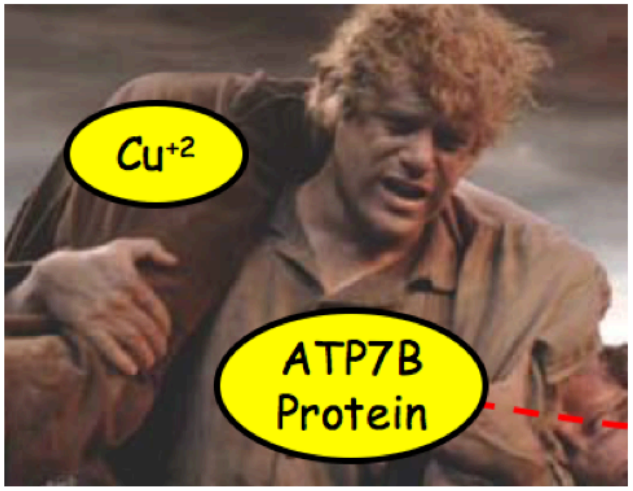
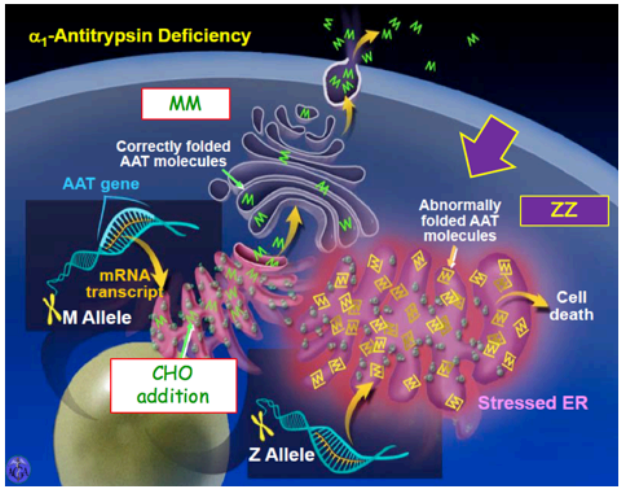
Podcast (Video Recorded Lecture Series):
Metabolic Liver Diseases (Part II): Wilson's Disease and α-1AT for the USMLE Step One Exam





Howard J. Sachs, MD
www.12DaysinMarch.com
Email: Howard@12daysinmarch.com

Stop Metabolic Liver Disease:
HH and Iron Regulation

Start Wilson Disease/A1AT

TV & MOVIES

Michael J. Fox's new NBC sitcom begins shooting in New York City

A report says the new show is loosely based on Fox's life. He'll play a former NYC local-news anchor who goes back to work after Parkinson's disease forced him to take time off.

Wilson's disease: Hepatolenticular Degeneration

What was MJF ceruloplasmin level?

Metabolic Liver Disorders,

Wilson's Disease – Hepatolenticular Degeneration

A Disease of Copper Transport – Can't get rid of the damn stuff

Disease of Copper Transport

Main player is ATP7B Protein.

In cytoplasm, it carries Copper into canalicular system.

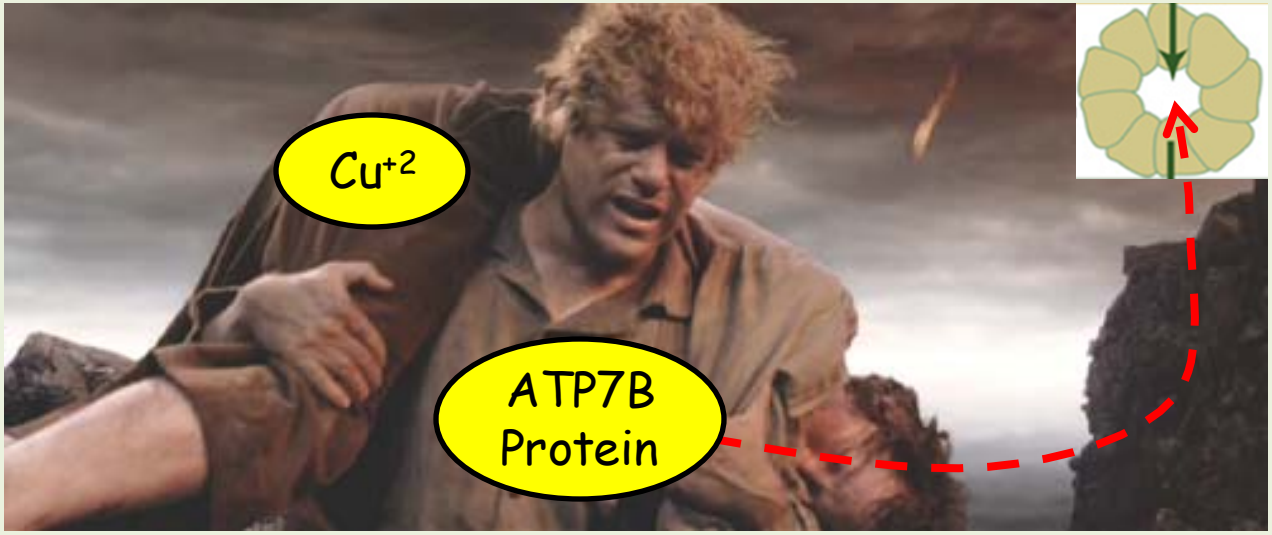
This is how we dump copper.

Disease of Copper Transport

Main player is ATP7B Protein.

In cytoplasm, it carries Copper into canalicular system.

This is how we dump copper.



Metabolic Liver Disorders,

Wilson's Disease – Hepatolenticular Degeneration

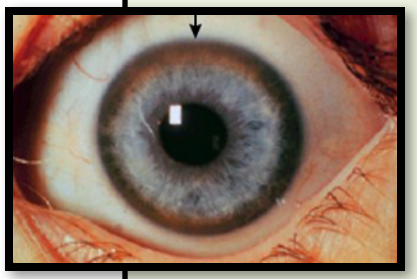
A Disease of Copper Transport – Can't get rid of the damn stuff

Disease of Copper Transport
Main player is ATP7B Protein.
In cytoplasm, it carries Copper into canalicular system.
This is how we dump copper.
In the Golgi, it ATP7B (Samwise Gamgee) mediates transfer of copper into apoceruloplasmin making ceruloplasmin, the main circulating form.

Deficient/mutated ATP7B Protein means
no ceruloplasmin and no dumping copper into bile.
If you can't dump it, it gets deposited.
That's the problem ☺

Wilson's Disease: Hepatolenticular Degeneration

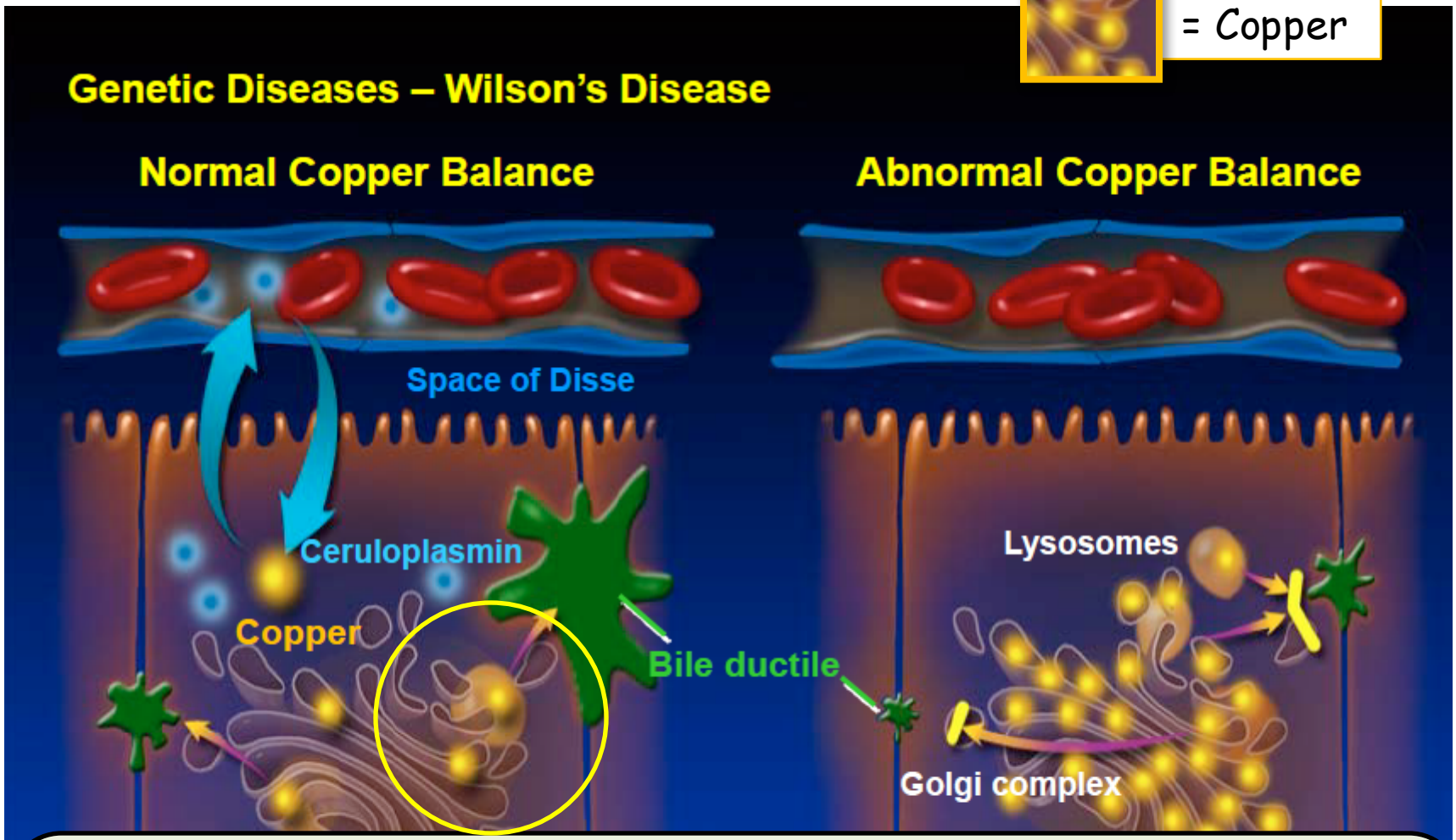
A Disease of Copper Transport – Can't get rid of the damn stuff



Kayser-Fleischer

If you can't dump it, it gets deposited.
That's the problem ☺

Eyes: Descemet's membrane
Brain (juvenile PD; hepatoLENTICULAR)
Liver (chronic ↔ acute FHF failure)
Joints



ATP7B Protein:

1. In Golgi, mediates Cu transport into apoceruloplasmin for transport in the blood as ceruloplasmin.

2. In the cytoplasm, sequesters Cu into vesicles for exocytosis into bile canniculus (principle method of elimination)

Wilson's Disease – Hepatolenticular Degeneration

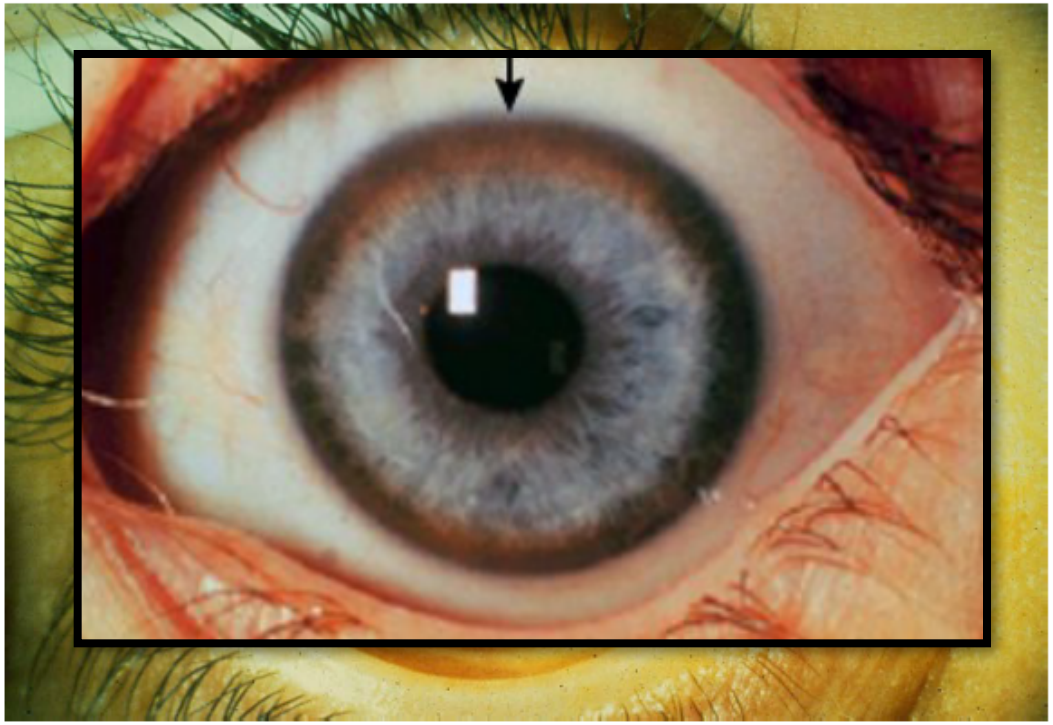
A Disease of Copper Transport – Can't get rid of the damn stuff

- Background:
  - AR characterized by excessive levels of copper w/ deposition in major organs including liver, brain, cornea, kidney and joints
  - The defect is a mutation of ATP7B gene (codes for P-type ATPase) responsible for transporting copper into bile and the incorporation into ceruloplasmin (thus, low measured levels).

- Presentation:
  - Liver chemistry abnormalities
  - Kayser-Fleischer rings (corneal deposits)
  - Neurodegenerative Disorder (basal ganglion degeneration; 'juvenile parkinson's')
- Diagnosis:
  - DECREASED ceruloplasmin
    - Disease marker not the pathogenic lesion
  - Increased serum, urine FREE copper

Wilson Disease

Kayser-Fleischer Ring



Green-brown deposits of copper in Desçemet's membrane in corneal limbus

Neurologic Manifestations of Wilson's Disease

- The neurologic hallmark of Wilson's disease is a progressive movement disorder characterized by dysarthria, dysphagia, apraxia and a tremor-rigidity syndrome ('juvenile Parkinsonism').

Within the brain, **the basal ganglia** (lenticular nuclei) is affected; this, plus liver involvement, give the disease its name, hepatolenticular degeneration

- Other symptoms may include
  - Tremor of the head, arms, or legs;
  - Impaired muscle tone,
  - Sustained muscle contractions that produce abnormal postures, twisting, and repetitive movements (dystonia);
  - Slowness of movements (bradykinesia).
- Individuals may also experience clumsiness (ataxia) and loss of fine motor skills.
- One-third of individuals with WD will also experience psychiatric symptoms
  - Abrupt personality change, bizarre and inappropriate behavior,
  - Depression accompanied by suicidal thoughts, neurosis, or psychosis.

Writing, speech, ψ-symptoms and abnormal liver chemistries → slit lamp

Neurologic Manifestations of Wilson's Disease

- The neurologic hallmark of Wilson's disease is a progressive movement disorder characterized by dysarthria, dysphagia, apraxia and a tremor-rigidity syndrome **('juvenile Parkinsonism').**

Within the brain, **the** is affected; this, plus liver involvement, give the **r degeneration**

- Other symptoms may incl
  - Tremor of the head, arms
  - Impaired muscle tone,
  - Sustained muscle contrac and repetitive movements (dystonia);
  - Slowness of movements (b
- Individuals may also expe fine motor skills.
- One-third of individuals v ric symptoms
  - Abrupt personality change, bizarre and inappropriate behavior,
  - Depression accompanied by suicidal thoughts, neurosis, or psychosis.

Did Sauron have Wilson's Disease?

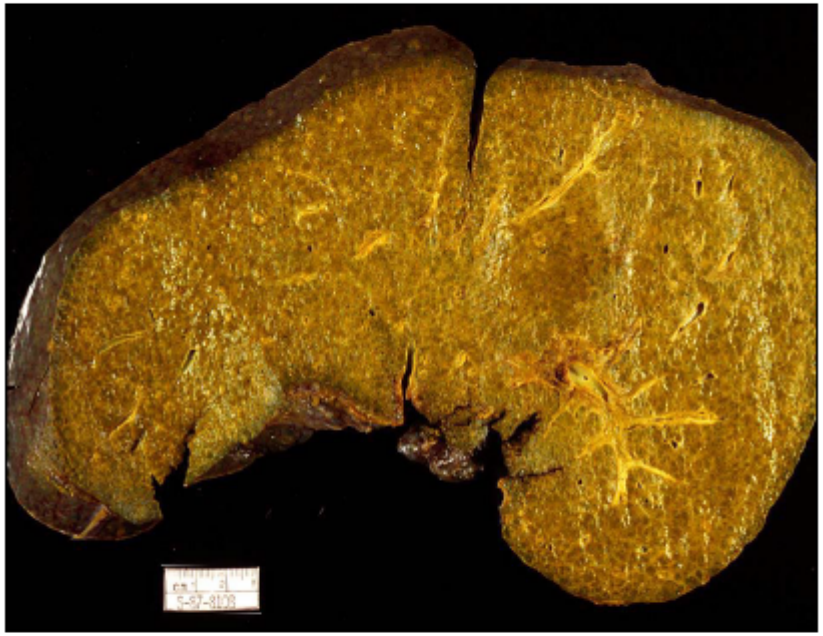
Writing, speech, ψ-symptoms and abnormal liver chemistries → slit lamp

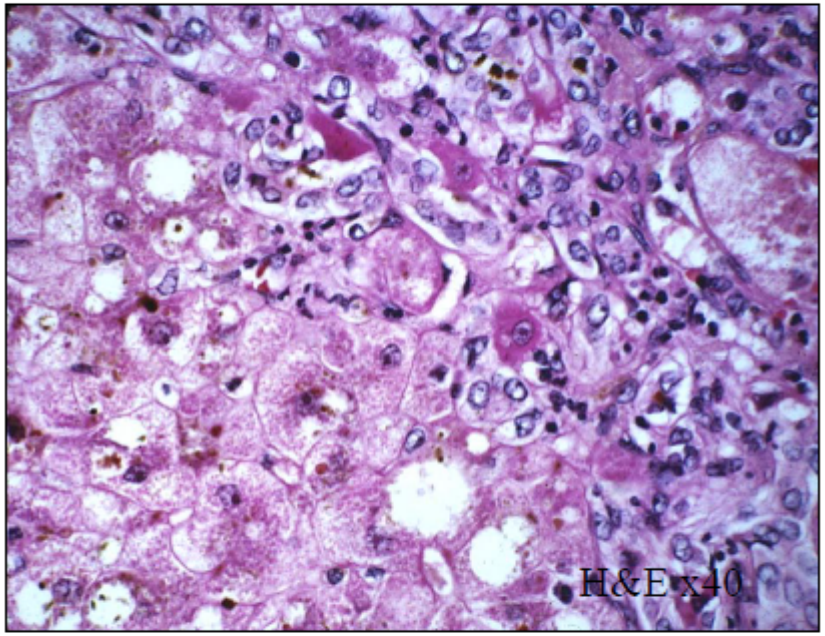
Usual Features in Wilson's Disease

- Ceruloplasmin <20 mg/dl
- Urine copper >100 mg/day
- Kayser-Fleischer rings
- Hepatic histology abnormal
- Hepatic copper >250 mg/g

Nonspecific;
Rhodam(n)ine stain

Wilson's Disease



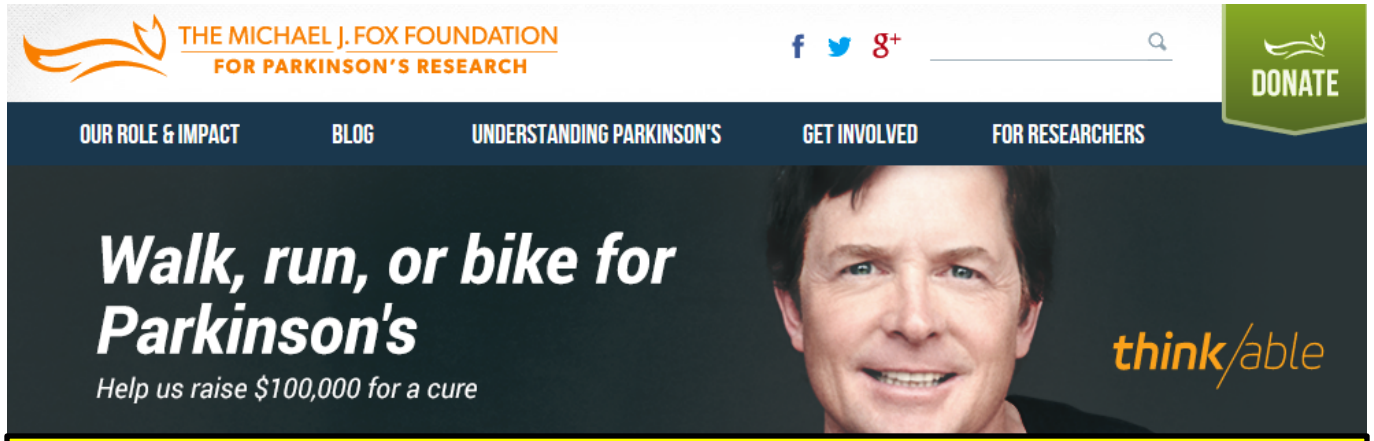


Mutation does not allow copper to be Excreted into the bile.

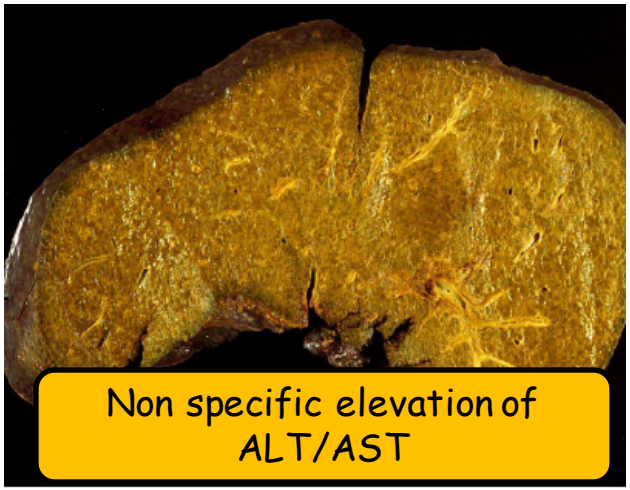
DX: serum ceruloplasmin < 20 mg/dl
urinary copper excretion
> 50 micrograms/24 hours

Histologically, changes are mild and Non specific.

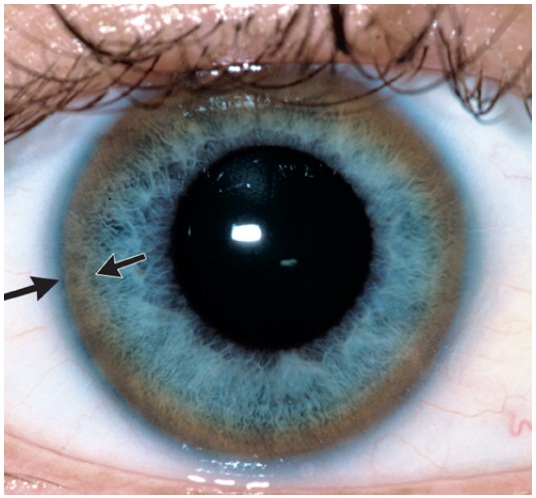
Dx: usually made clinically and sending liver biopsy off for quantitative copper analysis.

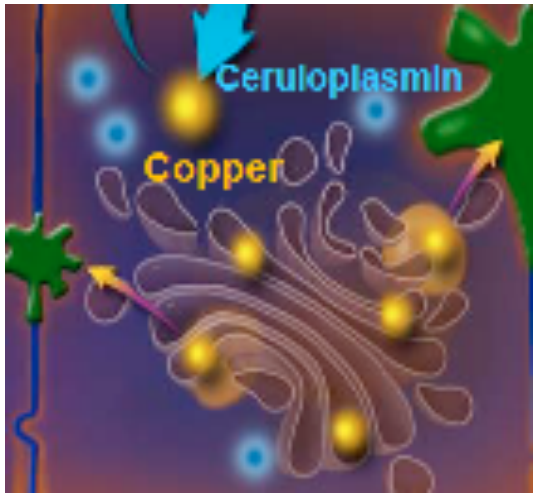


Hepatolenticular = Juvenile Parkinson's Disease



Non specific elevation of ALT/AST





What was MJF ceruloplasmin level: normal;
it is part of the work up in movement disorders

What is the body's principle mechanism of copper excretion?

1. ATP7B Transport into bile canniliculi
2. ATP7B Transport into Golgi for ceruloplasmin synthesis
3. Samwise Gamgee Transport to Mount Doom for disposal with other biohazard waste
4. Gollum Transport to Mordor

WYNTKFTB about α1-AT

Genetic Diseases

α_1-Antitrypsin

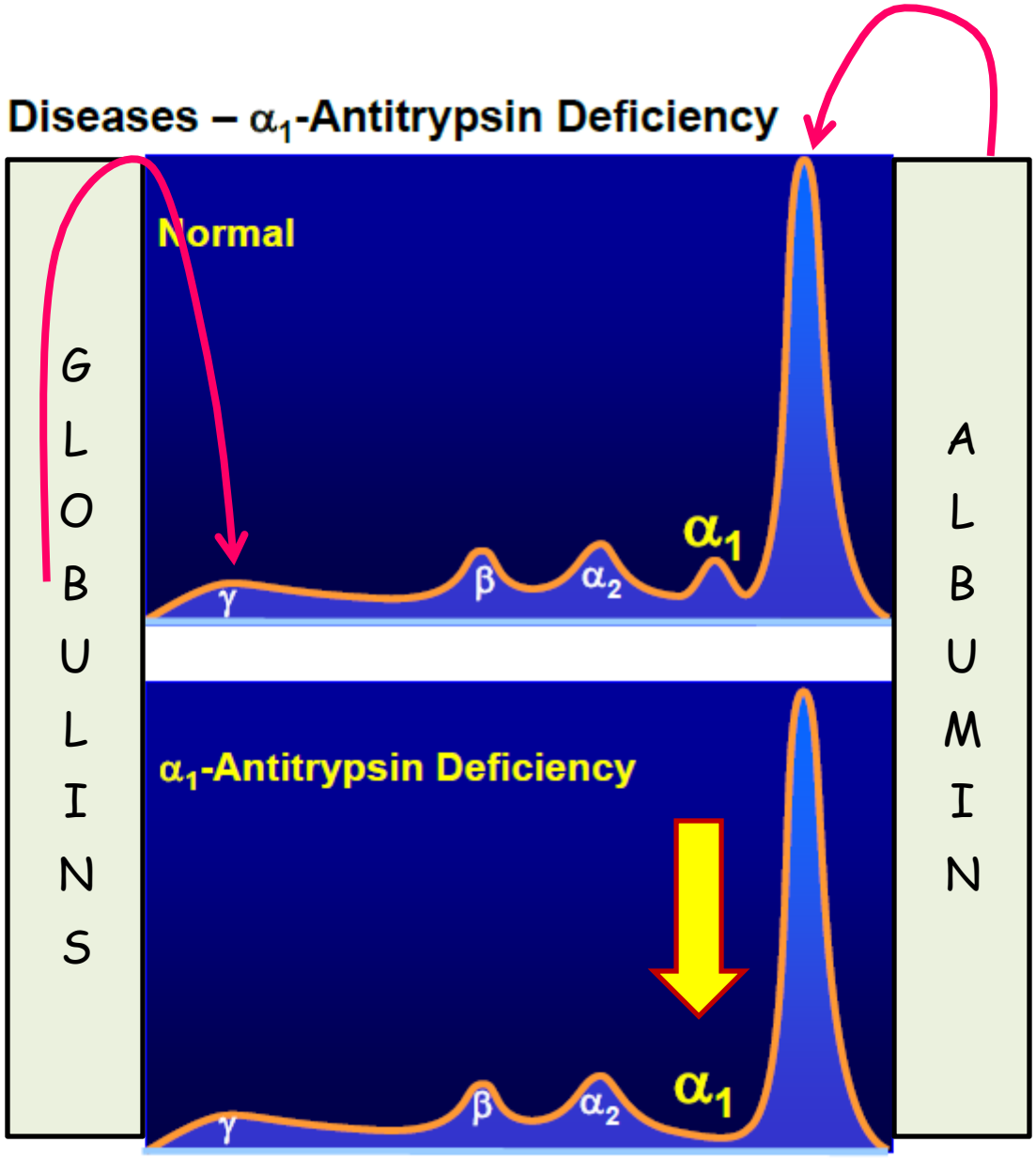
Dx:

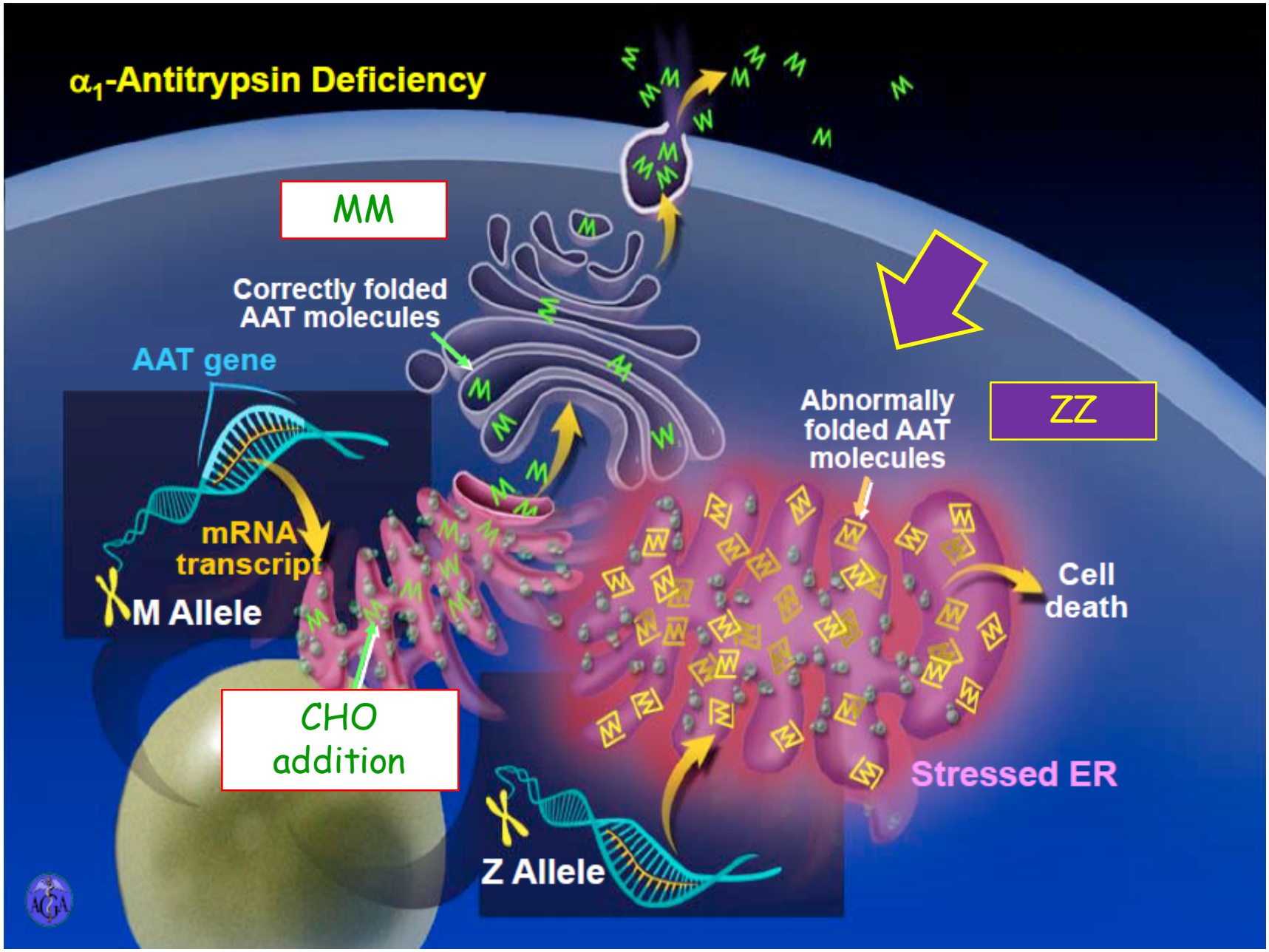
90% of α_1-globulin band on serum protein electrophoresis in normal subjects

Structure:	**52-kD glycoprotein, member of serpin supergene family**
Function:	**Inhibitor of specific proteases, e.g., neutrophil elastase, cathepsin G**
Synthesis:	**Hepatocytes, circulating monocytes, alveolar macrophages** Anti-elastase in lung

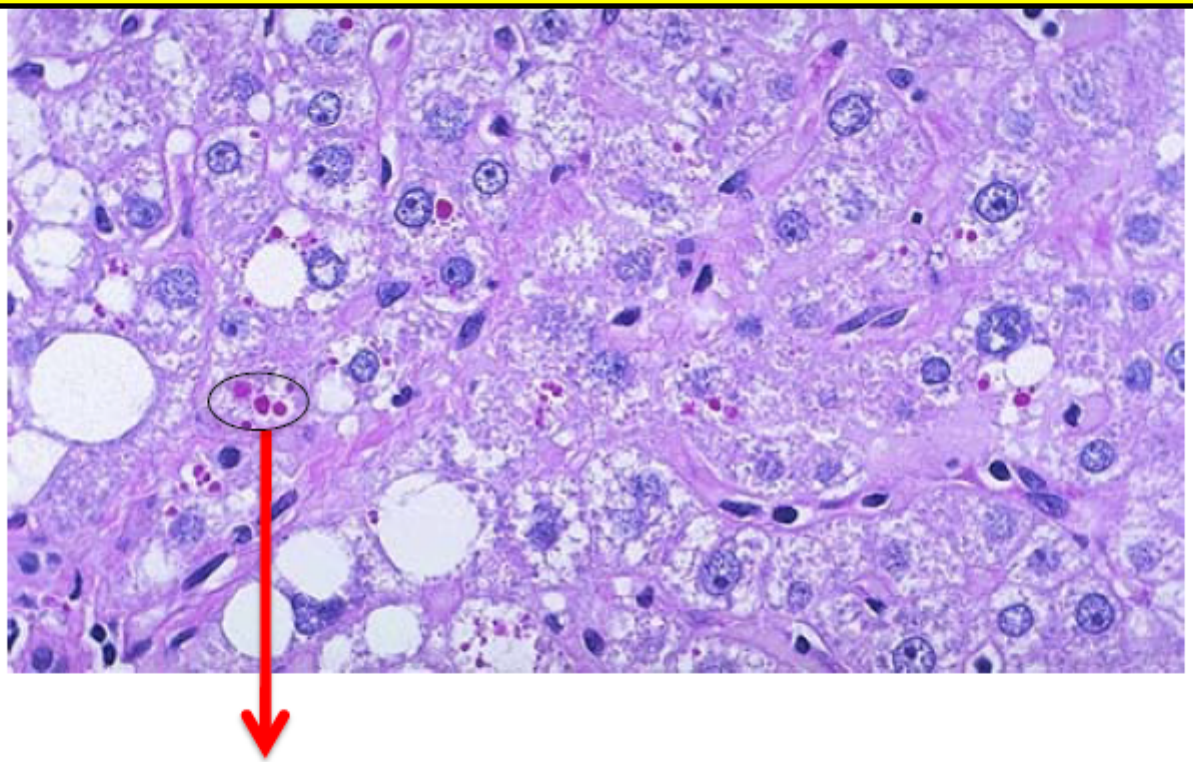
In the liver, not so much…

Genetic Diseases – α_1-Antitrypsin Deficiency




α1-Antitrypsin Deficiency
MM
Correctly folded AAT molecules
AAT gene
mRNA transcript
M Allele
CHO addition
Abnormally folded AAT molecules
ZZ
Cell death
Stressed ER
Z Allele

Question will include a patient with lung disease (COPD/basal segments) and abnormal AST/ALT. Biopsy will show…(or any variant on this theme)



- The periportal red hyaline globules seen here with periodic acid-Schiff (PAS) stain are characteristic for alpha-1-antitrypsin (AAT) deficiency.

Do not confuse PAS (+) liver bx with PAS (+) intestinal bx!

AAT Deficiency

- Pathogenesis
  - AD where each allele expresses itself.
    - MM is normal genotype
    - Z & S are deficient variant alleles
    - Severe deficiency of AAT in ZZ variant
      - Associated with panacinar emphysema and cirrhosis
      - AAT is not secreted properly from hepatocytes with accumulation of AAT
  - In contrast to lung disease (caused by loss as antielastase), liver disease is caused by pathologic polymerization of the variant AAT, resulting in intrahepatocyte accumulation of AAT molecules
  - Pathologically, the accumulated AAT appears as inclusions that stain positively with periodic acid-Schiff (PAS) reagent but resist digestion by diastase

fyi…

fyi…

Presentation

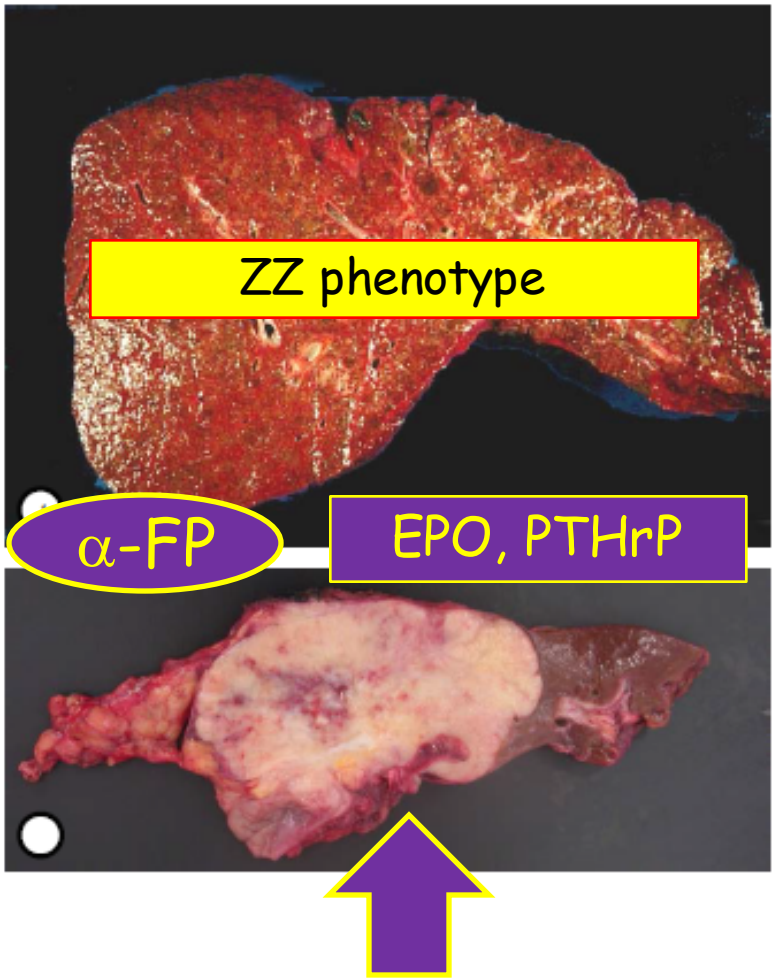
(varied phenotypic expression)

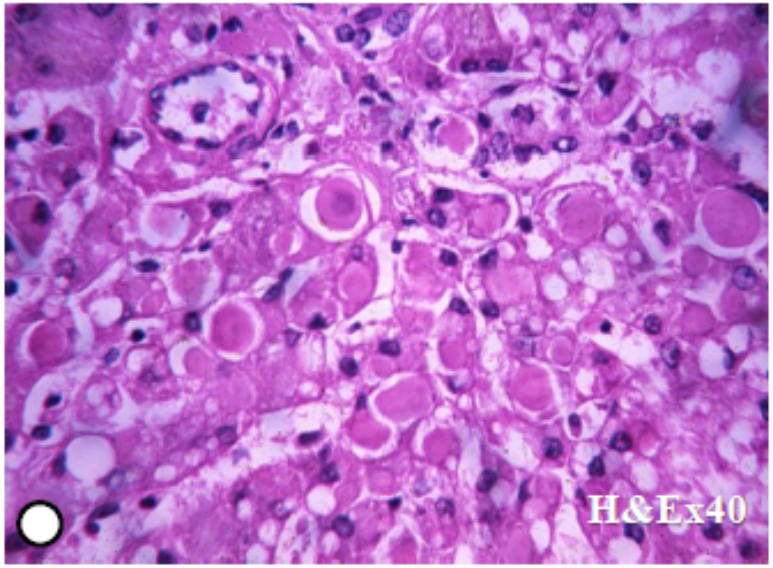
- The natural history (in equal proportion):
  - Resolution of hepatitis by ages 3 to 10 years
  - Development of cirrhosis between age six months and 17 years, often causing death from complications of end-stage liver disease
  - Histologic evidence of cirrhosis but with survival through the first decade with few sequelae
  - Persistent elevation of 'liver function tests' without cirrhosis

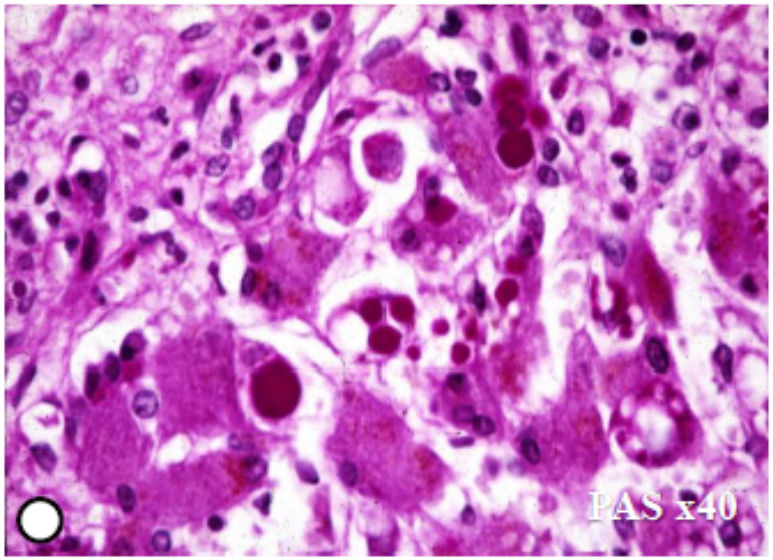
Patient with jaundice as a child now presents with SOB…

α_1-Antitrypsin deficiency

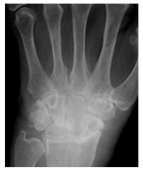
Morphology

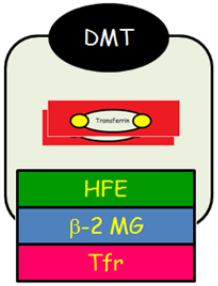


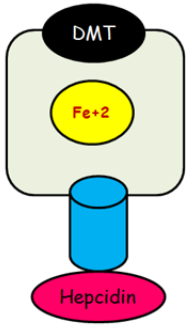




Metabolic Liver Diseases (for the Boards)







	Serum iron (µg/dL)	TIBC (µg/dL)	Transferrin saturation (%)	Ferritin (µg/dL)
Normal	60-180	230-370	20-50	20-200
Hemochromatosis	>180	<300	>50	>300

HH

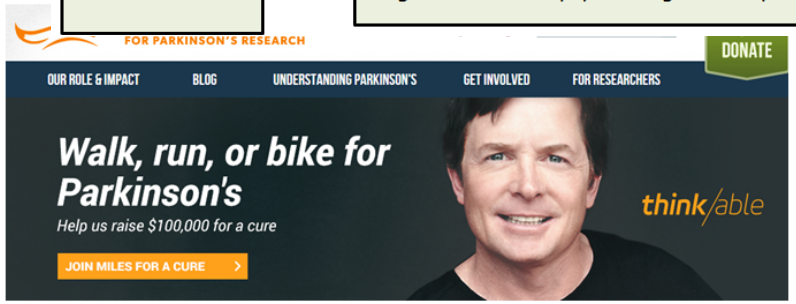
Iron dysregulation (understand the factors involved)
Multisystem (which systems?)
Diagnostic Lab Studies and key stains?
Complications

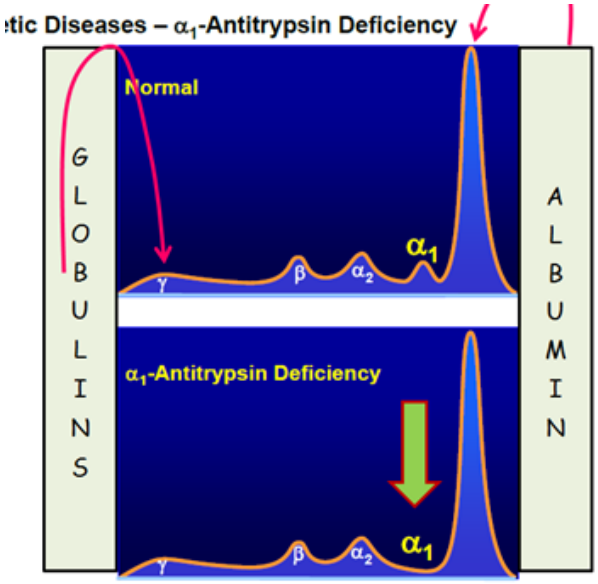
Wilson's

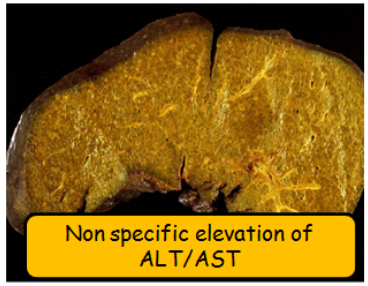
Copper dysregulation (understand the mechanisms involved)
Multisystem (which systems?)
Diagnostic Lab Studies?
Complications

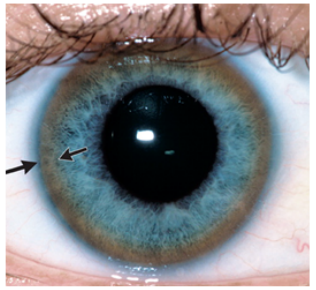
α-1-antitrypsin

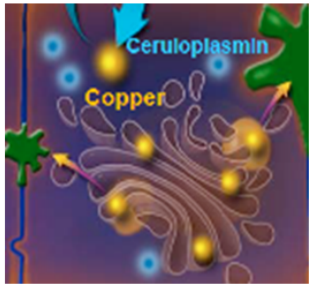
Protein dysregulation
Diagnostic Lab, Biopsy Findings and key stains.











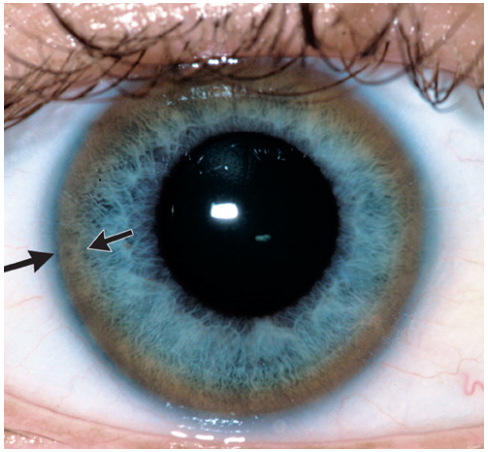
How will you know…?

A 20 y.o. is bought to your office with impaired balanced and speech difficulty. Symptoms developed slowly over the last several months. Noted with transaminase elevation, negative viral serology.

Which of the following would be most useful in establishing diagnosis?:

Subtle presentation, description BUT this is as good as it gets for Wilson's. Neuro PLUS Liver…boom!…Wilson's

1. MRI head
2. Transesophageal Echo
3. Nerve conduction studies
4. Blood cultures
5. Slit lamp exam



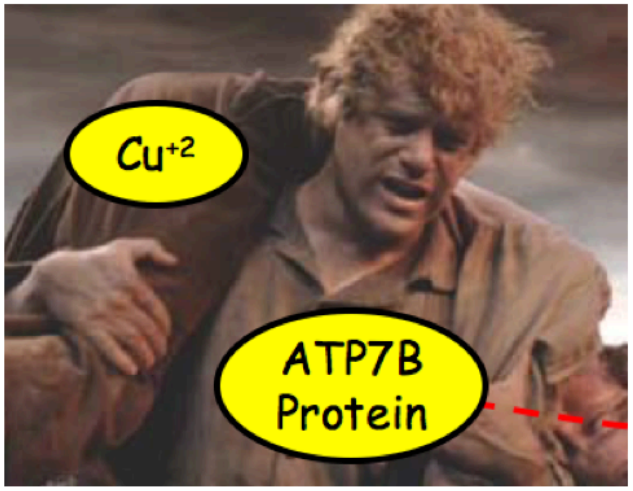
A 20 y.o. is bought to your office with impaired balanced and speech difficulty. Symptoms developed slowly over the last several months. Noted with transaminase elevation, negative viral serology. Which of the following would be most useful in establishing diagnosis?:

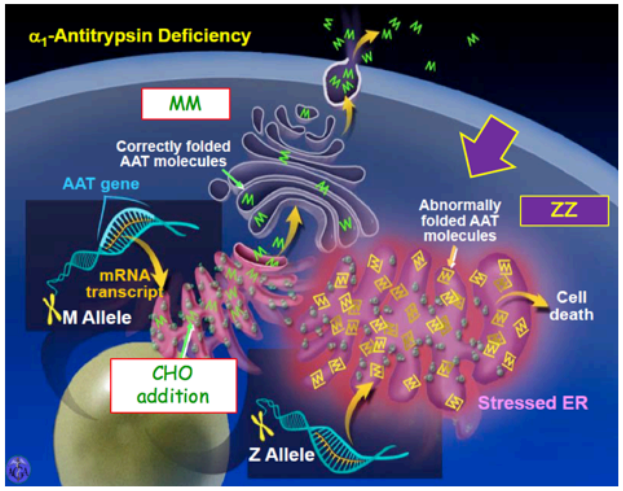
Rx: Pencillamine

Neuro Plus Liver:

Reye's Syndrome
Wilson's disease
Hepatic encephalopathy

Podcast (Video Recorded Lecture Series):
Metabolic Liver Diseases (Part II): Wilson's Disease and α-1AT for the USMLE Step One Exam





Howard J. Sachs, MD
www.12DaysinMarch.com
Email: Howard@12daysinmarch.com