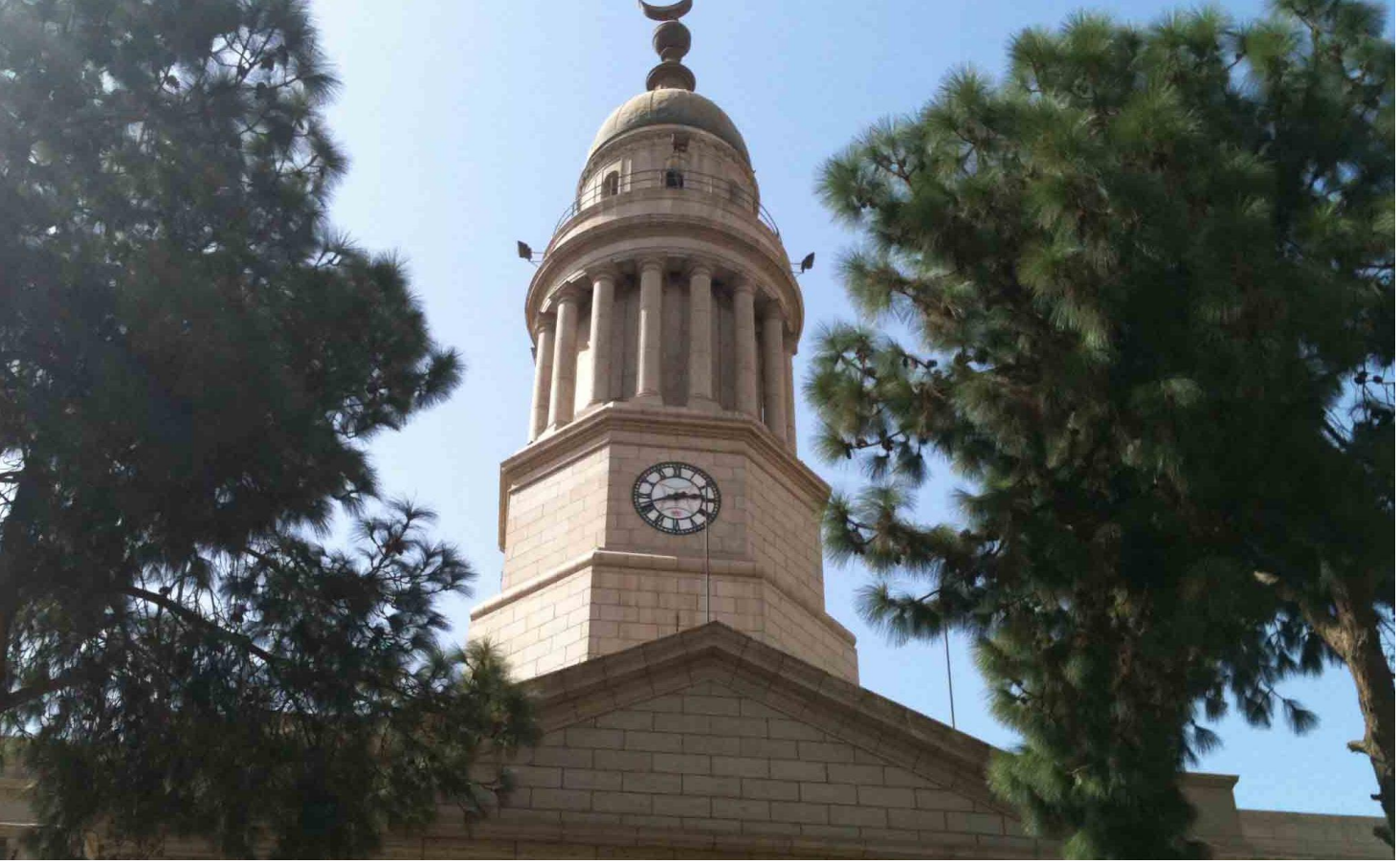
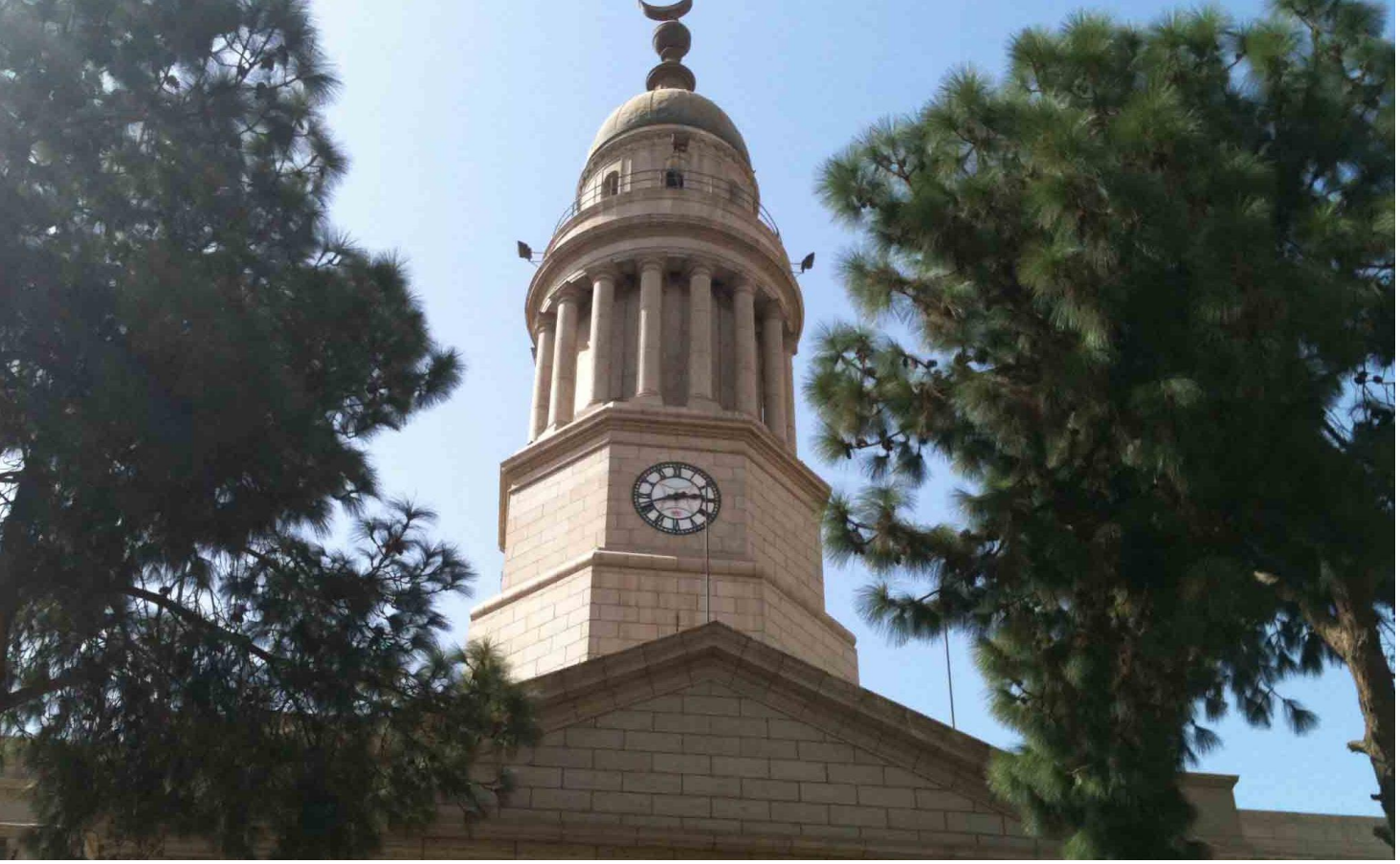


Wilson’s disease



Amr Hasan, MD,FEBN

Associate Professor of Neurology - Cairo University

BRAIN [MARCH, 1912.]

PART IV., VOL. 34.

Original Articles and Clinical Cases.

PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.[1]

BY S. A. KINNIER WILSON, M.D., B.Sc.EDIN., M.R.C.P.LOND.

Registrar to the National Hospital, Queen Square, London.

(*From the Laboratory of the National Hospital, Queen Square.*)

Samuel Alexander Kinnier Wilson (1878-1937)

Agenda

- Epideiology of Wilson's Disease
- Genetics of Wilson's Disease
- Pathophysiology of Wilson's Disease
- Clinical features
- Investigations
- Diagnostic criteria
- Treatment
- Prognosis

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Epidemiology

- 1 case per 30,000 live births in most populations
- One of the highest reported prevalences was from a small mountain village on the island of Crete, where Wilson disease was diagnosed in 1 in 15 births
- Men and women are equally affected, though women are more likely than men to develop acute liver failure due to Wilson disease

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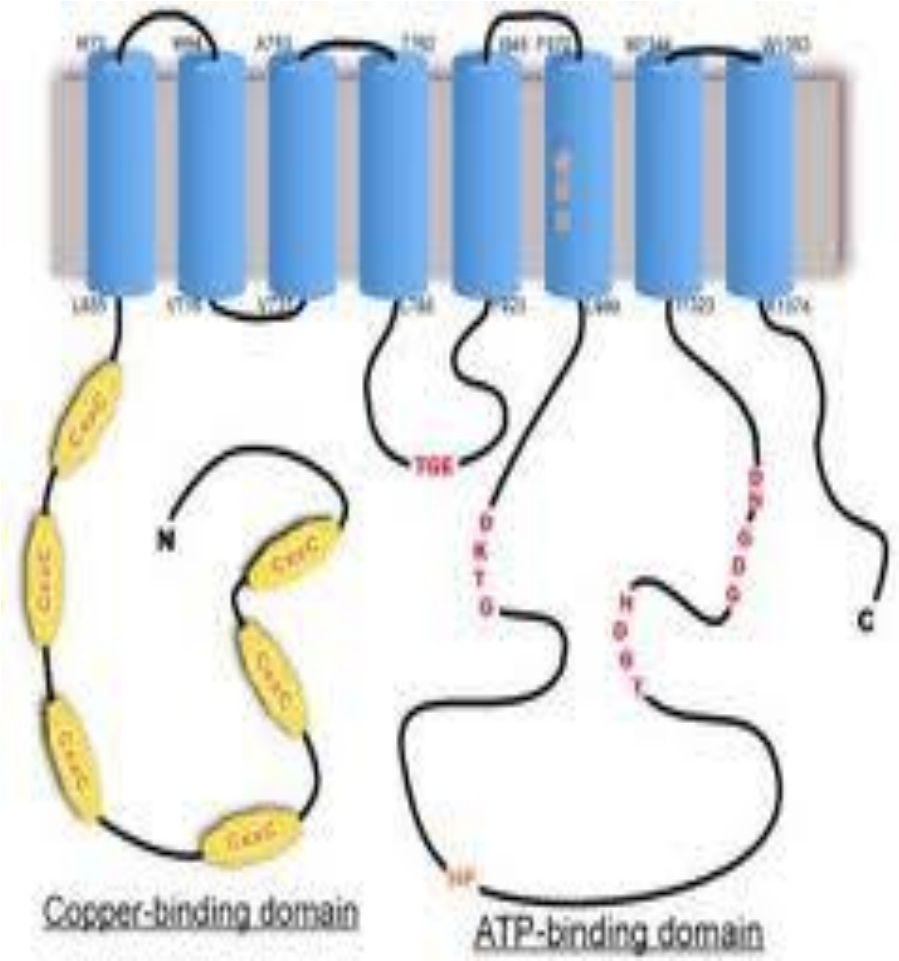
Genetics of Wilson's Disease *

- WD is caused by mutations to the gene coding for ATPase copper transporting beta polypeptide (*ATP7B*), which is located on chromosome 13.
- *ATP7B* is a relatively large gene at around 80 kb, and it contains 21 exons.



Genetics of Wilson's Disease *

- A variety of defects have been identified in the *ATP7B* gene of WD patients (over 300 mutations).
- These defects include insertion, deletion, splice site and point mutations.
- Frame shift deletions and nonsense mutations that cause a truncation of the translated protein product usually result in a severe form of the disease because of loss of the functional protein.

Genetics of Wilson's Disease *

- In most ethnic groups, either one or a small number of these *ATP7B* mutations are prevalent, in addition to many other more rare mutations.

- The H1069Q mutation is one of the most common mutations, with an allelic frequency of 10 to 40 percent (30 to 70 percent among Caucasians)

Genetics of Wilson's Disease *

- Compound heterozygotes for the *ATP7B* mutation are frequent in WD, which makes the genotype–phenotype correlation challenging.

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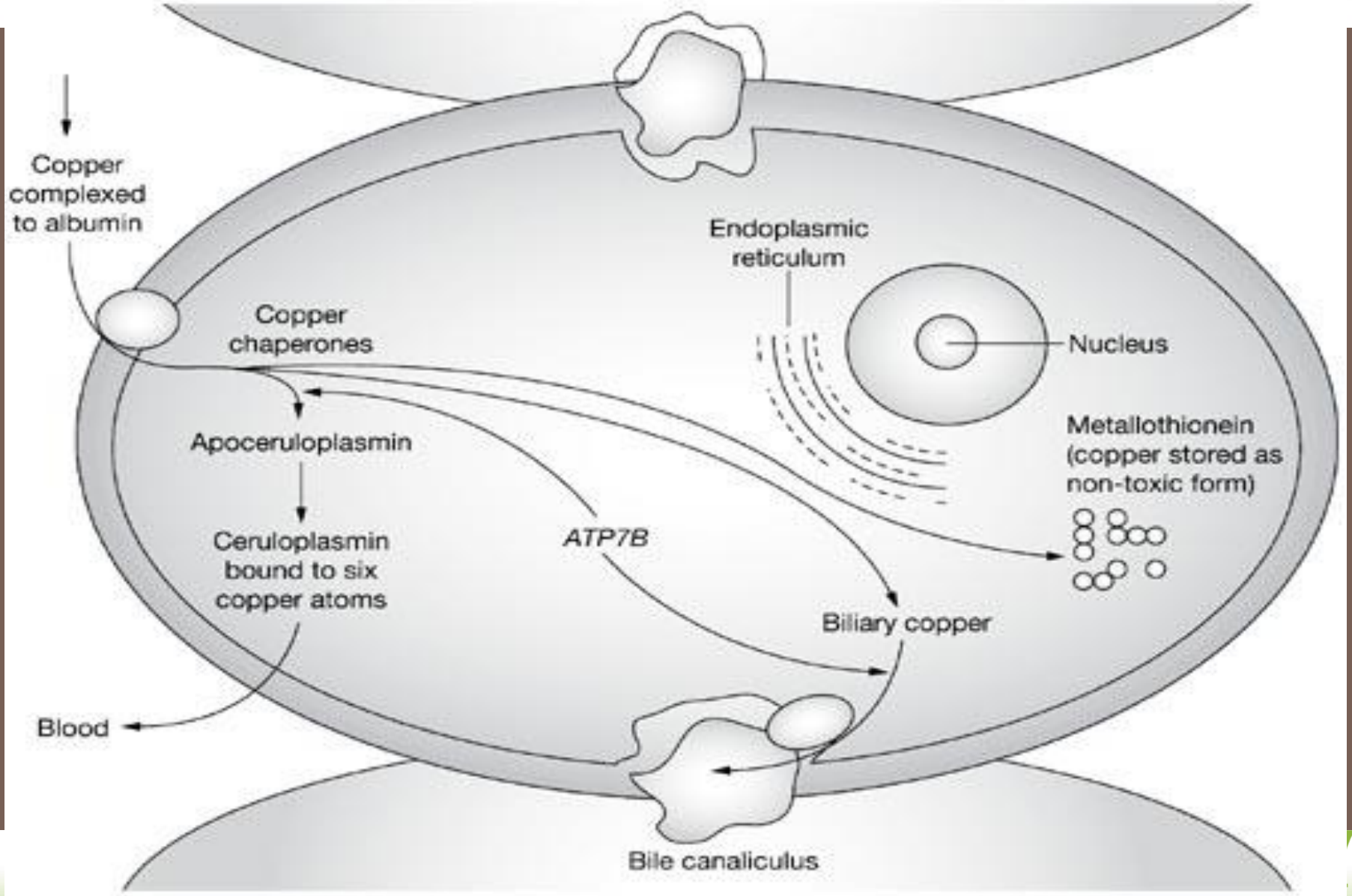
Schematic representation of copper metabolism within a liver cell



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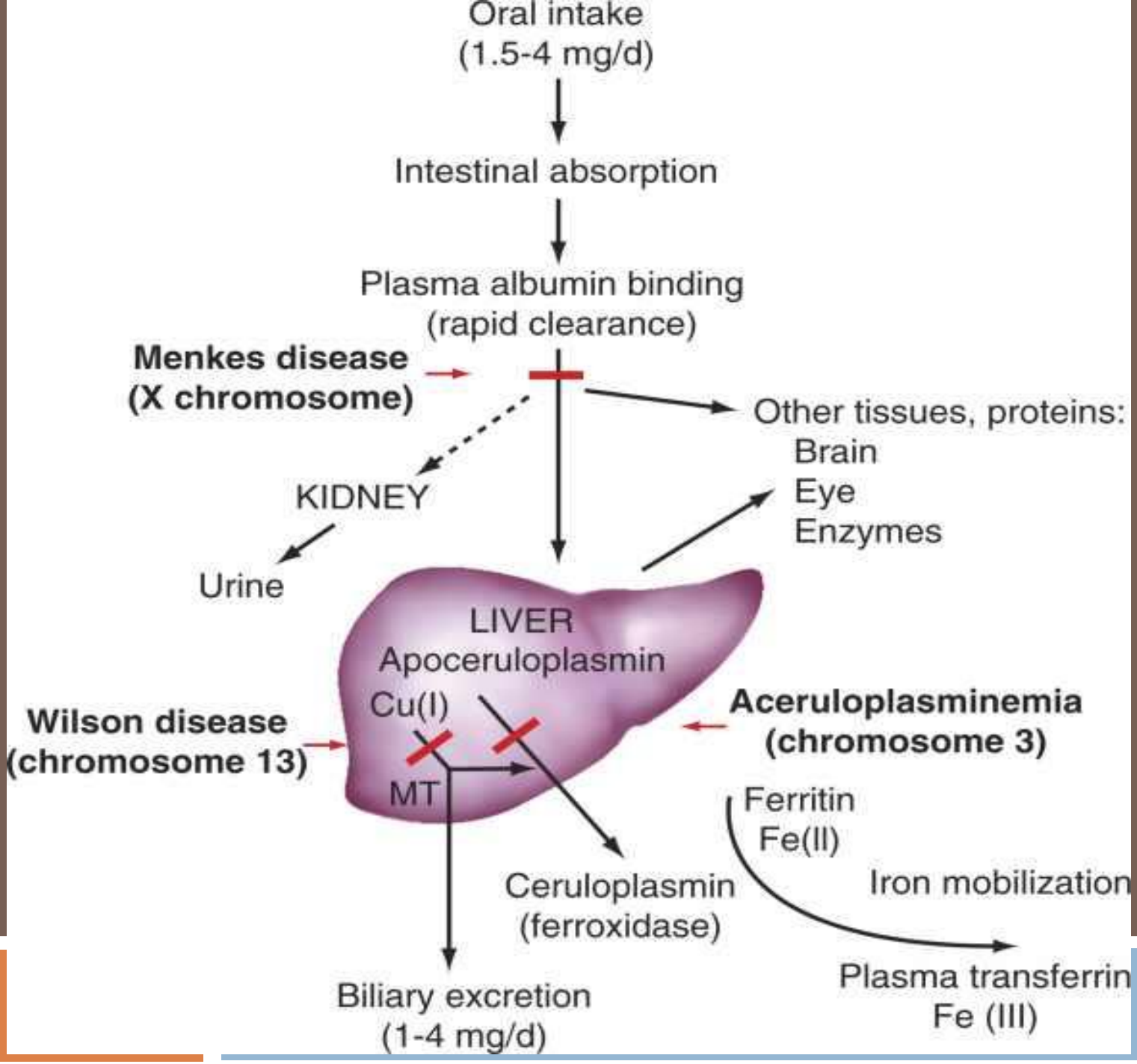
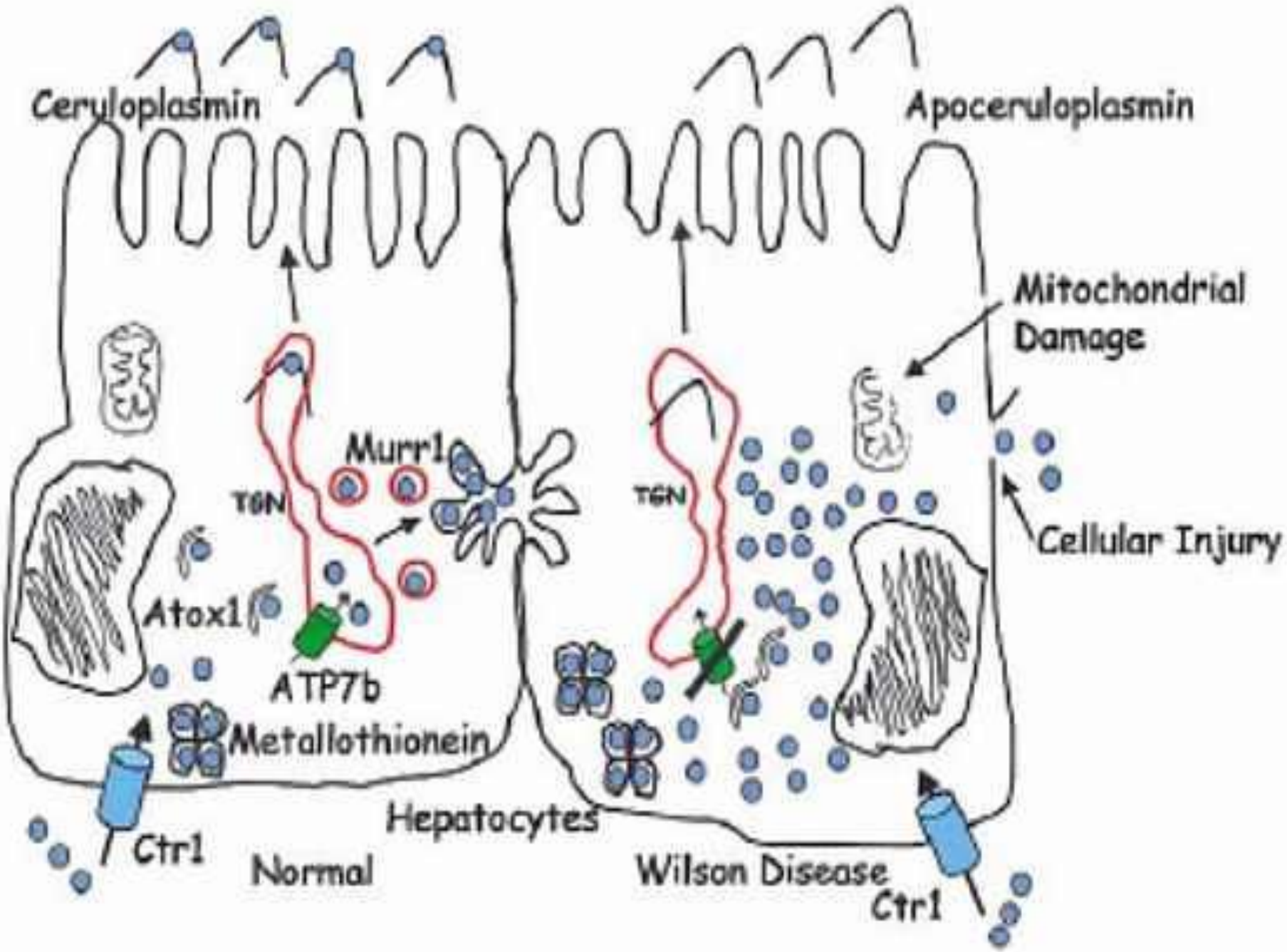
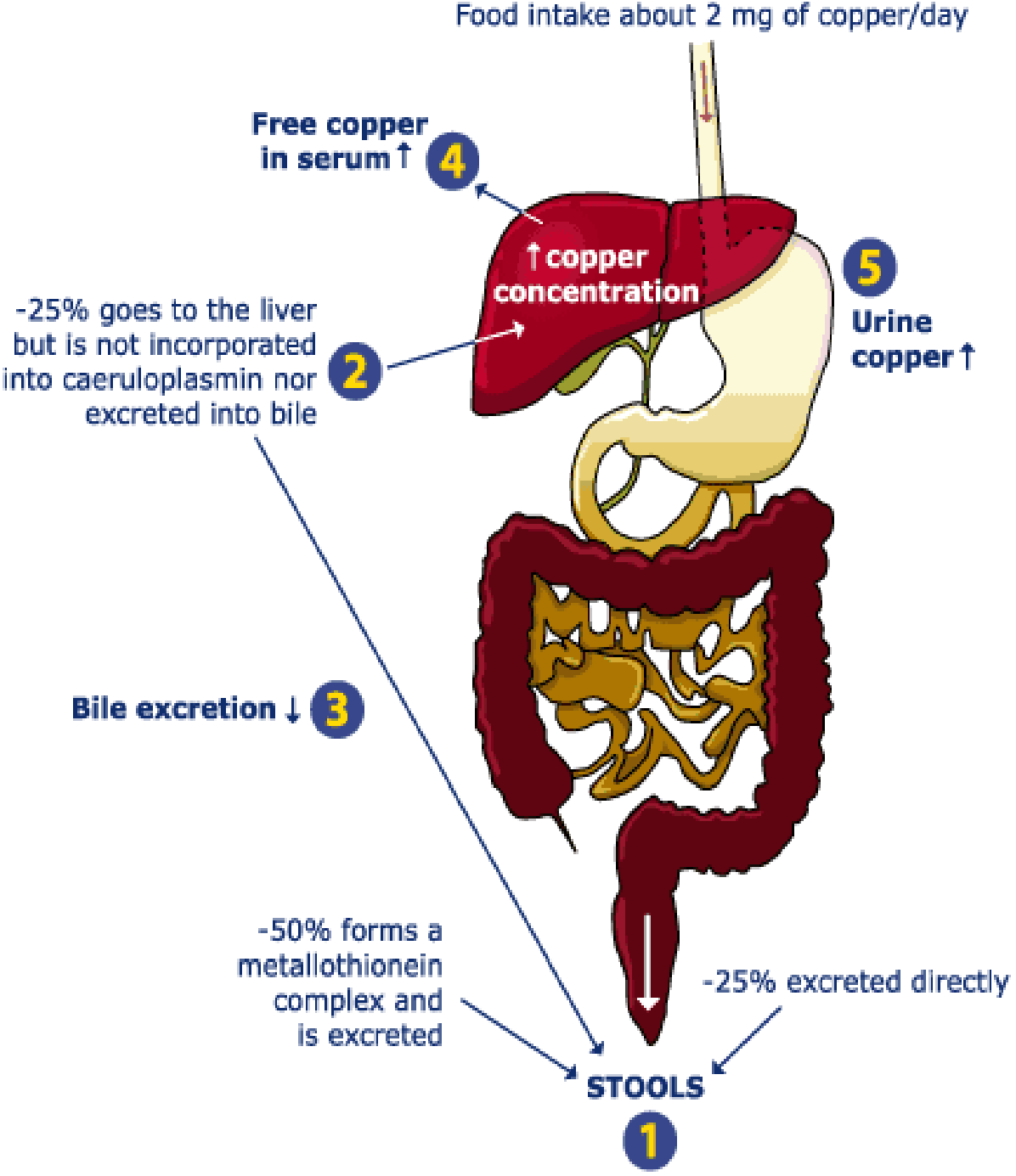
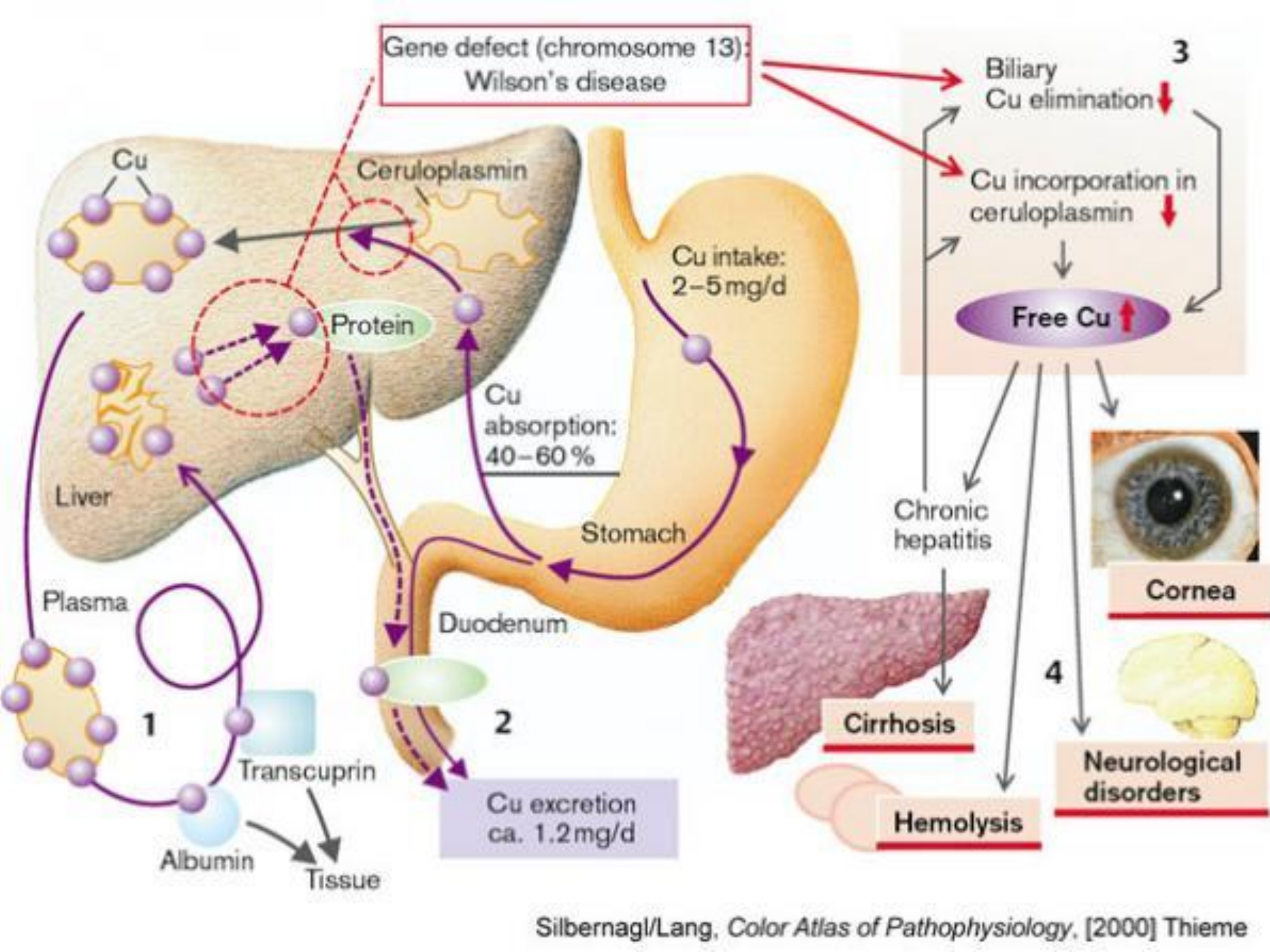

Oral intake
(1.5-4 mg/d)
Intestinal absorption
Plasma albumin binding
(rapid clearance)
Menkes disease
(X chromosome)
Other tissues, proteins:
Brain
Eye
Enzymes
KIDNEY
Urine
LIVER
Apoceruloplasmin
Cu(I)
Wilson disease
(chromosome 13)
Aceruloplasminemia
(chromosome 3)
MT
Ferritin
Fe(II)
Iron mobilization
Ceruloplasmin
(ferroxidase)
Plasma transferrin
Fe (III)
Biliary excretion
(1-4 mg/d)

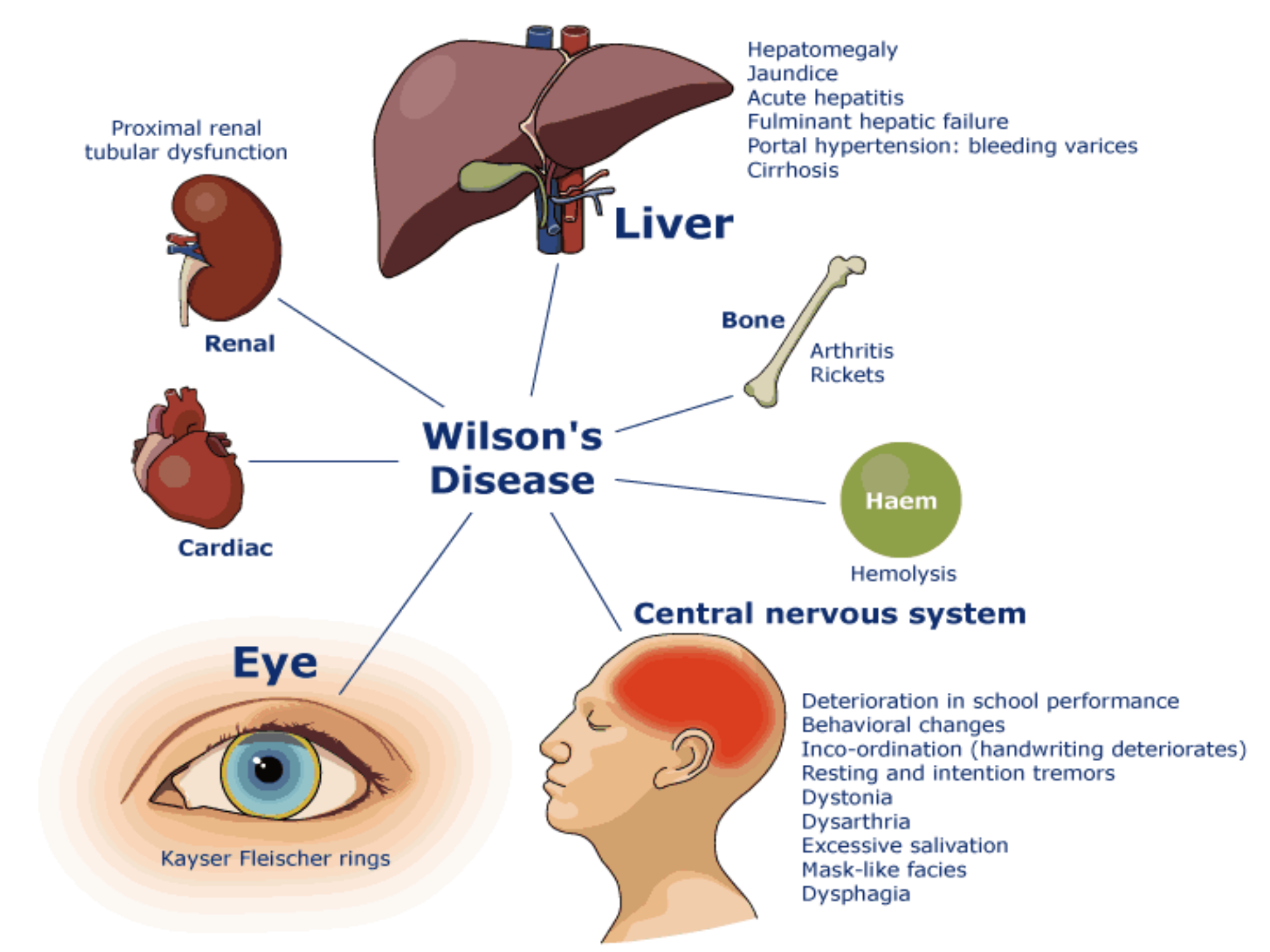

Ceruloplasmin
Apoceruloplasmin
Mitochondrial Damage
Murr1
TGN
TGN
Cellular Injury
Atox1
ATP7b
Metallothionein
Ctr1
Hepatocytes
Normal
Wilson Disease
Ctr1



1. Absorption of copper is normal
2. There is no incorporation of copper into caeruloplasmin not is it excreted into bile
3. The excretion of copper in bile is decreased
4. An increased copper concentration in the hepatocytes results in an overflow of copper into the blood. Consequently free Cu plasma concentration is increased
5. The increased free Cu plasma concentration will lead to an increased urinary concentration. Excretion of copper via the stools is decreased



Silbernagl/Lang, *Color Atlas of Pathophysiology*, [2000] Thieme


Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Portal hypertension: bleeding varices
Cirrhosis
Liver
Proximal renal tubular dysfunction
Renal
Bone
Arthritis
Rickets
Wilson's Disease
Cardiac
Haem
Hemolysis
Central nervous system
Eye
Kayser Fleischer rings
Deterioration in school performance
Behavioral changes
Inco-ordination (handwriting deteriorates)
Resting and intention tremors
Dystonia
Dysarthria
Excessive salivation
Mask-like facies
Dysphagia

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Hepatic Wilson disease

- Kayser-Fleischer rings, visible in 50 percent of patients with hepatic disease (seen with all forms of liver involvement)
- Asymptomatic (steatosis, chronic hepatitis, compensated cirrhosis)
- Abdominal pain (acute hepatitis, acute liver failure)
- Jaundice (acute hepatitis, acute liver failure, cirrhosis)
- Hepatomegaly (acute and chronic hepatitis, acute liver failure)
- Splenomegaly (cirrhosis)
- Ascites (cirrhosis)
- Upper gastrointestinal bleeding (cirrhosis with varices or portal hypertensive gastropathy)
- Peripheral stigmata of chronic liver disease (cirrhosis)
- Mental status changes due to hepatic encephalopathy (acute liver failure, cirrhosis)

Hepatic Wilson disease

- Children most often initially present with liver disease, at an average age of 9 to 13 years .
- **Acute hepatitis and acute liver failure —** Patients with Wilson disease, most often children or young adults, may develop acute hepatitis that is indistinguishable from acute viral hepatitis, with elevated aminotransferase levels, jaundice, and abdominal pain.
- Wilson disease accounts for 8 to 10 percent of **chronic active hepatitis** in children.
- **Chronic hepatitis and cirrhosis —** Patients with chronic hepatitis due to Wilson disease are often asymptomatic from their liver disease. Such patients are typically diagnosed through family screening, after being found to have abnormal liver tests, or after presenting with neurologic or psychiatric manifestations of Wilson disease.

Neurologic Wilson disease

- Dysarthria – 85 to 97 percent of patients with neurologic Wilson disease.
- Gait abnormalities/ataxia – 30 to 75 percent.
- Dystonia – 11 to 69 percent.
- Tremor – 22 to 55 percent.
- Parkinsonism – 19 to 62 percent.
- Drooling – 48 to 86 percent.

Neurologic Wilson disease

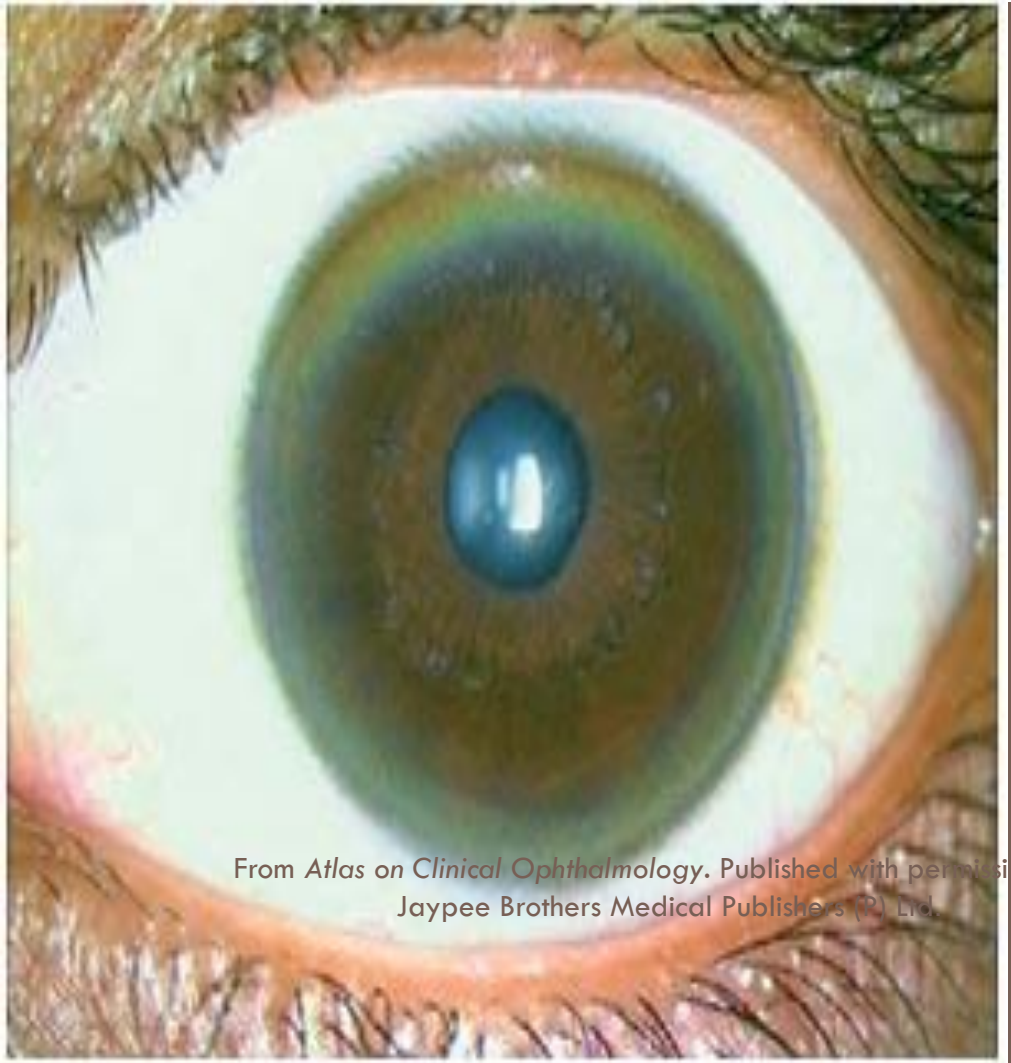
Other neurologic manifestations include:

- Risus sardonicus (sardonic expression produced by dystonic spasm of the facial muscles)
- Chorea
- Athetosis
- Cognitive impairment/dementia
- Seizures
- Hyperreflexia
- Myoclonia
- Urinary incontinence
- Autonomic dysfunction

4 Distinct diagnostic categories based on patients' major neurologic findings, as follows :

- Patients in the parkinsonian group (45%) - Distinguished by paucity of expression and movement.
- Patients in the pseudosclerotic group (24%) - Had tremor resembling multiple sclerosis.
- Patients in the dystonic group (15%) - Characterized by hypertonicity associated with abnormal limb movements.
- Patients in the choreic group (11%) - Predominantly characterized by choreoathetoid abnormal movements associated with dystonia.

The Kayser–Fleischer ring around the periphery of the cornea caused by deposition of copper in Descemet's membrane



From *Atlas on Clinical Ophthalmology*. Published with permissi
Jaypee Brothers Medical Publishers (P) Ltd.

Das SK and Ray K (2006) Wilson's disease: an update
Nat Clin Pract Neurol **2:** 482–493 10.1038/ncpneuro0291

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Kayser-Fleischer rings

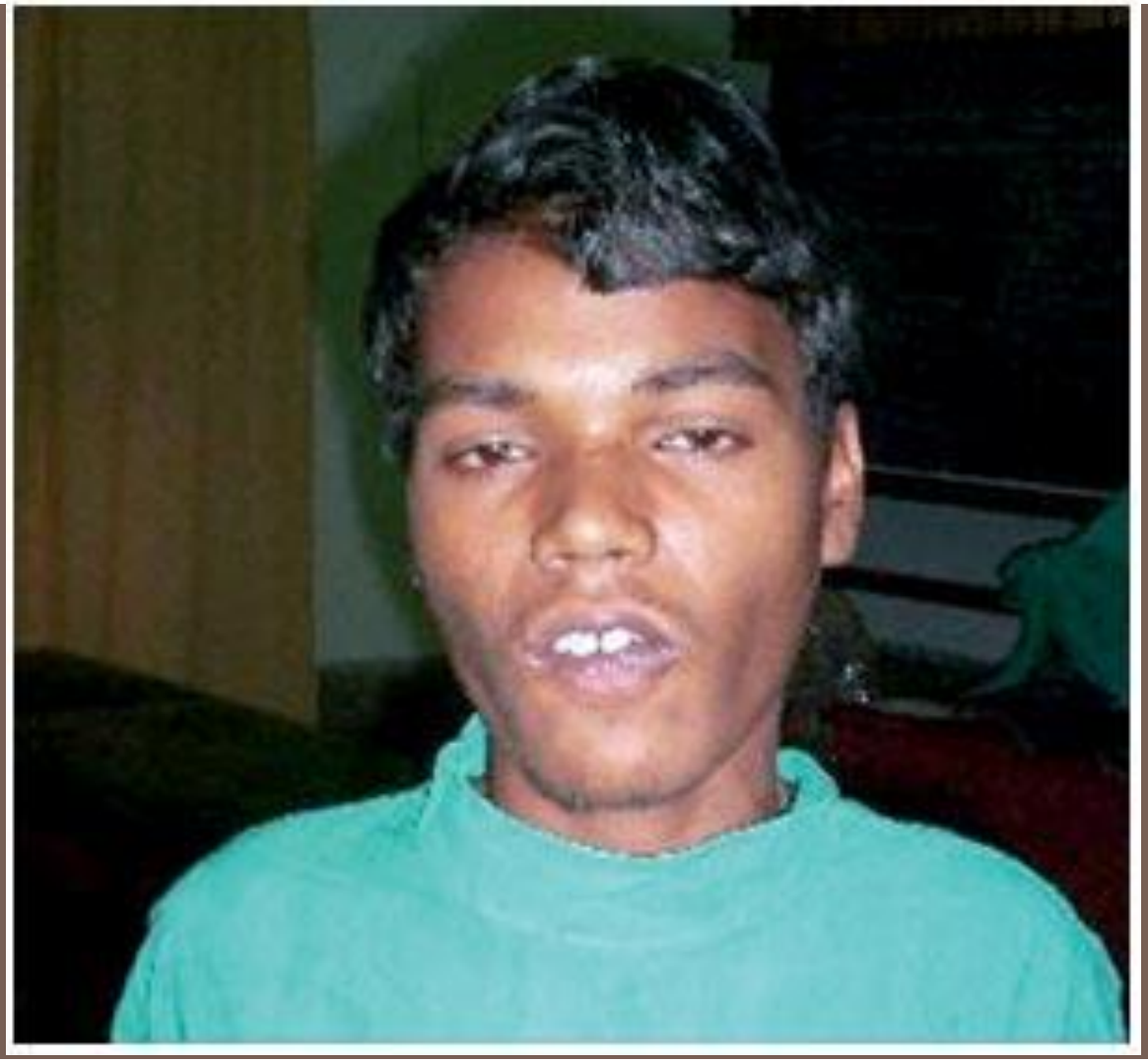
- Observed in up to 90% of individuals with symptomatic Wilson disease and almost invariably present in those with neurologic manifestations.

- No longer considered pathognomonic of Wilson disease unless accompanied by neurologic manifestations, as they may also be observed in patients with chronic cholestatic disorders.

Kayser-Fleischer rings

- Formed by the deposition of copper in the Descemet membrane in the limbus of the cornea.
- The color may range from greenish gold to brown.
- Well-developed rings may be readily visible to the naked eye or with an ophthalmoscope set at +40.
- When not visible to the unaided eye, the rings may be identified using slit-lamp examination or gonioscopy.

The 'vacuous smile' typified by mask facies with an open mouth caused by dystonia of the facial and mandibular muscles



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Rare presentations of Wilson's disease.

- **Hematological**

Acute non-immunological hemolytic anemia and epistaxis

- **Orthopedic**

Chondrocalcinosis, osteoarthritis, metabolic bone disease, juvenile polyarthritis, recurrent fracture and dislocation

- **Cardiovascular**

Arrhythmias, **rheumatic-fever-like manifestation**

- **Renal**

Renal tubular acidosis, hypercalciuria, microscopic hematuria and/or minimal proteinuria

- **Skin**

Hyperpigmentation (similar to Addison's disease)

- **Ocular**

Sunflower cataract

- **Gynecological**

Primary or secondary amenorrhea, repeated and unexplained spontaneous abortions

Staging

The natural history of Wilson disease may be considered in 4 stages, as follows:

- **Stage I -** The initial period of accumulation of copper within hepatic binding sites
- **Stage II -** The acute redistribution of copper within the liver and its release into the circulation
- **Stage III -** The chronic accumulation of copper in the brain and other extrahepatic tissue, with progressive and eventually fatal disease
- **Stage IV -** Restoration of copper balance by the use of long-term chelation therapy

Table 1 Differential diagnosis of Wilson's disease (noted usually in patients below 50 years of age).

Presentation	Differential diagnosis
Parkinsonian features	Juvenile Parkinson's disease Neurodegeneration with brain iron accumulation (NBIA)
Dystonia	Dopa-responsive dystonia Idiopathic torsion dystonia Lipid storage disease Post-encephalitic dystonia Dystonic cerebral palsy Focal dystonias such as writer's cramp
Ataxia	Degenerative or metabolic cerebellar disease Demyelinating disease Craniovertebral anomaly
Titubation or tremor	Degenerative cerebellar disease Demyelinating disease Essential tremor
Myoclonus and cognitive deterioration	Mitochondrial disease Neuronal ceroid lipofuscinosis Lafora's bodies disease Baltic myoclonus Subacute sclerosing panencephalitis (SSPE)
Chorea	Huntington's disease Sydenham's chorea Storage disorders Drug-induced chorea Neuroacanthocytosis Vasculitis (particularly systemic lupus erythematosus)

Psychiatric illness	Major psychosis Attention deficit hyperactive disorder Personality disorder Mental retardation
Proximal muscle weakness	Muscular dystrophy Metabolic myopathy Inflammatory myopathy
Liver disease	Acute hepatitis of unknown etiology Acute fulminant hepatic failure of unknown etiology Chronic active hepatitis of unknown etiology Cirrhosis of liver of unknown etiology

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Investigations

- Wilson disease should be considered in any patient with unexplained liver, neurologic, or psychiatric abnormalities.

- First-degree relatives of patients with Wilson disease should be screened for Wilson disease.

TEST	COMMENTS
Urinary Copper	24 hour copper excretion >100µg in 65% of WD patients
Urinary copper penicillamine challenge with two dosages of 500mg 12 hours apart and measure urine copper	24 hour copper excretion > 1600 µg in patients with active liver disease
Serum Copper	Serum copper may be low in asymptomatic cases (because caeruloplasmin is low) or high in cases with active liver disease (because free copper is raised)
Serum "free" copper Calculated on the basis that caeruloplasmin contains 0.3% copper	Free Copper >25µg/dl
Serum Caeruloplasmin	< 20 mg/dl (in 95% of WD patients)
KF rings	Identification in most patients requires an experienced observer
Liver Copper	>250 µg/gm of dry weight liver
Coombs negative haemolytic anaemia	
Biochemical indices	Abnormal liver function tests
MRI scan	Abnormal
Molecular diagnosis	Over 200 mutations are known

Penicillamine challenge

- The penicillamine challenge is performed by giving a 500 mg dose of penicillamine (regardless of the patient's weight) at the beginning of the 24-hour urine collection and then again at 12 hours.

- Urinary copper excretion greater than 1600 mcg per 24 hours (>25 micromol) is much more likely in Wilson disease compared with other types of liver disease.

Investigations

- In patients with clinical features suggestive of Wilson disease, we start by obtaining liver biochemical tests, a complete blood count, a serum ceruloplasmin level, a slit-lamp examination for Kayser-Fleischer rings, and a 24-hour urinary copper excretion.
- Serum ceruloplasmin and copper levels, slit-lamp examination results, and 24-hour urinary copper excretion determine the need for additional testing.

Investigations

- Approximately 85 to 90 percent of patients with Wilson disease have serum ceruloplasmin concentrations below the laboratory limit for normal, typically 20 mg/dL (200 mg/L).

- Among patients with less specific clinical manifestations, a serum ceruloplasmin level below 5 mg/dL (50 mg/L) is highly suspicious for Wilson disease. However, low ceruloplasmin levels can be seen in patients without Wilson disease, and normal or elevated ceruloplasmin levels may be seen in patients with Wilson disease.

Investigations

- Kayser-Fleischer rings are seen in 50 to 60 percent of patients with isolated hepatic Wilson disease and in >90 percent of patients with neurologic involvement.

- Wilson disease is typically associated with 24-hour urinary copper excretion of >100 mcg (>1.6 micromol), although lower values have been described in up to 25 percent of asymptomatic patients with confirmed disease. Values >40 mcg/24-hours (0.64 micromol/24-hours) are suggestive of Wilson disease.

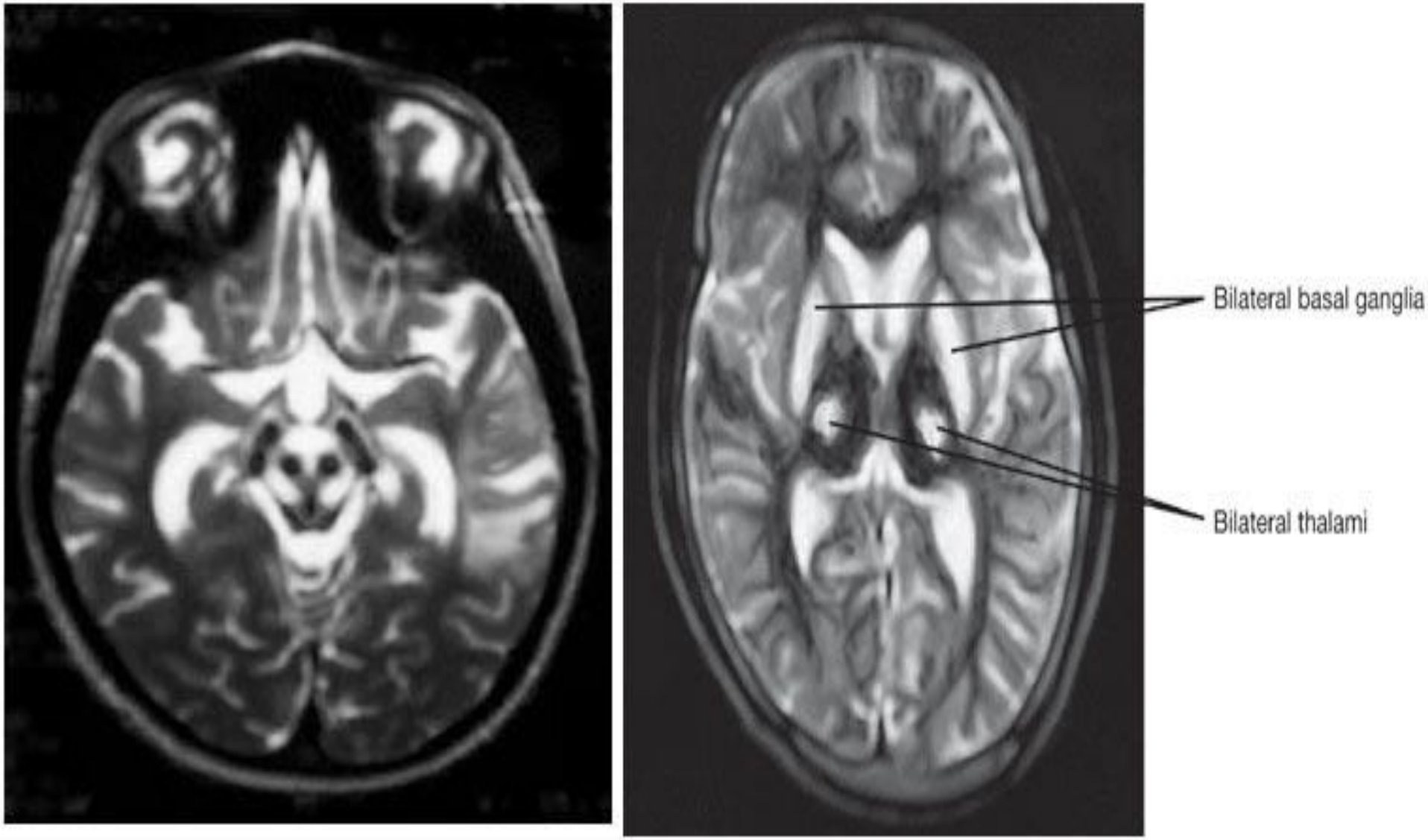
Investigations

- While a diagnosis of Wilson disease is established in patients with low serum ceruloplasmin levels, Kayser-Fleischer rings, and elevated urinary copper excretion, additional testing is required in patients with indeterminate results.
- Typically, this involves a liver biopsy to determine the hepatic copper concentration and to look for histologic changes suggestive of Wilson disease.

Investigations

- Genetic testing also has a role in the diagnosis of Wilson disease, but because of the large number of mutations seen in Wilson disease, it is generally reserved for those in whom a diagnosis cannot be established in other ways, or to screen family members when the mutation in *ATP7B* in the proband is known.

Hyperintensities in the bilateral BG ,BSand thalami shown by T2-weighted MRI of the brain



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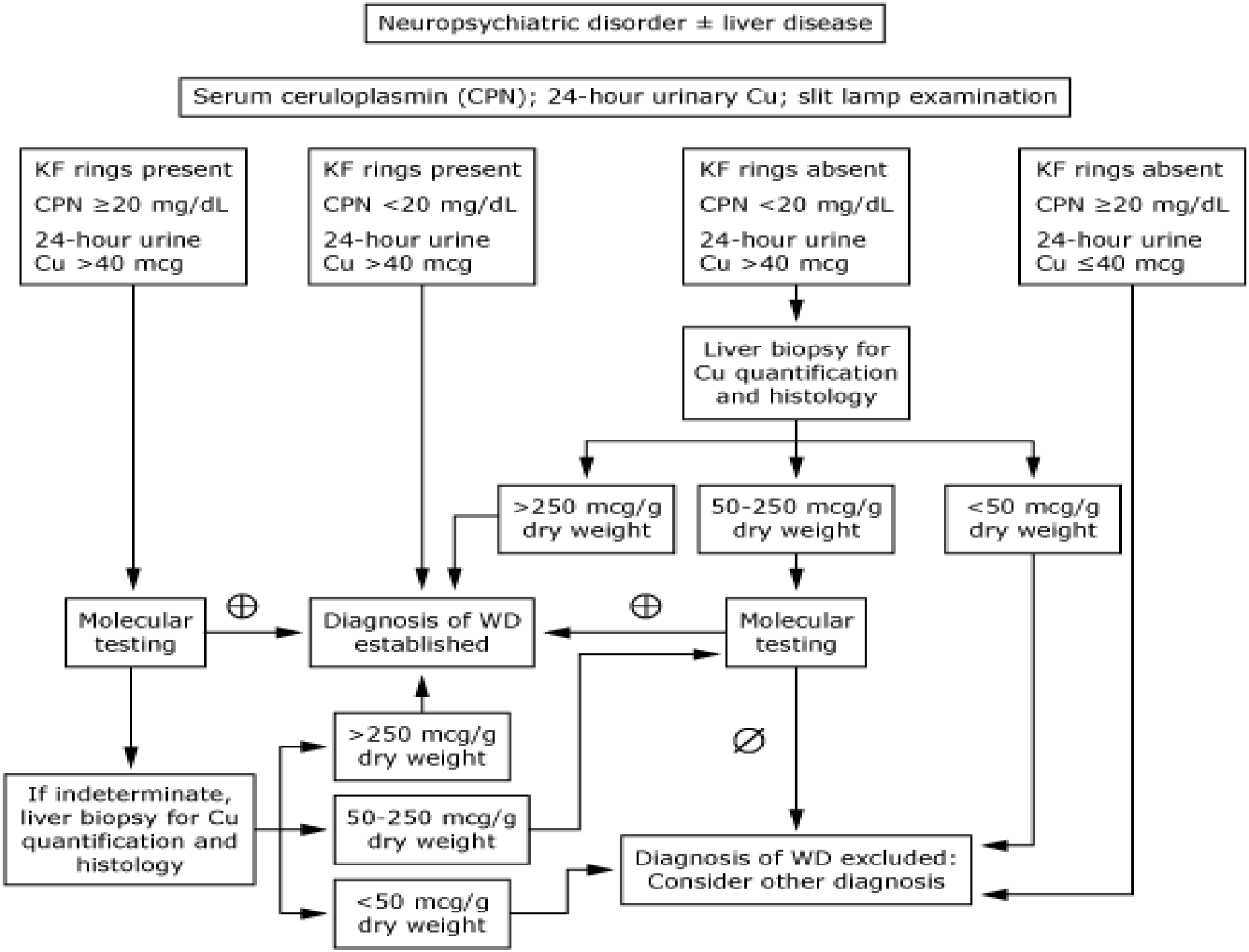
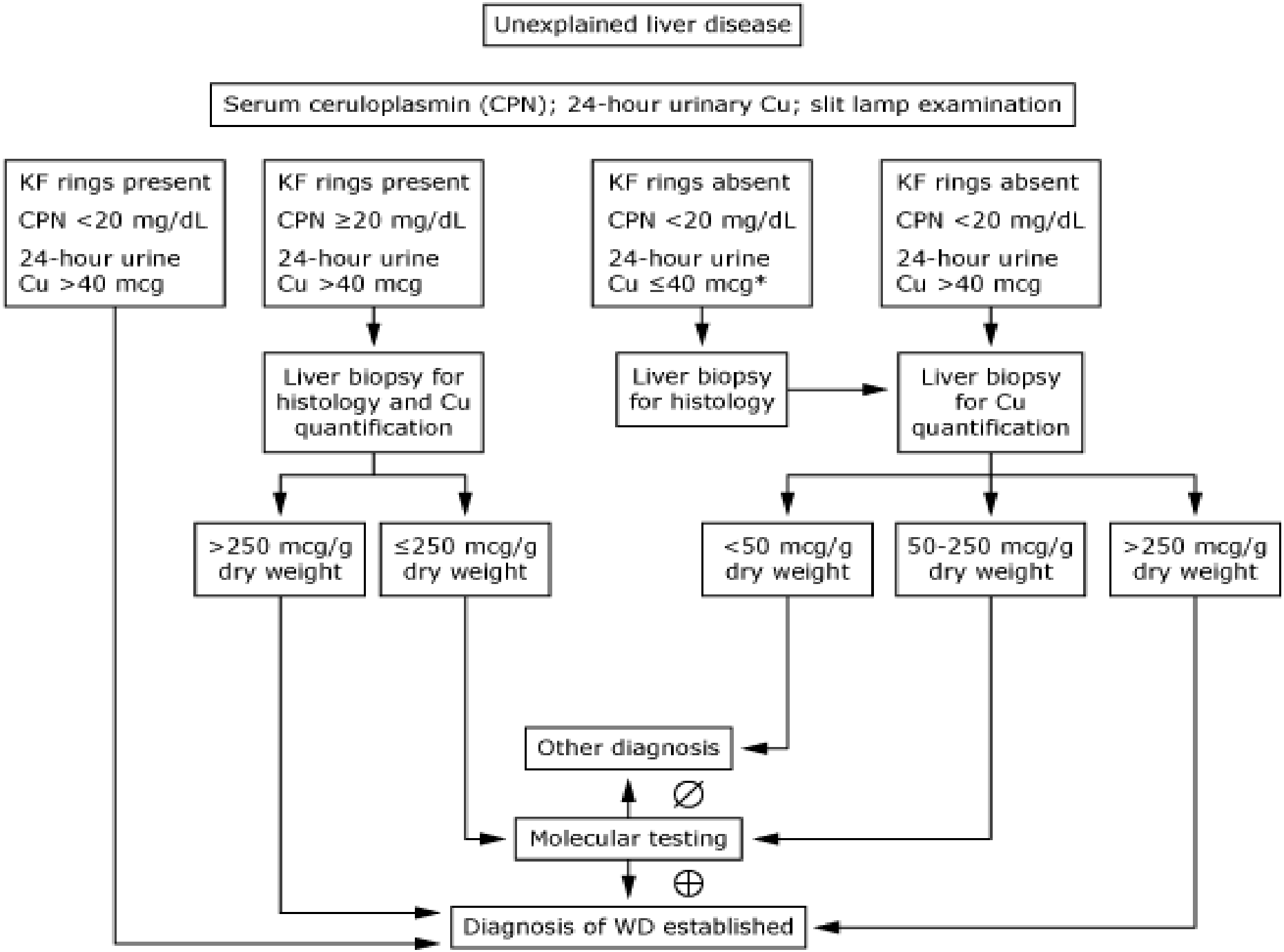

Neuropsychiatric disorder ± liver disease
Serum ceruloplasmin (CPN); 24-hour urinary Cu; slit lamp examination
KF rings present
CPN ≥20 mg/dL
24-hour urine Cu >40 mcg
KF rings present
CPN <20 mg/dL
24-hour urine Cu >40 mcg
KF rings absent
CPN <20 mg/dL
24-hour urine Cu >40 mcg
KF rings absent
CPN ≥20 mg/dL
24-hour urine Cu ≤40 mcg
Liver biopsy for Cu quantification and histology
>250 mcg/g dry weight
50-250 mcg/g dry weight
<50 mcg/g dry weight
Molecular testing
⊕
Diagnosis of WD established
⊕
Molecular testing
>250 mcg/g dry weight
If indeterminate, liver biopsy for Cu quantification and histology
50-250 mcg/g dry weight
<50 mcg/g dry weight
∅
Diagnosis of WD excluded: Consider other diagnosis


Unexplained liver disease
Serum ceruloplasmin (CPN); 24-hour urinary Cu; slit lamp examination
KF rings present
CPN <20 mg/dL
24-hour urine
Cu >40 mcg
KF rings present
CPN ≥20 mg/dL
24-hour urine
Cu >40 mcg
KF rings absent
CPN <20 mg/dL
24-hour urine
Cu ≤40 mcg*
KF rings absent
CPN <20 mg/dL
24-hour urine
Cu >40 mcg
Liver biopsy for histology and Cu quantification
Liver biopsy for histology
Liver biopsy for Cu quantification
>250 mcg/g dry weight
≤250 mcg/g dry weight
<50 mcg/g dry weight
50-250 mcg/g dry weight
>250 mcg/g dry weight
Other diagnosis
∅
Molecular testing
⊕
Diagnosis of WD established

- **Electrocardiography**
- Resting electrocardiographic abnormalities include left ventricular or biventricular hypertrophy, early repolarization, ST segment depression, T-wave inversion, and various arrhythmias.

PET Scanning

Positron emission tomography (PET) scanning reveals a significantly reduced regional cerebral metabolic rate of glucose consumption in the cerebellum, striatum, and, to a lesser extent, in the cortex and thalamus.

PET scan analyses of patients with Wilson disease have also demonstrated a marked reduction in the activity of dopa-decarboxylase, indicative of impaired function of the nigrostriatal dopaminergic pathway.

These abnormalities improve with chelation therapy, indicating a reversible component of striatal neuron injury.

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DENMARK
SWEDEN
North Sea
Baltic Sea
NETH.
U.K.
GERMANY
POLAND
Leipzig
BELG.
LUX.
CZECH REP.
SLVK.
FRANCE
SWITZ.
AUSTRIA
HUNG.
ITALY

Table 5. Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001 [44].

Typical clinical symptoms and signs	
KF rings	
Present	2
Absent	0
Neurologic symptoms**	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>0.2 g/L)	0
0.1-0.2 g/L	1
<0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

Other tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>4 µmol/g)	2
0.8-4 µmol/g	1
Normal (<0.8 µmol/g)	-1
Rhodanine-positive granules*	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0

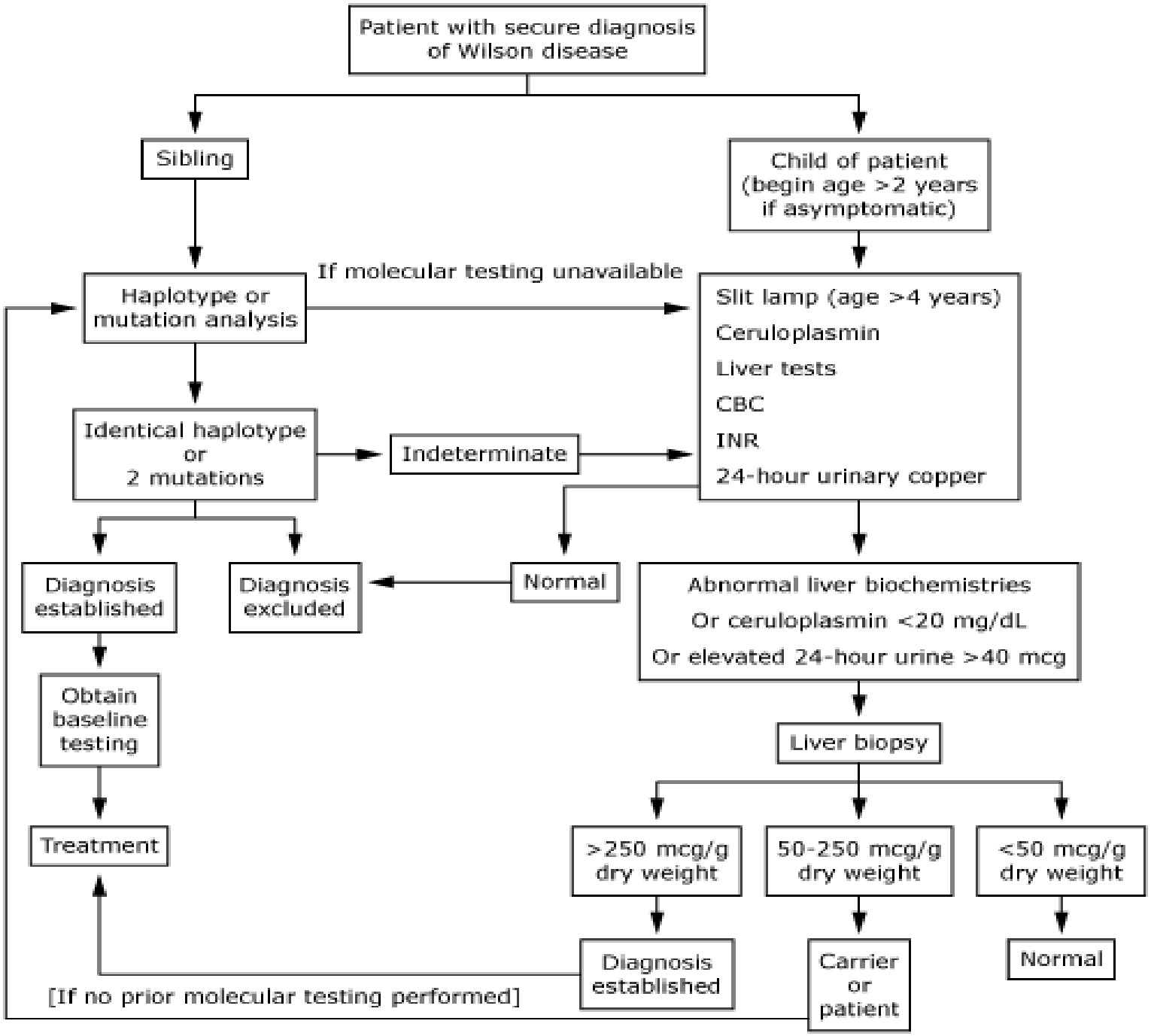
TOTAL SCORE	Evaluation:
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal.

AASLD recommendations for diagnosis and screening for Wilson disease (WD)

Clinical features:

- WD should be considered in any individual between the ages of 3 and *55** years with liver abnormalities of uncertain cause.
- Age alone should not be the basis for eliminating a diagnosis of WD.
- WD must be excluded in any patient with unexplained liver disease along with neurological or neuropsychiatric disorder.
- In a patient in whom WD is suspected, Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner.
- The absence of Kayser-Fleischer rings does not exclude the diagnosis of WD, even in patients with predominantly neurological disease.


Patient with secure diagnosis of Wilson disease
Sibling
Child of patient (begin age >2 years if asymptomatic)
If molecular testing unavailable
Haplotype or mutation analysis
Slit lamp (age >4 years)
Ceruloplasmin
Liver tests
CBC
INR
24-hour urinary copper
Identical haplotype or 2 mutations
Indeterminate
Diagnosis established
Diagnosis excluded
Normal
Abnormal liver biochemistries
Or ceruloplasmin <20 mg/dL
Or elevated 24-hour urine >40 mcg
Obtain baseline testing
Liver biopsy
Treatment
>250 mcg/g dry weight
50-250 mcg/g dry weight
<50 mcg/g dry weight
Diagnosis established
Carrier or patient
Normal
[If no prior molecular testing performed]

Screening family members of patients with Wilson's disease

Table 2 Screening family members of patients with Wilson's disease.

Tests	Homozygous or compound heterozygous		Heterozygous carrier	Non-carrier
	Symptomatic	Presymptomatic		
Clinical examination[a]	Might have either early hepatic or neurological features	Hepatomegaly in 38% of cases	No apparent clinical abnormality	Normal
Slit lamp examination for KF ring[a]	Commonly positive in neuropsychiatric presentations and in 50% of hepatic presentation	Positive KF ring in about 1/3 of cases	Usually negative	Negative
Serum ceruloplasmin level[a]	Low in about 85% of cases	Same as symptomatic	Low (<15 mg%) in about 15–20% of cases	Normal
Genetic analysis (haplotypic)[a]	Mutation in both Wilson's disease genes	Same as symptomatic	Abnormal mutation in one gene	No mutational change
24-hour urinary copper excretion	Usually high (>100 µg)	Same as symptomatic	Normal	Normal (20–50 µg)
Neuroimaging of brain	Commonly abnormal in neuropsychiatric presentation	Abnormal in 25% of cases	Normal	Normal

[a]Commonly used tests for family screening. Abbreviation: KF, Kayser–Fleischer.

Das SK and Ray K (2006) Wilson's disease: an update
Nat Clin Pract Neurol 2: 482–493 10.1038/ncpneuro0291

nature CLINICAL PRACTICE NEUROLOGY

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Anti-copper drugs used in the treatment of Wilson's disease

Table 3 Anti-copper drugs used in the treatment of Wilson's disease.

Drug	Mechanism of action	Dose	Toxicity
Zinc acetate	Blockage of copper absorption by inducing metallothionein in enterocytes	150 mg/day of elemental zinc in three divided doses	Mild abdominal discomfort in 10% of patients
Trientine	Chelation and urinary excretion of copper	1 g/day in three divided doses (range 750–2,000 mg)	Sideroblastic anemia. Autoimmune disorders same as D-penicillamine but occur less frequently
D-Penicillamine	Chelation and urinary excretion of copper	0.75–1.5 g/day (children: 20 mg/kg/body weight)	Initial neurological worsening, acute hypersensitivity, proteinuria. Delayed side effects: Goodpasture's syndrome, polymyositis, neuropathy and neuromuscular junction defect, systemic lupus erythematosus, bone marrow suppression effects on immune system, collagen and on skin during prolonged therapy (aging effect)
Ammonium tetrathiomolybdate	Complex with copper and protein within intestine and circulation, thereby detoxifying copper in plasma and blocking copper absorption from the intestine	2–3 mg/kg/body weight given in six doses along with meal and in the interval between meals	Overtreatment produces reversible anemia. Long-term safety and efficacy unknown

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nature CLINICAL PRACTICE NEUROLOGY

D-penicillamine

Therapeutic indications

a) Severe, active rheumatoid arthritis, including juvenile forms

b) Wilson's disease (hepatolenticular degeneration) in adults and children (0 to 18 years)

c) Cystinuria-dissolution and prevention of cystine stones in adults and children (0 to 18 years)

d) Lead poisoning in adults and children (0 to 18 years)

e) Chronic active hepatitis in adults

D-penicillamine

- *Adults:* 1500 to 2000mg daily in divided doses. The optimum dose to achieve a negative copper balance (measured by analysis of 24 hour urinary copper excretion and subsequently by monitoring free copper in the serum) should be chosen.
- The dose may be reduced to 750-1000 mg daily when disease control is achieved as evidenced by urinary copper excretion.
- A dose of 2000mg daily should not be continued for more than one year.

D-penicillamine

- *Children:* 20mg/kg/day in two or three divided doses, given 1 hour before meals.
- For older children (>12 years) the usual maintenance dose is 0.75-1g daily.
- *Elderly:* Up to 20 mg per kg body weight daily in divided doses. The dosage should be adjusted to minimal level necessary achieve disease control.
- *Renal Insufficiency:* Extra precautions should be taken to monitor for adverse effects in patients with Wilson's disease and renal insufficiency.

D-penicillamine

Both the frequency and severity of many side-effects and adverse reactions to penicillamine are found to be **dose-related** and vary according to the nature of the disease under treatment.

hence the importance of initiating therapy at **low doses and gradually increasing the quantity** of drug given to optimum level.

D-penicillamine

- Penicillamine should not be given with other drugs capable of causing similar serious haematological or renal adverse effects, for example gold salts, chloroquine, clozapine or hydroxychloroquine, or immunosuppressive drugs.
- Patients who are allergic to penicillin may react similarly to penicillamine, but cross-sensitivity appears to be rare.

D-penicillamine

- Because of the potential for serious haematological and renal adverse reactions to occur at any time full blood count and urinalysis should be performed weekly for at least the first 2 months of therapy, (or after any change in dose) and should be repeated monthly thereafter.

D-penicillamine

- Patients should be instructed to report promptly the development of signs and symptoms of granulocytopaenia and/or thrombocytopenia such as fever, chills, sore throat, easy bruising or unexplained bleeding, mouth ulcers or rashes. Laboratory tests should be repeated in this case.

- Consider withdrawing therapy if platelet count falls below 120 000/mm^3 or WBC below 2500/mm^3, or if either parameter shows 3 successive falls within the reference range.
- Therapy can be re-introduced at a lower dose, when the count returns to normal, but should be discontinued permanently if neutropaenia or thrombocytopenia recurs.

D-penicillamine

- Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage
- In the treatment of rheumatoid arthritis, response to penicillamine is often slow and the use of existing analgesics, anti-inflammatories or steroids should be continued and later gradually withdrawn, subject to patient improvement.

D-penicillamine

- Pyridoxine 25 mg daily may be given to patients taking penicillamine for long periods, especially if they are on a restricted diet, (e.g. Wilson's disease or cystinuria) since penicillamine increases the requirement for this vitamin

D-penicillamine

- It has been suggested that doses of penicillamine should be reduced to 250 mg daily for 6 weeks prior to elective surgery because of possible effects of penicillamine on collagen and elastin (and thereby on wound healing).

D-penicillamine

- Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended.
- Haematuria is rare but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately.
- A late rash, described as "acquired epidermolysis bullosa" and "penicillamine dermopathy" may occur, after several months or years of therapy and may necessitate discontinuation of treatment

D-penicillamine

- Breast enlargement has been reported as a rare complication of penicillamine therapy in both women and men.

- Danazol has been used successfully to treat breast enlargement which does not regress on drug discontinuation.

D-penicillamine

Early side effects

- a hypersensitivity reaction characterized by fever, skin rash and lymphadenopathy that commonly occurs within 3 weeks of commencing medication.
- An early hypersensitivity reaction can be managed by temporary withdrawal of the drug, followed by its reintroduction after a course of oral steroids.

D-penicillamine

Early side effects

- In 20–30% of cases, an exacerbation of the neurological symptoms occurs over a period of 2 weeks to 12 months (commonly after 6 weeks).

- This occurrence is caused by the rapid mobilization of liver copper in the circulation, and can sometimes be permanent.

-

- Neurological deterioration can be attenuated by withdrawing the drug, and then reinstituting it at a smaller dosage with a slow escalation to the optimum dosage. If neurological deterioration recurs, D-penicillamine should be withdrawn and substituted with other chelators or zinc salt alone.

D-penicillamine

Delayed side effects

- side effects occur in about 5% of cases, and can be caused by immunological factors, interference with collagen and elastin synthesis, or idiopathic factors .
- Immunological side effects are managed with steroids and a reduction in the D-penicillamine dosage. In cases in which the patient cannot tolerate treatment with D-penicillamine, trientine can be used as a substitute, which is usually effective except in cases with systemic lupus erythematosus or elastosis perforans.

D-penicillamine

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: Very common (> 1/10), Common (1/100, < 1/10), Uncommon (1/1000, < 1/100), Rare (1/10,000, < 1/1000), Very rare (< 1/10,000), including isolated reports. Not known (where no valid estimate of the incidence has been derived)

D-penicillamine

Blood and lymphatic system disorders:

Common: Thrombocytopenia

Not known: Neutropenia[8], agranulocytosis[1], aplastic anaemia[1], haemolytic anaemia, leucopoenia

Immune system disorders:

Rare: Allergic reactions including hypersensitivity

Metabolism and nutrition disorders:

Not known: Anorexia[2]

Psychiatric disorders:

Not known: Confusion[2]

Nervous system disorders:

Not known: Loss of taste[4], headache[2], dizziness[2]

Eye disorders:

Not known: Abnormal vision[2]

D-penicillamine

Ear and labyrinth disorders:

Rare: Deafness

Vascular disorders:

Not known: Pulmonary haemorrhage

Respiratory, thoracic and mediastinal disorders:

Not known: Dyspnoea, pleural effusion, alveolitis, pulmonary fibrosis, bronchiolitis, pneumonitis

Gastrointestinal disorders:

Rare: Mouth ulceration, stomatitis, glossitis

Not known: Pancreatitis, nausea, vomiting, diarrhoea.

Hepatobiliary disorders:

Not known: Cholestatic jaundice

D-penicillamine

Blood and lymphatic system disorders:Skin and subcutaneous tissue disorders:

Rare: Alopecia, pseudoxanthoma elasticum, elastosis perforans, skin laxity

Not known: Rash[2], urticarial reactions[3], epidermolysis bullosa[6], penicillamine dermopathy[6], dermatomyositis, pemphigus, Stevens-Johnson syndrome.

Musculoskeletal, connective tissue and bone disorders:

Not known: Drug induced lupus erythamatosus, myasthenia gravis, polymyositis, rheumatoid arthritis

Renal and urinary disorders:

Very common: Proteinuria

Rare: Haematuria[5]

D-penicillamine

Reproductive system and breast disorders:

Rare: Breast enlargement[7]

General disorders and administration site conditions:

Not known: Fever

D-penicillamine

Blood and lymphatic system disorders:Skin and subcutaneous tissue disorders:

Rare: Alopecia, pseudoxanthoma elasticum, elastosis perforans, skin laxity

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Renal and urinary disorders:

Very common: Proteinuria

Rare: Haematuria·

Long-Term Monitoring

- Perform a physical examination, 24-hour urinary copper excretion assay, complete blood count (CBC), urinalysis, serum free copper measurement, and renal and liver function tests on a weekly basis for the first 4-6 weeks following initiation of chelation therapy.
- The best way to monitor efficacy is to measure serum nonceruloplasmin-bound copper. This is measured by the following formula: Total serum copper (mcg/dL) - 3[ceruloplasmin (mg/dL)]. The reference range is less than 15 mcg/dL.

Long-Term Monitoring

- An adjunctive way to monitor efficacy is to measure urinary copper excretion. Urinary chelator levels usually measure 200-500 mcg/day. Urinary zinc levels usually measure less than 75 mcg/day.
- Bimonthly evaluations are recommended through the first year, followed by yearly examinations thereafter. In patients with Kayser-Fleischer rings, a yearly slit-lamp examination should document fading or disappearance if patients are being adequately "decoppered."

Long-Term Monitoring

- Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease.
- This is one of the major causes of fulminant liver failure.
- Patients must avoid most alcohol consumption and potential hepatotoxic drug therapy.

Diet

- Patients should generally avoid eating foods with a high copper content, such as liver, chocolate, nuts, mushrooms, legumes, and shellfish (especially lobster).

- Drinking water from atypical sources (eg, well water) should be analyzed for copper content and replaced with purified water if the copper content is greater than 0.2 parts per million.

Pregnancy

- Excessive intrauterine copper concentrations may be responsible for the high rate of spontaneous abortions in patients with Wilson disease.

- D-penicillamine (0.75-1.5 g/day) appears to pose no major risk to the fetus and should be continued throughout the pregnancy.

Pregnancy

- Abrupt cessation of the drug treatment can be fatal. If the patient is completely free of toxic copper, she should be advised to take only zinc salt.
- Although D-penicillamine and trientine are potentially teratogenic, there are currently insufficient data concerning their teratogenic effects in pregnant patients with WD to warrant cessation of treatment.

Trientine

- safer alternatives
- a less potent copper remover

Ammonium tetrathiomolybdate

- Ammonium tetrathiomolybdate, an agent previously used to treat copper toxicosis in animals, has been advocated because of its lower toxic profile, but it is still an experimental drug that is not routinely available, and its long-term safety and efficacy is unknown.

Hepatic transplantation

- progressive liver failure
- acute liver failure from fulminant hepatitis with or without intravenous hemolysis.
- also indicated in the absence of liver failure in patients with neurological WD in whom chelation therapy has proved ineffective, and significant improvements in neurological features have been reported, which include the disappearance of the KF ring.

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Prognosis

- WD has a fatal outcome if not treated appropriately and in a timely manner.

- Symptomatic WD patients require lifelong treatment, because an interruption to therapy or inadequate treatment can lead to fatalities within 9 months to 3 years.

Prognosis

- The severity of disease at the start of treatment determines the level of disability, and an early onset is worse than a late onset in terms of prognosis.

- If treatment is begun early enough, symptomatic recovery is usually complete, leading to a normal life expectancy. Residual dysarthria and mild dystonia are relatively common in neurological WD (SK Das, personal experience).

- A prognostic index using the Nazer score has been proposed to differentiate between fatal and nonfatal cases of WD, and is based on the severity of the abnormality of serum aspartate aminotransferase, bilirubin and prothrombin time at admission.

http://www.wilsonsdisease.org/


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THANK YOU