INE | INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Micronutrients: Copper

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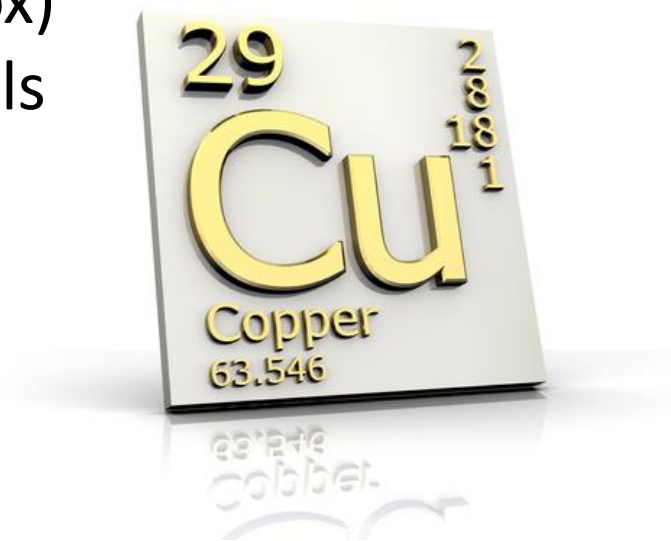
Medical Disclaimer: The information in this presentation is not intended to replace a one-on-one relationship with a qualified health care professional and is not intended as medical advice. It is intended as a sharing of knowledge and information from the research and experience of Dr. Ritamarie Loscalzo, drritamarie.com, and the experts who have contributed. We encourage you to make your own health care decisions based upon your research and in partnership with a qualified health care professional.

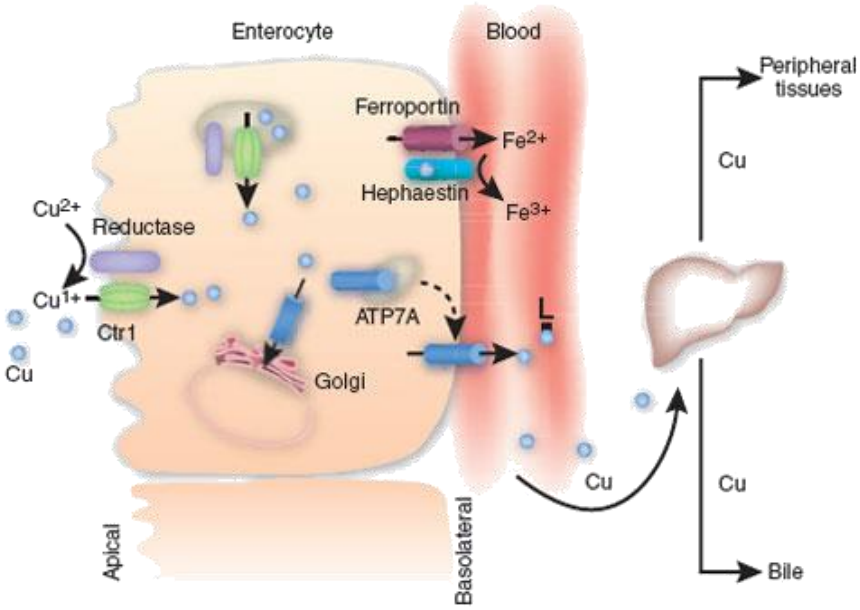
Copper (CU) Basics

- ✓ An essential trace element
- ✓ Found in the body in either the cuprous (Cu1+) form or the cupric (Cu2+) form
- ✓ Majority of the body's copper is in the Cu2+ form (cupric)
- ✓ Copper can easily accept and donate electrons and is important in oxidation-reduction (redox) reactions and in scavenging free radicals
- ✓ Hippocrates is said to have prescribed copper compounds to treat diseases as early as 400 B.C.



Digestion and Absorption of Copper

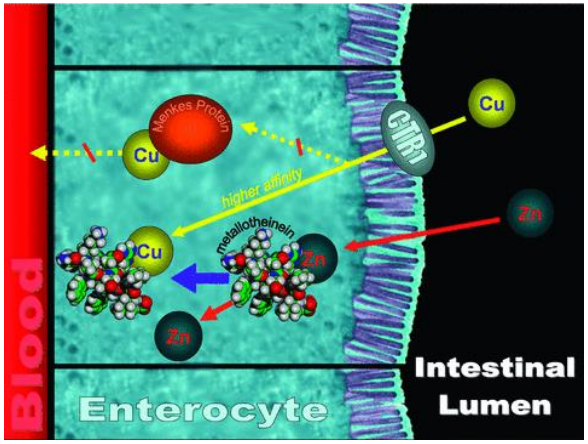
- ✓ Bound to amino acids in foods
- ✓ HCl and pepsin in stomach required to break the bonds
- ✓ Proteolytic enzymes in small intestine hydrolyze to further release bonds
- ✓ Passive diffusion in small intestine, mainly in duodenum, when present in high concentrations
- ✓ Active transport in low concentrations
- ✓ Usually over 50% is absorbed



Factors that Impact Copper Absorption

Enhancers of Copper Absorption

- ✓ **Amino Acids:**
  - Histidine
  - Cysteine
  - Methionine
- ✓ **Organic Acids:**
  - Citric
  - Gluconic
  - Lactic
  - Acetic
  - Malic



Inhibitors of Copper Absorption

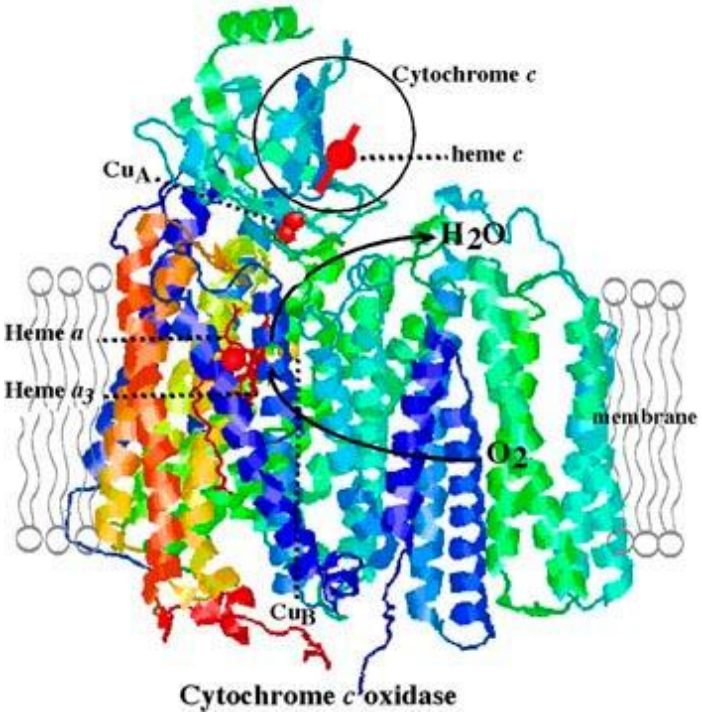
- ✓ Phytate
- ✓ Zinc (over 40 mg, sometimes as little as 18.5 mg)
- ✓ Iron (large amounts)
- ✓ Molybdenum
- ✓ Calcium (2382 mg as glucarate)
- ✓ Phosphorus (2442 mg as glycerol phosphate)
- ✓ Vitamin C

Functions of Copper

- ✓ Part of cuproenzymes
- ✓ Aids in the formation of bone, hemoglobin, and red blood cells
- ✓ Works in balance with zinc and vitamin C to form elastin, an important skin protein
- ✓ Involved in the healing process
- ✓ Important for energy production
- ✓ Role in hair and skin coloring
- ✓ Important for taste sensitivity
- ✓ Required for healthy nerves and joints
- ✓ Essential for the formation of collagen

Copper and Energy Production

- ✓ Copper-dependent enzyme, cytochrome c oxidase, plays a critical role in cellular energy production
- ✓ Cytochrome c oxidase catalyzes the reduction of molecular oxygen (O2) to water (H2O)
- ✓ Cytochrome c oxidase generates an electrical gradient used by the mitochondria to create the vital energy-storing molecule ATP



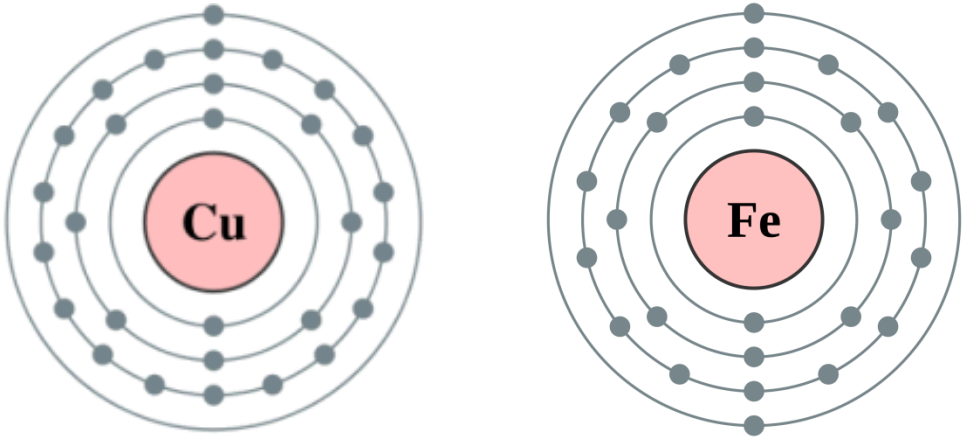
Copper and Connective Tissue Formation

- ✓ Cuproenzyme - lysyl oxidase
  - ➢ Required for the cross-linking of collagen and elastin
  - ➢ Essential for the formation of strong and flexible connective tissue
- ✓ Lysyl oxidase helps maintain the integrity of connective tissue in the heart and blood vessels
- ✓ Plays a role in bone formation

Copper and Iron Metabolism

Enzymes: Copper oxidases (MCO) or ferroxidases

- ✓ Oxidize ferrous iron (Fe2+) to ferric iron (Fe3+), the form of iron that can be loaded onto iron carrying protein transferrin for red blood cell formation
  - ✓ Circulating ceruloplasmin (~90% of plasma copper)
  - ✓ Membrane-bound ceruloplasmin (called GPI-ceruloplasmin)
  - ✓ Hephaestin and Zyklopen, found in the intestine and the placenta
- ✓ Lack of ceruloplasmin causes iron overload in liver, brain, and retina
- ✓ Iron mobilization from storage sites is impaired in copper deficiency
- ✓ Ferroxidase activity of ceruloplasmin is essential to the flux of iron in the body

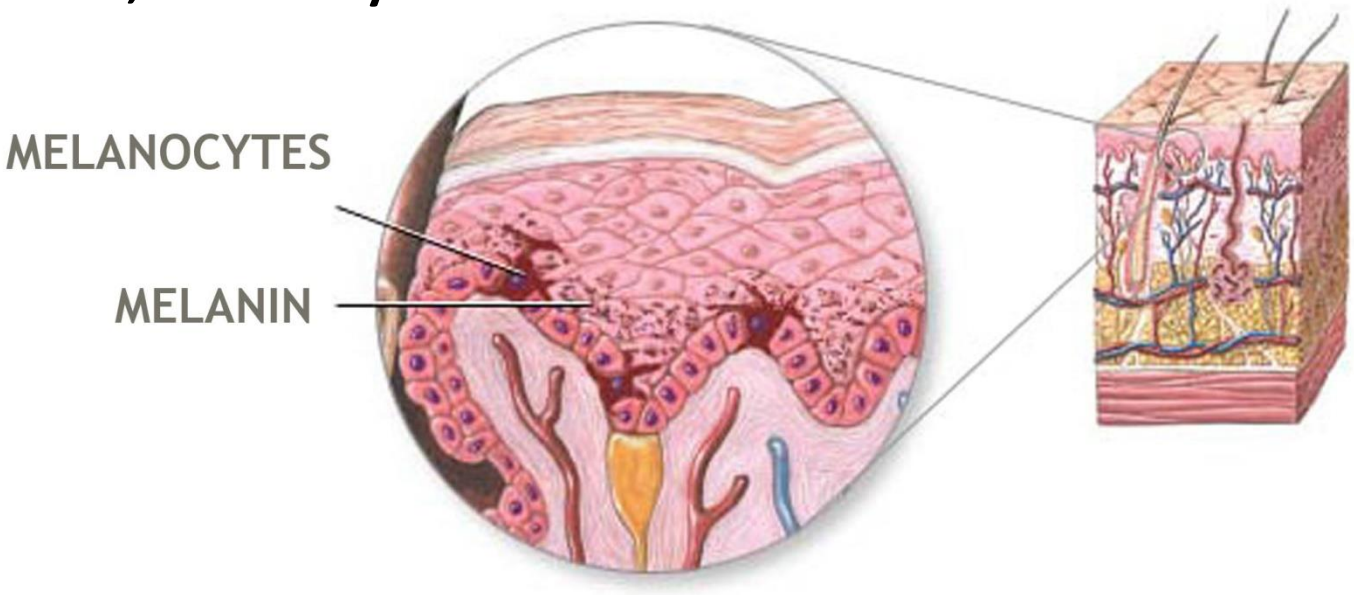


Copper and the Central Nervous System

- ✓ **Neurotransmitter synthesis**
  - ➢ Dopamine β-hydroxylase, a cuproenzyme, catalyzes the conversion of dopamine to norepinephrine
- ✓ **Formation and maintenance of myelin**
  - ➢ The myelin sheath is made of phospholipids whose synthesis depends on cytochrome c oxidase activity

Copper and Pigmentation

- ✓ The cuproenzyme, tyrosinase is required for the formation of melanin
- ✓ Tyrosinase is formed in melanocytes
- ✓ Melanin plays a role in the pigmentation of the hair, skin, and eyes

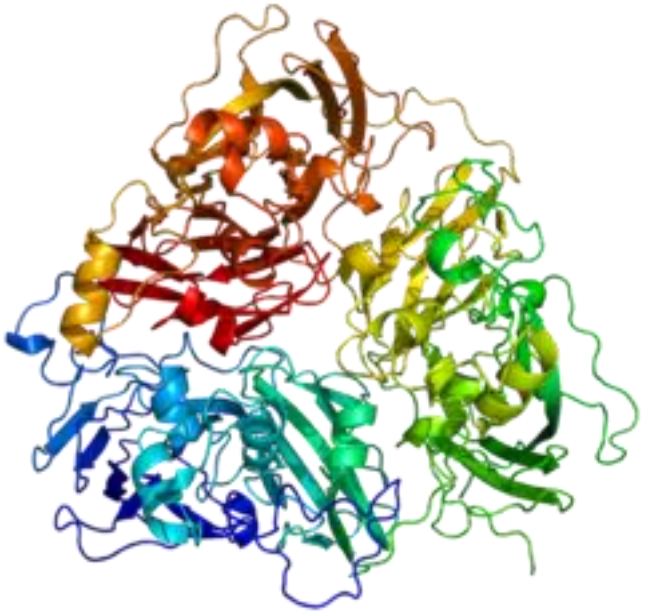


Copper and Superoxide Dismutase

- ✓ Superoxide dismutase (SOD)
  - ➢ Functions as an antioxidant
  - ➢ Catalyzes the conversion of superoxide radicals to hydrogen peroxide
  - ➢ Can subsequently be reduced to water by other antioxidant enzymes
- ✓ Two forms of SOD contain copper:
  - ➢ Copper/zinc SOD is found within most cells of the body, including red blood cells
  - ➢ Extracellular SOD is a copper-containing enzyme found at high levels in the lungs and low levels in plasma

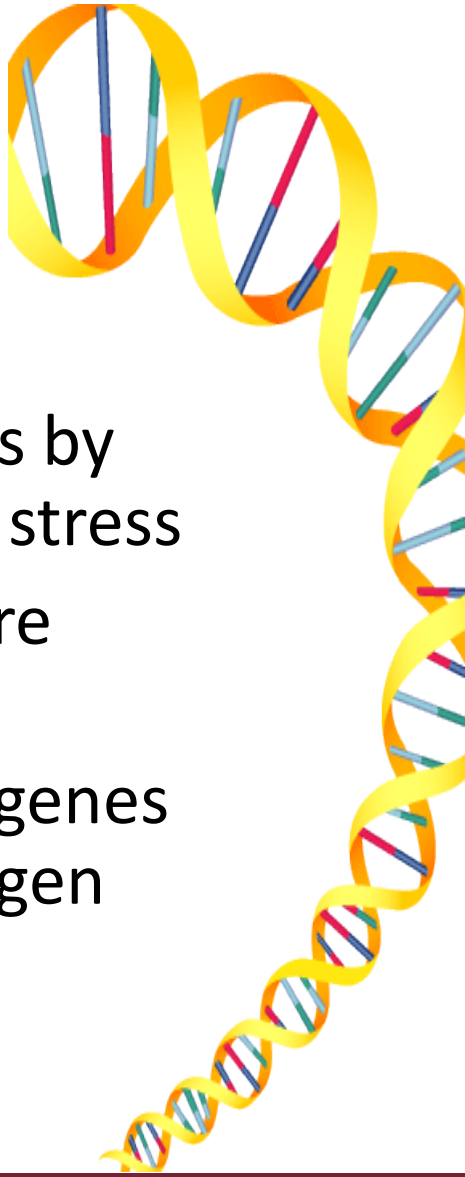
Copper and Ceruloplasmin

- ✓ Ceruloplasmin prevents free copper ions from catalyzing oxidative damage by binding copper
- ✓ Free copper and iron ions are powerful catalysts of free radical damage
- ✓ The ferroxidase activity of ceruloplasmin (oxidation of ferrous iron)
  - ➢ Facilitates iron loading onto its transport protein, transferrin
  - ➢ May prevent free ferrous ions (Fe2+) from participating in harmful free-radical-generating reactions



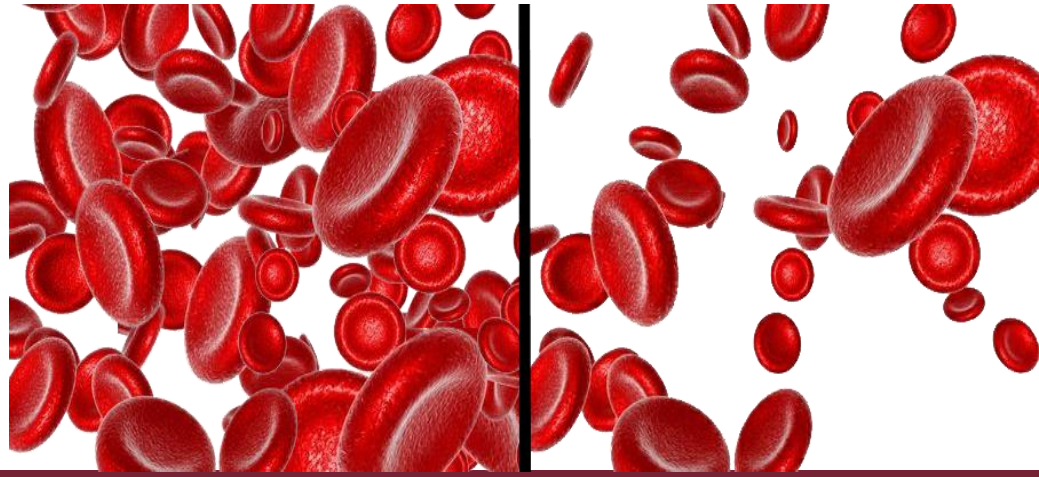
Copper and Regulation of Gene Expression

- ✓ Cellular copper levels enhance or inhibit the transcription of specific genes
- ✓ May affect the synthesis of proteins
- ✓ Copper may regulate the expression of genes by increasing the level of intracellular oxidative stress
- ✓ A number of signal transduction pathways are activated in response to oxidative stress
- ✓ Can lead to an increase in the expression of genes involved in the detoxification of reactive oxygen species



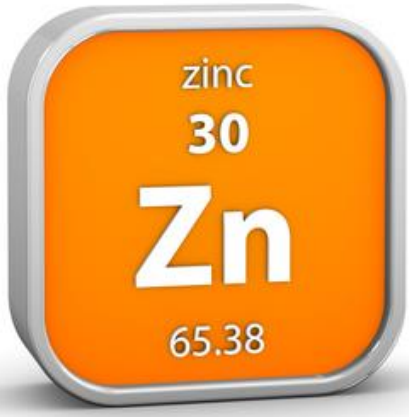
Copper and Iron Interactions

- ✓ Adequate copper nutritional status is necessary for normal iron metabolism and red blood cell formation
- ✓ Ceruloplasmin required for iron transport to the bone marrow for red blood cell formation
- ✓ Anemia is a clinical sign of copper deficiency
- ✓ Copper deficiency can lead to secondary ceruloplasmin deficiency and hepatic iron overload and/or cirrhosis
- ✓ High iron intakes may interfere with copper absorption



Copper and Zinc Interactions

- ✓ Zinc intake of 50 mg/day or more for extended periods of time may result in copper deficiency
  - ➢ Increase the synthesis of an intestinal cell protein called metallothionein
  - ➢ Binds certain metals and prevents their absorption by trapping them in intestinal cells
- ✓ Metallothionein
  - ➢ Has a stronger affinity for copper than zinc
  - ➢ High levels of metallothionein induced by excess zinc cause a decrease in copper absorption
  - ➢ High copper intakes have not been found to affect zinc nutritional status

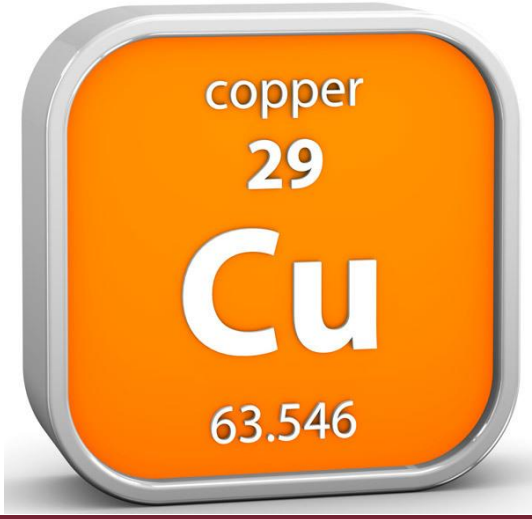


Copper and Vitamin C Interactions

- ✓ Vitamin C may decrease absorption of copper (reduces copper from Cu^{2+} to $Cu^{1+)}$
- ✓ Vitamin C supplementation of 1,500 mg/day for two months resulted in a significant decline in ceruloplasmin oxidase activity
- ✓ Supplements of 605 mg/day of vitamin C for three weeks resulted in decreased ceruloplasmin oxidase activity, although copper absorption did not decline
- ✓ Neither of these studies found vitamin C supplementation to adversely affect copper nutritional status

Copper Deficiency Signs

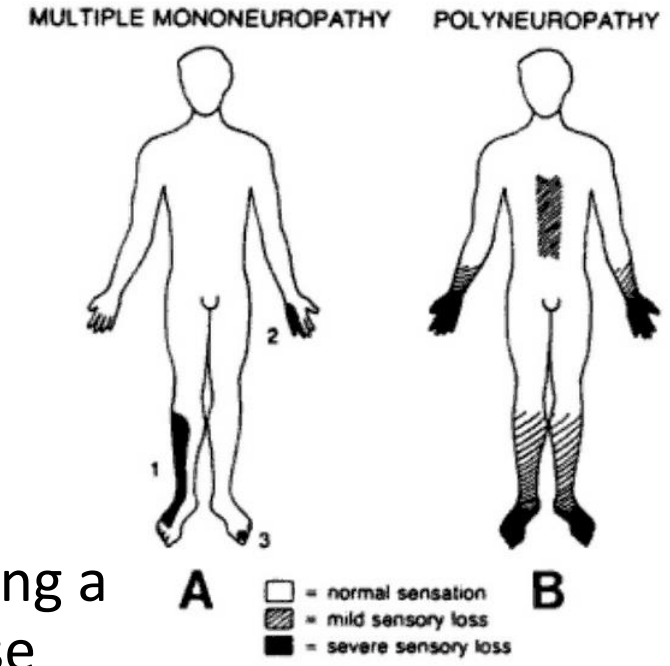
- ✓ Most common in low-birth-weight infants and young children (uncommon)
- ✓ Serum copper and ceruloplasmin levels may fall to 30% of normal in cases of severe copper deficiency
- ✓ Hypocupremia is also observed in genetic disorders of copper metabolism like aceruloplasminemia and Wilson's disease
- ✓ The most common clinical signs of copper deficiency
  - ➢ An anemia that is unresponsive to iron therapy but corrected by copper supplementation
  - ➢ Abnormally low numbers of neutrophils (neutropenia)
  - ➢ Increased susceptibility to infection
  - ➢ Loss of pigmentation, neurological symptoms, and impaired growth (less common)
  - ➢ Osteoporosis and other abnormalities of bone development
  - ➢ Cardiovascular dysfunction



Individuals at Risk of Deficiency

- ✓ High-risk individuals
  - ➢ High-risk infants and children fed only cow's milk formula
  - ➢ Premature infants (especially low-birth-weight infants)
  - ➢ Infants with prolonged diarrhea
  - ➢ Infants and children recovering from malnutrition
- ✓ Individuals with malabsorption syndromes
  - ➢ Celiac disease
  - ➢ Sprue
  - ➢ Short bowel syndrome due to surgical removal of large portions of the intestine
- ✓ Cystic fibrosis patients
- ✓ IV total parenteral nutrition lacking copper (infants with cholestasis link)
- ✓ Excessive zinc intake (over 50 mg per day)

Acquired Copper Deficiency



- ✓ A neurologic syndrome
- ✓ The symptoms include:
  - ➢ Central nervous system demyelination
  - ➢ Polyneuropathy
  - ➢ Myelopathy
  - ➢ Inflammation of the optic nerve
- ✓ Increased intestinal copper content suggesting a malabsorption syndrome like Menkes disease
- ✓ Oral copper replacement (2 mg/day of elemental copper)
  - ➢ Normalizes serum copper and ceruloplasmin concentrations
  - ➢ Stabilizes the condition
  - ➢ Significantly improves the quality of life of affected subjects

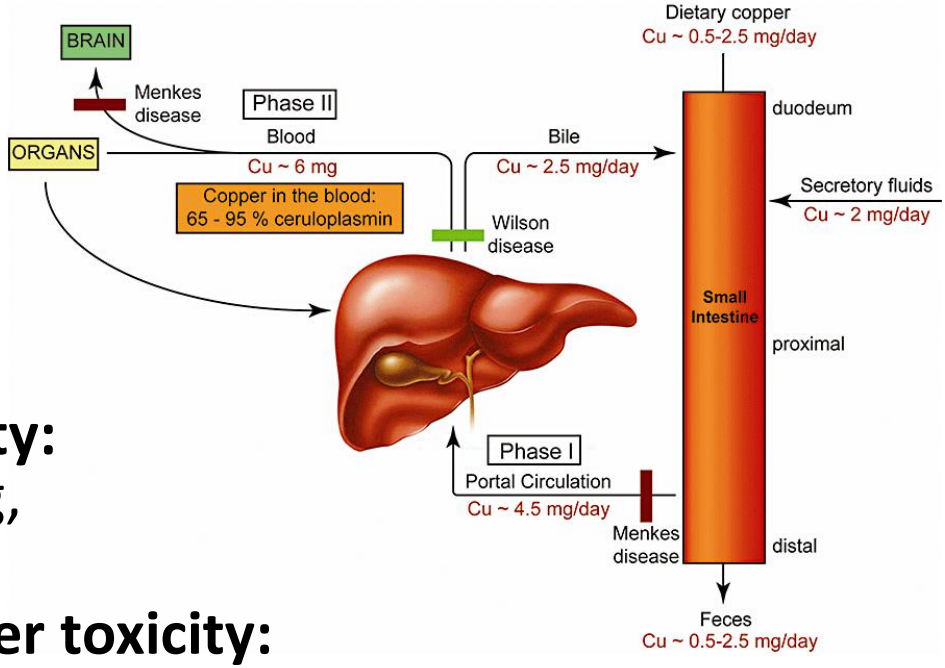
Inherited Copper Deficiency –
Menkes Disease (MD) and Occipital Horn Syndrome (OHS)

- ✓ **Mutations in the *ATP7A* gene** (ATPase enzyme in most cells except liver)
  - ➢ Impair the transport of intracellular copper
  - ➢ Accumulates in the cytosol of enterocytes and vascular endothelial cells
  - ➢ Results in systemic copper deficiency and decreased cuproenzyme activity
- ✓ **Copper transport into the brain is also affected**
  - ➢ Copper accumulation in the blood-brain barrier
  - ➢ Reduced cuproenzyme activity in neurons

- ✓ Clinical features of MD include intractable seizures, connective tissue disorders, subdural hemorrhage, and hair abnormalities ("kinky hair")
- ✓ OHS patients exhibit muscular hypotonia and connective tissue abnormalities, including exostosis on occipital bones
- ✓ **Subcutaneous injections of copper-histidine** are used to bypass the defective intestinal absorption and improve copper metabolic function in patients
- ✓ Copper entry into the brain remains limited

Copper Toxicity

- ✓ Rare in the general population
- ✓ **Acute copper poisoning due to:**
  - ➢ Contamination of beverages stored in copper-containing containers
  - ➢ Contaminated water supplies
- ✓ **Symptoms of acute copper toxicity:** Abdominal pain, nausea, vomiting, and diarrhea
- ✓ **More serious signs of acute copper toxicity:** Severe liver damage, kidney failure, coma, and death
- ✓ **Long term complications:** Liver damage
- ✓ **Genetic disorders** like Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis, may lead to adverse effects of chronic copper toxicity at significantly lower intake levels



Copper and the Endocrine System

- ✓ Women tend to have higher levels of copper and more symptoms related to copper imbalance, including yeast infections, migraine headaches, adult acne, menstrual dysfunction, and depression
- ✓ Copper-toxic women are often estrogen dominant
- ✓ Women with bio-unavailable copper are often low in estrogen
- ✓ Men tend to be zinc-dominant, although many men do have symptoms of copper toxicity including depression, anxiety, and other symptoms

Recommended Daily Allowance

- ✓ 0-6 months: 0.2 mg
- ✓ 6-12 months: 0.22 mg
- ✓ 1-3 years: 0.34 mg
- ✓ 4-8 years: 0.4 mg
- ✓ 9-13 years: 0.7 mg
- ✓ 14-18 years: 0.89 mg
- ✓ 19+ years: 0.9 mg
- ✓ Pregnant women: 1.0 mg
- ✓ Lactating women: 1.3 mg

The DRI report also established a Tolerable Upper Intake Level (UL) of 10 mg per day for adult men and women.

The Daily Value (DV) for copper is 2 mg per 2000 calories. This is the value that you will see on nutrition labels on foods.

Food Sources

- ✓ Cashews
- ✓ Sunflower seeds
- ✓ Hazelnuts
- ✓ Almonds
- ✓ Walnuts
- ✓ Lentils
- ✓ Garbanzo beans
- ✓ Lima beans
- ✓ Soybeans
- ✓ Tempeh
- ✓ White mushrooms
- ✓ Beet greens
- ✓ Turnip greens
- ✓ Spinach
- ✓ Kale

Adult RDA 0.9 mg

Food	Serving Size	Cals	Amount (mg)	DRI/DV (%)
Sesame Seeds	0.25 cup	206.3	1.47	163
Cashews	0.25 cup	221.2	0.88	98
Soybeans	1 cup	297.6	0.70	78
Mushrooms, Shiitake	0.50 cup	40.6	0.65	72
Beet Greens	1 cup	38.9	0.36	40
Turnip Greens	1 cup	28.8	0.36	40
Mushrooms, Crimini	1 cup	15.8	0.36	40
Spinach	1 cup	41.4	0.31	34
Asparagus	1 cup	39.6	0.30	33
Swiss Chard	1 cup	35.0	0.29	32
Kale	1 cup	36.4	0.20	22
Mustard Greens	1 cup	36.4	0.20	22
Summer Squash	1 cup	36.0	0.19	21
Sunflower Seeds	0.25 cup	204.4	0.63	70
Tempeh	4 oz	222.3	0.61	68
Garbanzo Beans	1 cup	269.0	0.58	64
Lentils	1 cup	229.7	0.50	56
Walnuts	0.25 cup	196.2	0.48	53
Lima Beans	1 cup	216.2	0.44	49
Pumpkin Seeds	0.25 cup	180.3	0.43	48
Tofu	4 oz	164.4	0.43	48

http://www.drritamarie.com/go/WHFoodsCopper

Testing for Copper Levels

- ✓ **Blood test** – along with ceruloplasmin
  - ➢ Wilson's disease
  - ➢ Excess copper storage
  - ➢ Copper poisoning
  - ➢ Copper deficiency
- ✓ **24-hour urine test**
  - ➢ Copper elimination
  - ➢ Copper storage in the liver
- ✓ **Hair analysis**

Copper/Drug Interactions

- ✓ Penicillamine
  - ➢ Used to bind copper and enhance its elimination in Wilson's disease, a genetic disorder resulting in hepatic copper overload
  - ➢ Dramatically increases the urinary excretion of copper
- ✓ Antacids may interfere with copper absorption when used in very high amounts

References

- ✓ *Advanced Nutrition and Human Metabolism*: Gropper, Smith And Groff (suggested textbook for Nutrient part of the course)
- ✓ *Handbook of Nutritionally Essential Minerals*: Boyd L. O'Dell (Editor), Roger A. Sunde http://www.drritamarie.com/go/MineralElementHandbook
- ✓ Linus Pauling Institute website: http://www.drritamarie.com/go/LPICopper
- ✓ http://www.drritamarie.com/go/NCBICopperTransport
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