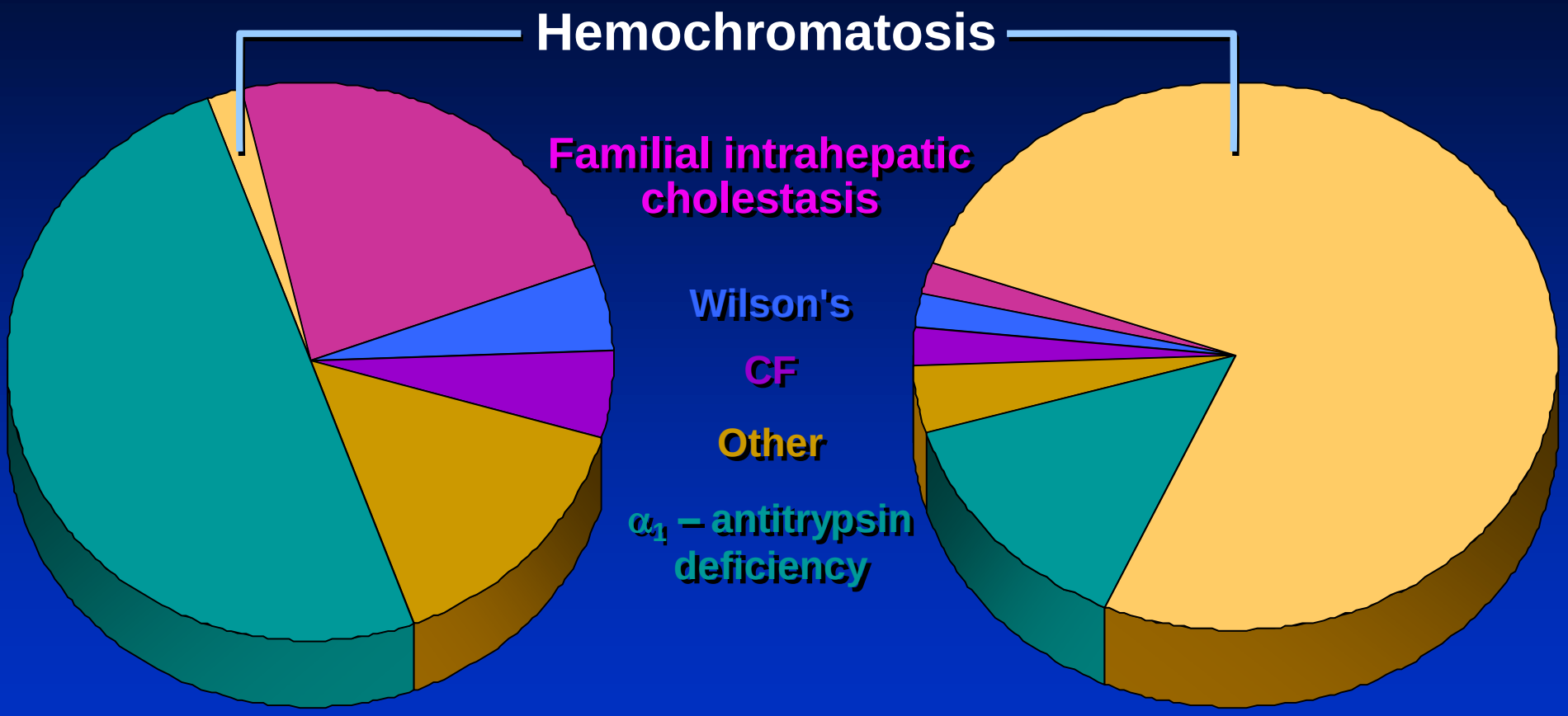
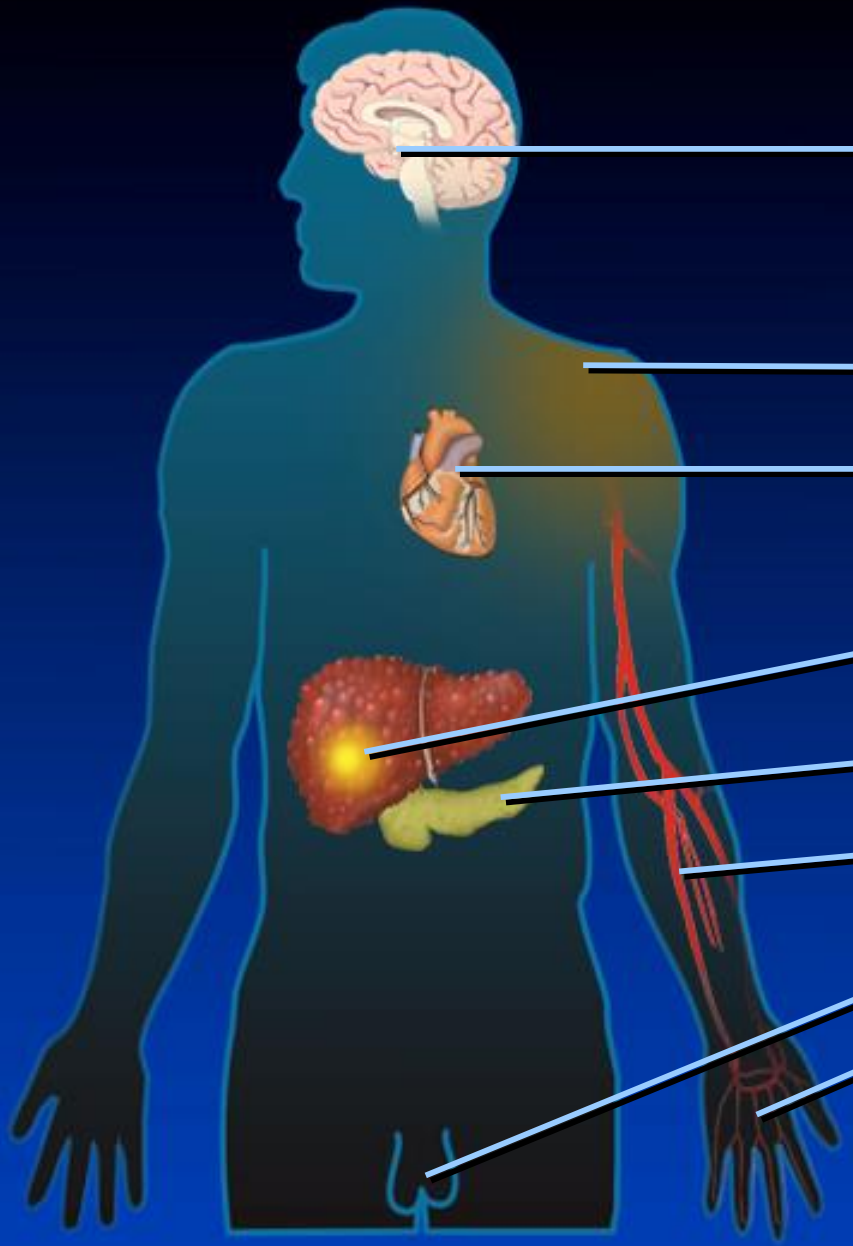
Genetic Diseases - Liver

Inherited Causes of Cirrhosis



Genetic Diseases - Hemochromatosis - Clinical Manifestations



- Pituitary
  - Gonadotropin deficiency
- Skin bronzing
- Cardiomyopathy
- Conduction disorders
- Cirrhosis
- Hepatocellular carcinoma
- Diabetes mellitus
- Bacteremia
- Testicular atrophy
- Arthropathy
  - Arthritis
  - Pseudogout

Iron Overload Disorders

- Transfusion
- Ineffective erythropoiesis
- African iron overload

Hemochromatosis

- Incidence is population-dependent
- Inheritance is autosomal recessive
- HFE gene mutations are present
- Functional defect results in increased iron absorption

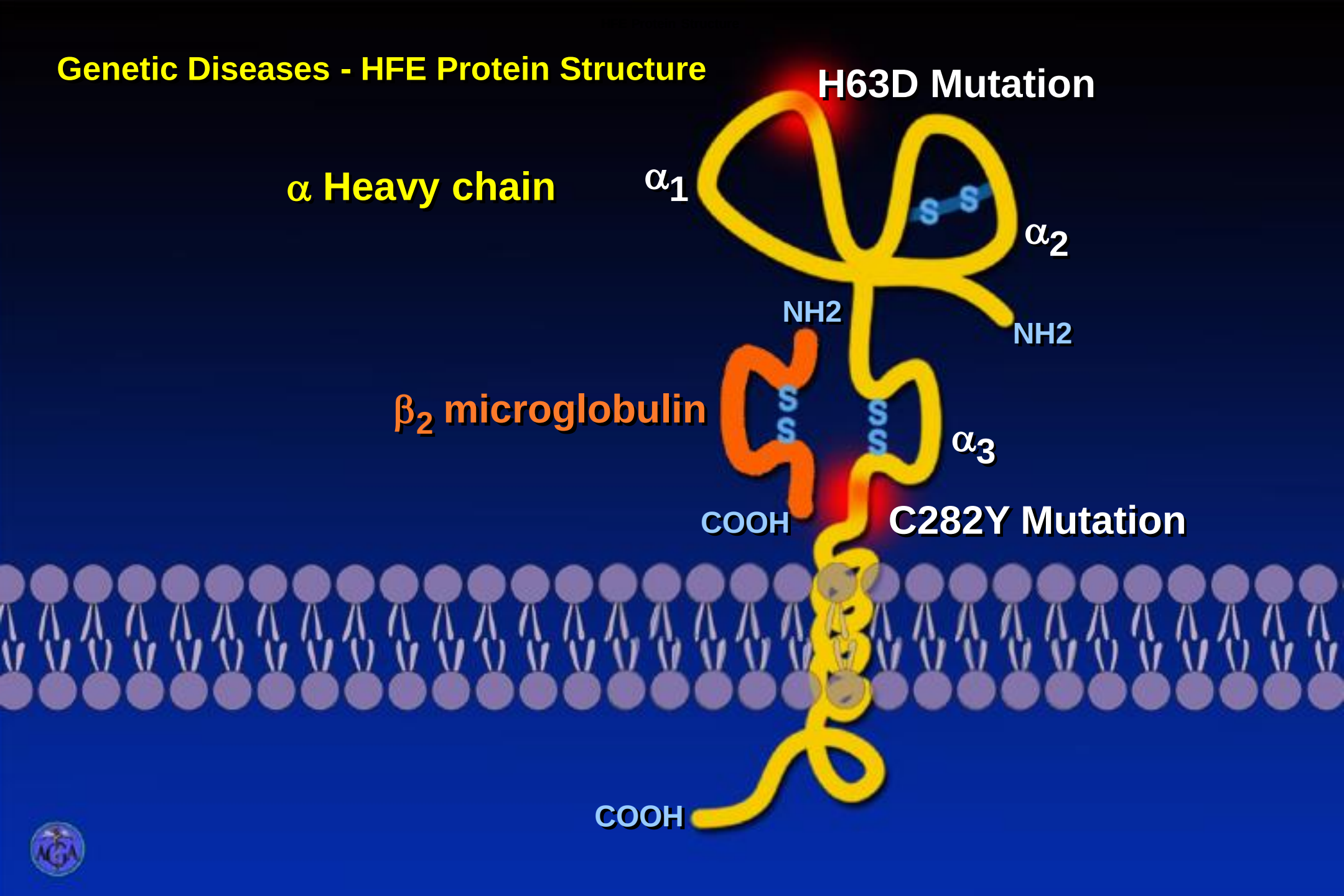
Genetic Diseases - Hemochromatosis

Frequency

Very common in Caucasians

Heterozygote - 1 in 12

Homozygote - 1 in 400


Genetic Diseases - HFE Protein Structure
H63D Mutation
α Heavy chain
α1
α2
S S
NH2
NH2
β2 microglobulin
S S
S S
α3
COOH
C282Y Mutation
COOH

Genetic Diseases - Hemochromatosis

HFE Gene Mutations

Abnormal intestinal epithelial protein

Increased intestinal iron absorption

Iron-induced tissue injury and fibrogenesis

Bacon BR and Britton RS, 2002

Genetic Diseases

Stages of Hemochromatosis

- Iron overload without organ injury
- Iron overload with organ injury without clinical manifestations
- Iron overload with organ injury and clinical manifestations

Bacon BR and Britton RS, 2002

Genetic Diseases – Hemochromatosis - Normal Iron Balance

Ingested
- 10-20 mg/day

Absorbed
- 1-2 mg/day

Lost
- Gut, skin, urine - 1-2 mg/day
- Menses - 30 mg/month

Iron Transport and Storage

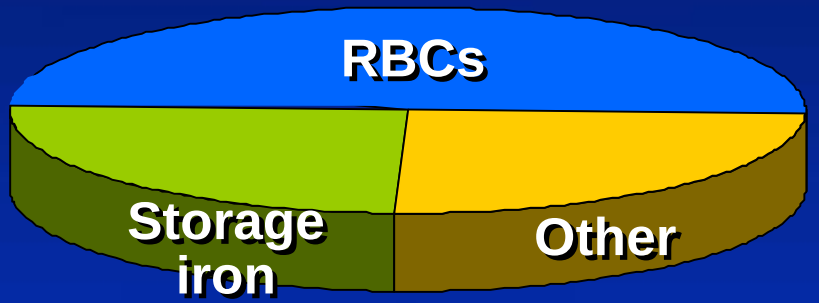
Transport

Transferrin - two iron atoms

Intracellular storage

Ferritin - thousands of iron atoms

Total body iron - 4g



Phenotype Expression

- Men > women
- Increases with age
- Correlates with amount of iron in the diet
- Chronic hemolysis, alcoholism, steatohepatitis, hepatitis C

Hereditary Forms of Iron Overload

Familial or hereditary forms of hemochromatosis

- Hereditary hemochromatosis (HFE-related)
  - C282Y homozygosity
  - C282Y / H63D compound heterozygosity
- Hereditary hemochromatosis, non-HFE related
- Juvenile hemochromatosis
- Neonatal iron overload
- Autosomal dominant hemochromatosis (Solomon islands)

Bacon BR, et al. Gastroenterology 1999; 116: 193

Acquired Causes of Iron Overload

Acquired iron overload

- Iron-loading anemias
  - Thalassemia major
  - Sideroblastic anemia
  - Chronic hemolytic anemia
- Dietary iron overload
- Chronic liver diseases
  - Hepatitis C
  - Alcoholic liver disease
  - NAFLD

Genetic Diseases – Hemochromatosis – Iron Measurements

	Normal	Hereditary hemochromatosis
Serum		
Iron		
(μg/dL)	60-180	180-300
(μmol/L)	11-32	32-54
Transferrin saturation %	20-50	55-100
Ferritin		
Males (ng/mL or μg/L)	20-200	300-3000
Females (ng/mL or μg/L)	15-150	250-3000
Liver		
Iron stains	0,1+	3+, 4+
Iron concentration		
(μg/g dry weight)	300-1500	3000-30,000
(μmol/g dry weight)	5-27	53-536
Iron index		
(μmol/g dry weight ÷ age in years)	<1.1	>1.9

Diagnosis

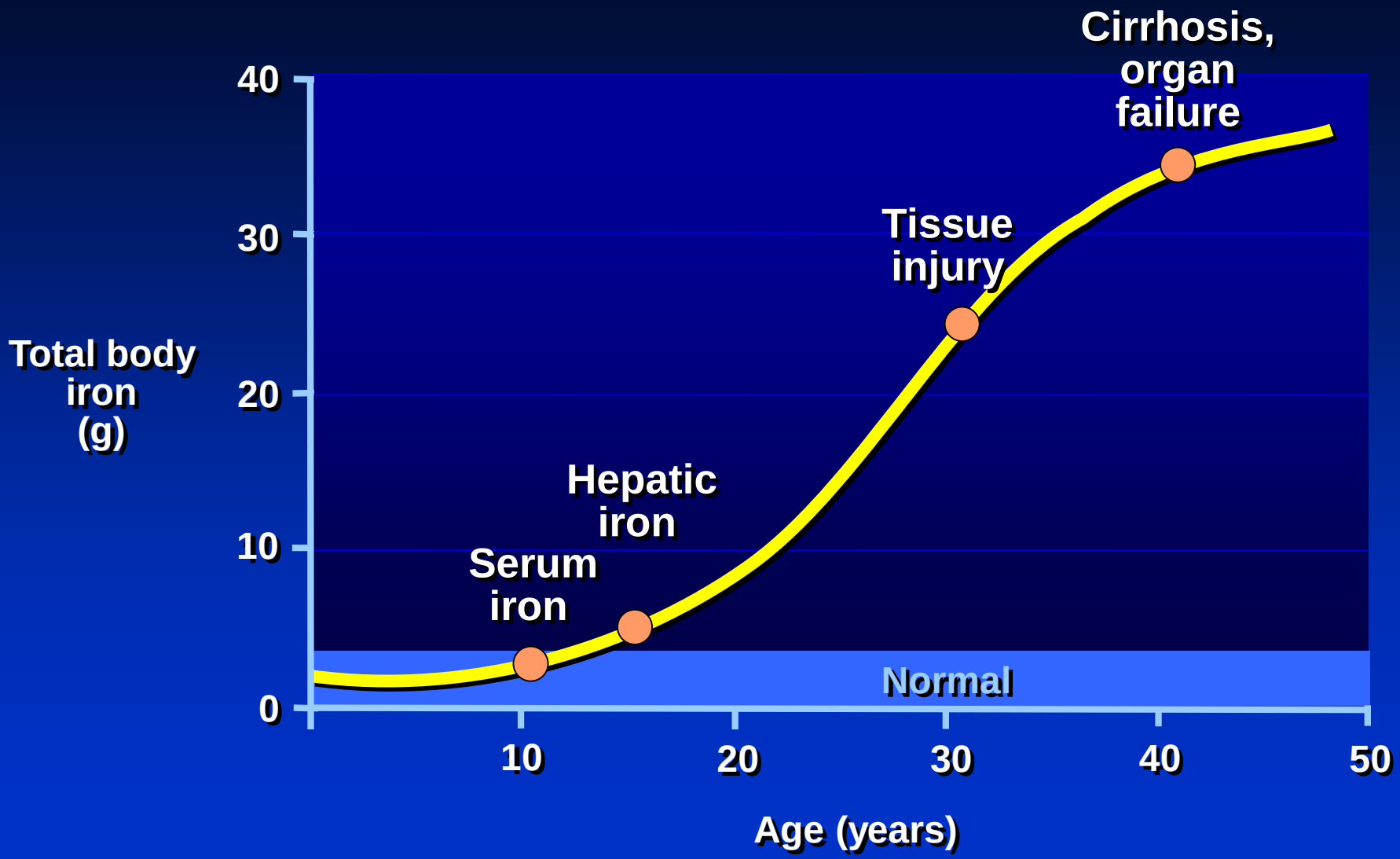
- Homozygous C282Y HFE mutations
- Heterozygous for both C282Y and H63D mutations

Genetic Diseases – Hemochromatosis - Iron Balance Values

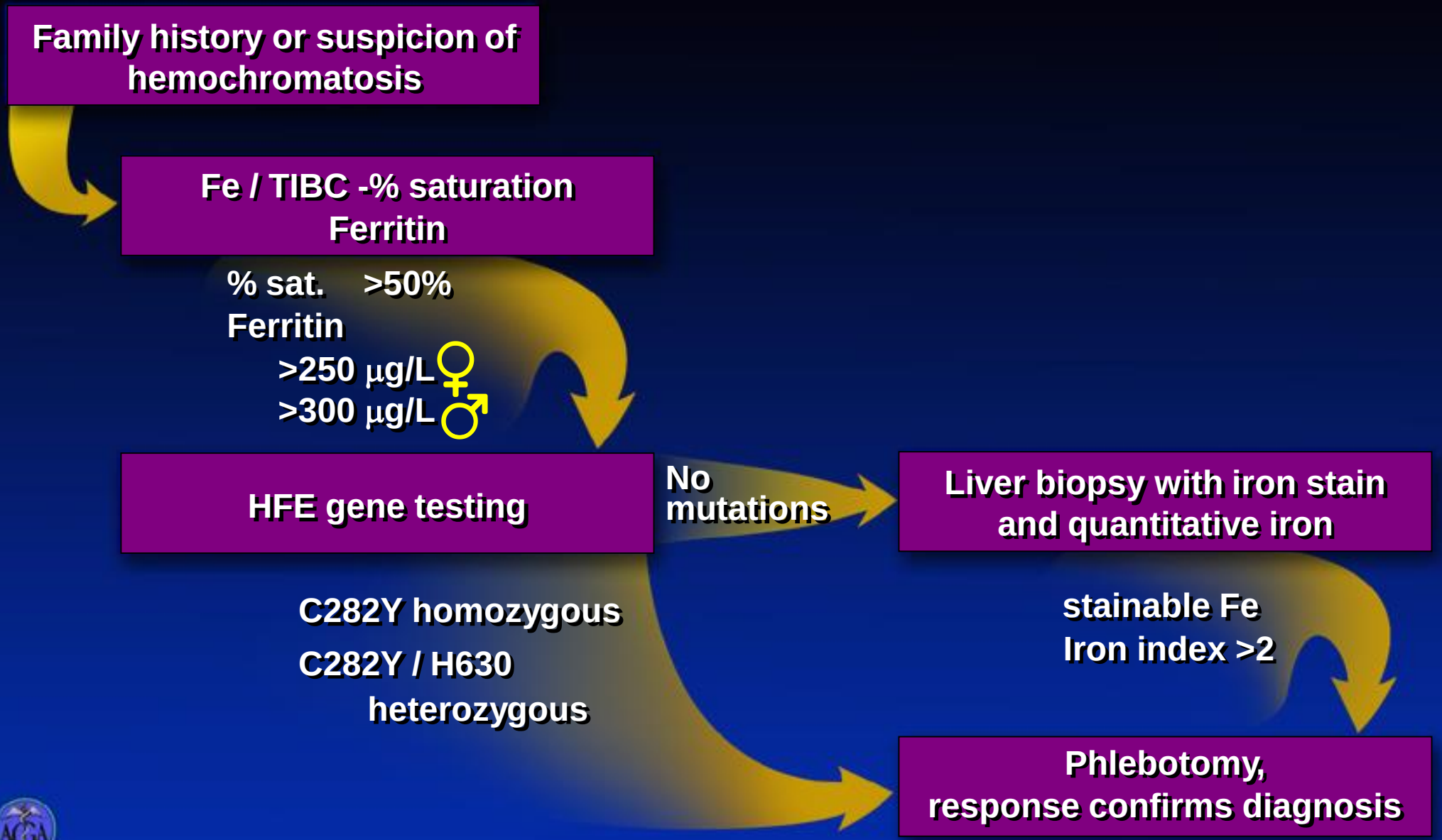
	Serum iron (μg/dL)	TIBC (μg/dL)	Transferrin saturation (%)	Ferritin (μg/dL)	Quantitative hepatic iron (μg/g dry wt)
Normal	60-180	230-370	20-50	20-200	300-1500
Hemochromatosis	>180	<300	>50	>300	>3000

Bacon BR and Britton RS, 2002

Genetic Diseases – Hemochromatosis



Genetic Diseases – Hemochromatosis – Diagnostic Testing



Indications for HFE Genetic Testing in Appropriate Clinical Setting

- Family history of hemochromatosis
- Chronic liver disease
- Abnormal liver tests
- Abnormal serum iron studies
- Diabetes mellitus
- Arthropathy
- Heart disease

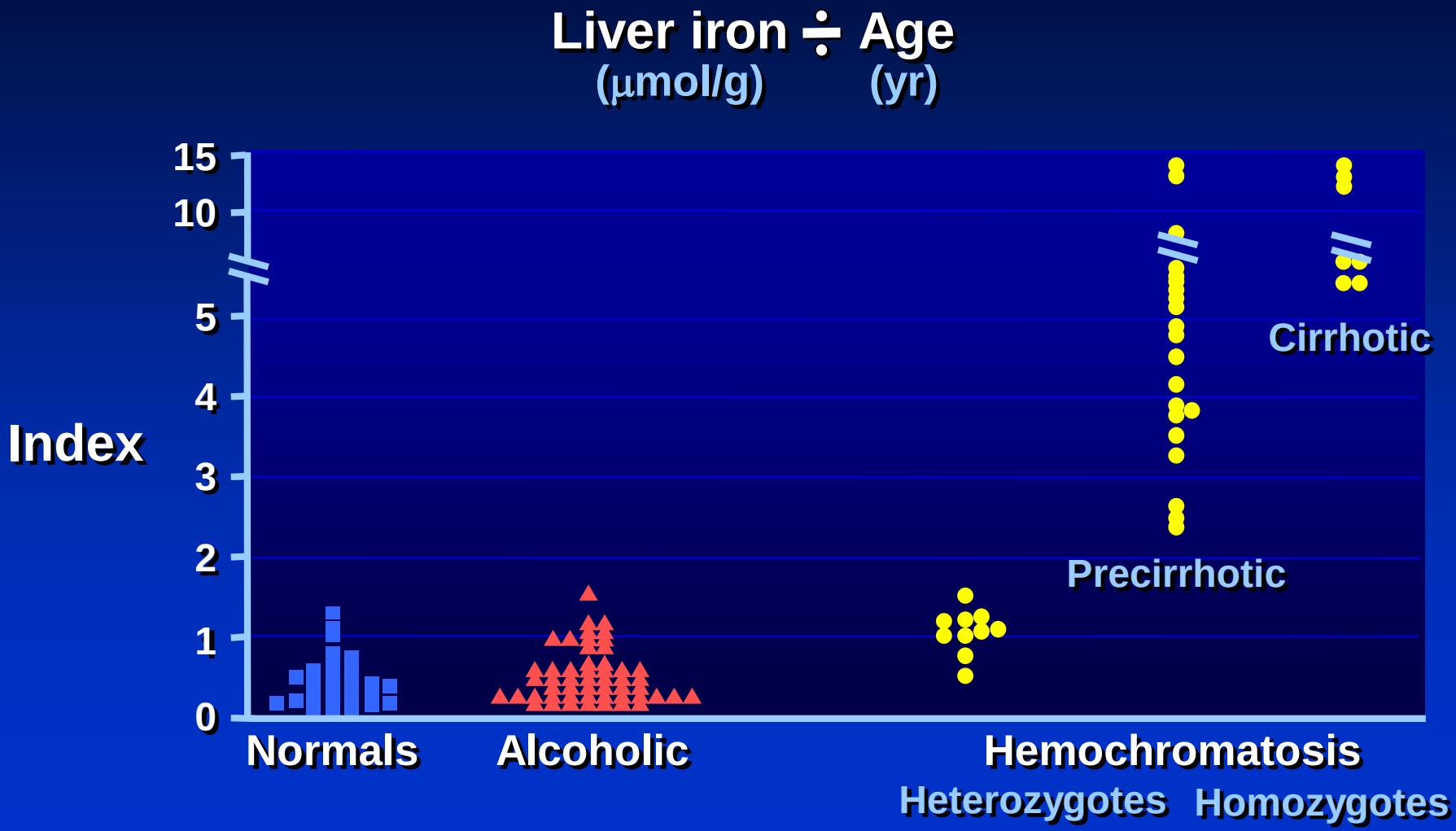
Bacon BR and Britton RS, 2002

Genetic Diseases – Hemochromatosis

Interpretation of Ferritin Levels

High Ferritin and	High iron	Hemochromatosis
		Acute liver injury
	↓ iron	Acute phase reactant
Normal ferritin and ↓ iron		Chronic disease
↓ Ferritin and ↓ iron		Iron deficiency

Hepatic Iron Index



Phlebotomy

Acute

1 unit (250 mg Fe) weekly or biweekly until mildly anemic

Maintenance

Once iron stores are depleted (ferritin <50ng/ml, transferrin sat <50%) continue with phlebotomy every 2-3 months. Monitor hemoglobin, ferritin and transferrin saturation

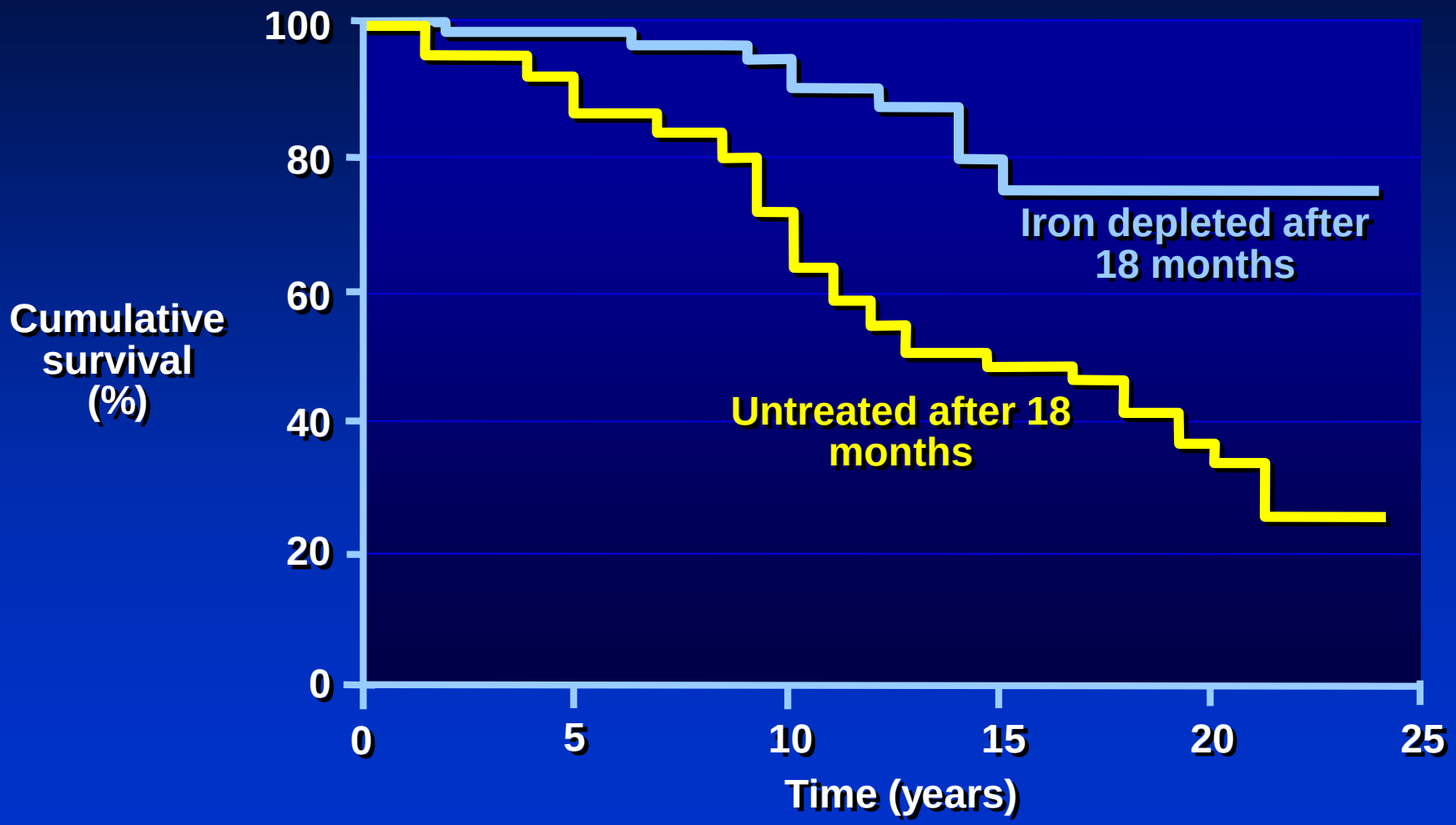
Bacon BR and Britton RS, 2002

Genetic Diseases – Hemochromatosis

Phlebotomy Improves Survival

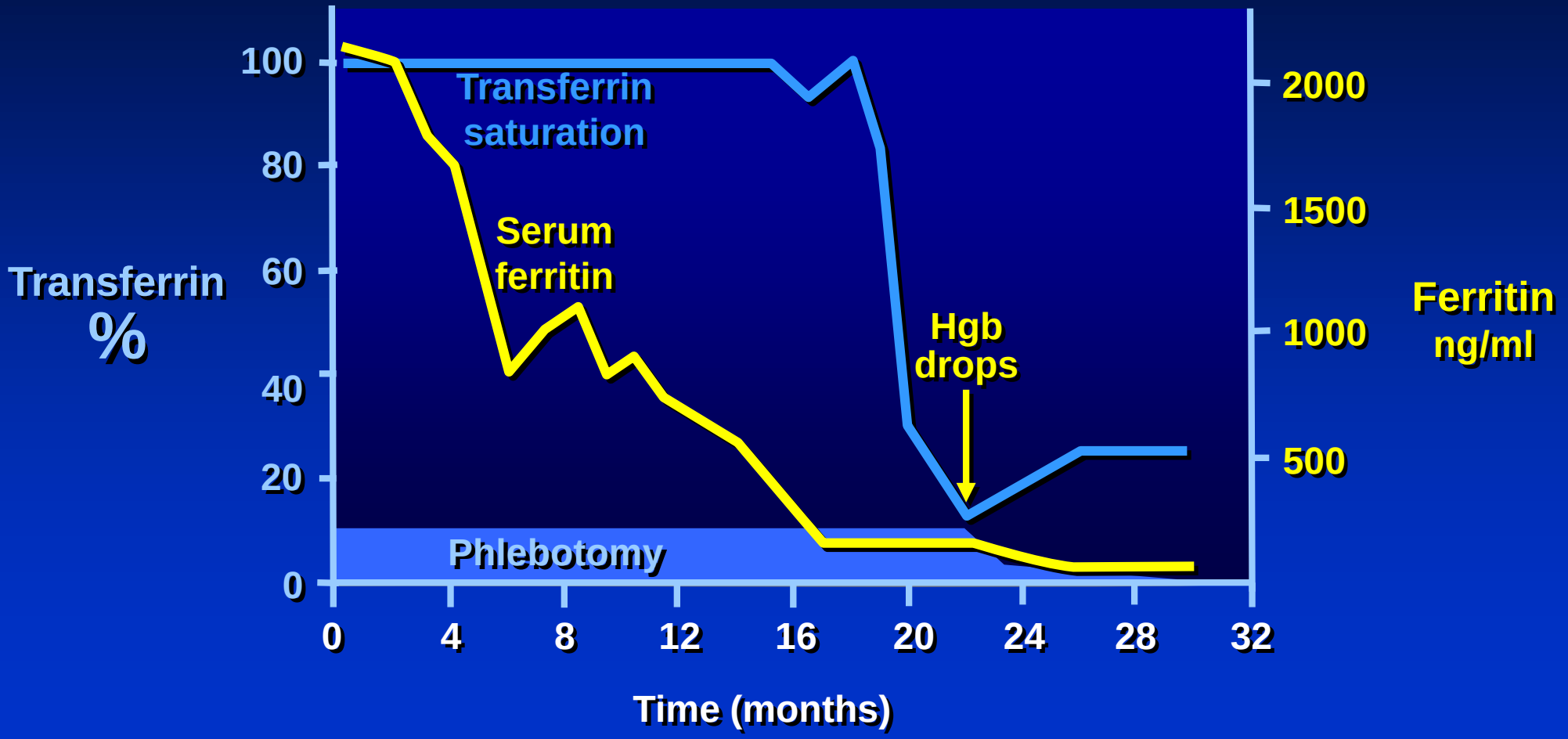
Preventable:	**all clinical manifestations**
Reversible:	**cardiac dysfunction, glucose intolerance, hepatomegaly, skin pigmentation**
Irreversible:	**cirrhosis** **risk of hepatocellular carcinoma** **arthropathy, hypogonadism**

Iron Depletion Improves Survival



Niederau C, et al. N Engl J Med 1985; 313:1256

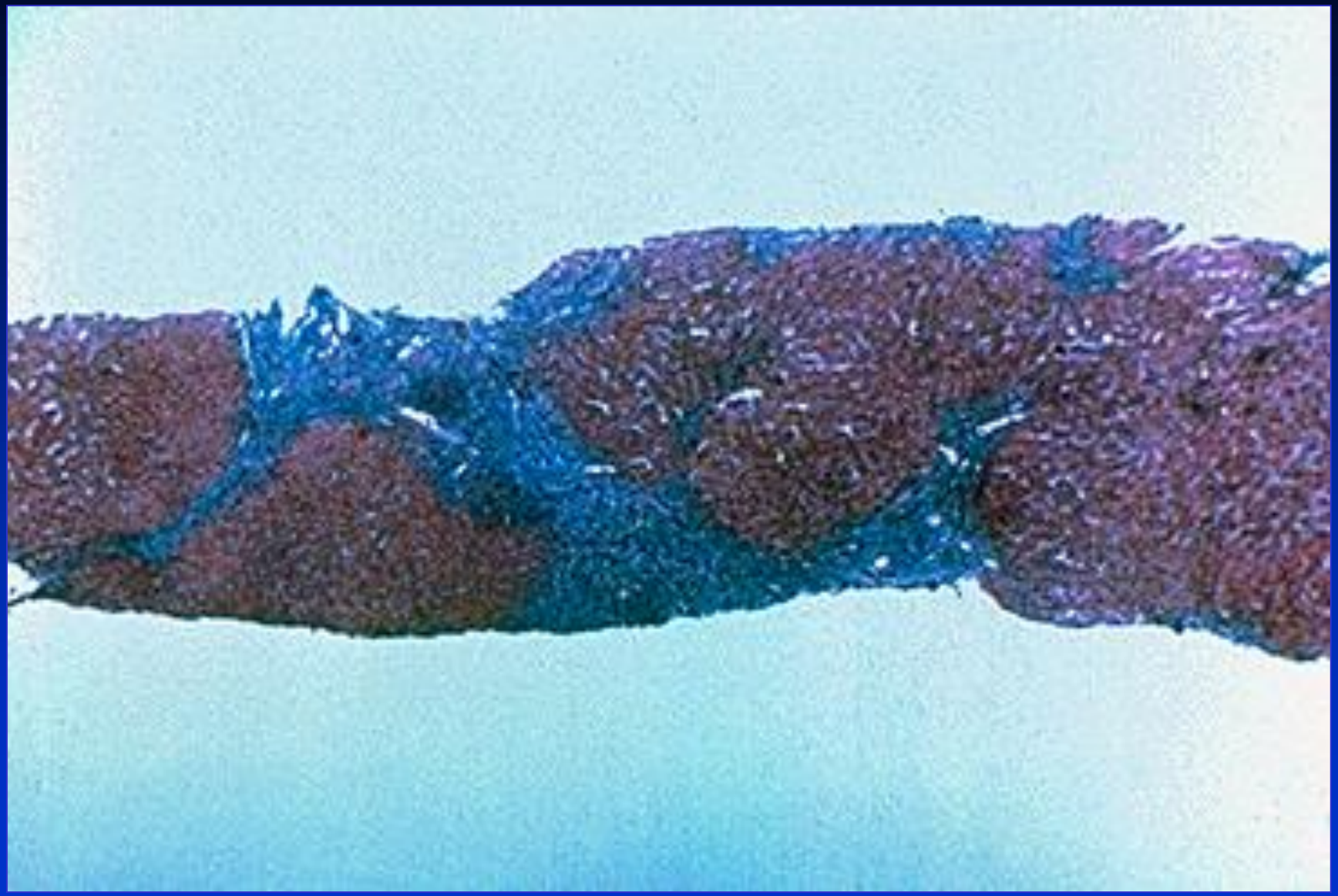
Response to Phlebotomy



Edwards CQ, et al. Hospital Practice 1991; 26:30

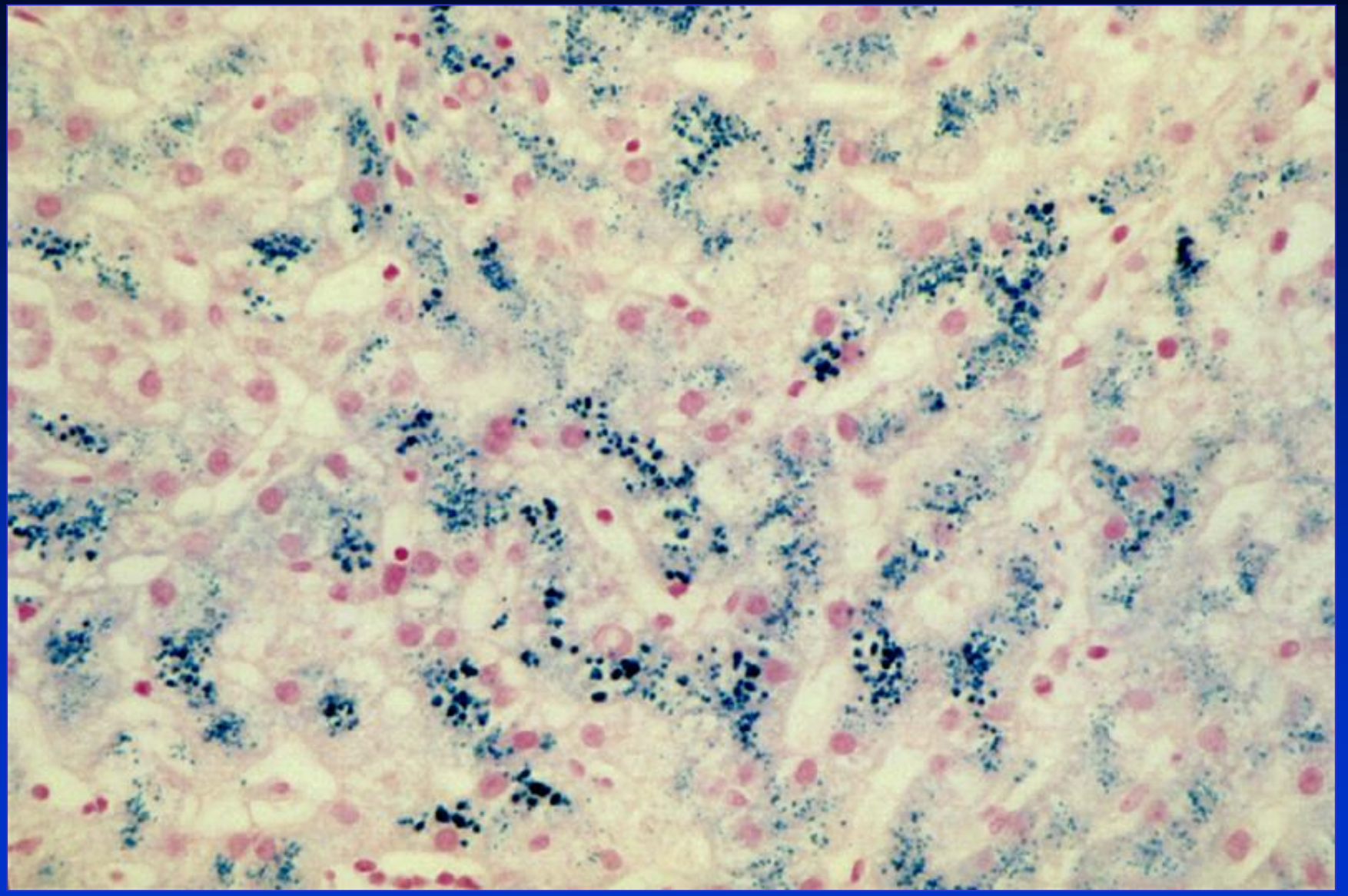
Trichrome Stain - Liver

Trichrome Stain - Liver

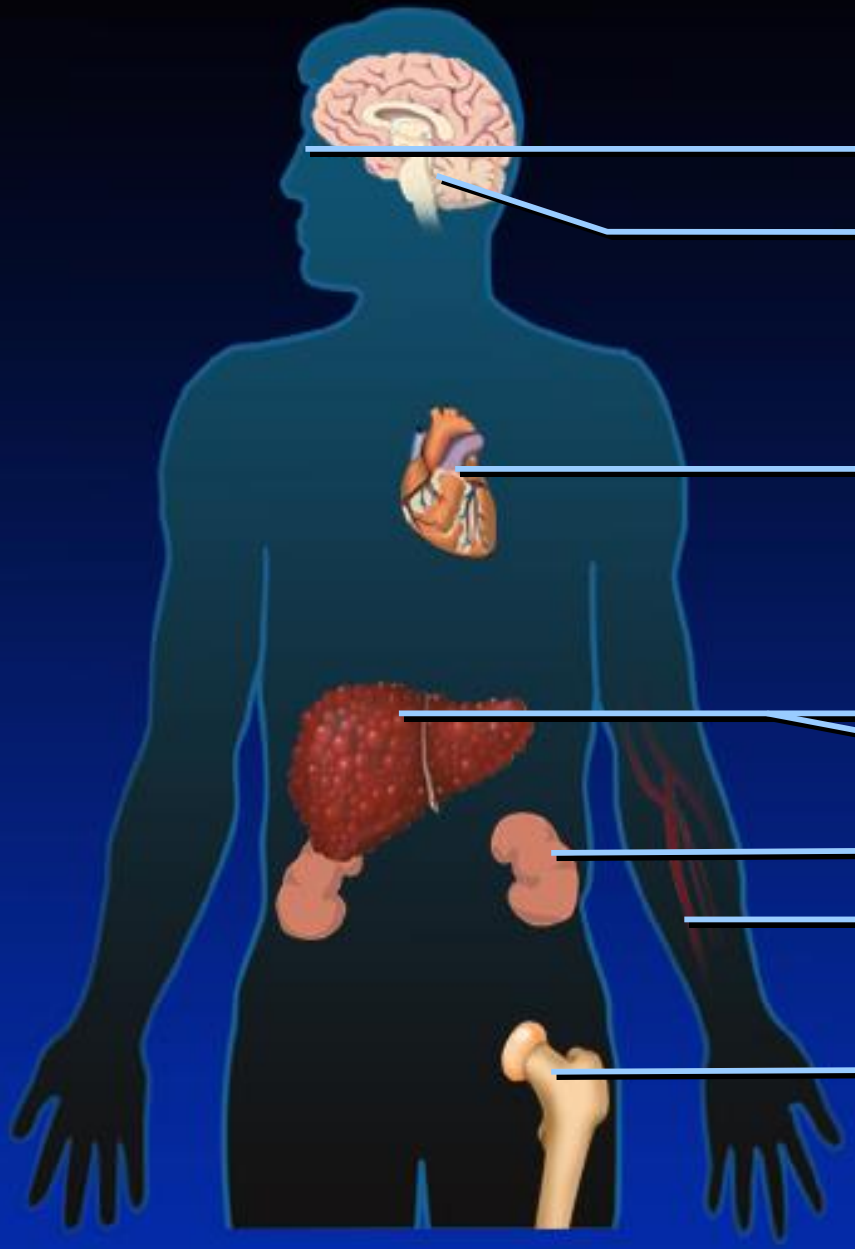


Liver Biopsy - Prussian Blue Stain for Iron

Liver Biopsy - Prussian Blue Stain for Iron



Genetic Diseases – Wilson's Disease



Kayser-Fleischer rings

Neuropsychiatric disorders

Cardiomyopathy

Hepatitis

Cirrhosis

Fanconi syndrome

Hemolysis

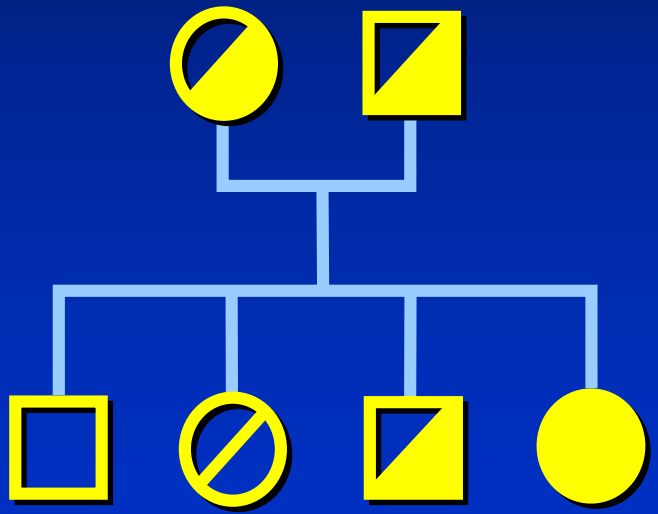
Osteoporosis and arthropathy

Genetic Diseases – Wilson's Disease

Copper Overload Disorders

Primary

Wilson's Disease

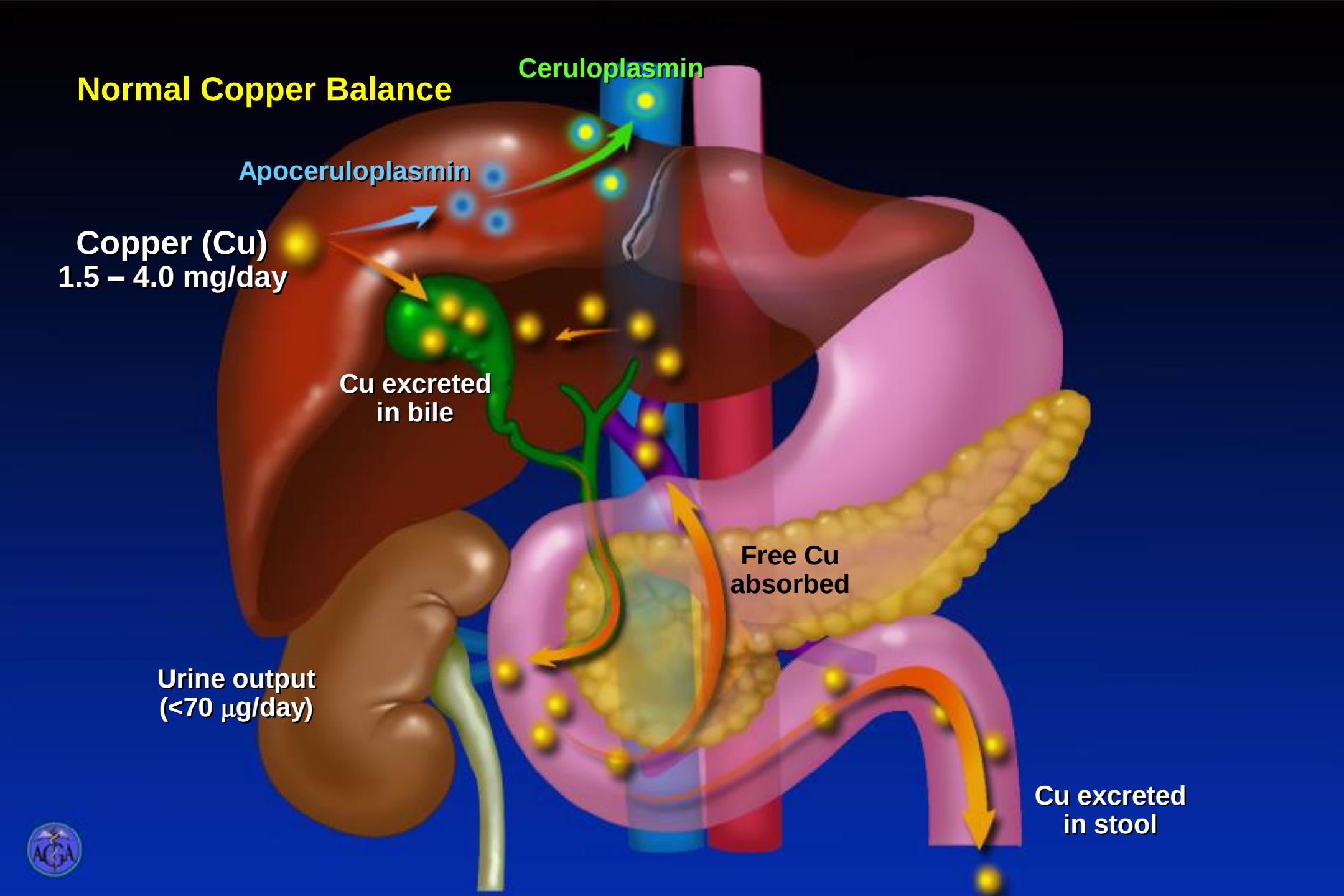


Autosomal recessive inheritance

Secondary

Chronic cholestasis

- Primary biliary cirrhosis
- Byler's syndrome


Normal Copper Balance
Ceruloplasmin
Apoceruloplasmin
Copper (Cu)
1.5 – 4.0 mg/day
Cu excreted
in bile
Free Cu
absorbed
Urine output
(<70 μg/day)
Cu excreted
in stool

Genetic Diseases – Wilson's Disease

Ceruloplasmin

A blue α_2 globulin

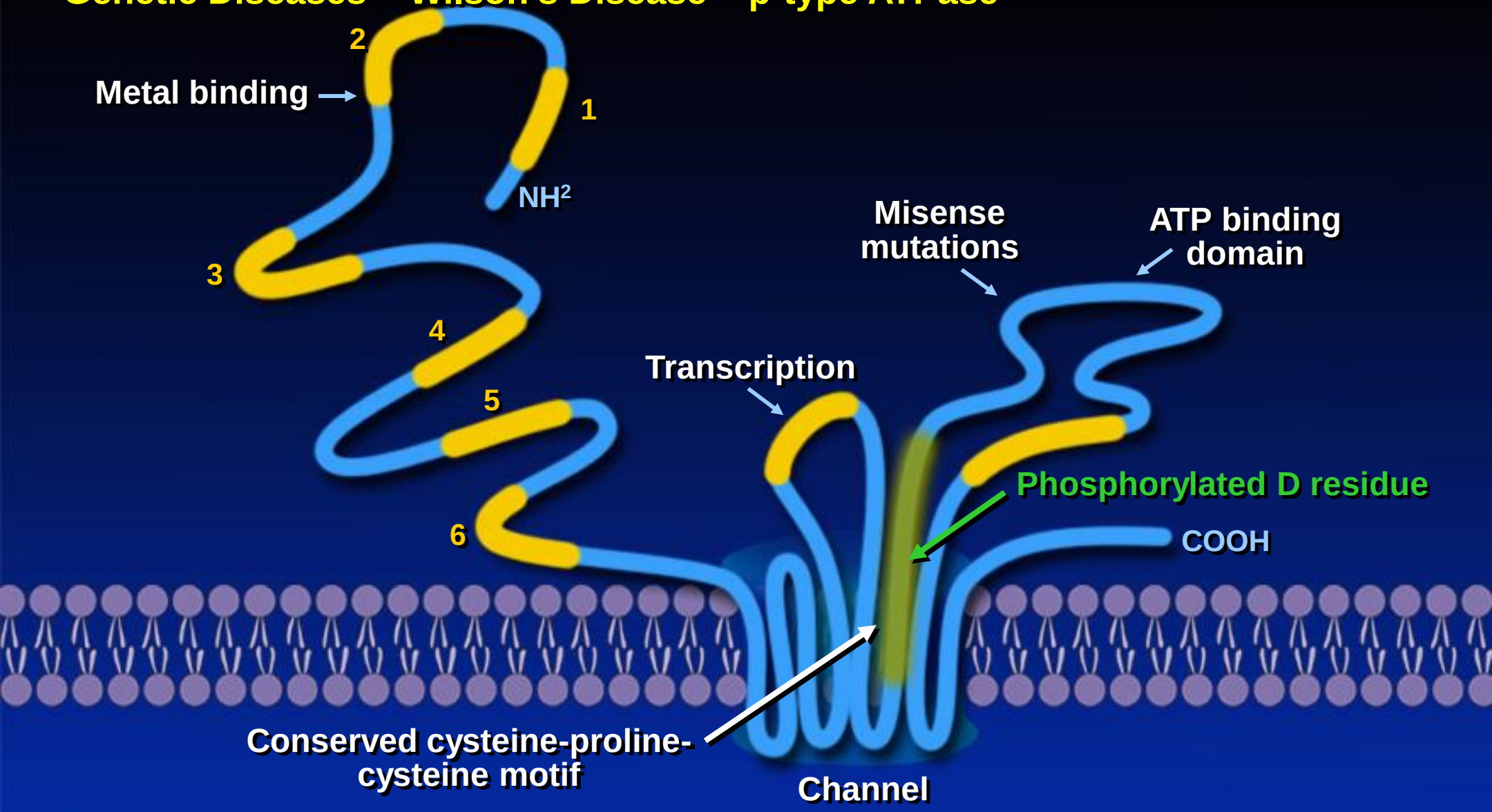
Binds copper irreversibly

Normal serum level = 20-40 mg/dL

Decreased serum ceruloplasmin is seen in:

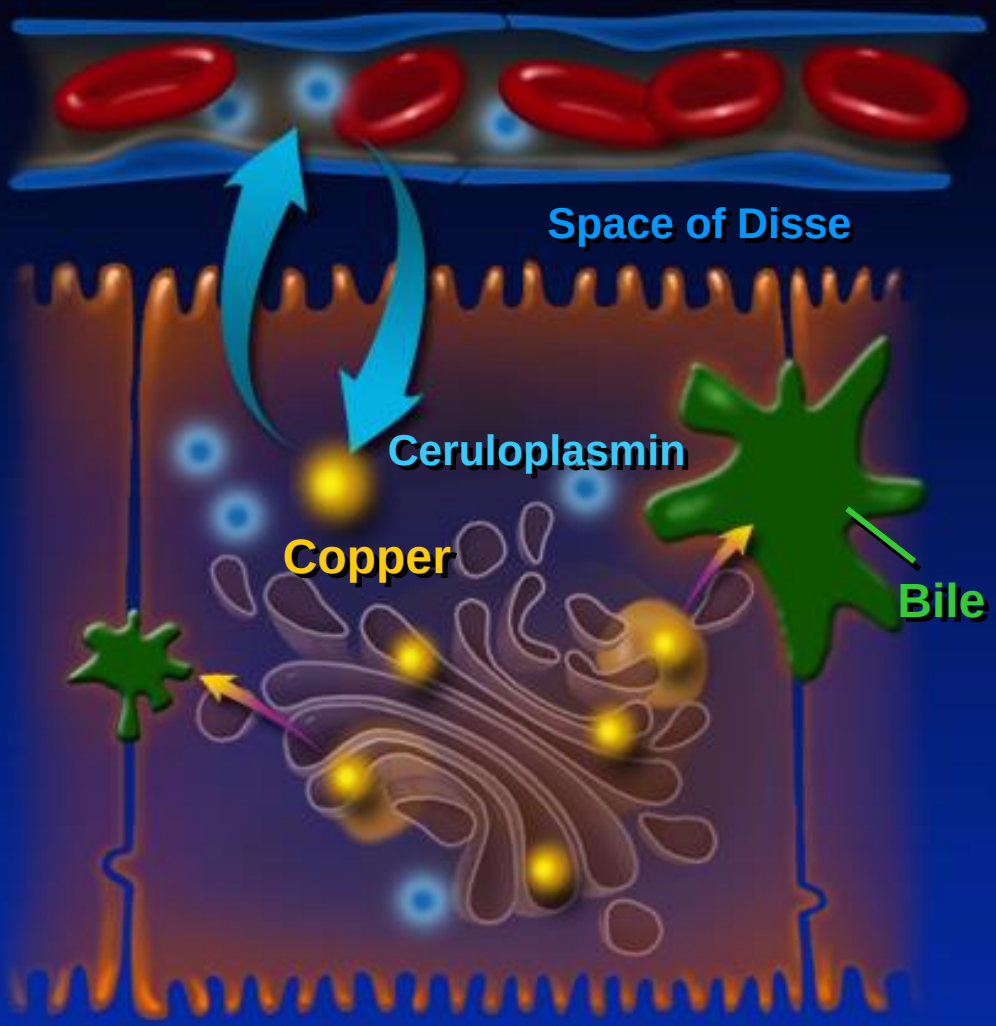
- Wilson's disease
  - 95% of homozygotes
  - 20% of heterozygotes
- Protein loss
- Hepatic failure
- Menkes syndrome

Genetic Diseases – Wilson's Disease – p-type ATPase

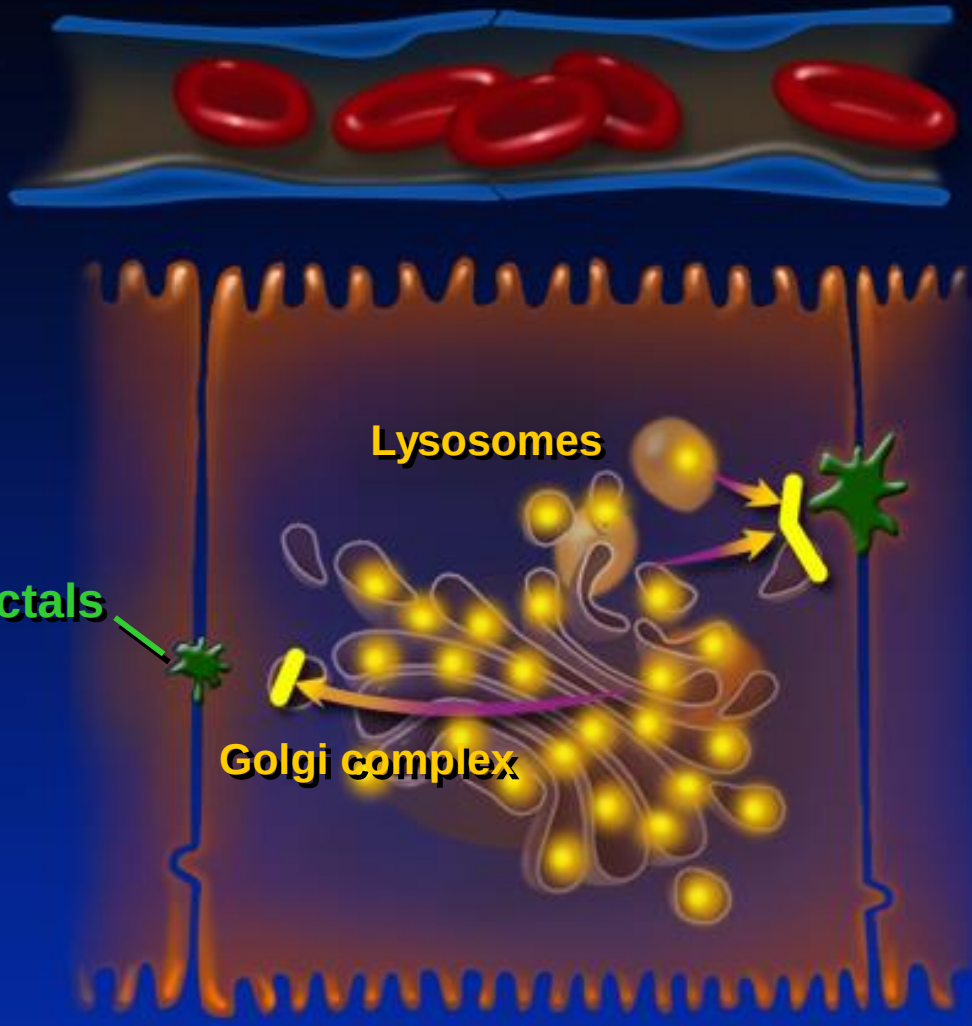


Genetic Diseases – Wilson's Disease

Normal Copper Balance



Abnormal Copper Balance



Copper build-up leads to cell stress and death

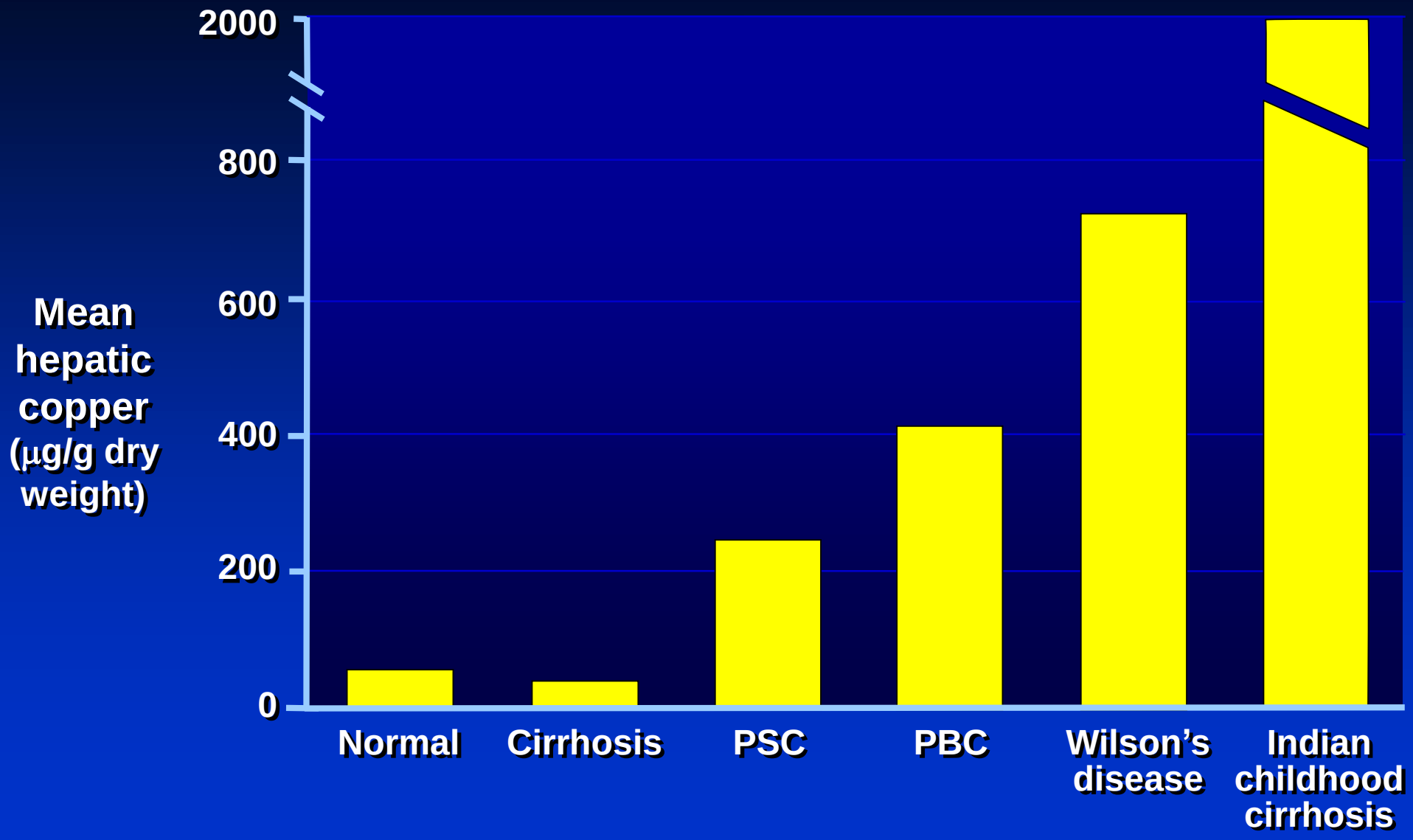
Genetic Diseases – Wilson's Disease

Usual Features in Homozygotes	Usual Features in Heterozygotes
Ceruloplasmin <20 mg/dl	Rarely
Urine copper >100 mg/day	Rarely
Kayser-Fleischer rings	Never
Hepatic histology abnormal	Never
Hepatic copper >250 mg/g	Rarely

Indications for Testing

- Liver disease in children, adolescents, young adults
- Hemolysis with liver disease
- Neurologic disease in the young
  - Parkinsonian tremor
  - Gait disturbance
  - Psychosis or other mental disorders
- Fanconi syndrome
- Hypouricemia
- Kayser-Fleischer rings
- Sunflower cataracts
- Siblings of affected patients

Genetic Diseases – Wilson's Disease



Genetic Diseases – Wilson's Disease

Presentations

Liver	Abnormal liver tests Acute hepatitis Acute hepatic failure Liver disease with hemolysis Chronic hepatitis Cryptogenic cirrhosis
CNS	Parkinson-like disorders Psychiatric disorders
Eye	Kayser-Fleischer rings Sunflower cataracts
Kidney	Fanconi syndrome with hypouricemia

Genetic Diseases – Wilson's Disease

Diagnostic Testing

Ceruloplasmin
Slit lamp examination
Urine copper

Ceruloplasmin <20 mg/dL
(5% of Wilson's patients have normal ceruloplasmin levels)
Kayser-Fleischer rings
Urine copper >100 μg/24 hr

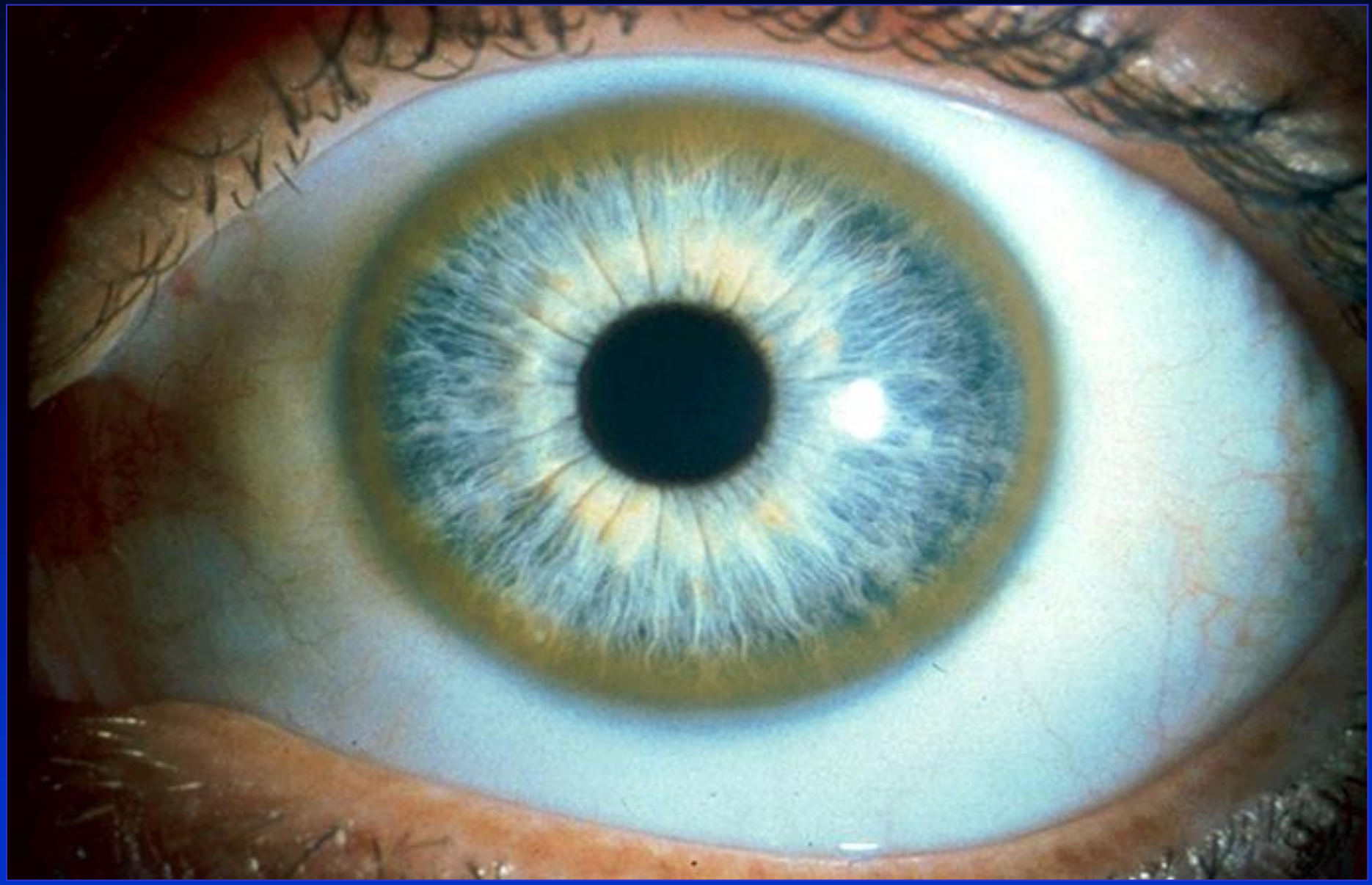
Liver biopsy with quantitative copper determination confirms diagnosis

Genetic Diseases – Wilson's Disease

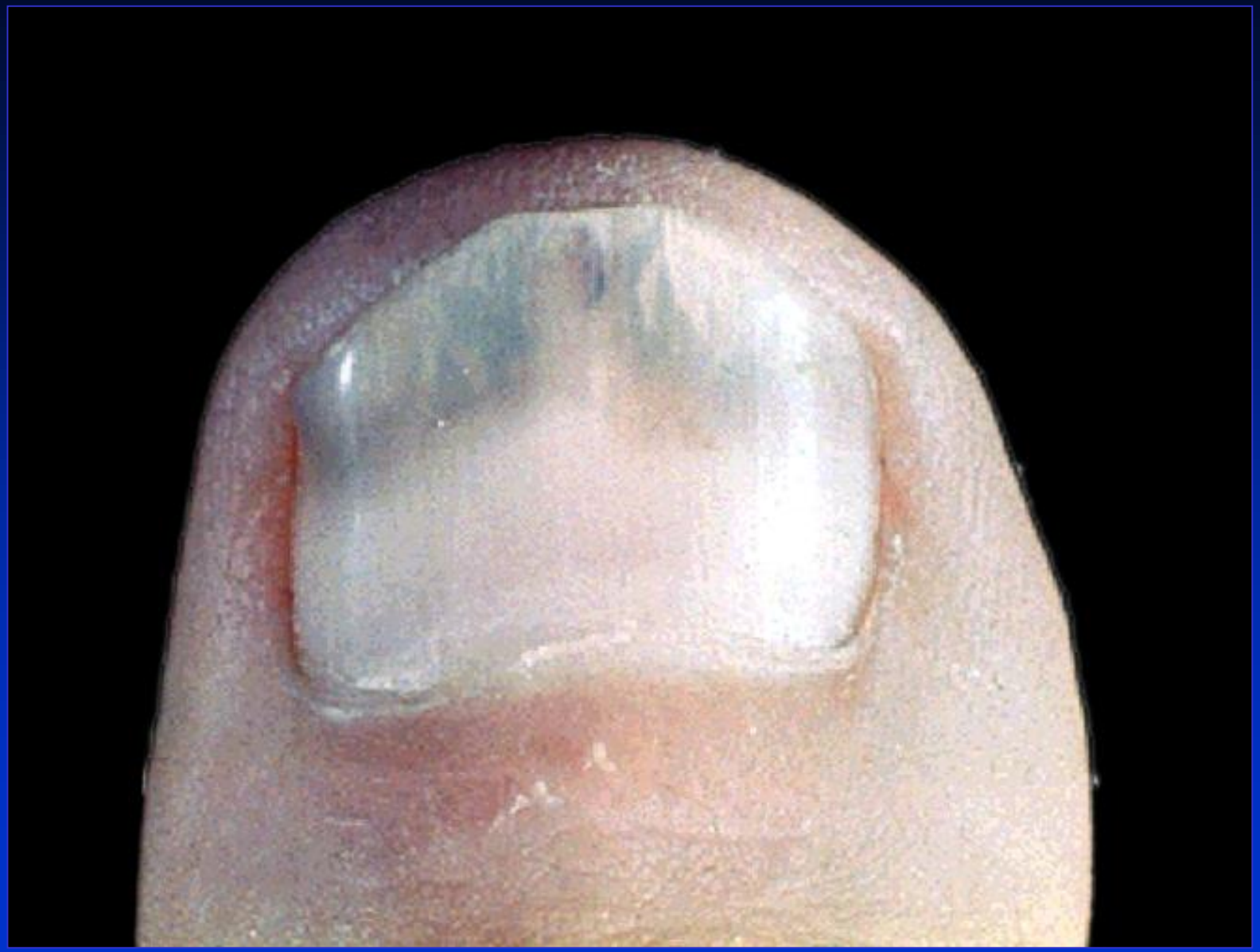
Management

Therapy	Chelation + pyridoxine Zinc Avoid high copper foods Transplantation in selected cases Family screening
Monitoring	Urine copper Non-ceruloplasmin copper Do NOT monitor Kayser-Fleischer rings
Results	Treatment prevents disease Improves liver and CNS disease Prolongs life

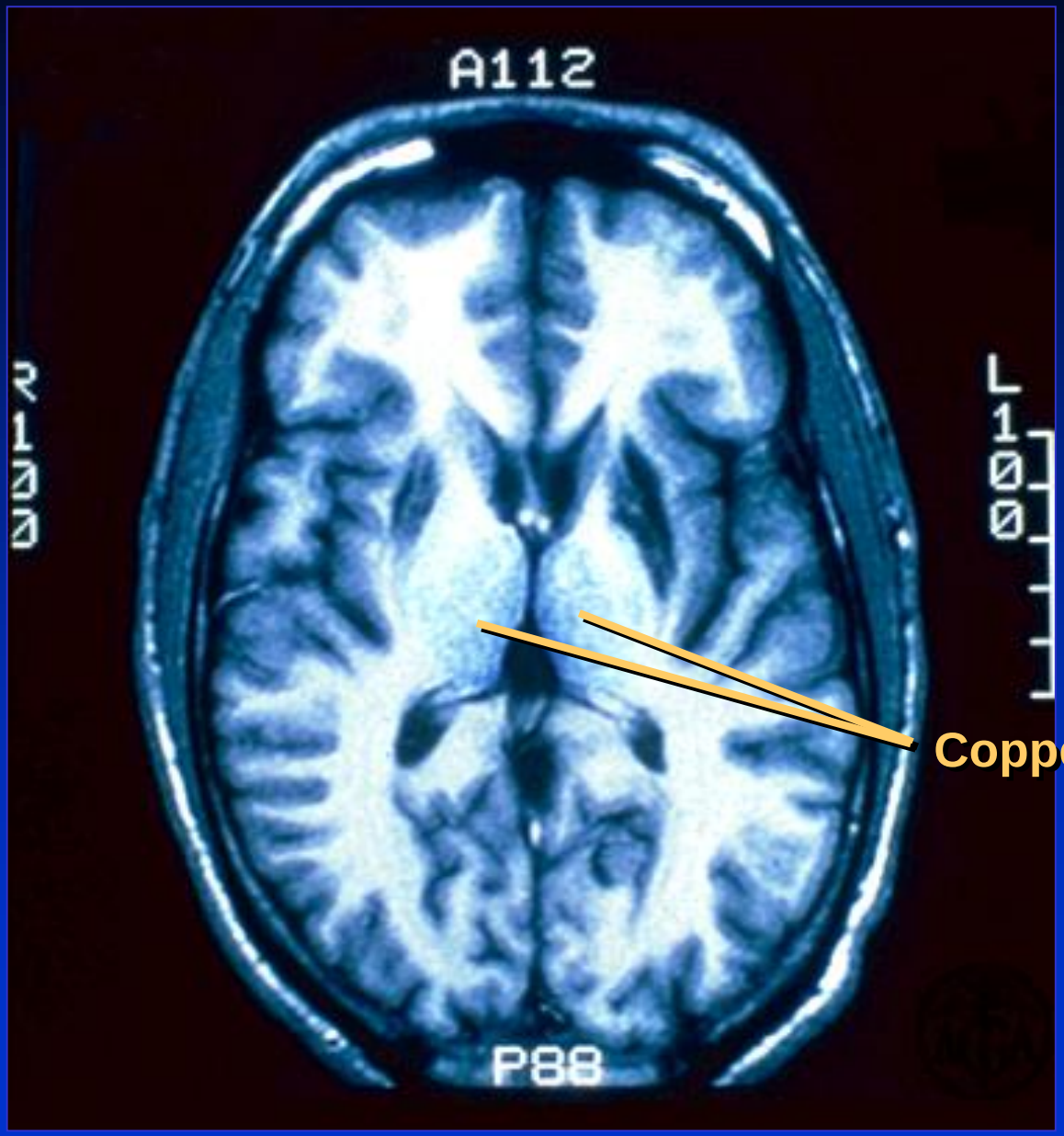
Genetic Diseases – Wilson's Disease



Genetic Diseases – Wilson's Disease

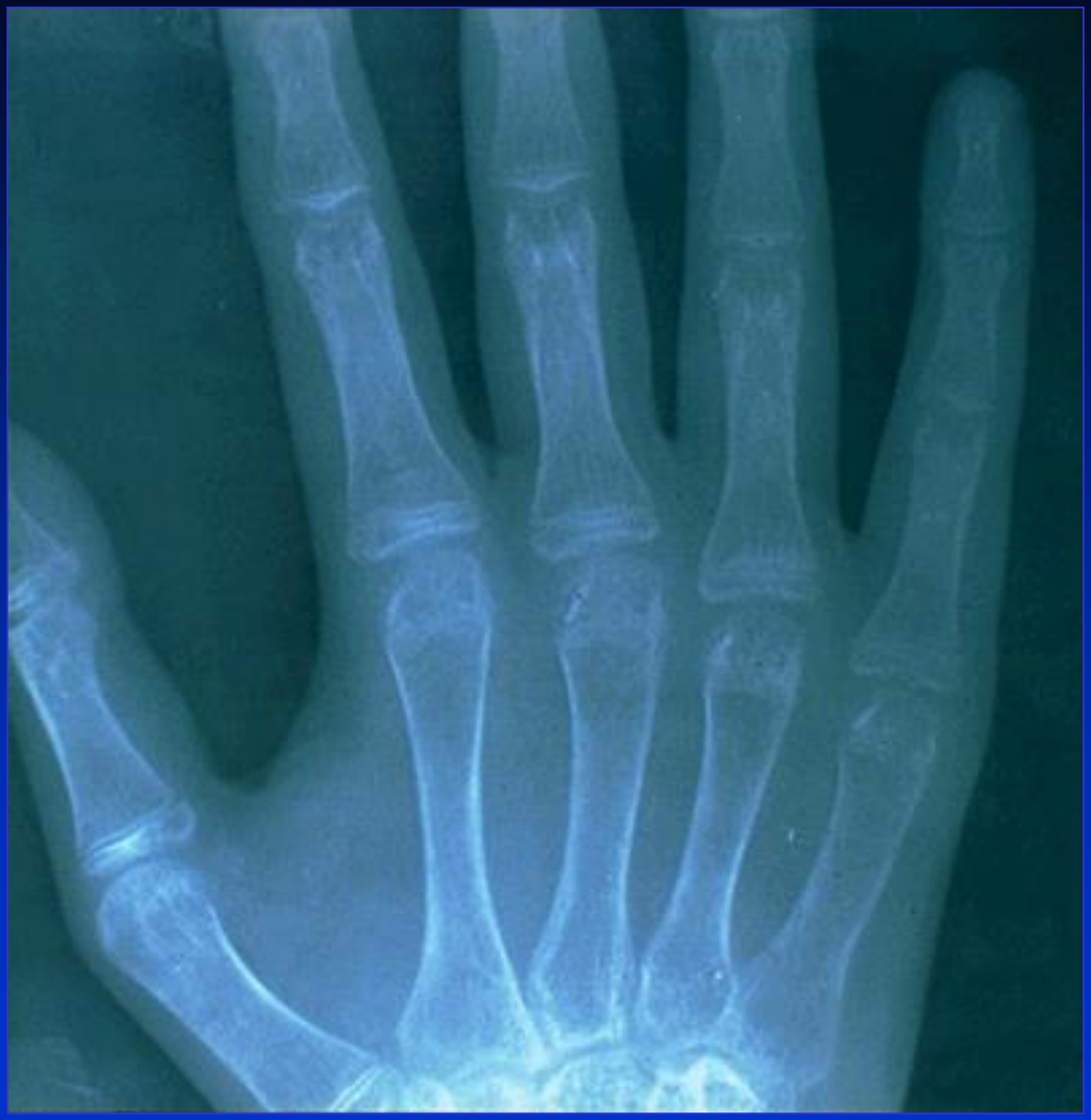


Genetic Diseases – Wilson's Disease



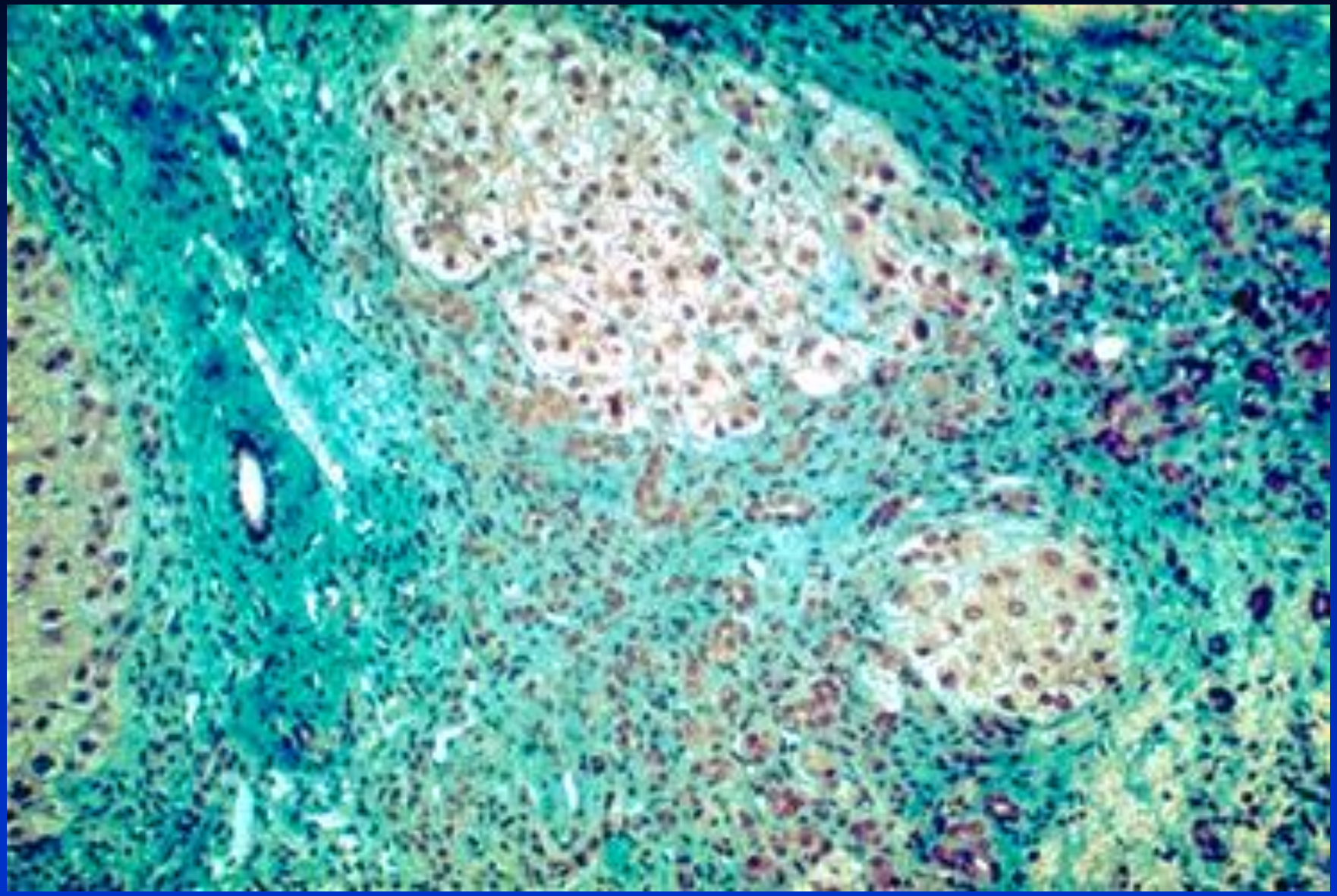
CM - Hand Radiograph

Genetic Diseases – Wilson's Disease



Resnick, 1998

Genetic Diseases – Wilson's Disease



Genetic Diseases – Wilson's Disease