AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Pearl Title : Disorders of Copper metabolism

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DOI:

Outline

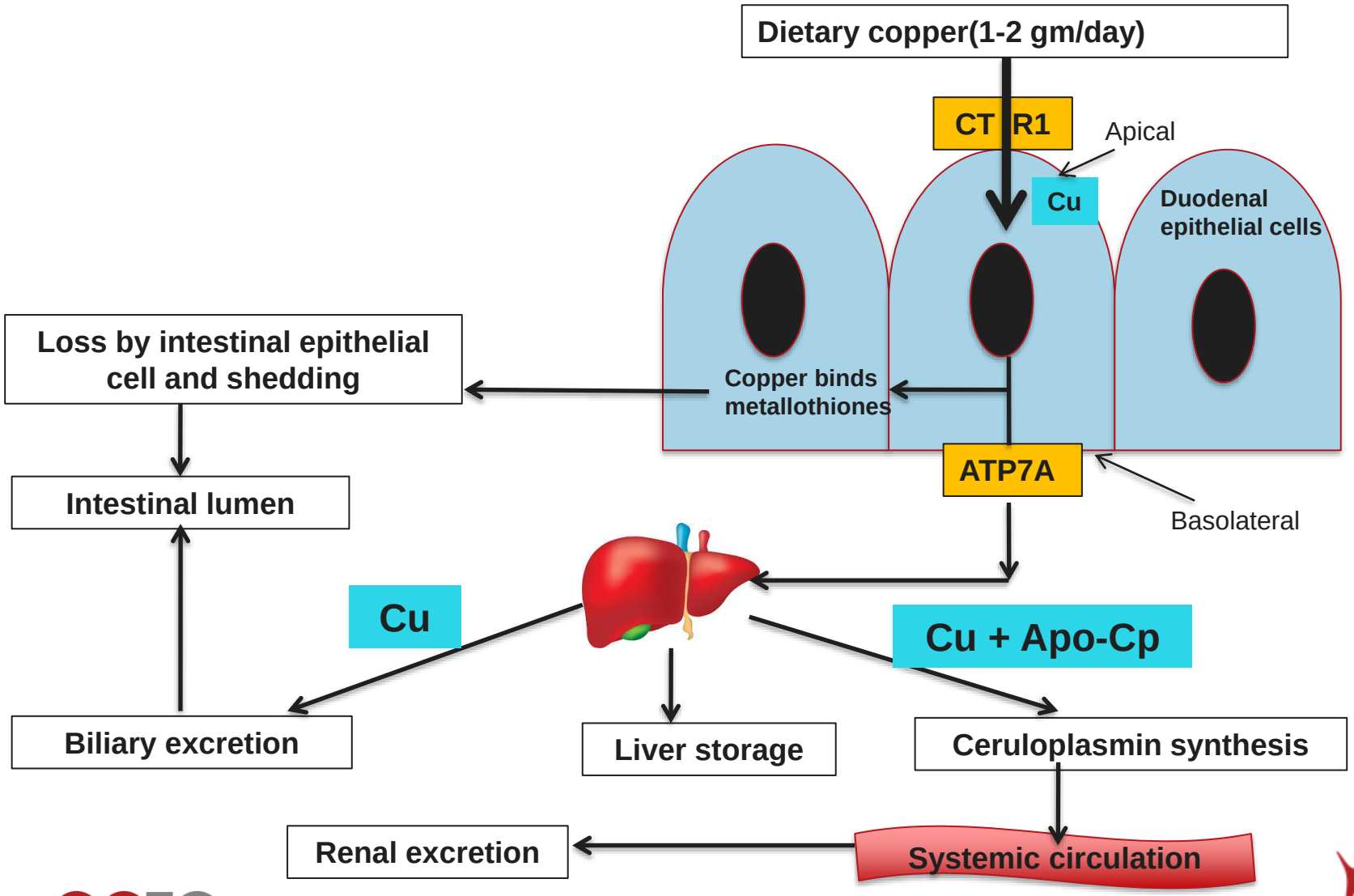
- Copper metabolism
- Disorders of copper metabolism
  - Pathogenesis
  - Clinical features and diagnosis
  - Treatment

Introduction

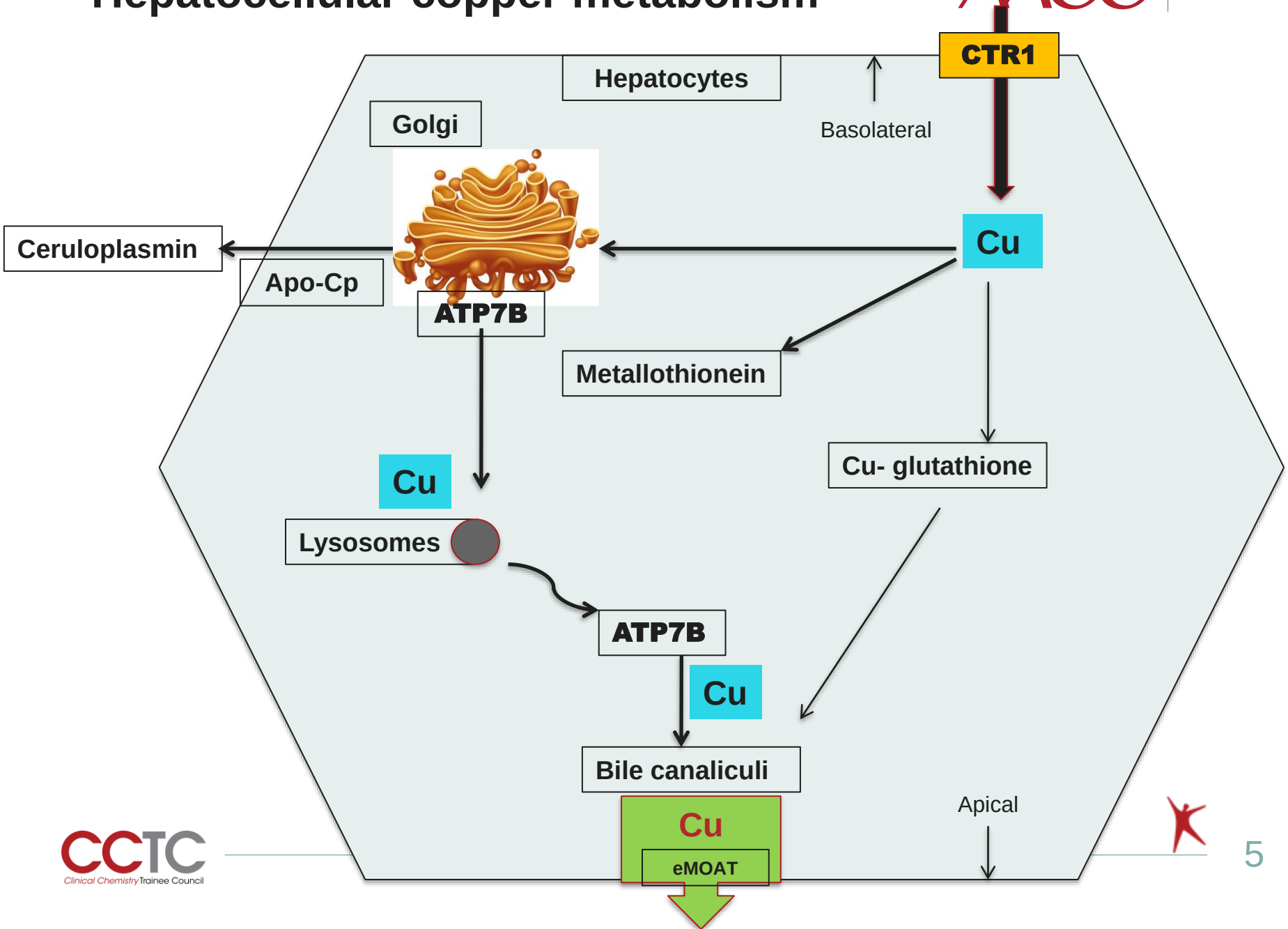
- Important trace element of the biological systems.

- Functions
  - Role in redox reaction (cytochrome C oxidase: electro transport chain)
  - Superoxide dismutase: Cell detoxification
  - Ferroxidase
  - Dopamine beta hydroxylase: secretion of Adrenalin, Nor-adrenalin
  - MAO; catecholamines metabolism
  - Tyrosinase: Melanin
  - Lysol Oxidase: cross linking collagen
  - Regulation of gene expression

Copper absorption and excretion



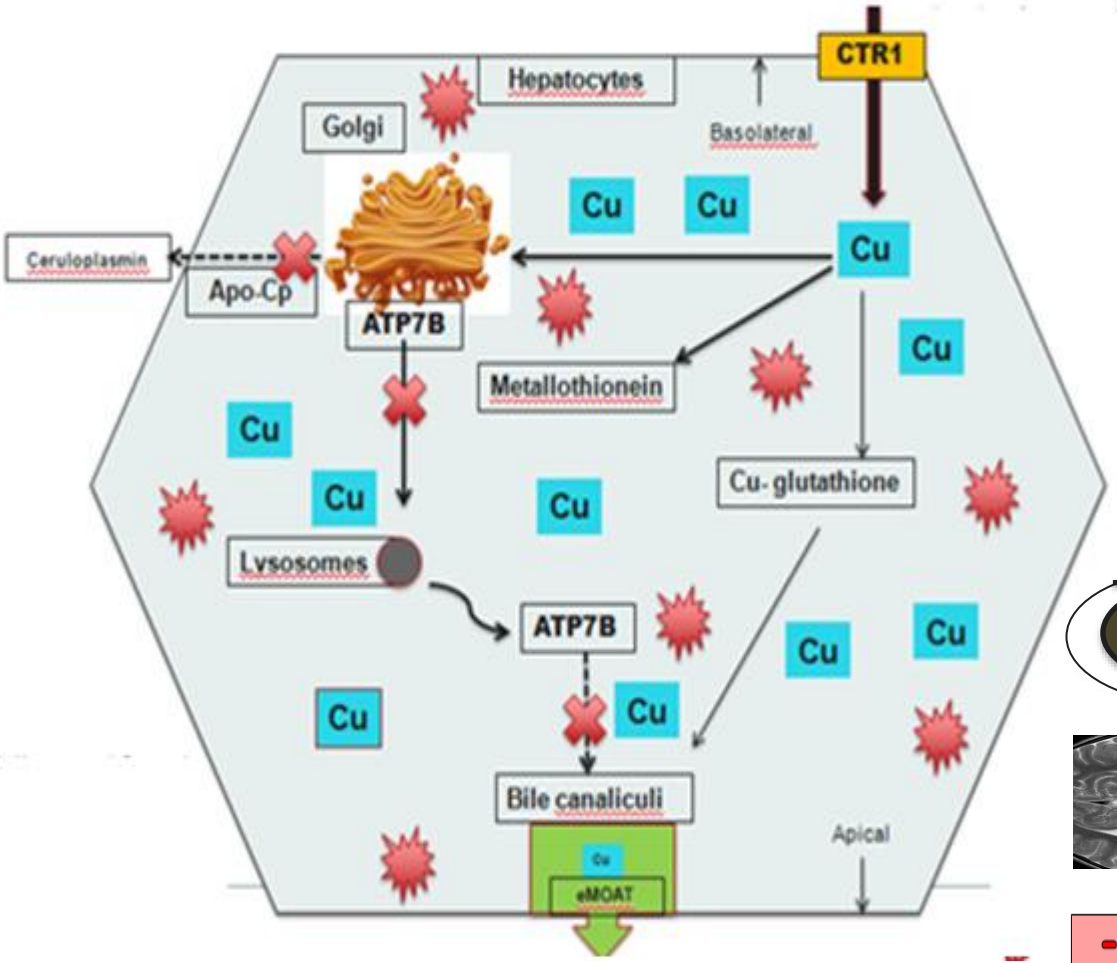
Hepatocellular copper metabolism



Disorders of Copper metabolism

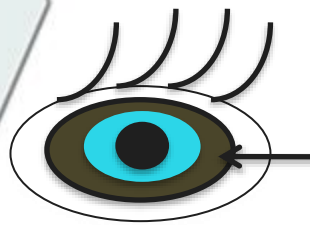
- Wilson's disease - mutation of ATP7B
- Menkes disease - mutation of ATP7A
    - Inborn errors of copper metabolism

- Infantile and childhood copper toxicosis syndrome
    - Indian childhood cirrhosis (ICC)
    - Idiopathic copper toxicosis (ICT)
    - Tyrolean infantile cirrhosis (TIC)

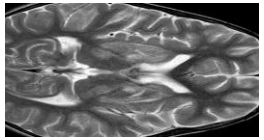


Copper excretion in feces reduced

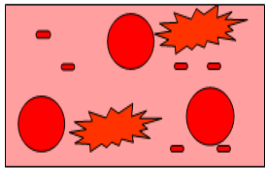
- Decreased copper excretion into bile
- Decreased copper binding with ceruloplasmin
- Increased unbound copper



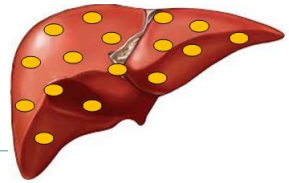
Kayser-Fleischer Ring



Hepatolenticular degeneration



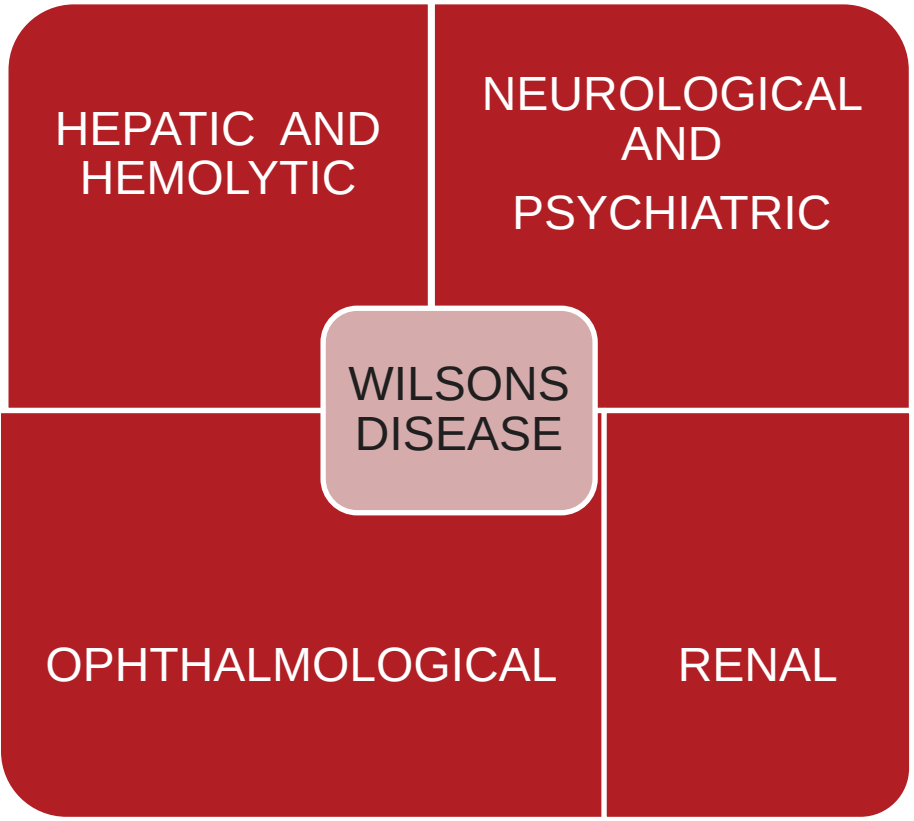
Hemolysis



Cirrhosis

Hepatocyte inflammation and death (ROS mediated)

Clinical features



- Hepatic - Fatigue, anorexia, abdominal pain, nausea, jaundice(self limiting), severe coagulopathy and encephalopathy.
- Hemolytic -Coombs-negative Hemolytic Anemia
- Neurological - dysarthria, clumsiness, tremor, drooling, gait disturbance, masklike facies and deterioration of handwriting.
- Psychiatric - changes in personality, depression and anxiety.
- Ophthalmologic - Kayser-Fleischer Rings; granules rich in copper and sulfur deposited in the Descemet membrane of the cornea, giving golden brown or has a greenish discoloration in the limbus.
- Renal – microscopic hematuria and Fanconi syndrome.

Diagnostic criteria to establish Wilson's disease

(The **Leipzig criteria** considers both clinical and laboratory data for diagnosis)

Clinical or Laboratory Finding		Points
Kayser-Fleischer Rings	Present Absent	2 0
Neurologic Symptoms or MRI Findings	Severe Mild Absent	2 1 0
Serum ceruloplasmin(g/L)	<0.1 0.1–0.2 Normal (>0.2)	2 1 0
24-h Urinary Copper	>2 ×ULN 1–2 ×ULN Normal Normal, but >5 ULN after D-penicillamine	2 1 0 2

ULN – upper limit of normal

Leipzig criteria….contd

Clinical or Laboratory Finding		Points
Coombs-negative Hemolytic Anemia	Present Absent	1 0
Total Liver Copper Level (µmol/g)	>5 × UNL(>4) Increased (0.8–4) Normal (<0.8) Rhodanine-positive granules present	2 1 -1 1
Genetic Mutation	Present on both chromosomes Present on 1 chromosome Absent	4 1 0
Evaluation and Total Score	**Diagnosis established** **Diagnosis possible, more tests needed** **Diagnosis unlikely**	**4** **3** **2 or less**

ULN – upper limit of normal

Mutation analysis

- More than 600 mutations of *ATP7B* gene.
- Majority are missense mutations with few mutations for specific populations.
- Large deletions are rare.
- Accurate molecular diagnosis of Wilson disease can be made if mutations at both alleles are identified in the patient.
- Direct genetic testing, focusing on sequence analysis of *ATP7B* mutation hotspots.

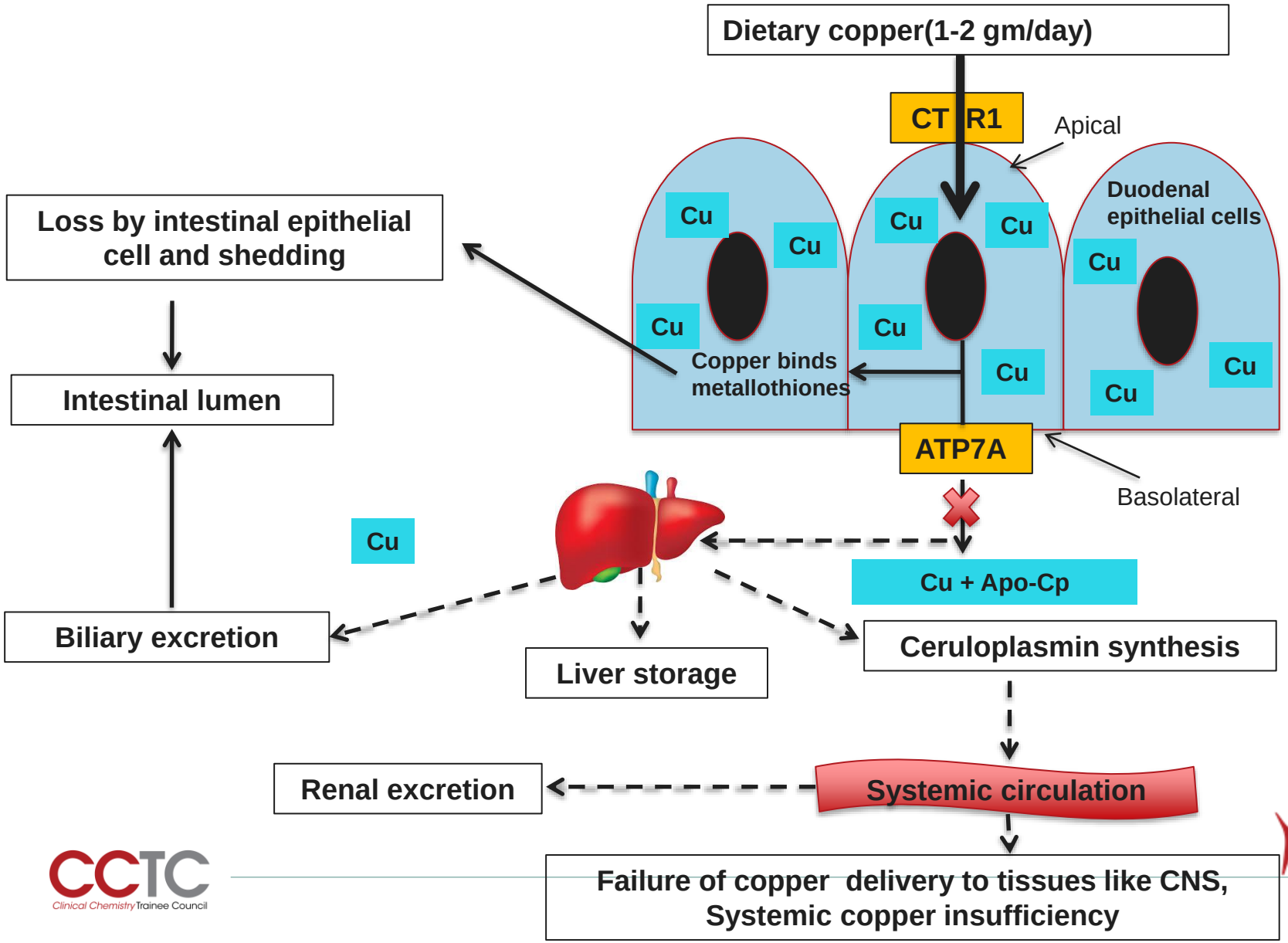
Treatment

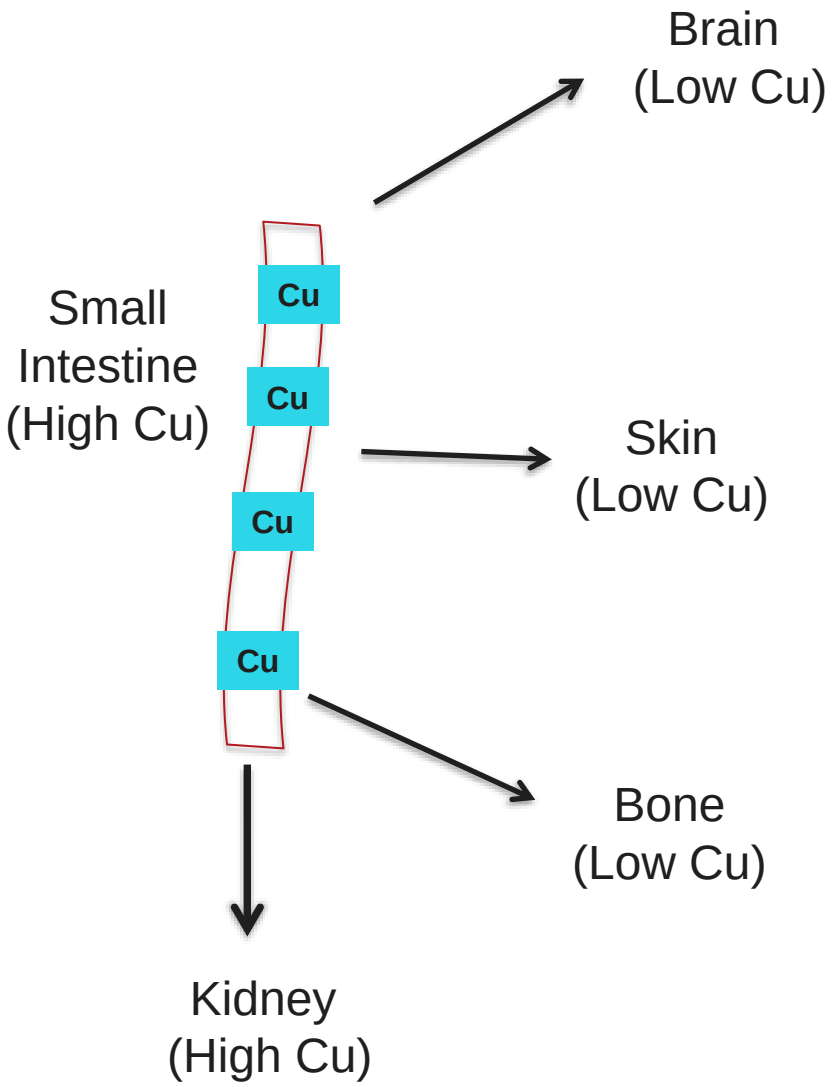
- Copper chelators like penicillamine.
- Trientine - second-line treatment for patients who are intolerant of d-penicillamine.
- Zinc salts.
- Pyridoxine supplementation.
- In extreme cases of liver failure there may be a need of liver transplantation.
- With good compliance, prognosis is excellent.

Menkes disease

- X linked recessive disease defect in ATP7A(Xq21.1)
- The N-terminal domains of the protein ATP7A, and of ATP7B, specifically bind copper and serve as sensors of intracellular copper concentration.
- ATP7A is expressed in all tissues except the liver.
- Localized in the trans-Golgi network and cycles between the trans-Golgi and plasma membrane localizations in response to basal conditions or conditions of copper excess, respectively.

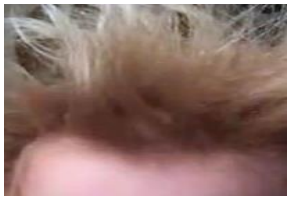
Pathogenesis and clinical features





- Demyelination
- Neuron loss in cerebral hemispheres, cerebellum and spinocerebellar tract

- Cherubic face
- Depigmented steely hair
- Fragile and frequently broken hair



- Wormian bones in lambdoid and saggital sutures
- Anterior rib flaring or cupping
- Lateral or medial spur formation on the proximal or distal femoral and humoral metaphyses

Biochemical parameters in Menkes disease

- Decreased serum copper and ceruloplasmin beyond first 6 weeks of life.
- Hepatic copper markedly decreased; urine copper excretion may be increased.
- Elevated dihydroxyphenylalanine(DOPA) and diydroxyphenylacetic acid(DOPAC) with decreased nor-epinephrine or epinephrine and of their metabolites.
- Faulty dopamine-beta-hydroxylase leads to increased urine ratios of HVA/VMA(homovanillic acid/vanillylmandelic acid)
- Increased urine β2- microglobulin excretion.

Mutation analysis and Treatment

- Diverse mutations in *ATP7A* (0–15% residual activity).
- Administration of Copper Histidinate, as early as possible after birth.
- In absence of early diagnosis and treatment, prognosis is bad.

Occipital horn syndrome

- Milder allelic variant of Menkes disease.
- Leaky splice junction or hypomorphic missense mutations in *ATP7A.*
- ATP7A-mediated copper transport occurs but spares the central nervous system.
- Symptoms of dysautonomia, related to dopamine-beta-hydroxylase deficiency, and connective tissue seen.

Indian Childhood Cirrhosis (ICC)

- Restricted to Indian subcontinent.
- Ingestion of excess copper and brass due to eating from these vessels along with a genetic predisposition.
- Increased hepatic, urinary and serum copper, with rapidly progressive liver cirrhosis.
- Presently a very rare entity.

Idiopathic copper toxicity (ICC like disease)

- Rare disorder due to unidentified genetic defect or excessive environmental copper exposure(contaminated spring water in endemic Tyrolean infantile cirrhosis).
- Within two years of age the child develops severe progressive cirrhosis without neurological disease.

Future directions

- New born screening to enable early detection and hence early treatment of patients for Menkes disease and Occipital horn syndrome.
- Adeno virus-mediated gene therapy.
- Liver directed gene therapy for Wilsons disease.

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