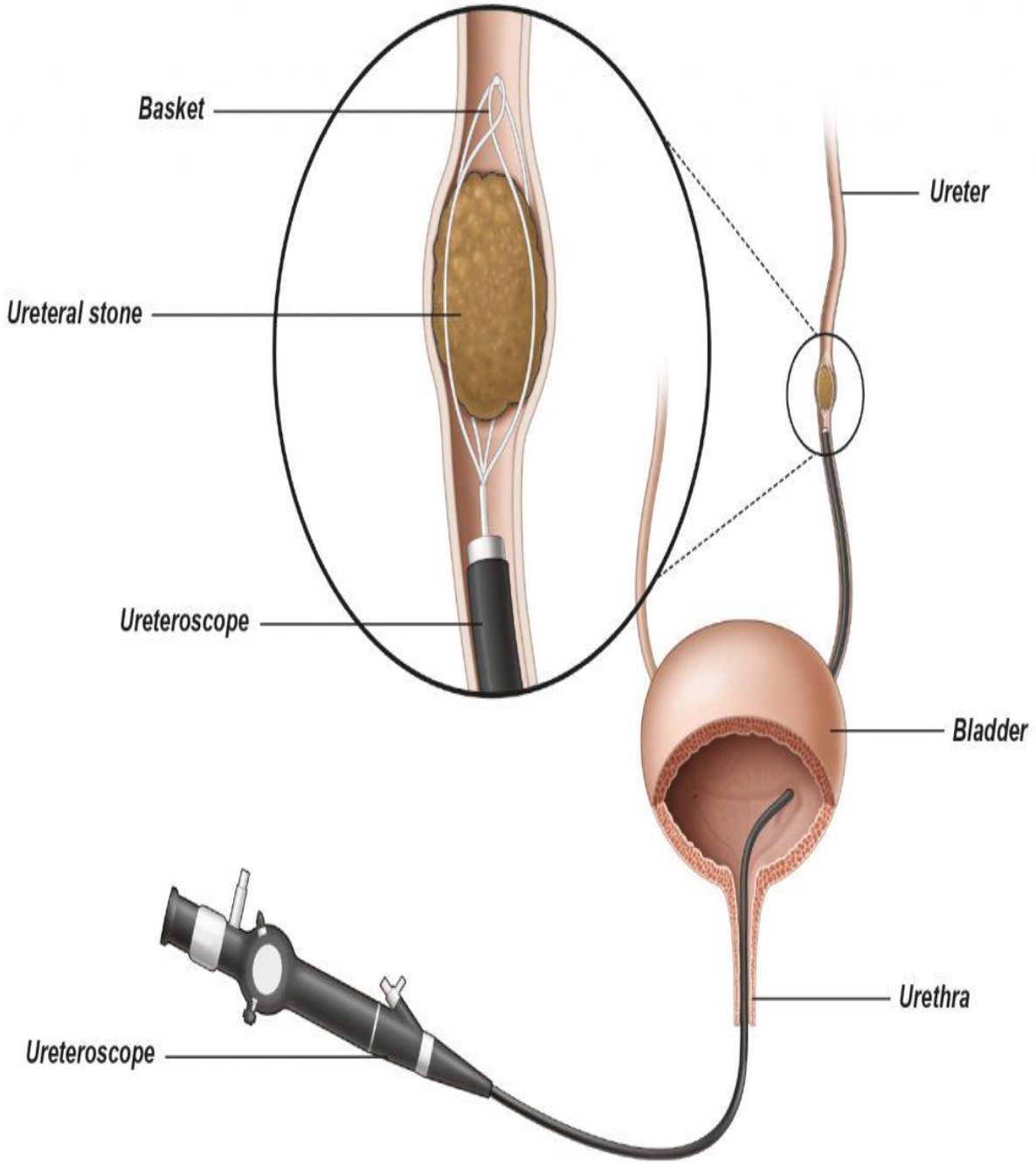

Abbott
Febuxostat Tablets 40 mg
Febustat™ 40
40 mg
5 x 2 x 15 Tablets
फेबुस्टाट ४०
Abbott
Febuxostat Tablets 40 mg
Febustat™ 40

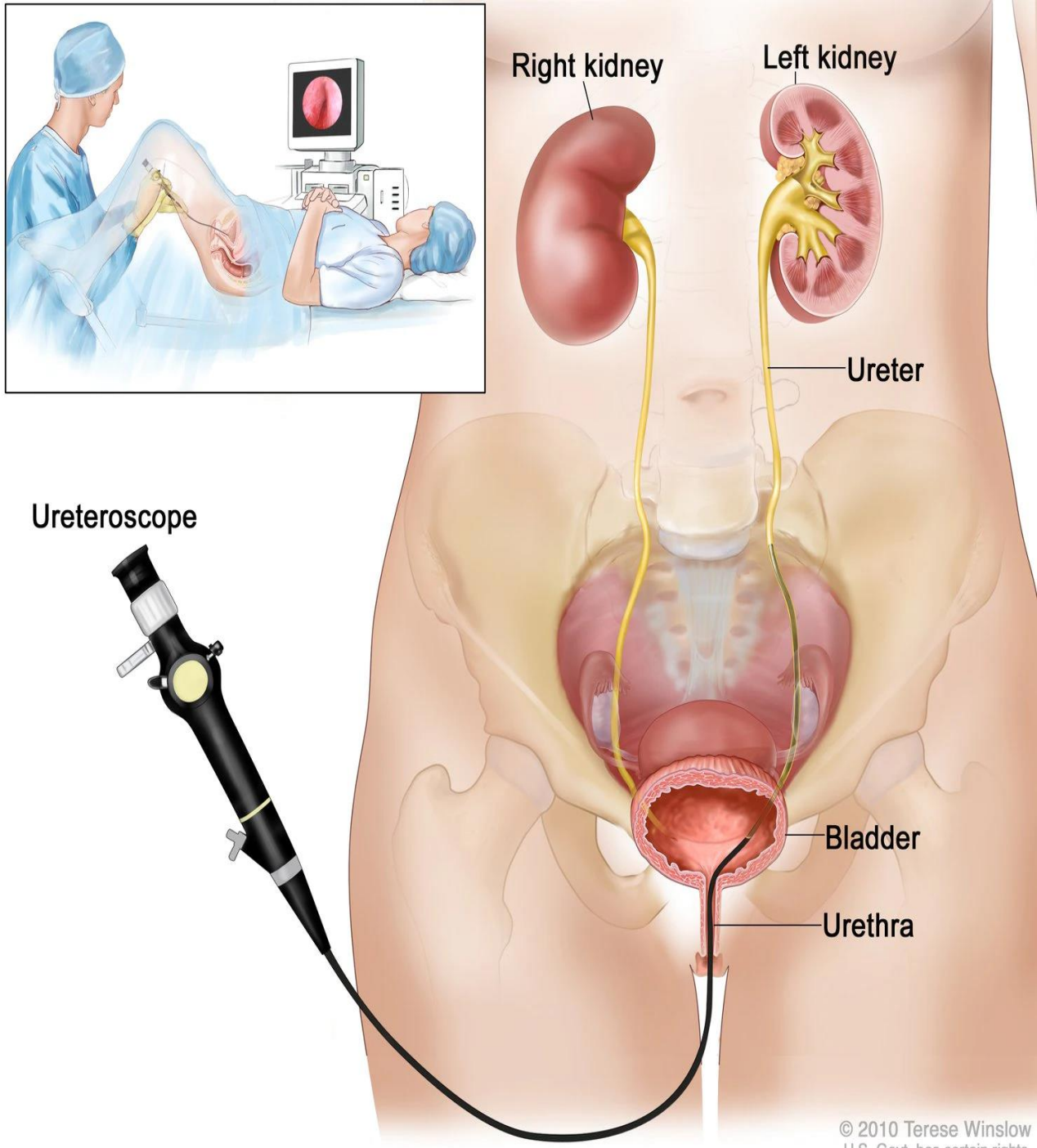
Kidney stones

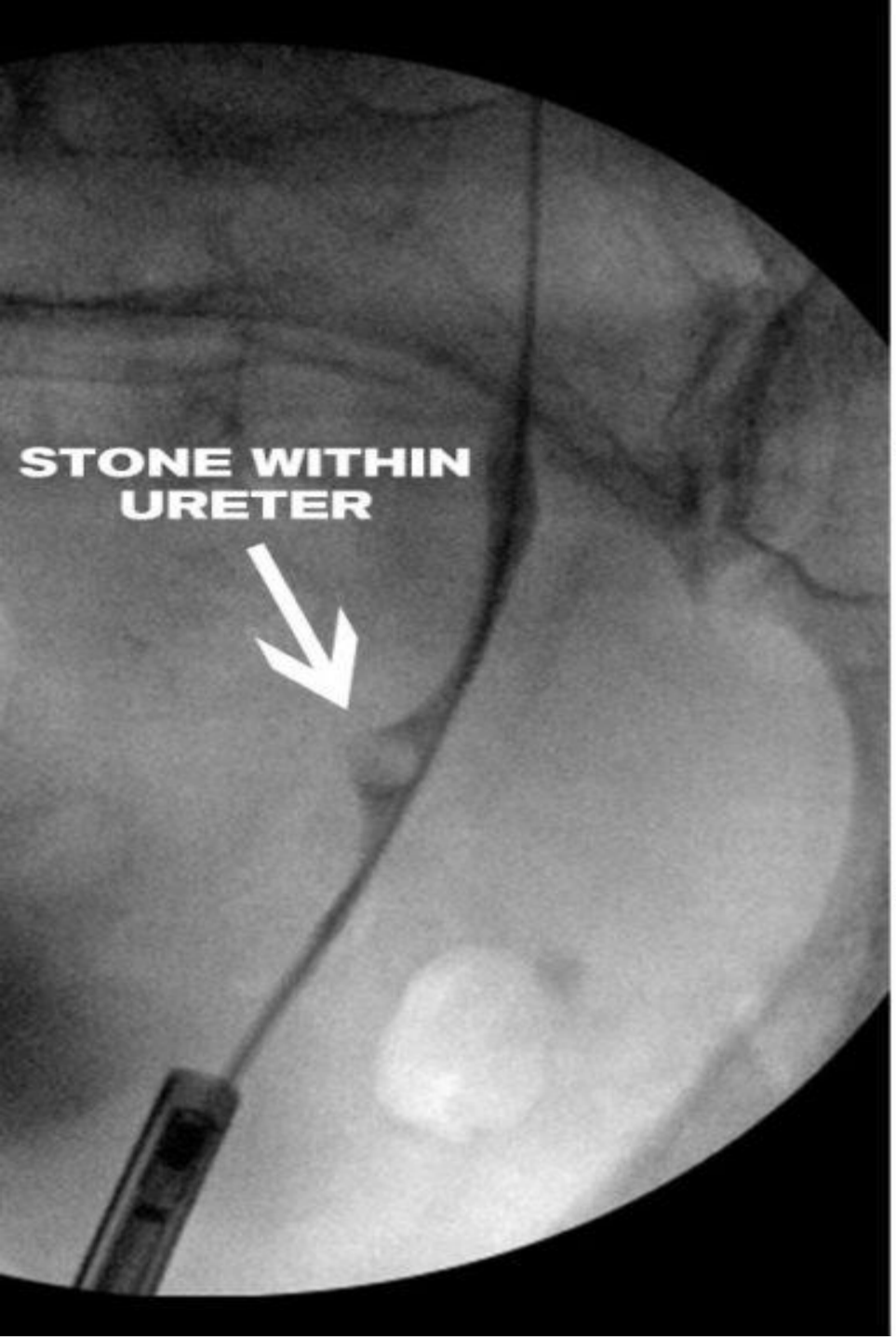
- If you have kidney stones smaller than 5 mm, your doctor may advise you to drink a lot of water and take over-the-counter pain medications until the stones pass.
- Some doctors prescribe medications such as **tamsulosin** (Flomax) to relax the muscles in your urinary tract. This can make it easier and less painful to pass the stones.
- **Extracorporeal shock wave lithotripsy** is a non-invasive procedure where ultrasonic energy or shock waves are directed through your skin at the kidney stone. The shock waves break the large stone into smaller pieces that can pass more easily through your urinary system.
- If the stones are greater than **10 mm**, you may need to have them surgically removed.
- Ureteroscopic surgery is performed by passing a 2 mm scope through your urethra. It goes through your bladder and directly into the ureters, which are the tubes connecting your kidneys to your bladder.

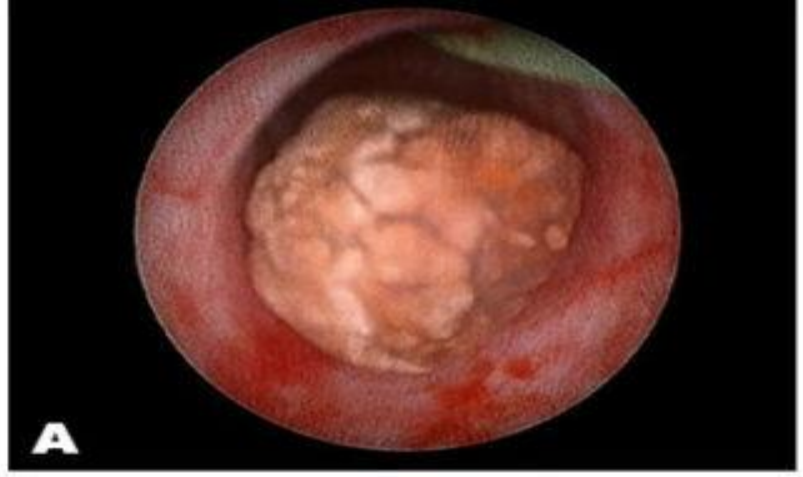


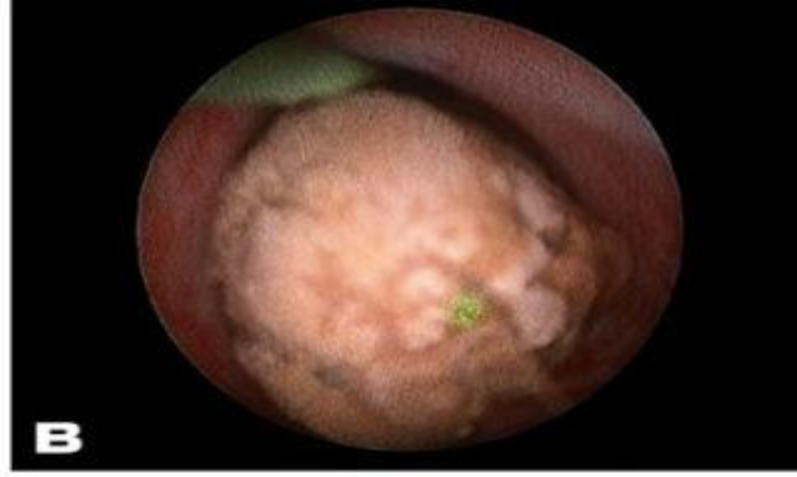
Extracorporeal shock wave lithotripsy (ESWL) machine

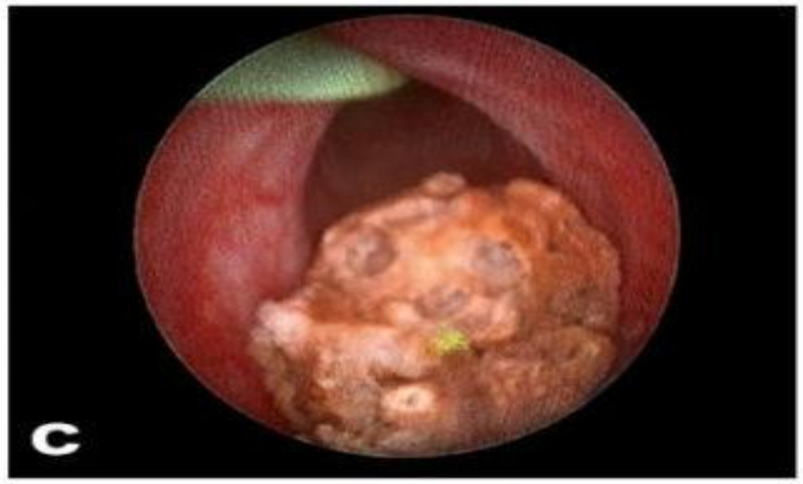


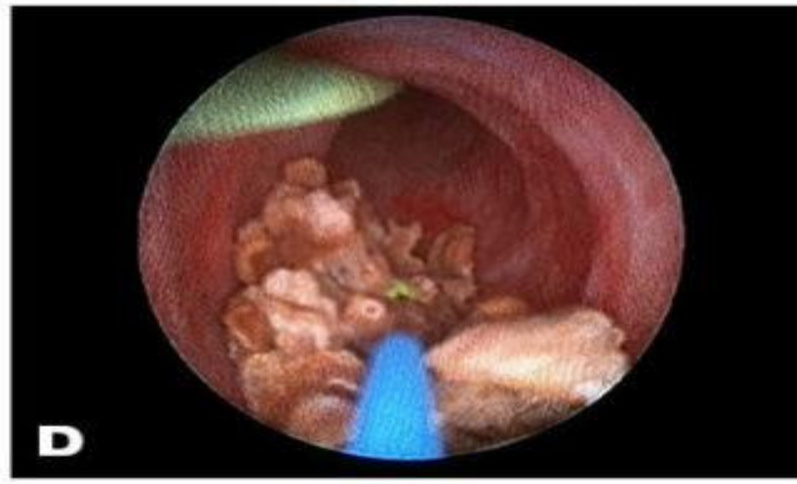


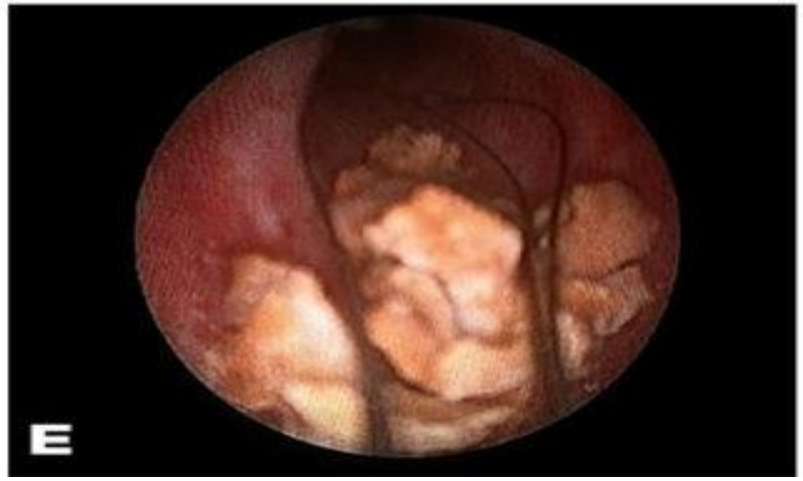

STONE WITHIN
URETER

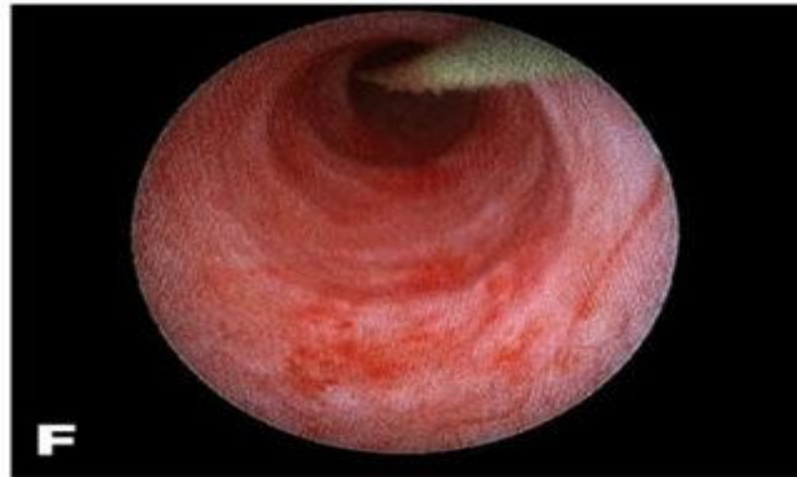

A

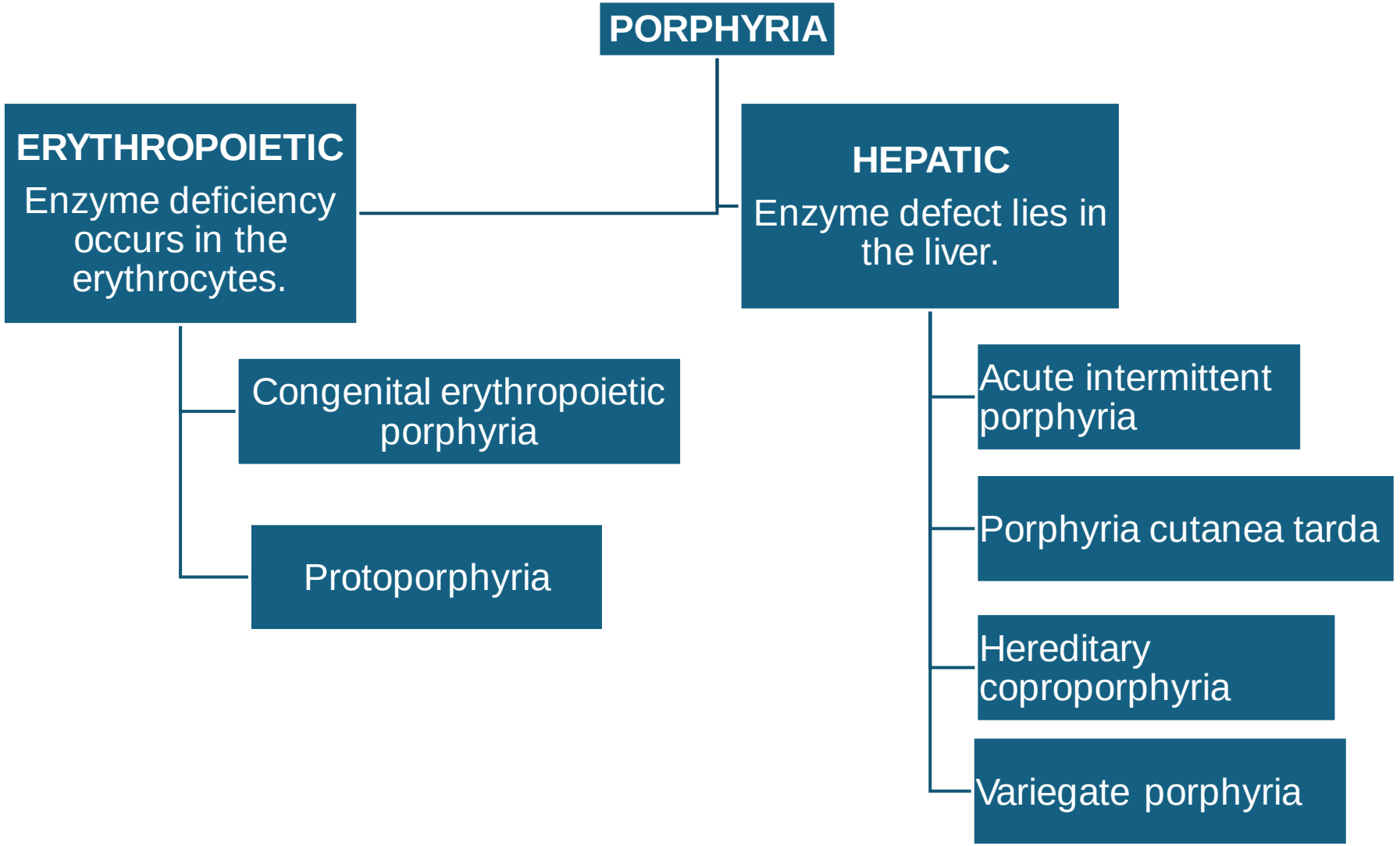

B


C

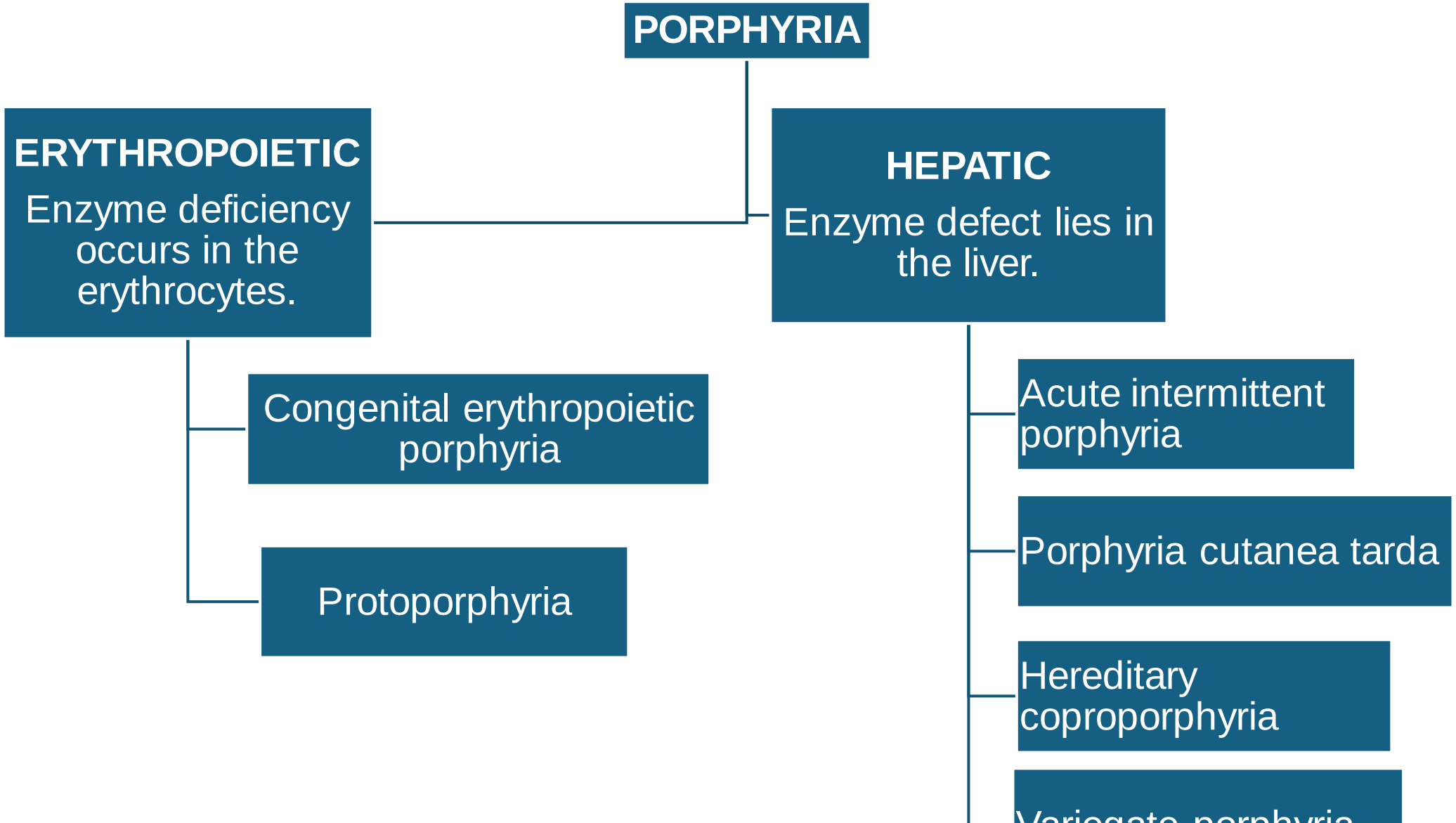

D


E


F

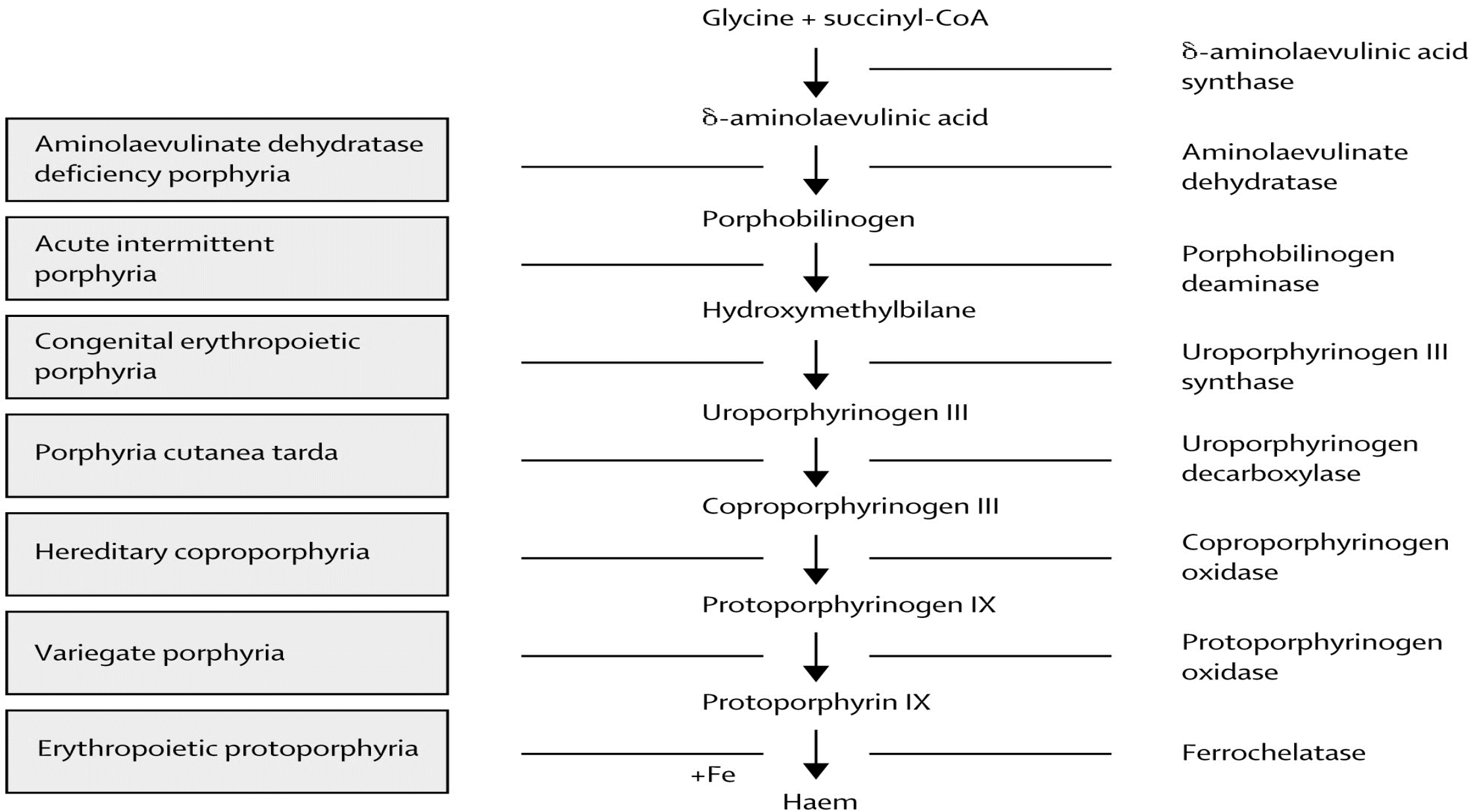

PORPHYRIA
ERYTHROPOIETIC
Enzyme deficiency occurs in the erythrocytes.
Congenital erythropoietic porphyria
Protoporphyria
HEPATIC
Enzyme defect lies in the liver.
Acute intermittent porphyria
Porphyria cutanea tarda
Hereditary coproporphyria
Variegate porphyria

Porphyria


PORPHYRIA
ERYTHROPOIETIC
Enzyme deficiency occurs in the erythrocytes.
Congenital erythropoietic porphyria
Protoporphyria
HEPATIC
Enzyme defect lies in the liver.
Acute intermittent porphyria
Porphyria cutanea tarda
Hereditary coproporphyria

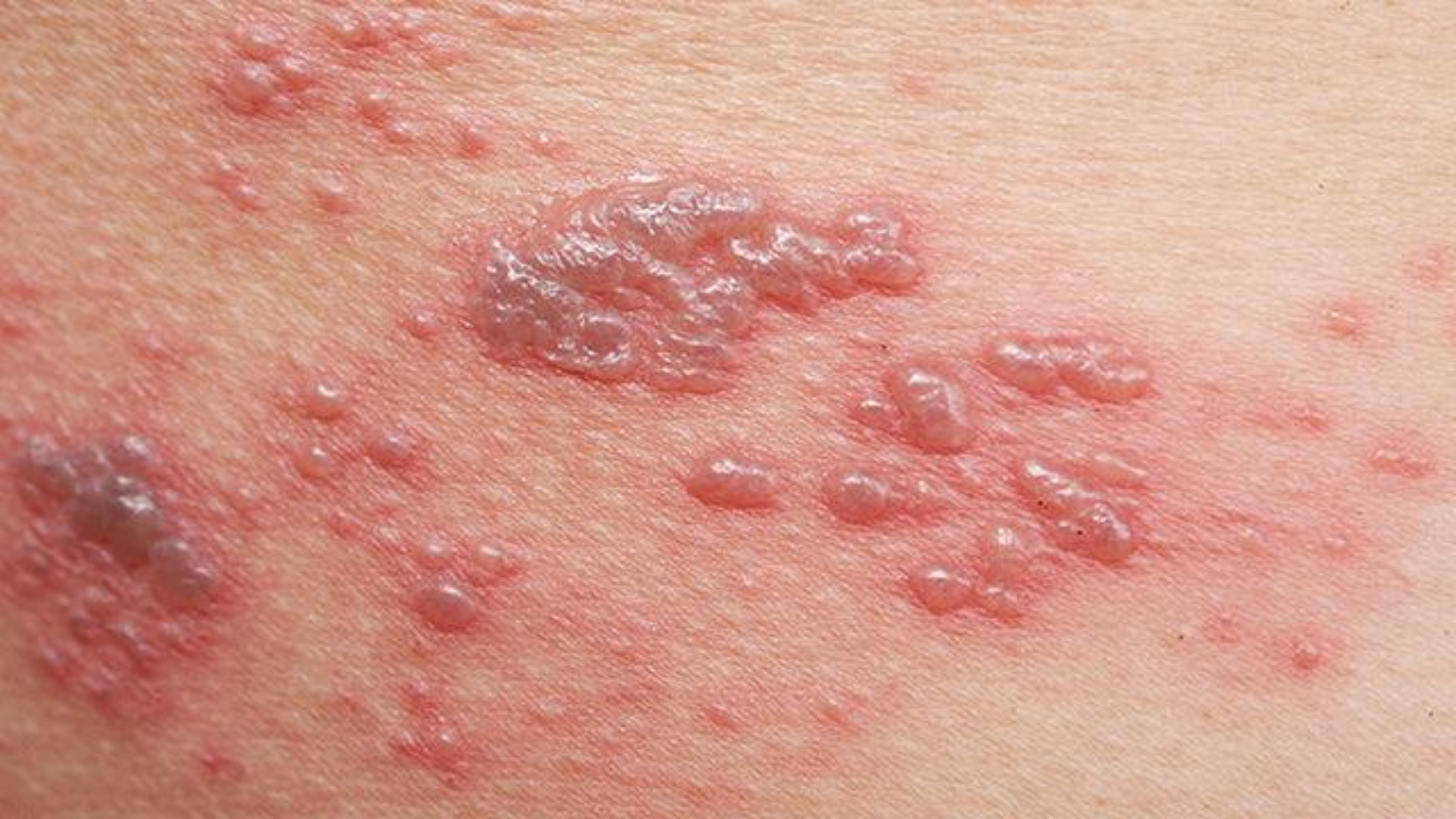
Porphyria

- Mutation in gene encoding enzymes involved in **heme** synthesis.
- Inheritable disorder
- 8 types

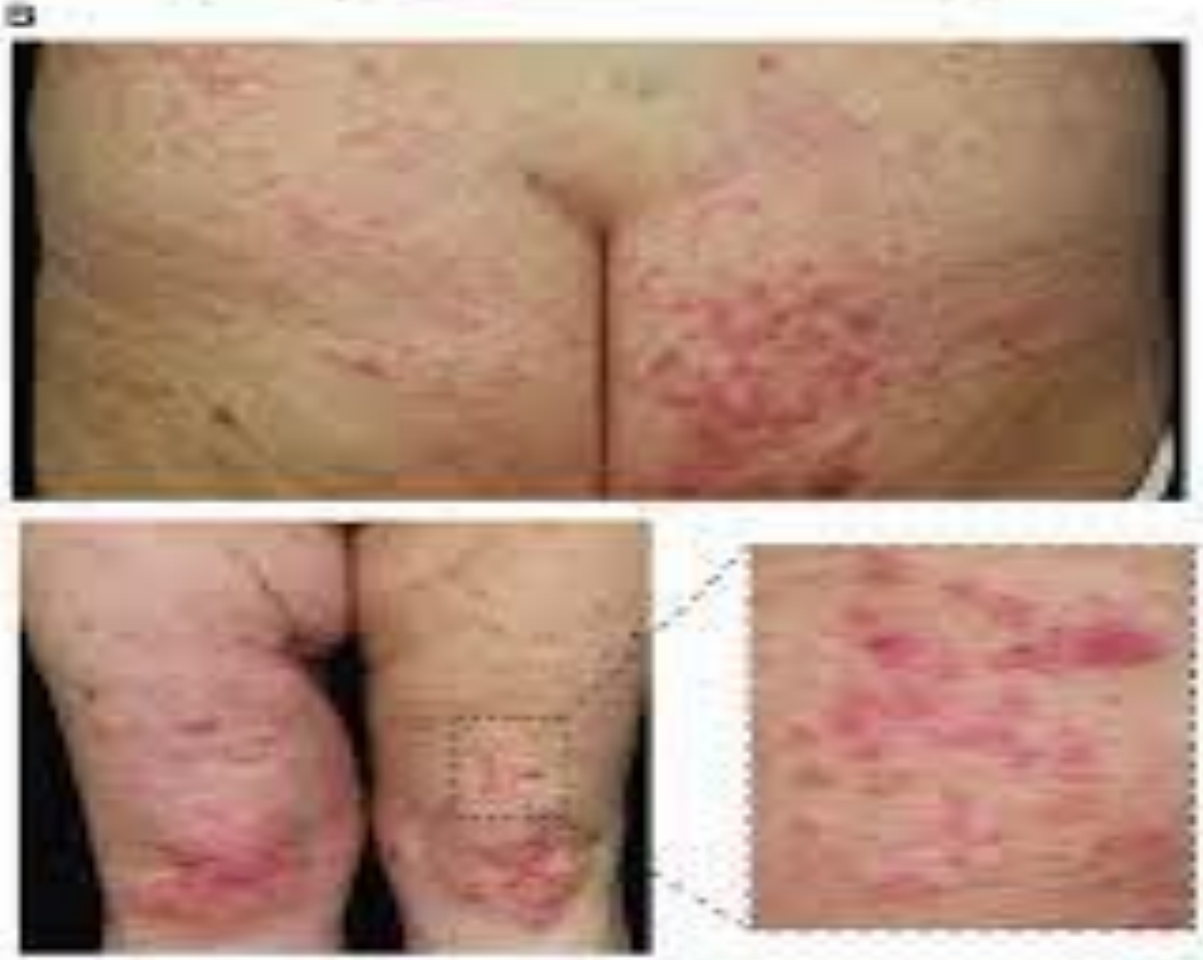

Glycine + succinyl-CoA
δ-aminolaevulinic acid synthase
δ-aminolaevulinic acid
Aminolaevulinate dehydratase
Porphobilinogen
Porphobilinogen deaminase
Hydroxymethylbilane
Uroporphyrinogen III synthase
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
Coproporphyrinogen III
Coproporphyrinogen oxidase
Protoporphyrinogen IX
Protoporphyrinogen oxidase
Protoporphyrin IX
Ferrochelatase
+Fe
Haem
Aminolaevulinate dehydratase deficiency porphyria
Acute intermittent porphyria
Congenital erythropoietic porphyria
Porphyria cutanea tarda
Hereditary coproporphyria
Variegate porphyria
Erythropoietic protoporphyria

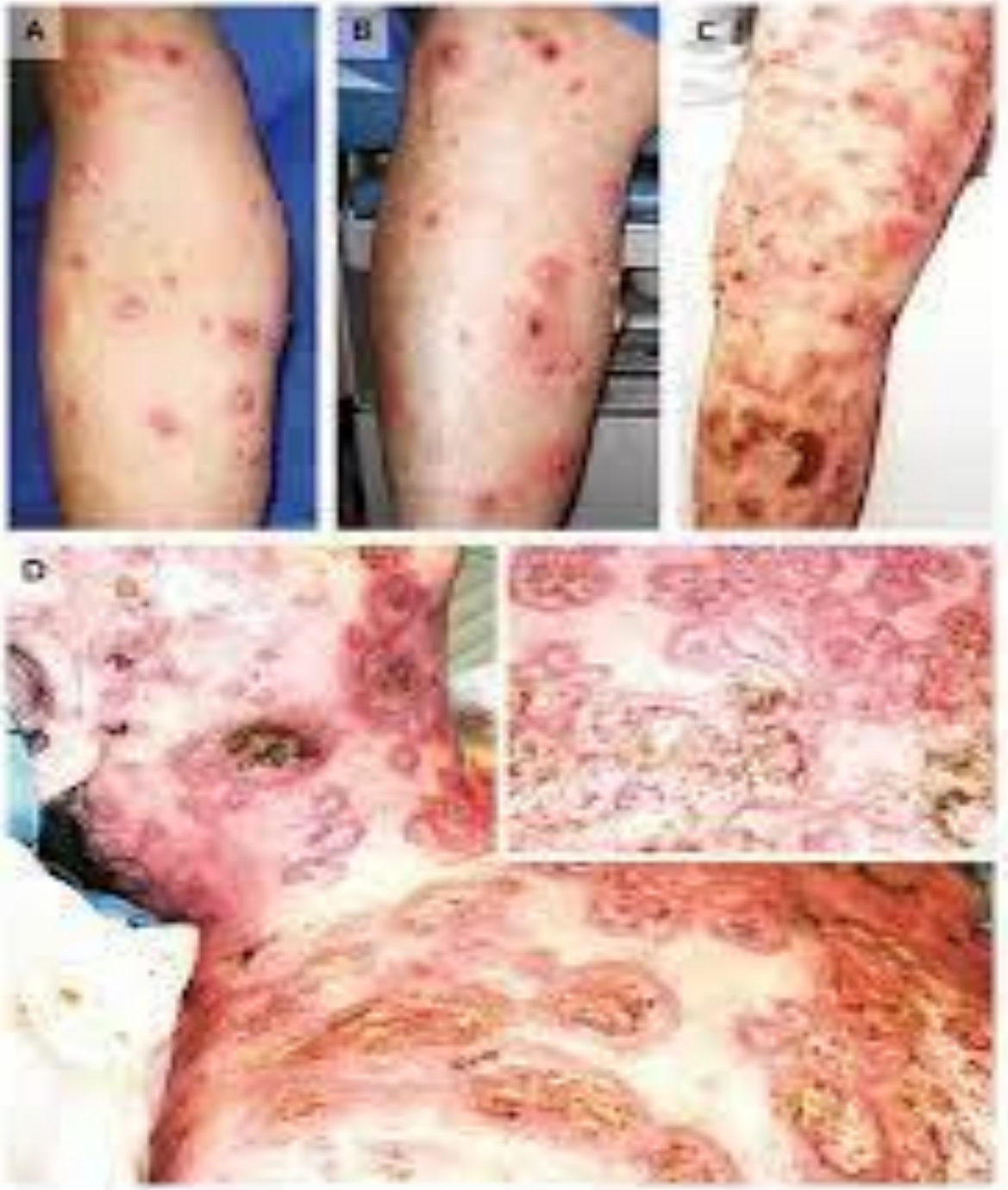
Symptoms

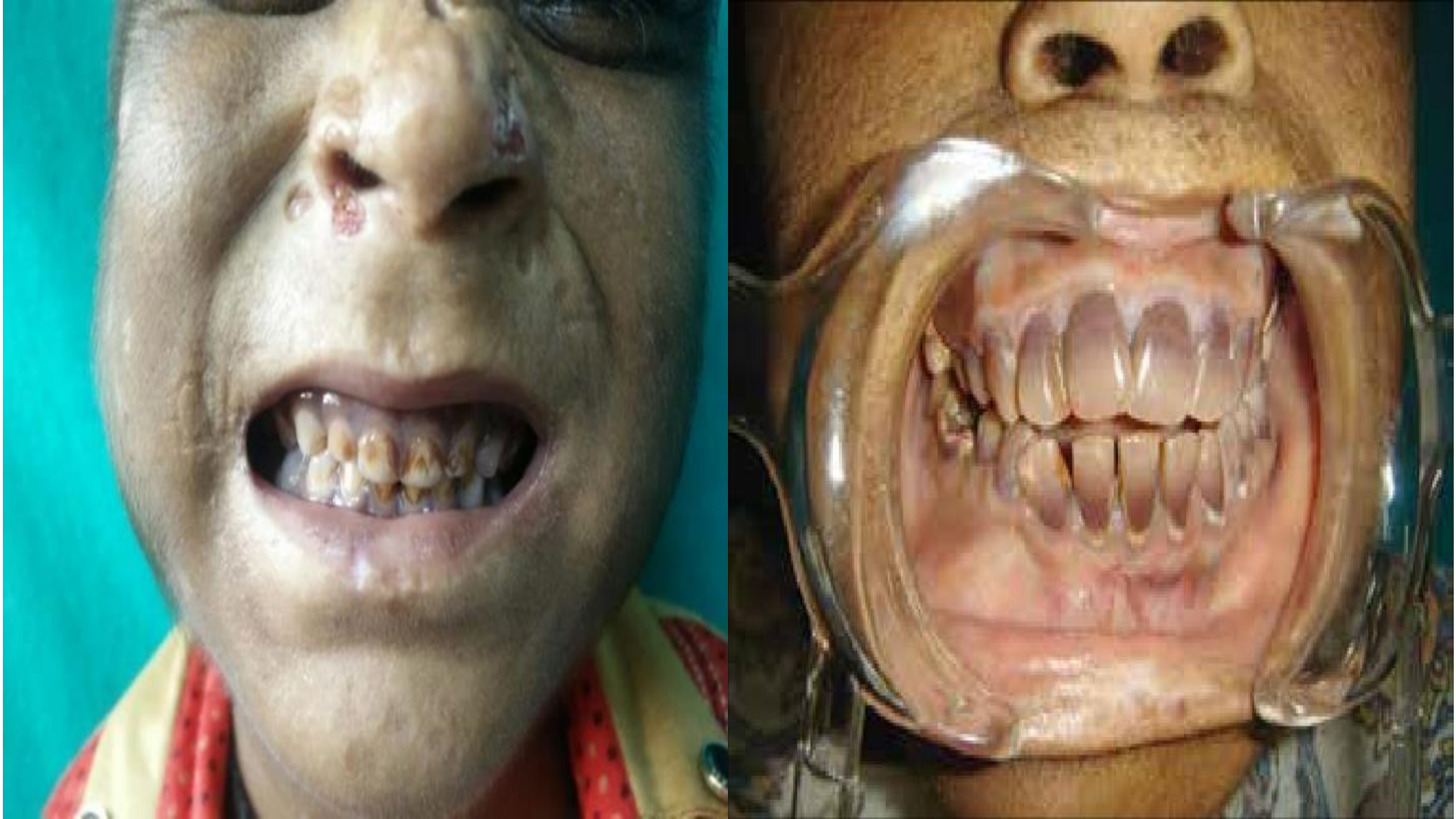
- Anemia
- Neurological disorder –due to the inhibition of **ATPase**
- Abdominal pain – due to the inhibition of **tryptophan pyrulase**
- Skin lesion
- Erythrodontia




A


B


A
B
C
C



Diagnosis

- Urinary ALA and PBG – urine test
- Plasma porphyrin – blood test
- Enzyme and mutation analysis

Treatment

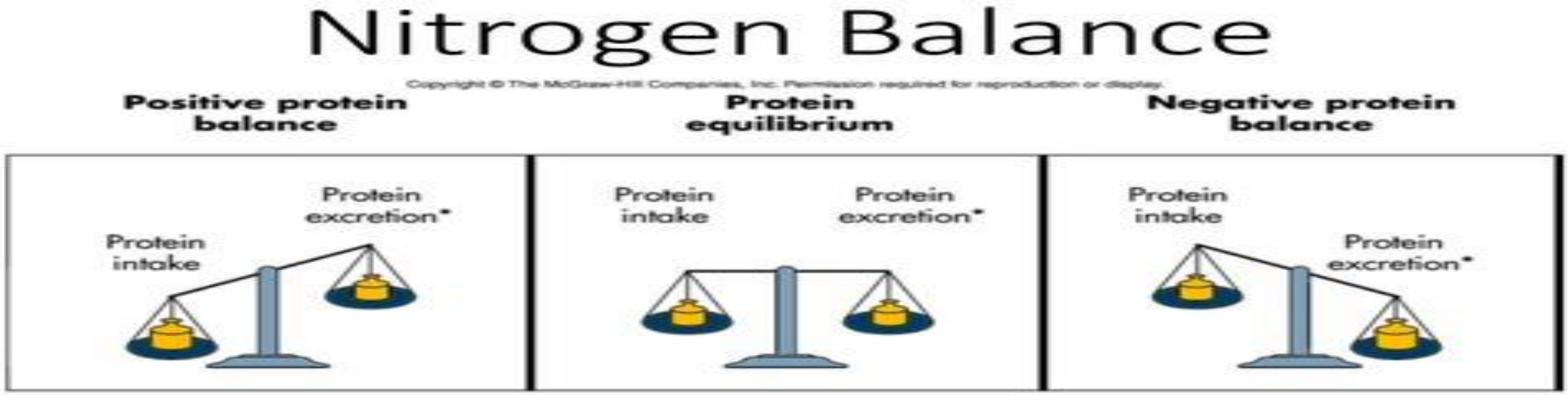
- Hematin- inhibits porphyrin synthesis
- Antioxidants vitamins(A,C,E) – decrease photosensitivity (skin lesion).
- sunscream

Factors affecting nitrogen balance

1. Insufficient caloric intake
2. Lack of non-essential nitrogen
3. Potassium depletion
4. Corticosteroid administration (used to provide relief for inflamed areas of the body.)
5. Infection
6. Cardiac insufficiency (heart muscle's pump function is reduced)

- These factors affect the nitrogen balance and increase plasma urea concentration.

FACTORS INFLUENCING NITROGEN BALANCE:



Situations in which protein balance is positive:

Growth
Pregnancy
Recovery stage after illness
Athletic training**
Increased secretion of hormones, such as insulin, growth hormone, and testosterone

Situations in which protein balance is negative:

Inadequate intake of protein (fasting, intestinal tract diseases)
Inadequate energy intake
Conditions such as fevers, burns, and infections
Bed rest (for several days)
Deficiency of essential amino acids (e.g., poor-quality protein consumed)
Increased protein loss (as in some forms of kidney disease)
Increased secretion of certain hormones, such as thyroid hormone and cortisol

Disorders of Porphyrias

Disorder	Incidence	Age of onset	Important aspects
Acute porphyrias			
Acute intermittent porphyria	0.5–1 per 100 000	Second to fourth decade of life; rarely before puberty	Most common acute porphyria worldwide; acute neurologic attacks but no photosensitivity/cutaneous manifestations
Variegate porphyria	~1 per 300 in South Africa; relatively rare elsewhere	Second to third decade of life; usually not before puberty	*Cutaneous manifestations similar to porphyria cutanea tarda* , and acute attacks similar to acute intermittent porphyria can occur (neurocutaneous porphyria); founder mutations identified in South Africa and Chile
Hereditary coproporphyria	Very rare (<75 cases reported)	Usually not before puberty	Acute attacks similar to acute intermittent porphyria; *cutaneous manifestations, including erythema and blistering in sun-exposed areas, can occur* (neurocutaneous porphyria)
ALA-D deficiency porphyria	Extremely rare (<10 cases reported)	Early and late onset have been described	Neurologic symptoms similar to acute intermittent porphyria can occur; no photosensitivity/cutaneous manifestations

Non-acute porphyrias (all can have cutaneous features)			
Porphyria cutanea tarda	Most common porphyria worldwide	Third to fourth decade of life; usually not before puberty	Acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous findings in sun-exposed areas include skin fragility, erosions, crusts, vesicles and bullae, milia, scarring, hyperpigmentation and hypertrichosis; indistinguishable from variegate porphyria
Erythropoietic protoporphyria	Second-highest incidence of the cutaneous porphyrias	Early childhood (1 to 4 years); late onset extremely rare	Cutaneous manifestations include erythema, edema, crusts, purpura, skin thickening, and waxy scars, primarily on the dorsal hands and face; usually no blistering; in ~5% of patients, severe liver disease can occur; cholelithiasis; palmar keratoderma in rare AR form; adult-onset form associated with underlying MPD or MDS
Congenital erythropoietic porphyria	Very rare (~170 cases reported)	Infancy/first decade of life	Very severe clinical course; in sun-exposed sites, vesicles and bullae, erosions, ulcerations, crusts, milia, scarring, hyperpigmentation and hypertrichosis; mutilation; hemolytic anemia; hepatosplenomegaly; porphyrin deposition in bones and teeth (erythrodontia); pink, red or violet staining of diapers
Hepatoerythropoietic porphyria	Extremely rare (~35 cases reported)	Early infancy	Recessive variant of porphyria cutanea tarda; markedly increased photosensitivity and severe clinical course possible; in sun-exposed sites, vesicles and bullae, skin fragility, erosions, crusts, milia, scarring and hypertrichosis; mutilation can occur; diapers stained by darkly colored urine
X-linked dominant protoporphyria	Very rare	Early childhood	Skin symptoms indistinguishable from erythropoietic protoporphyria; most recent type of porphyria to be recognized; liver disease appears to occur more frequently than in erythropoietic protoporphyria

PLASMA LIPOPROTEIN

PLASMA LIPOPROTEIN:

- Plasma lipoproteins, often referred to as lipoproteins, are complexes of lipids and proteins that transport lipids, such as cholesterol and triglycerides, through the bloodstream.
- **Chylomicrons**: Transport dietary lipids from the intestines to other tissues.
- **Very Low-Density Lipoproteins (VLDL)**: Carry triglycerides synthesized by the liver to tissues.
- **Low-Density Lipoproteins (LDL)**: Often termed "bad cholesterol," they deliver cholesterol to cells but can contribute to atherosclerosis if levels are too high.
- **High-Density Lipoproteins (HDL)**: Known as "good cholesterol," they help remove cholesterol from the bloodstream and transport it to the liver for excretion.

- Inherited disorders of plasma lipoproteins are encountered in some individuals resulting in primary hyper- or hypolipoproteinemias.
- These are due to genetic defects in lipoprotein metabolism and transport.
- The secondary acquired lipoprotein disorders are due to some other diseases (e.g. diabetes mellitus, nephrotic syndrome, atherosclerosis, hypothyroidism etc.), resulting in abnormal lipoprotein pattern which often resembles the primary inherited condition.

HYPERLIPOPROTEINEMIA:

- Hyperlipoproteinemia Elevation in one or more of the lipoprotein fractions constitutes hyperlipoproteinemia.
- These disorders may be either primary or secondary.
- ***Type l:*** is due to familial lipoprotein lipase deficiency. The enzyme defect causes increase in plasma chylomicron and triacylglycerol levels
- ***Type ll a :*** This is also known as hyperbetalipoproteinemia and is caused by a defect in LDL receptors. Secondary type II a hyperlipoproteinemia is observed in association with diabetes mellitus, hypothyroidism, nephrotic syndrome etc. This disorder is characterized by hypercholesterolemia.
- ***Type ll b :*** Both LDL and VLDL increase along with elevation in plasma cholesterol and triacylglycerol is due to overproduction of apo B.

- ***Type Ill :*** This is commonly known as broad beta disease and characterized by the appearance of a broad -band corresponding to intermediate density lipoprotein (IDL) on electrophoresis.
- ***Type IV:*** This is due to overproduction of endogenous triacylglycerols with a concomitant rise in VLDL.
- Type IV disorder is usually associate with obesity, alcoholism, diabetes mellitus etc.
- ***Type V*** : Both chylomicrons and VLDL are elevated.
- This is mostly an acquired condition, due to disorders such as obesity, diabetes and excessive alcohol consumption etc.

HYPOLIPOPROTEINEMIA:

- Hypolipoproteinemias Are Although low levels of plasma lipids (not HDL!) within the normal range may be beneficial to the body, very low lipid levels are undesirable.
- These are commonly associated with certain abnormalities

✓ ***Abetalipoproteinemia :***

- This is a rare disorder due to a defect in the synthesis of apoprotein B.
- It is characterized by a total absence of B-lipoprotein (LDL) in plasma.
- Triacylglycerols are not found in plasma, but they accumulate in liver and intestine.
- Serum cholesterol level is low.
- Abetalipoproteinemia is associated with decreased absorption of fat and fat-soluble vitamins.
- Impairment in physical growth and mental retardation are commonly observed.

✓ ***Familial alpha-lipoprotein deficiency (Tangier disease) :***

- The plasma HDL particles are almost absent.
- Due to this, the reverse transport of cholesterol is severely affected leading to the accumulation of cholesteryl esters in tissues.
- An absence of apoprotein C Il-which activates lipoprotein lipase is also found.
- The plasma triacylglycerol levels are elevated.
- The affected individuals are at an increased risk for atherosclerosis

HYPERLIPIDEMIA:

- Hyperlipidemia, also known as high cholesterol, is a condition where there are high levels of fats or cholesterol in the blood.
- It's a common disorder that can be caused by genetics or acquired disorders.
- Hyperlipidemia can lead to serious illnesses, including heart attack, stroke, and coronary artery disease.
- This is because high cholesterol can build up in arteries, narrowing them and making it difficult for blood to flow.

CHOLESTEROL:

- A waxy, fat-like substance made in the liver, and found in the blood and in all cells of the body.
- Cholesterol is important for good health and is needed for making cell walls, tissues, hormones, vitamin D, and bile acid.
- Cholesterol also comes from eating foods taken from animals such as egg yolks, meat, and whole-milk dairy products.
- Too much cholesterol in the blood may build up in blood vessel walls, block blood flow to tissues and organs, and increase the risk of developing heart disease and stroke.

- Cholesterol is produced by the **liver** and also made by most cells in the body. It is carried around in the blood by little ‘couriers’ called lipoproteins.
- A small amount of blood cholesterol in the body uses it to:
- Build the structure of cell membranes
- Make hormones like estrogen, testosterone and adrenal hormones
- Help your **metabolism** work efficiently, for example, cholesterol is essential for your body to produce vitamin D
- Produce bile acids, which help the body digest fat and absorb important nutrients

✓ **Atherosclerosis**:

The buildup of cholesterol and other substances in the walls of arteries, leading to narrowing and hardening, which can restrict blood flow.

✓**Coronary Artery Disease (CAD):**

A condition where the coronary arteries become narrowed due to atherosclerosis, increasing the risk of heart attacks.

✓**Stroke**:

Reduced blood flow to the brain caused by a blocked artery can lead to a stroke. High cholesterol can contribute to the formation of blood clots that block these arteries.

✓ **Peripheral Artery Disease (PAD)**:

Reduced blood flow to the limbs, often due to atherosclerosis, leading to pain and mobility issues.

✓ **Heart Attack**:

A sudden blockage of blood flow to the heart muscle, often due to a ruptured plaque caused by high cholesterol.

✓ **Biliary Tract Disease**:

High cholesterol can lead to the formation of gallstones, which can block the bile ducts.

TRIGLYCERIDES:

- Triglycerides are fats from the food we eat. Most of the fats we eat (like butter) are in triglyceride form.
- Extra calories, alcohol and sugar in our body turn into triglycerides.
- our body stores them in fat cells throughout the body like stocking shelves in a pantry.
- High triglycerides (hypertriglyceridemia) can put us at a higher risk of heart and vascular (blood vessel) disease.
- This includes heart attack and stroke. About 25% of people in the U.S. have high triglycerides.

- Triglycerides and cholesterol are both fatty substances called lipids. But triglycerides are fats; cholesterol isn't.
- ***Normal and high triglyceride levels:***
- For adults, classifies high triglyceride levels as:
- **Mild:** 150-199 (mg/dL).
- **Moderate:** 200-499 mg/dL.
- **Severe:** Greater than 500 mg/dL.
- For adults, a normal triglyceride level is below 150 mg/dL. For young people between ages 10 and 19, a normal number for triglycerides is below 90 mg/dL.

DISEASE:

- High levels of triglycerides increase your risk of pancreatitis. This severe and painful inflammation of the pancreas can be life-threatening.
- High triglyceride levels also increase your risk of heart and vascular disease, including:
- Carotid artery disease.
- Coronary artery disease (CAD) and heart attack.
- Metabolic syndrome (a combination of high blood pressure, diabetes and obesity).
- Peripheral artery disease (PAD).
- Strokes.

CAUSES:

- Excessive alcohol use.
- Unmanaged diabetes.
- A diet high in sugar, saturated fat and simple carbohydrates.
- Liver disease.
- Kidney disease.
- Medications like diuretics, hormones, corticosteroids, beta blockers and some HIV medications.
- A body mass index (BMI) greater than 25.
- Inflammatory diseases like rheumatoid arthritis.
- Smoking.
- Thyroid disease.
- Lack of physical activity.

PHOSPHOLIPIDS:

- Phospholipids are compound lipids, consisting of phosphoric acids, nitrogen base, alcohol and fatty acids.
- These compound lipids are major components of the cell membrane and also provide a fluid character to the membranes.
- Glycerophospholipids (containing glycerol as the alcohol) .
- Sphingophospholipids (containing sphingosine as the alcohol).

Disease:

- Antiphospholipid syndrome (APS) is an autoimmune disorder that can be caused by a deficiency of phospholipids.
- ***Cause:***
- The body's immune system produces abnormal antibodies that attack the body's own tissues, which can increase the risk of blood clots.
- ***Symptoms:***
- Blood clots, repeated miscarriages, low blood platelet levels, anemia, and a lace-like pattern on the skin called livedo reticularis.
- ***Diagnosis:***
- A blood test that checks for antiphospholipid antibodies. Three types of blood tests are typically performed, each looking for the antibodies in different ways.
- ***Treatment:***
- There's no cure for APS, but medications can reduce the risk of blood clots and miscarriage.

KETONE BODIES:

- Ketone bodies are metabolic products that are produced in excess during excessive breakdown of fatty acids.
- Acetoacetate, acetone and β- hydroxybutyrate are collectively known as ketone bodies (acetone bodies).
- Only the first two are true ketones while β-hydroxybutyrate does not possess a keto (C=O) group.
- Ketone bodies are water-soluble and energy yielding.
- In a normal man, concentration of ketone bodies in the blood is usually less than 3 mg/100ml.
- In normal individuals, there is a constant production of ketone bodies by liver and their utilization by extrahepatic tissues.
- The concentration of ketone bodies in blood is maintained around 1 mg/dl.
- Their excretion in urine is very low and undetectable by routine tests (Rothera's test).

- Ketoacidosis (Ketosis) Definition- It is a metabolic disorder characterized by a triad of :

  1. Ketonemia (increase ketone bodies in blood).

  2. ketonuria (increase ketone bodies in urine).

  3. acetone (fruity) Odor of breath. There are also dehydration, acidosis, coma, and death (if untreated).

- When the rate of synthesis of ketone bodies exceeds the rate of utilization, their concentration in blood increases, this is known as ketonemia.
- Ketonemia is predominantly due to increased production of ketone bodies rather than the deficiency in their utilization. The overall picture of ketonemia and ketonuria is commonly referred to as ketosis.
- Smell of acetone in breath is a common feature in ketosis.
- Ketosis is most commonly associated with starvation and severe uncontrolled diabetes mellitus.

- Ketonuria and weight loss : The appearance of ketone bodies in urine is an indication of active fat metabolism.
- Some programs designed for body weight loss encourage reduction in carbohydrate and total calorie intake until ketone bodies appear in urine.
- The ketogenic substances (promote ketogenesis) include fatty acids and certain amino acids (leucine, lysine, tyrosine etc.).
- The antiketogenic substances (inhibit ketogenesis) are glucose, glycerol and glucogenic amino acids (e.g. glycine, alanine, serine, glutamate etc.)

FATTY LIVER:

- Fatty liver are known is more medical terms as steatosis, is the build up of fat in the liver.
- Liver has some amount of fat in it, but presence of fat which makes more than 5%-10% of fat in the liver can be a bit dangerous.
- It is a common and reversible process and can be changed with some changes in the lifestyle and diet .
- It may not have any symptoms and doesn’t cause any permanent damage.

Types:

- Alcoholic liver disease (ALD)-

This disease occur by drinking too much of alcohol. As heavy drinking damages the liver, liver can't breakdown the fat resulting in the accumulation of fat in the liver.

- Non-alcoholic fatty liver disease (NAFLD)-

The cause of this fatty liver is not known, it can caused due to obesity, diabetes, high cholesterol or can be genetic (run into families). But this is not caused due to alcohol.

- But there are other types which are:

Nonalcoholic steatohepatitis (NASH)-As the fat build up enough in liver, the liver swells up.

The actual cause of the disease is not known and it impairs the liver function.

Symptoms:

- Weight loss
- Abdominal pain
- Feeling tired
- Weakness
- Nausea
- Vomiting
- Confusion, poor judgement or trouble concentrating

Causes:

- Drinking too much alcohol
- Obesity
- Hyperlipidemia, or high levels of fat in the body
- Diabetes
- Rapid weight loss
- Genetic inheritance
- Side effects of certain medicines
- Too much iron in the body
- Hepatitis C (which cause inflammation in the body)

Diagnosis:

- Techniques to diagnose fatty liver are:
- Blood tests: Certain liver enzymes might be treated which may be higher than normal. Presence of higher level of such enzymes may denote fatty liver.
- Ultrasound: Fatty liver may be found by seeing the image of liver in ultrasound. The fat in the liver will be seen as white area.
- Liver biopsy: A needle will be inserted in to the liver, and a tissue will be taken out for certain tests.

Treatment:

- There is no certain treatment of fatty liver.
- Preventing the risk factors such loosing weight
- Quitting alcohol,
- Managing cholesterol and sugar level
- Eating a healthy and balanced diet can help to reduce fatty liver.

Major cardiovascular diseases – Atherosclerosis, Myocardial infarction

Cardiovascular diseases

- **Cardiovascular diseases (CVD)** refer to a group of disorders affecting the heart and blood vessels. These conditions can involve blocked or narrowed blood vessels, leading to heart attacks, chest pain (angina), or strokes. They are among the leading causes of death globally.

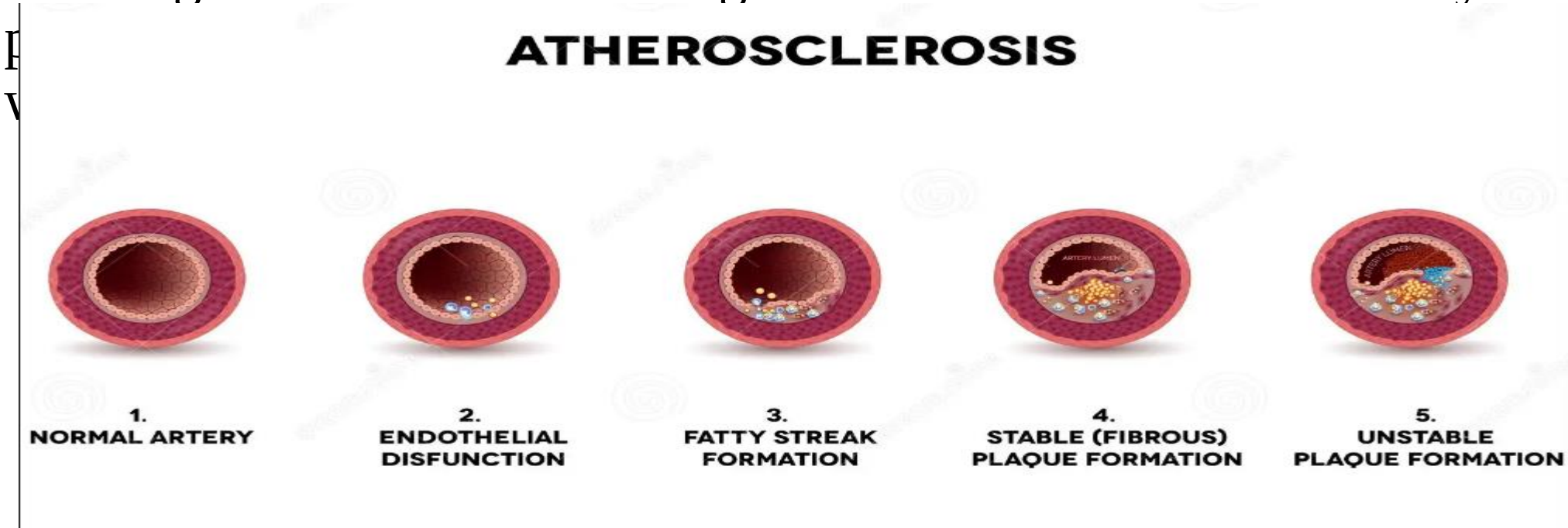
Major Types of Cardiovascular Diseases:

- **Coronary Artery Disease (CAD)**: Blockages in the coronary arteries that supply blood to the heart muscle.
- **Heart Attack (Myocardial Infarction)**: This occurs when a part of the heart muscle doesn’t receive enough blood, often due to a blockage in the arteries.
- **Stroke**: This occurs when the blood supply to part of the brain is interrupted or reduced.

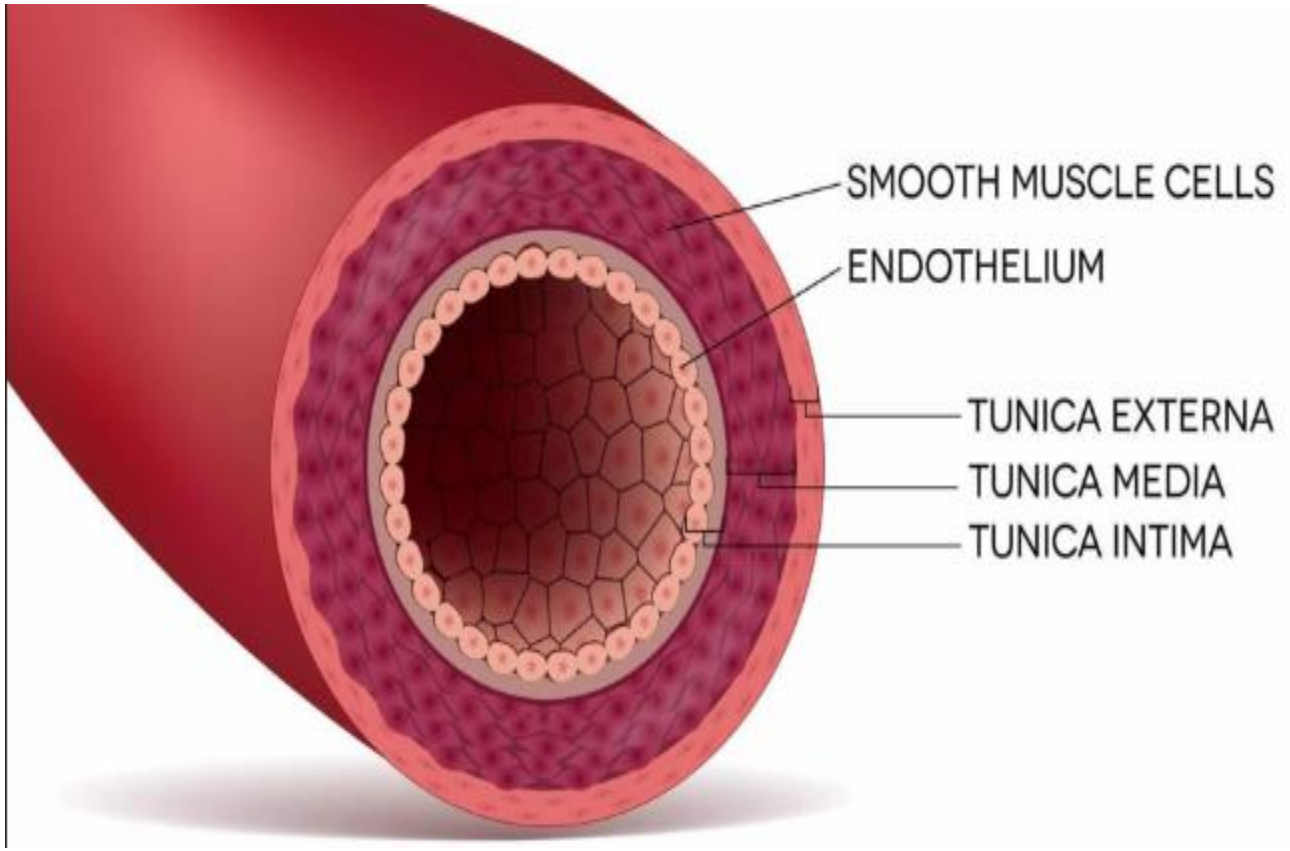
- **Heart Failure**: The heart's inability to pump enough blood to meet the body's needs.
- **Arrhythmias**: Abnormal heart rhythms, such as atrial fibrillation.
- **Hypertension (High Blood Pressure)**: Consistently elevated blood pressure can damage blood vessels over time.
- **Congenital Heart Disease**: Structural problems of the heart present from birth.

Atherosclerosis

- **Atherosclerosis** is a condition in which plaque—a mixture of fat, cholesterol, calcium, and other substances—builds up in the inner walls of arteries. Over time, this plaque hardens and narrows the arteries, restricting blood flow to vital organs and tissues.
- Atherosclerosis is a chronic, degenerative, inflammatory condition affecting medium-sized and large arteries. It involves the slowly p
v



Artery Structure



Risk factors

there are mainly two types of categories that are

Modifiable risk factors

- Factors that can be controlled or changed, such as smoking, physical inactivity, poor diet, and high cholesterol.

Non-modifiable risk factors

- Factors that cannot be changed, such as age, gender, and family history.

Risk factors

•**High Blood Pressure (Hypertension)**: Elevated blood pressure puts extra strain on the heart and blood vessels, leading to damage over time, which can result in heart attacks, strokes, and heart failure.

•**High Cholesterol**: Excess cholesterol, particularly low-density lipoprotein (LDL or "bad" cholesterol), can accumulate in the walls of arteries, forming plaques that narrow and harden the arteries, leading to atherosclerosis (hardening of the arteries).

•**Smoking**: Smoking damages the lining of the blood vessels, raises blood pressure, and reduces the amount of oxygen the heart receives, making it a significant risk factor for heart disease and stroke.

•**Obesity**: Excess body fat, particularly around the abdomen, is linked to increased blood pressure, high cholesterol, and insulin resistance, all of which are risk factors for CVD.

•**Unhealthy Diet**: Diets high in saturated fats, trans fats, sodium, and sugar increase the risk of developing conditions such as obesity, hypertension, and high cholesterol, which contribute to CVD.

•**Age**: The risk of cardiovascular diseases increases as a person ages, especially after the age of 50, due to the gradual weakening of the heart and blood vessels over time.

•**Family History**: A family history of heart disease increases the risk, especially if close relatives were diagnosed with CVD at a young age. Genetic factors play a role in predisposition to conditions like high blood pressure or high cholesterol.

•**Gender**: Men are generally at a higher risk of developing cardiovascular diseases at an earlier age compared to women. However, the risk for women increases and becomes similar to men's after menopause.

- **Chronic Inflammation**: Conditions like rheumatoid arthritis or chronic infections can cause inflammation, which may increase the risk of damage to blood vessels and arteries, contributing to CVD

- **Alcohol Consumption**: Excessive alcohol intake can raise blood pressure, contribute to weight gain, and increase the risk of developing CVD. Moderate consumption may have protective effects, but this is debated and varies by individual.

- **Stress**: Chronic stress can contribute to high blood pressure and other heart disease risk factors, such as poor lifestyle habits (e.g., smoking, overeating, lack of exercise)

- **Physical Inactivity**: A sedentary lifestyle can contribute to weight gain, high cholesterol, and elevated blood pressure, all increasing the risk of heart disease.

pathogenesis

The response-to-injury hypothesis :

- The endothelium can become damaged by factors such as high blood pressure, smoking, or high cholesterol. This damage can lead to an increased permeability of the artery walls, which allows lipoproteins (e.g., LDL cholesterol) to enter the artery wall. In response, inflammatory cells (like macrophages) are recruited to the site of injury.
- These cells absorb cholesterol and form foam cells, eventually creating a fatty streak. The continuous cycle of damage, inflammation, and lipid deposition leads to plaque formation and progression.

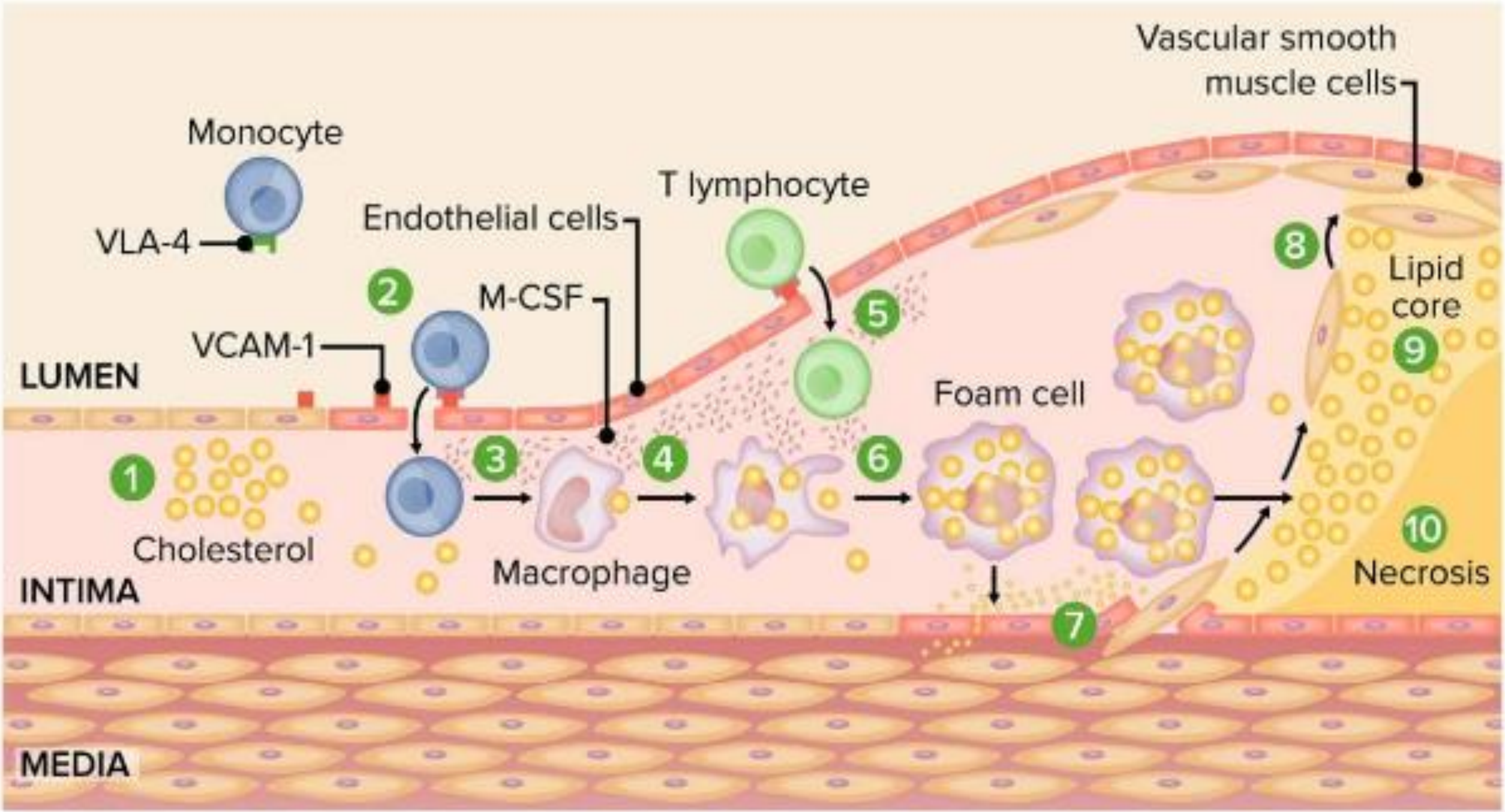
- ***The lipid oxidation hypothesis***, developed by **Steinberg and colleagues**, offers a mechanism for endothelial injury and explains the formation of macrophage-derived foam cells, which are characteristic of the early stages of atherosclerosis.
- In the initial phase of the process**, monocytes adhere to the endothelium and accumulate in the subendothelial space**. Along with smooth muscle cells, these monocytes absorb cholesterol uncontrollably and transform into lipid-laden foam cells, leading to the appearance of the first visible lesion, known as the fatty streak.
- Goldstein and Brown proposed the presence of a **"scavenger receptor"** that enables unregulated cholesterol uptake in the form of modified LDL.

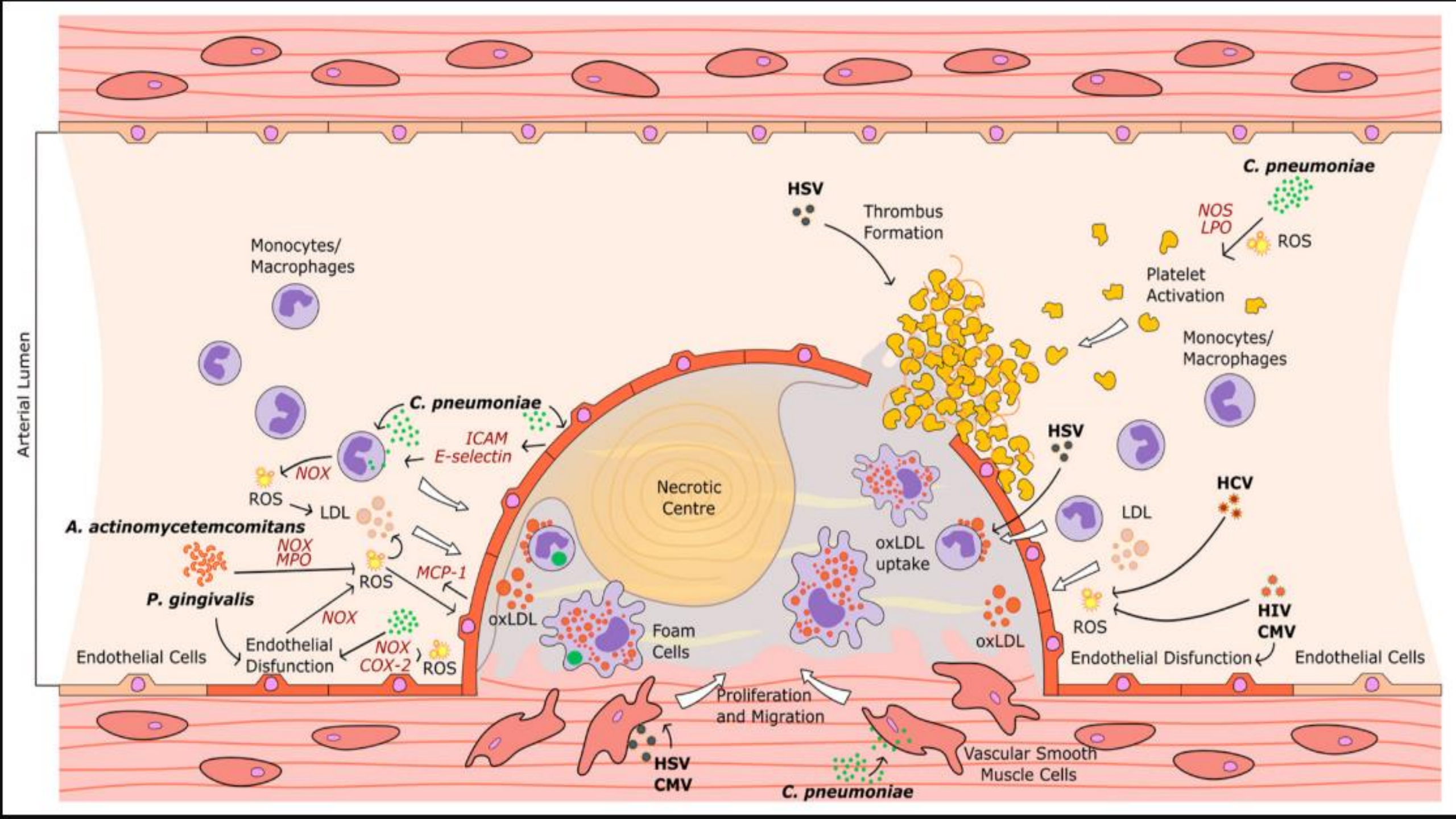
- Several scavenger receptors have since been identified, with CD36 (also called scavenger receptor B) being one of the most significant.
- These receptors allow the uptake of modified LDL particles through processes like enzymatic changes, oxidation, glycosylation, or glycoxidation.
- The oxidation of LDL alters the lysine residues on apolipoprotein B, a key protein in the LDL particle.
- LDL oxidation can occur in various cells within the artery, such as endothelial cells, macrophages, smooth muscle cells, and T lymphocytes
- The oxidation of LDL leads to the production of **isoprostanes**, which are chemically stable, free radical-catalyzed products of **arachidonic acid** and structural isomers of

Oxidized LDL promotes atherosclerosis through several mechanisms, including:

- Acting as a **chemoattractant for monocytes**.
- Stimulating inflammatory and immune responses through **cytokine release from macrophages** and **antibody production**.
- Facilitating unregulated cholesterol uptake via the **scavenger receptor pathway**, leading to foam cell formation (foam cells can rupture, releasing oxidized LDL, enzymes, and free radicals that further damage the arterial wall).
- Inducing **apoptosis** in vascular smooth muscle cells and endothelial cells, contributing to the response-to-injury hypothesis of atherosclerosis.

- Disrupting the endothelial cell surface, impairing function by reducing the release of **nitric oxide (NO)**, a key mediator of endothelium-dependent vasodilation. Endothelial damage also promotes **platelet adherence** and cytokine release, which stimulates smooth muscle proliferation.
- **Increasing platelet aggregation** and **thromboxane release**, which promotes vasoconstriction and thrombus formation.


Vascular smooth muscle cells
Monocyte
VLA-4
Endothelial cells
T lymphocyte
2
M-CSF
VCAM-1
LUMEN
5
8
Lipid core
9
Foam cell
1
3
4
6
Cholesterol
Macrophage
INTIMA
10
Necrosis
7
MEDIA

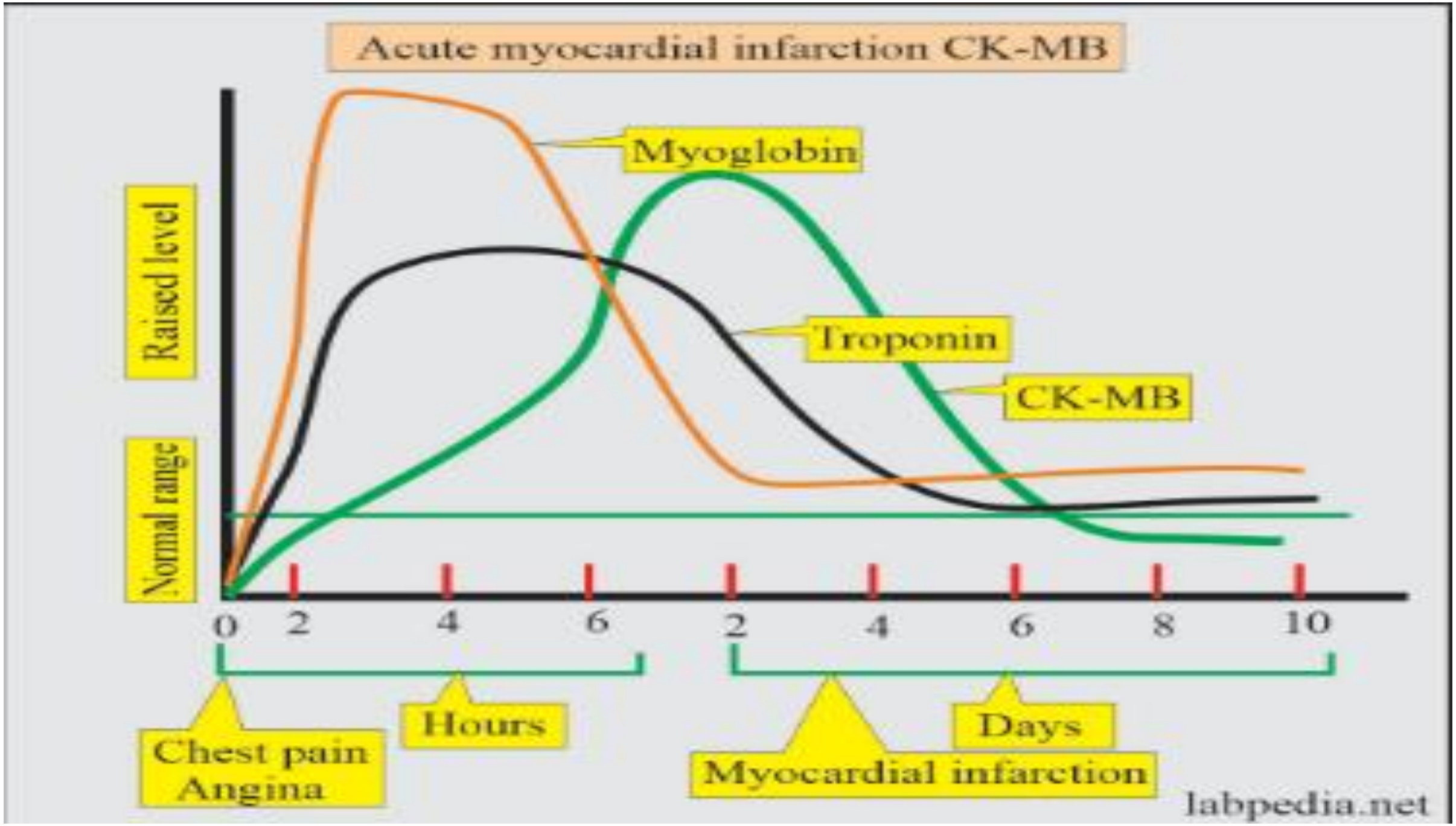

Arterial Lumen
Monocytes/
Macrophages
C. pneumoniae
ICAM
E-selectin
NOX
ROS
LDL
A. actinomycetemcomitans
NOX
MPO
P. gingivalis
ROS
MCP-1
NOX
Endothelial Cells
Endothelial
Disfunction
NOX
COX-2
ROS
Necrotic
Centre
oxLDL
Foam
Cells
HSV
Thrombus
Formation
C. pneumoniae
NOS
LPO
ROS
Platelet
Activation
Monocytes/
Macrophages
HSV
oxLDL
uptake
HCV
LDL
HIV
CMV
ROS
oxLDL
Endothelial Disfunction
Endothelial Cells
Proliferation
and Migration
HSV
CMV
C. pneumoniae
Vascular Smooth
Muscle Cells

Myocardial infarction

- It is commonly known as a heart attack, which occurs when blood flow to a part of the heart muscle (myocardium) is blocked, leading to tissue damage or death due to a **lack of oxygen**. This blockage is typically caused by the rupture of an atherosclerotic plaque in a coronary artery, and the formation of a blood clot (thrombus) at the site of the rupture. As a result, the affected area of the heart muscle becomes deprived of oxygen and nutrients, which can cause **irreversible damage** if the blood flow is not quickly restored.
- The severity of an MI depends on the size of the blockage and the amount of heart muscle affected.
- **ST-elevation myocardial infarction (STEMI)** : A complete blockage of a coronary artery where characteristic changes appear on an ECG.
- **non-ST elevation myocardial infarction (NSTEMI)** Partial blockages, where blood flow is reduced but not completely cut off.

Laboratory diagnosis for myocardial infarction

- Biomarkers are substances released into the bloodstream when the heart muscle (myocardium) is damaged, such as during a myocardial infarction (heart attack). Measuring these biomarkers helps in the early diagnosis, management, and prognosis of MI.
- The most commonly used cardiac biomarkers include:
  - Cardiac Troponins (cTnI and cTnT)
  - Creatine Kinase-MB (CK-MB)
  - Myoglobin
  - Lactate Dehydrogenase (LDH)
  - B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP)


Acute myocardial infarction CK-MB
Raised level
Normal range
Myoglobin
Troponin
CK-MB
0
2
4
6
2
4
6
8
10
Hours
Days
Chest pain
Angina
Myocardial infarction
labpedia.net

PHENYLKETONURIA

- Phenylketonuria is a also called as the PKU.
- PKU, is a rare inherited disorder that causes an amino acid called phenylalanine to build up in the body.
- PKU is caused by a change in the phenylalanine hydroxylase (PAH) gene.
- This gene helps create the enzyme needed to break down phenylalanine.

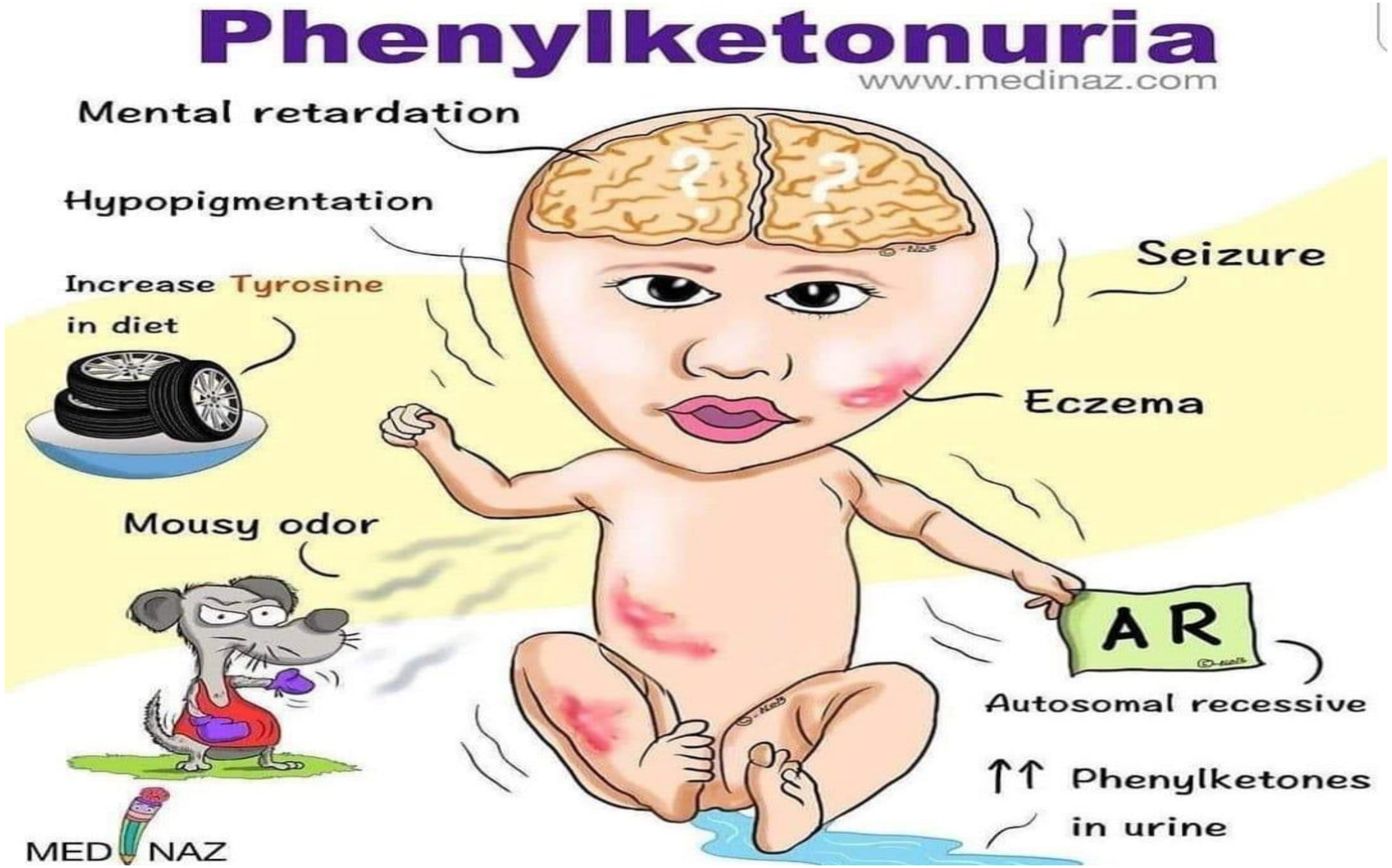
- Without the enzyme necessary to break down phenylalanine, a dangerous buildup can develop when a person with PKU eats foods that contain protein or eats aspartame, an artificial sweetener.

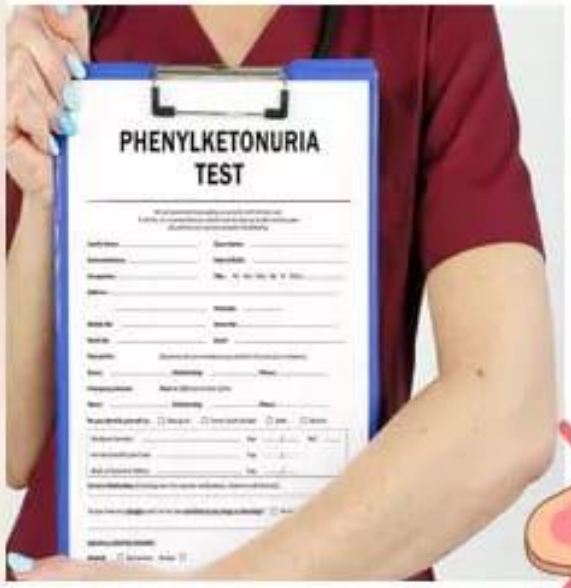
- This can eventually lead to serious health problems.

- For the rest of their lives, people with PKU — babies, children and adults — need to follow a diet that limits phenylalanine, which is found mostly in foods that contain protein.

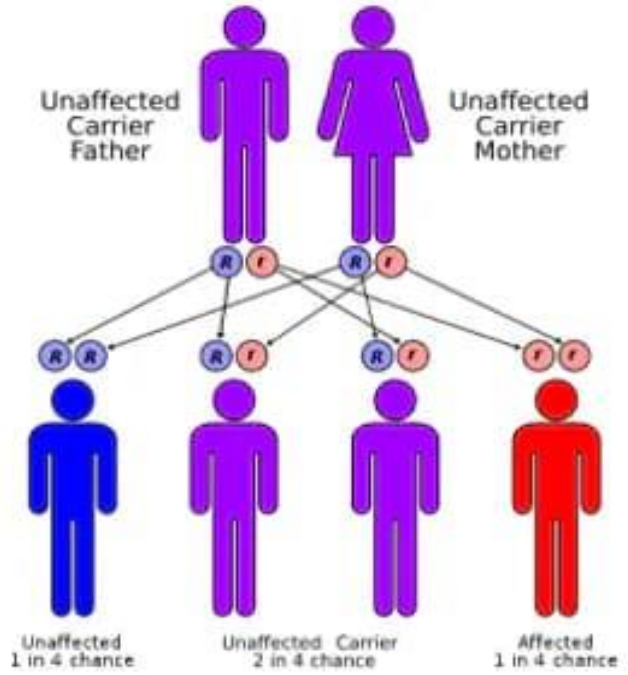
Phenylketonuria

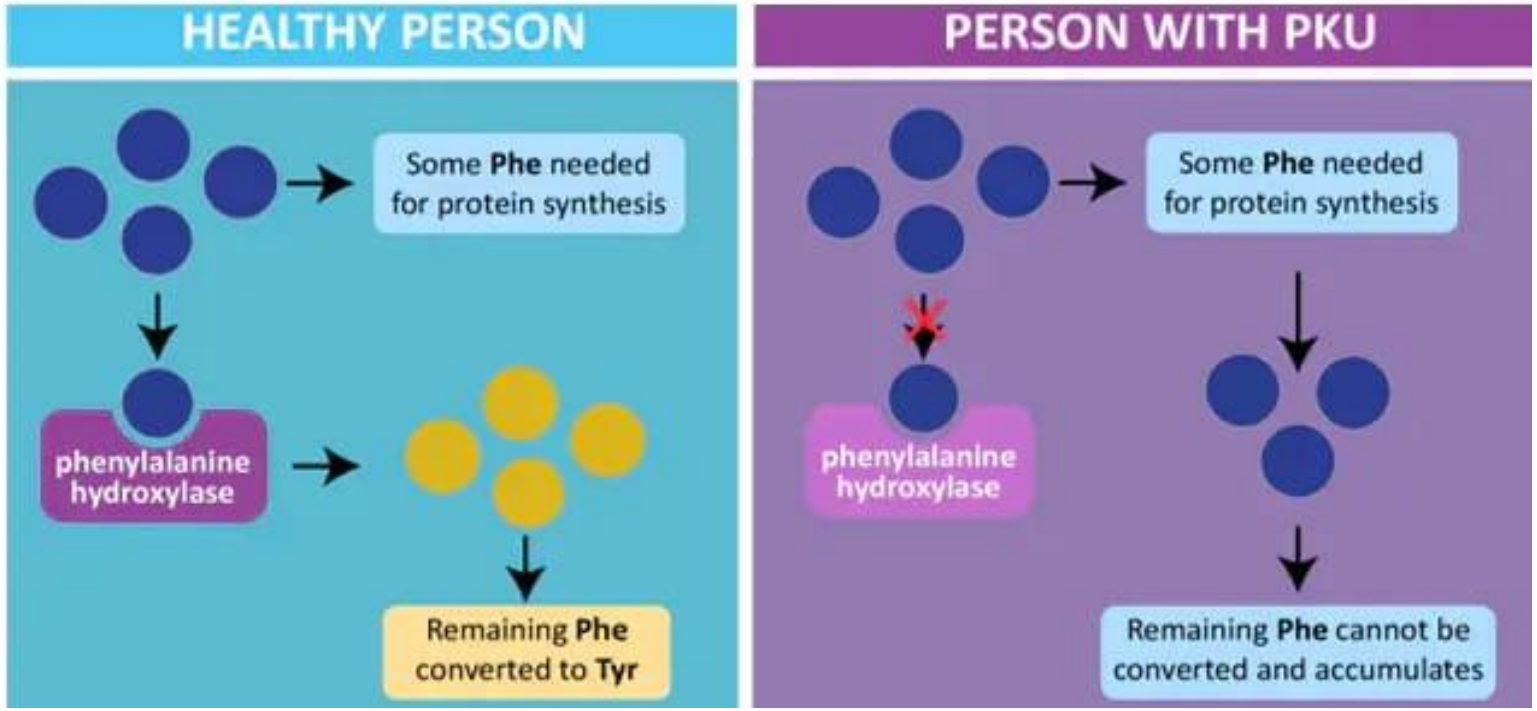
www.medinaz.com




PHENYLKETONURIA
TEST


milk


Unaffected
Carrier
Father
Unaffected
Carrier
Mother
R
r
R R
R r
R r
r r
Unaffected
1 in 4 chance
Unaffected Carrier
2 in 4 chance
Affected
1 in 4 chance

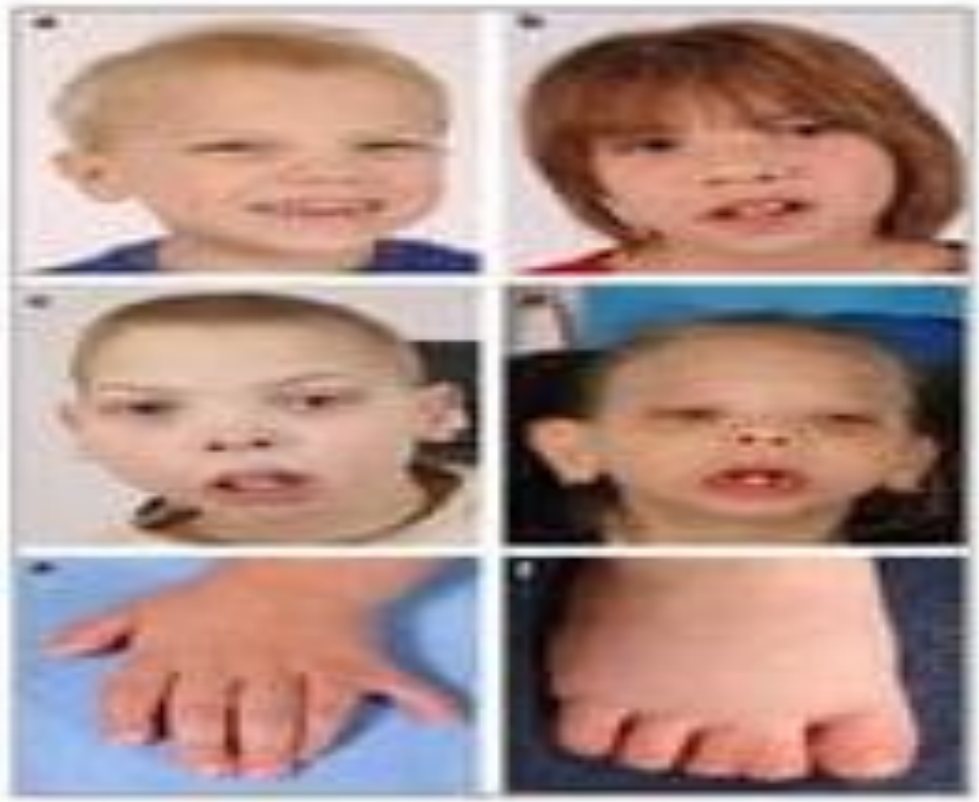

HEALTHY PERSON
Some Phe needed
for protein synthesis
phenylalanine
hydroxylase
Remaining Phe
converted to Tyr
PERSON WITH PKU
Some Phe needed
for protein synthesis
phenylalanine
hydroxylase
Remaining Phe cannot be
converted and accumulates

SYMPTOMS

- Newborns with PKU initially don't have any symptoms. However, without treatment, babies usually develop signs of PKU within a few months.

- Signs and symptoms of untreated PKU can be mild or severe and may include:
- A musty odor in the breath,
- skin or urine,
- caused by too much phenylalanine in the bodyNervous system (neurological) problems that may include seizuresSkin rashes,
- such as eczemaLighter skin, hair and eye color than family members,
- because phenylalanine can't transform into melanin — the pigment responsible for hair and skin toneUnusually small head size (microcephaly)HyperactivityIntellectual disabilityDelayed developmentBehavioral, emotional and social problemsMental health disorders

Symptoms of PKU



CAUSES

- Autosomal recessive inheritance pattern
- Autosomal recessive inheritance pattern
- Enlarge image
- A gene change (genetic mutation) causes PKU, which can be mild, moderate or severe.
- In a person with PKU, a change in the phenylalanine hydroxylase (PAH) gene causes a lack of or reduced amount of the enzyme that's needed to process phenylalanine, an amino acid.

INHERITANCE

- For a child to inherit PKU, both the mother and father must have and pass on the changed gene.
- This pattern of inheritance is called autosomal recessive.
- It's possible for a parent to be a carrier — to have the changed gene that causes PKU, but not have the disease.
- If only one parent has the changed gene, there's no risk of passing PKU to a child, but it's possible for the child to be a carrier.

Diagnosis

- Newborn screening identifies almost all cases of phenylketonuria.
- All 50 states in the United States require newborns to be screened for PKU.
- Many other countries also routinely screen infants for PKU.
- Testing your baby after birthA PKU test is done a day or two after your baby's birth. For accurate results, the test is done after your baby is 24 hours old and after your baby has had some protein in the diet.A nurse or lab technician collects a few drops of blood from your baby's heel.

Prevention

- If you have PKU and are considering getting pregnant:
- Follow a low-phenylalanine diet.
- Women with PKU can prevent harm to their developing baby by sticking to or returning to a low-phenylalanine diet before becoming pregnant.
- Nutritional supplements designed for people with PKU can ensure enough protein and nutrition during pregnancy.
- If you have PKU, talk to your health care provider before you start trying to conceive.

ALKAPTONURIA

- Alkaptonuria is also called black urine disease.
- Alkaptonuria is a genetic metabolic disorder in which body cells cannot break down two amino acids called tyrosine and phenylalanine.
- This metabolic disorder results in the collection of homogentisic acid in the body.
- Due to the presence of excess homogentisic acid, urine and other parts of the body turn dark coloured and it leads to a range of problems over time.

Causes

- AlkaptonuriaAlkaptonuria is a rare inherited disorder caused by a mutation in the homogentisate 1,2-dioxygenase (HGD) gene.

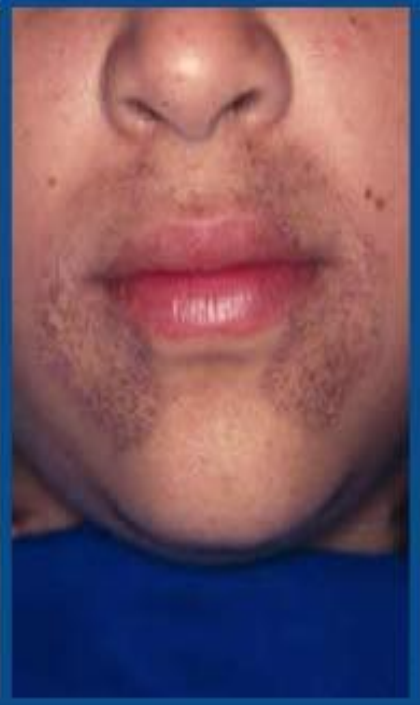
- It is an autosomal recessive condition, which implies that both the parents must have the gene to pass the disease on to their infants.

Symptoms of Alkaptonuria

- Arthritis
- Black earwax
- Prostate and kidney stones
- Signs of early-onset osteoarthritis
- Dark spots in the sclera of the eyes
- Dark-coloured sweat or sweat stainsT
- hickened and darkened cartilage in the ears
- Chronic stiffness or pain in your lower back or large joints
- Blue speckled discolouration of the skin, particularly around sweat glands

Symptoms & Signs of Alkaptonuria

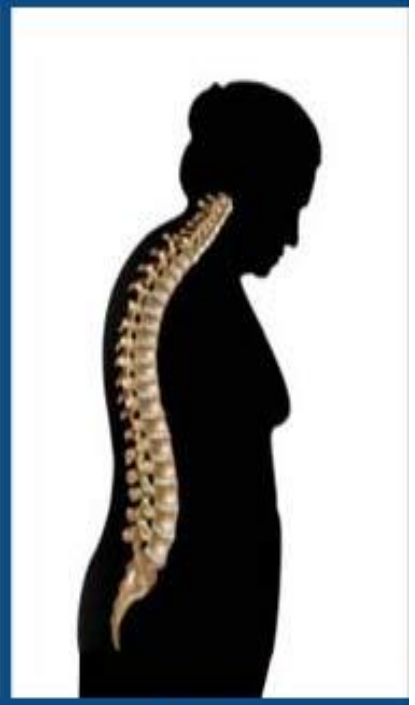
Black colored urine



Ochronosis

Tendinitis

Kidney & prostate stones



Kyphosis or hunchback

source : wikipedia.org

Treatment for Alkaptonuria

- Arthritis
- Heart disease
- Prostate and kidney stones
- Anti-inflammatory medications can be used for joint pain.
- Along with these medications, specific physical and occupational therapies may help maintain strength and flexibility in the muscles and joints.

ALBINISM

ALBINISM

- albinism usually refers to oculocutaneous (ok-u-low-ku-TAY-nee-us) albinism (OCA).
- OCA is a group of disorders passed down in families where the body makes little or none of a substance called melanin.
- The type and amount of melanin in your body determines the color of your skin, hair and eyes.
- Melanin also plays a role in the development and function of the eyes, so people with albinism have vision problems.

Symptoms of albinism

Albinism are usually seen in a person's skin, hair and eye color, but sometimes differences are slight.

People with albinism are also sensitive to the effects of the sun, so they're at higher risk of getting skin cancer.

Although there's no cure for albinism, people with the disorder can take steps to protect their skin and eyes and get proper eye and skin care.

The Many Shades of Albinism

Complications

- Albinism can include skin and eye complications.

- Eye complications
- Problems with vision can impact learning, employment and the ability to drive.

- Skin complications
- People with albinism have skin that is very sensitive to light and sun. Sunburn is one of the most serious complications of albinism. Sun exposure can cause sun damage, which may result in rough and thickened skin. Sunburn also can increase the risk of developing skin cancer.

Diagnosis of albinism

- A physical exam that includes checking skin and hair pigmentation.
- A thorough eye exam.
- Comparison of your child's pigmentation to that of other family members.
- Review of your child's medical history, including whether there has been bleeding that doesn't stop, frequent or large bruises, or unexpected infections.

Treatment

- Albinism is a genetic disorder, and there is currently no cure.
- Treatment focuses on getting proper eye care and monitoring skin for problems.
- Your care team may include your primary care provider, a specialist in eye care called an ophthalmologist and a specialist in skin care called a dermatologist.
- A specialist in genetics can help identify the specific type of albinism.
- This information can help guide care, identify possible complications and determine the risk of the condition in future children.

TYROSINOSIS OR TYROSINEMIA

- Tyrosinemia or tyrosinaemia is an error of metabolism, usually inborn, in which the body cannot effectively break down the amino acid tyrosine.
- Symptoms of untreated tyrosinemia include liver and kidney disturbances.
- Without treatment, tyrosinemia leads to liver failure.
- tyrosinemia is increasingly detected on newborn screening tests before any symptoms appear.
- With early and lifelong management involving a low-protein diet, special protein formula, and sometimes medication, people with tyrosinemia develop normally, are healthy, and live normal lives

SYMPTOMS

- Bloody stools
- Cabbage like odor
- DiarrheaFatigue
- Poor weight gain
- Failure to thrive
- Vomiting
- Painful lesions on the skin
- Red eyes and light sensitivity
- Corneal cloudingI

CAUSES

- All tyrosinemias result from dysfunction of various genes in the phenylalanine and tyrosine catabolic pathway, and are inherited in an autosomal-recessive pattern

- Type I tyrosinemia results from a mutation in the FAH gene, which encodes the enzyme fumarylacetoacetase.
- As a result of FAH deficiency, the substrate fumarylacetoacetate can accumulate in proximal renal tubular cells and hepatocytes, resulting in damage to the kidney and liver, respectively.

- Type II tyrosinemia results from a mutation in the TAT gene, which encodes the enzyme tyrosine aminotransferase.
- As a result of TAT deficiency, the substrate tyrosine accumulates, causing ophthalmologic and dermatologic abnormalities.

- Type III tyrosinemia results from a mutation in the HPD gene, which encodes the enzyme 4- hydroxyphenylpyruvate dioxygenase.
- Type III tyrosinemia is the rarest of the three conditions, with only a few cases ever reported.
- Most of those cases have included intellectual disability and neurologic dysfunction.

Diagnosis

- Type I tyrosinemia can be detected via blood tests for the presence of a fumarylacetoacetate metabolite, succinylacetone, which is considered a pathognomonic indicator for the disease.

- Type II tyrosinemia can be detected via the presence of significantly elevated plasma tyrosine levels, and the diagnosis can be confirmed by detection of a mutation in TAT in cultured fibroblasts.

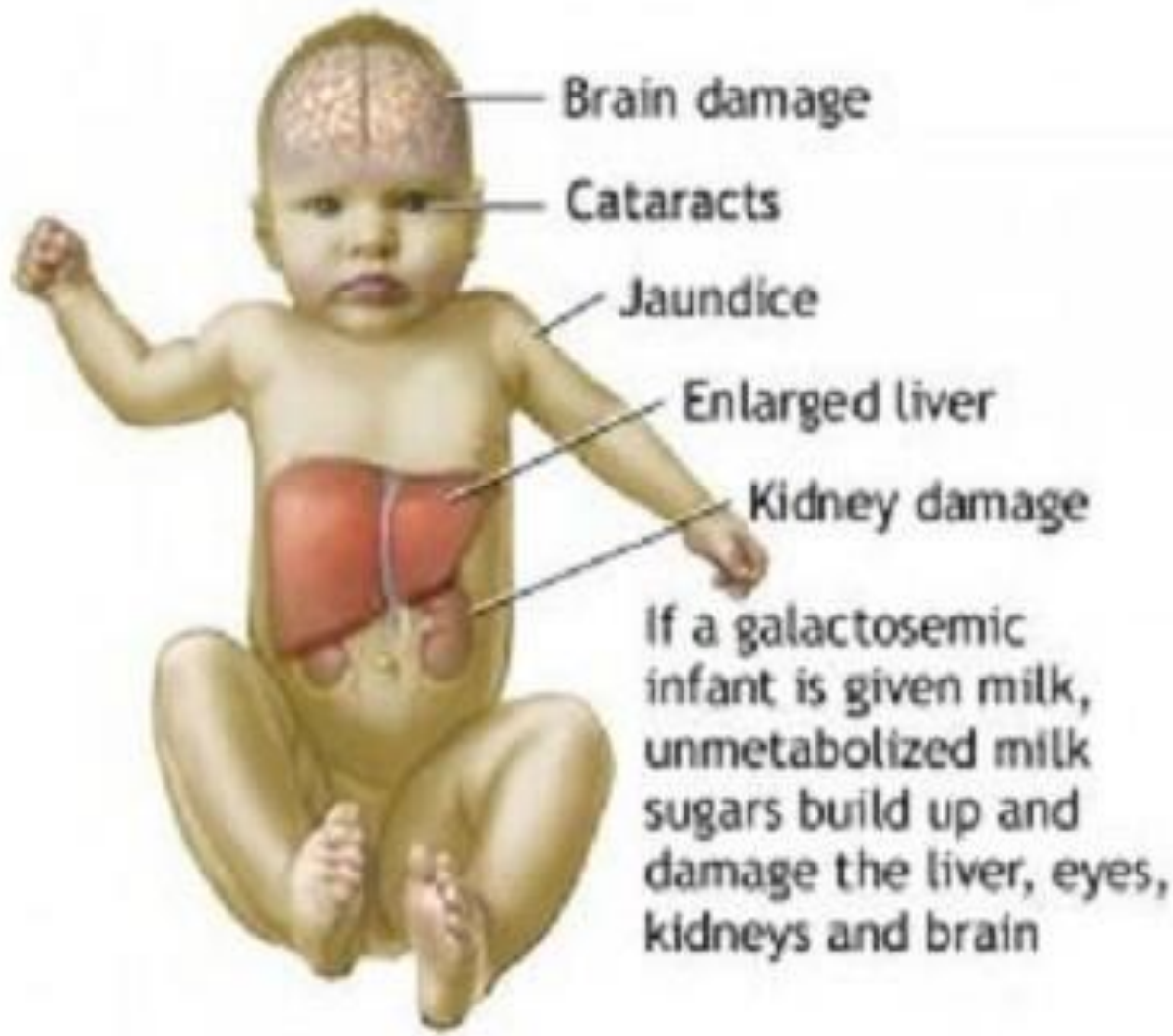
- Type III tyrosinemia can be diagnosed by detection of a mutation in HPD in cultured fibroblasts

Treatment

- Treatment varies depending on the specific type;
- A low-protein diet combined with the use of a specially engineered formula to supply protein is required in most cases.
- Experience with nitisinone has shown it to be effective, especially when started within the first month of life, and it is now the standard course of treatment.
- It is a 4-hydroxyphenylpyruvate dioxygenase inhibitor indicated for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.
- Liver transplant is indicated for patients with tyrosinemia type I who do not respond to nitisinone, as well as those with acute liver failure and hepatomas.

MAPLE SYRUP URINE DISEASE

- **Maple syrup urine disease (MSUD) is a rare but serious inherited condition.**
- It means the body cannot process certain amino acids (the "building blocks" of protein), causing a harmful build-up of substances in the blood and urine.
- Normally, our bodies break down protein foods such as meat and fish into amino acids. Any amino acids that are not needed are usually broken down and removed from the body.
- Babies with MSUD are unable to break down amino acids called leucine, isoleucine and valine. Very high levels of these amino acids are harmful.
- One of the characteristic symptoms of MSUD is sweet-smelling urine, which gives the condition its name.


Brain damage
Cataracts
Jaundice
Enlarged liver
Kidney damage
If a galactosemic infant is given milk, unmetabolized milk sugars build up and damage the liver, eyes, kidneys and brain

SYMPTOMS

- Symptoms of MSUD usually appear within the first few days or weeks after birth. More general symptoms include:
- sweet-smelling urine and sweat
- poor feeding or loss of appetite
- weight loss
- Babies with MSUD may also have episodes known as a "metabolic crisis", sometimes early in their life. Symptoms of a metabolic crisis include:
- lack of energy
- vomiting
- irritability
- breathing difficulties


Maple Syrup Urine Disease (MSUD)
For Information, Visit: www.epainassist.com
Normal Urine
Maple Syrup Disease Urine

TREATMENT

- If your child becomes ill, they might have an episode of a metabolic crisis. This can lead to serious illness and long-term brain damage, and can be life threatening.
- It's possible to reduce this risk by changing to an emergency diet while they're ill.
- Your dietitian will provide detailed instructions for a low-protein diet and dietary supplements.
- This may include replacing milk and foods containing protein with special high-sugar drinks and taking amino acid supplements.

DIAGNOSIS

- Healthcare providers diagnose classic MSUD with newborn screenings (blood tests) soon after a baby is born.

- Prenatal testing can show if the fetus has classic MSUD.

- Depending on how far along you are in your pregnancy, providers test a tissue sample from the placenta (chorionic villus sampling) or amniotic fluid

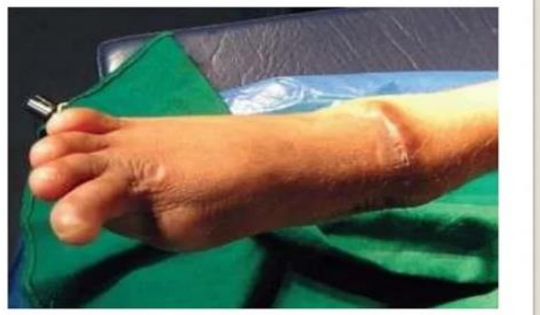
Inborn error of metabolism: Lesch – Nyhan syndrome, Histidinemia, Gaucher's disease, Tay – sachs and Niemann – Pick disease

Inborn error of Metabolism

- Inborn errors of metabolism (IEM) are a group of genetic disorders that disrupt the body's ability to convert food into energy or to remove waste products effectively.
- These conditions arise due to defects in specific enzymes, which are proteins that facilitate chemical reactions necessary for metabolism.
- When these enzymes do not function properly, it can lead to the accumulation of toxic substances in the body or a deficiency in essential compounds, resulting in a wide range of symptoms and health issues.

Lesch-Nyhan Syndrome

- Lesch-Nyhan syndrome (LNS) is a rare, X-linked inherited metabolic disorder characterized by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT).
- This enzyme is crucial for the recycling of purines, which are essential components of DNA and RNA.
- The deficiency leads to an accumulation of uric acid in the body, resulting in various neurological and behavioral symptoms.



Overproduction and accumulation of uric acid

Causes

- Lesch-Nyhan syndrome is caused by mutations in the *HPRT1* gene located on the X chromosome.
- This gene is responsible for producing the HGPRT enzyme, which facilitates the conversion of hypoxanthine and guanine into their respective nucleotides.
- When this enzyme is deficient, purines are not recycled effectively, leading to excessive uric acid production.
- This condition primarily affects males, as they have only one X chromosome, while females are typically carriers and may exhibit milder symptoms later in life.

Symptoms

- Poor muscle control
- Increased muscle tone
- Dystonia (involuntary muscle contractions)
- Chorea (involuntary movements) are also common.
- Speech difficulties (dysarthria)
- **Gout and Kidney Issues**: The excess uric acid can lead to gout, and the formation of urate crystals in the kidneys, potentially causing kidney stones and urinary tract infections.

Treatment

•Medication: Allopurinol is commonly prescribed to reduce uric acid levels and prevent gout attacks. Other medications may be used to address neurological symptoms, such as carbidopa/levodopa for movement disorders.

DIAGNOSIS

•Blood and Urine Tests: These tests typically reveal elevated levels of uric acid. Urine may show orange crystals indicative of urate.
•Genetic Testing: Confirmatory testing for mutations in the *HPRT1* gene can establish a definitive diagnosis.

HISTIDINEMIA

- Histidinemia is a rare inherited metabolic disorder characterized by elevated levels of the amino acid histidine in the blood, urine, and cerebrospinal fluid.
- It results from a deficiency of the enzyme histidase, which is necessary for the metabolism of histidine.
- This condition is typically benign, with most individuals remaining asymptomatic.

CAUSES

- Histidinemia is caused by mutations in the *HAL* gene, which encodes the enzyme histidase.
- This enzyme is primarily active in the liver and skin and is responsible for converting histidine into urocanic acid.
- When histidase is deficient or inactive, histidine accumulates in the body, leading to elevated levels in various bodily fluids.

SYMPTOMS

- Learning disabilities
- Speech Disorders: There may be a slight risk of speech impairments.
- Increased Levels of Histidine: Blood tests typically show elevated histidine levels (normal range is 70-120 µM, while histidinemia levels can range from 290 to 1420 µM).
- Decreased Urocanic Acid: Alongside elevated histidine, levels of urocanic acid are often decreased in the blood, urine, and skin cells.

DIAGNOSIS

- **Blood and Urine Tests**: These tests measure the levels of histidine and its metabolites. Elevated histidine levels and decreased urocanic acid levels are indicative of the disorder.

- **Genetic Testing**: Confirmatory testing for mutations in the *HAL* gene can establish a definitive diagnosis.

TREATMENT

- Dietary Management:

A low-histidine diet may be recommended to reduce histidine levels, although this is typically unnecessary for the majority of patients.

- Supportive Care:

For those with developmental or behavioral issues, supportive therapies such as speech therapy or behavioral interventions may be beneficial.

GAUCHER'S DISEASE

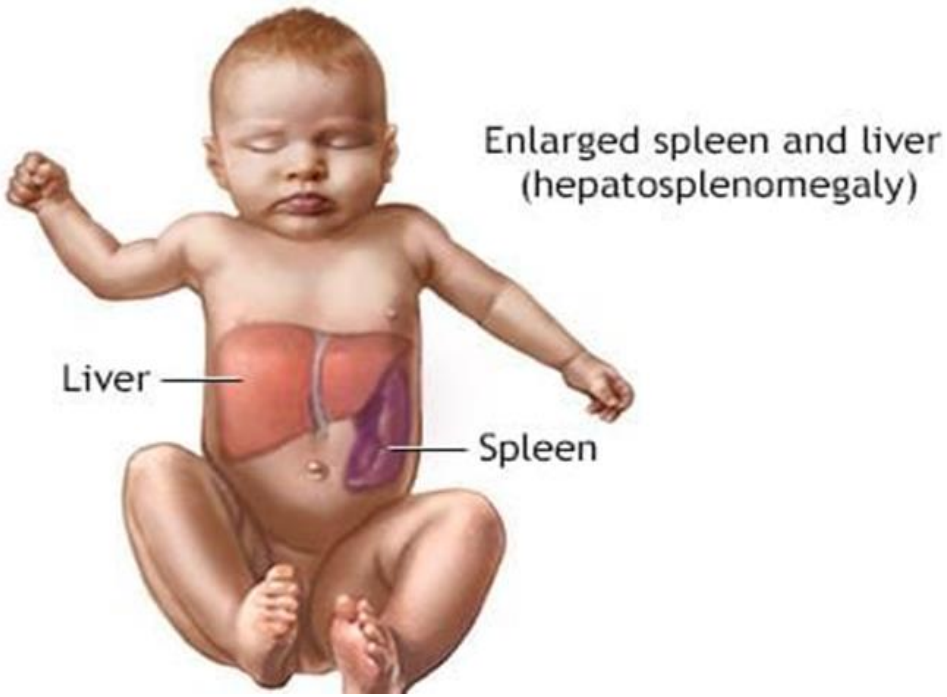
- Gaucher disease is a rare inherited metabolic disorder caused by a deficiency of the enzyme glucocerebrosidase (GCase).
- This enzyme is responsible for breaking down a fatty substance called glucocerebroside.
- When GCase is deficient, glucocerebroside accumulates in various organs and tissues, particularly the spleen, liver, and bone marrow, leading to a wide range of symptoms.

TYPES

1. **Type 1 (Non-Neuronopathic):** It is characterized by an enlarged spleen and liver, anemia, low platelet count, and bone problems. Type 1 does not affect the brain or nervous system.
2. **Type 2 (Acute Neuronopathic):** This rare, severe form begins in infancy and progresses rapidly. Symptoms include brain damage, seizures, and severe neurological problems. Affected infants usually die by 2 years of age.
3. **Type 3 (Chronic Neuronopathic):** This form has a wide range of symptoms and can begin at any age. It is characterized by neurological problems, an enlarged spleen and liver, and lung and heart complications. The progression is slower than type 2.

SYMPTOMS

- Enlarged spleen and liver
- Anemia and easy bruising/bleeding
- Bone pain, fractures, and osteoporosis
- Lung and heart complications
- Neurological problems (types 2 and 3)



DIAGNOSIS

- Blood tests to enzyme activity
- Genetic testing to measure GCase identify mutations in the *GBA* gene
- Imaging tests like MRI or CT scans to assess organ size and bone involvement

TREATMENT

1. **Enzyme Replacement Therapy (ERT):** Intravenous infusions of a modified version of the GCase enzyme, given every 2 weeks. ERT can help reduce organ size, improve blood counts, and reduce bone pain.
2. **Substrate Reduction Therapy (SRT):** Oral medications that reduce the production of glucocerebroside.
3. **Supportive Care:** Treatments for specific symptoms, such as pain management, blood transfusions, and orthopedic interventions.

TAY SACHS DISEASE

- Tay-Sachs disease is a rare genetic disorder that primarily affects the nervous system.
- It is classified as an inborn error of metabolism due to a deficiency of the enzyme hexosaminidase A (Hex-A), which is crucial for the breakdown of a fatty substance called GM2 ganglioside.
- This accumulation of GM2 gangliosides leads to the progressive destruction of nerve cells in the brain and spinal cord.

TYPES

1. **Infantile Tay-Sachs Disease**: The most common and severe form, typically presenting between 3 to 6 months of age.
2. **Juvenile Tay-Sachs Disease**: Onset occurs between ages 2 and 10, with symptoms that progress more slowly than the infantile form.
3. **Late-Onset Tay-Sachs Disease**: Symptoms can appear in late adolescence or adulthood, and the progression is generally milder.

SYMPTOMS

- **Infantile Tay-Sachs Disease**
- **Early Symptoms**: Include muscle weakness, decreased muscle tone (hypotonia).
- Vision loss (often accompanied by a characteristic "cherry-red spot" in the retina)
- Hearing loss
- Seizures
- Difficulty swallowing
- Paralysis and severe cognitive decline

- **Juvenile Tay-Sachs Disease:**

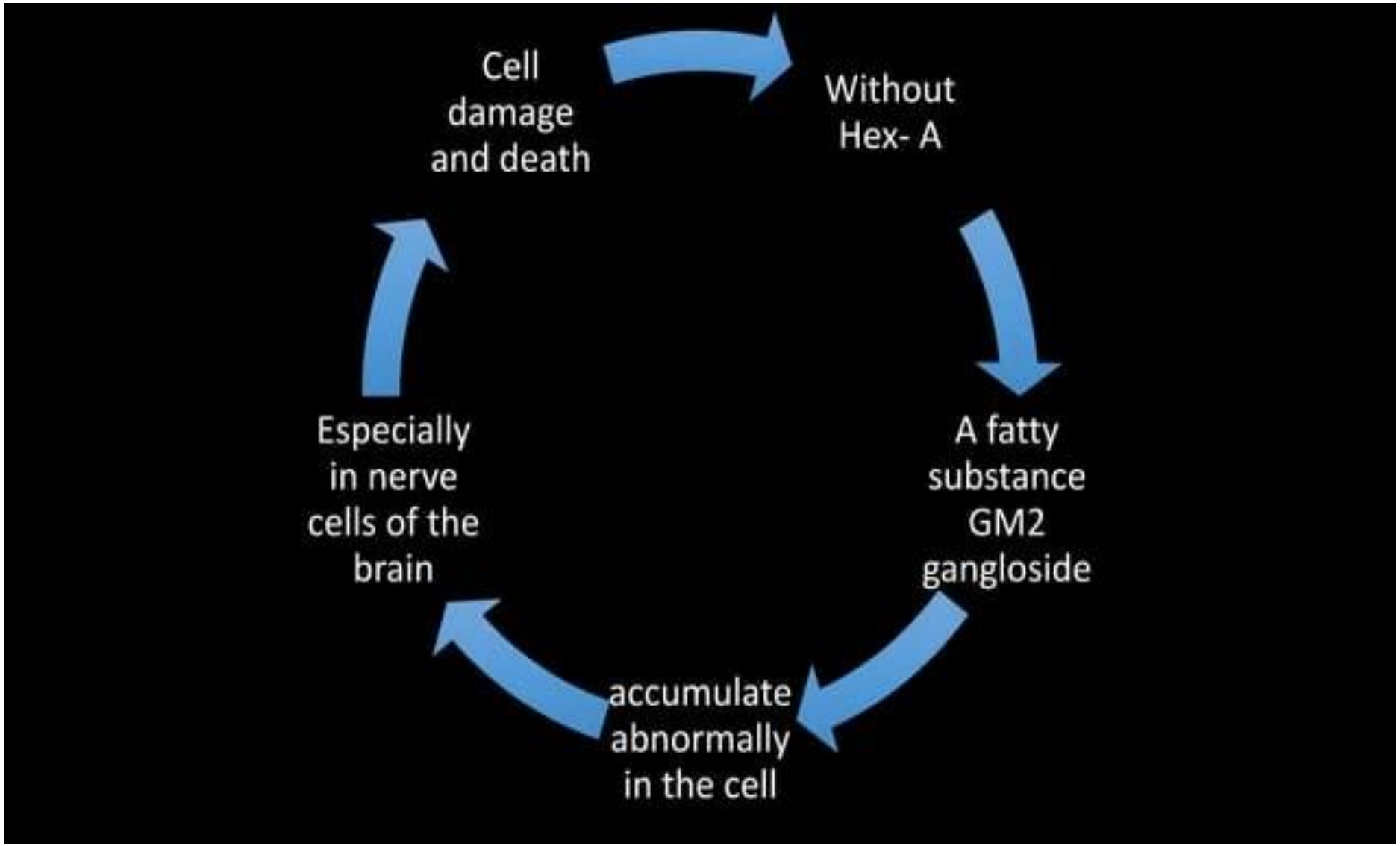
Include clumsiness, ataxia (loss of coordination), progressive loss of speech and motor skills, and potential cognitive decline.

- **Late-Onset Tay-Sachs Disease:**

Include progressive muscle weakness, ataxia, speech difficulties, and psychiatric symptoms. This form tends to progress more slowly and may not be fatal.

CAUSES

- Tay-Sachs disease is caused by a genetic mutation in the *HEXA* gene located on chromosome 15.
- This gene provides instructions for making a protein called hexosaminidase A (Hex-A), which is essential for breaking down a fatty substance called GM2 ganglioside.
- When the *HEXA* gene has mutations, it leads to a deficiency of the Hex-A enzyme.
- Without sufficient Hex-A, GM2 gangliosides accumulate in the nerve cells of the brain and spinal cord, causing progressive damage and destruction of these cells.


Without
Hex- A
A fatty
substance
GM2
ganglioside
accumulate
abnormally
in the cell
Especially
in nerve
cells of the
brain
Cell
damage
and death

DIAGNOSIS

- Enzyme Activity Testing:

  Blood tests to measure Hex-A enzyme activity are the first step in diagnosing the disease.

- Genetic Testing:

  Identifying mutations in the *HEXA* gene can confirm the diagnosis.

- Ophthalmological Examination:

  A characteristic cherry-red spot in the retina can be identified through eye examination

TREATMENT

- **Medications**: Anticonvulsants for seizures and medications to manage muscle stiffness.
- **Therapies**: Physical therapy to improve mobility and speech therapy for feeding and communication difficulties.
- **Nutritional Support**: Special feeding techniques may be required for those with swallowing difficulties.

NIEMANN - PICK DISEASE

- Niemann-Pick disease (NPD) is a group of rare inherited metabolic disorders characterized by the accumulation of lipids, particularly sphingomyelin and cholesterol, in various organs and tissues.
- These conditions are classified as lysosomal storage disorders and are caused by deficiencies in specific enzymes or proteins involved in lipid metabolism.

TYPES

1.Type A (Infantile Neurovisceral):

Caused by mutations in the *SMPD1* gene, leading to a severe deficiency of the enzyme acid sphingomyelinase (ASM). This results in the accumulation of sphingomyelin in the brain, liver, spleen, and other organs.

1.Type B (Chronic Visceral):

Also caused by *SMPD1* gene mutations and ASM deficiency. Type B is less severe than type A, with primarily visceral symptoms such as an enlarged liver and spleen, lung disease, and blood abnormalities.

- **Type C:**

Caused by mutations in the *NPC1* or *NPC2* genes, which disrupt the transport of cholesterol and other lipids within cells.

This leads to the accumulation of unesterified cholesterol and other lipids in the liver, spleen, and brain.

Type C has a wide range of symptoms, including neurological problems, and can occur at any age.

CAUSES

- Niemann-Pick disease is caused by genetic mutations affecting lipid metabolism.
- Types A and B result from mutations in the *SMPD1* gene, leading to a deficiency of acid sphingomyelinase and sphingomyelin accumulation.
- Type C is caused by mutations in *NPC1* or *NPC2* genes, disrupting lipid transport and causing cholesterol accumulation.
- All types are inherited in an autosomal recessive manner.

DIAGNOSIS

- **Enzyme Assays**: Measuring ASM activity in white blood cells or fibroblasts for types A and B.
- **Genetic testing**: Identifying mutations in the *SMPD1*, *NPC1*, or *NPC2* genes.
- **Filipin staining**: Detecting accumulation of unesterified cholesterol in type C.

TREATMENT

- There is no cure for Niemann-Pick disease, and treatment focuses on managing symptoms and complications:
- **Supportive care**: Addressing specific symptoms and complications, such as respiratory support for lung disease.
- **Enzyme replacement therapy**: Investigational treatments using recombinant ASM for types A and B.
- **Substrate reduction therapy:** Reducing the production of lipids to limit accumulation in type C.

REFERENCE

- MN Chatterjea, Ranashinde – (2012). Textbook of Medical Biochemistry, 8thedition, JAYPEE.
- By William J. Marshall, S. K. Bangert – (1995). Clinical Biochemistry: Metabolic and Clinical Aspects, 1stedition, Churchillivingstone.
- Michael Lieberman, Allan D. Marks – (2009). Marks'Basic Medical Biochemistry: A Clinical Approach, 3rdedition, Lippincott Williams &Wilkins.
- https://www.ncbi.nlm.nih.gov/books/NBK430900/
- https://www.ncbi.nlm.nih.gov/books/NBK245

THANK YOU