TABLE 429-1 USEFUL TESTS FOR WILSON'S DISEASE

Test	Usefulness[a]	Normal Value	Heterozygous Carriers	Wilson's Disease
Serum ceruloplasmin	+	180–350 mg/L (18–35 mg/dL)	Low in 20%	Low in 90%
Kayser- Fleischer rings	++	Absent	Absent	Present in >99% if neurologic or psychiatric symptoms are present Present in 30–50% in hepatic presentation and presymptomatic state
Urine copper (24-h)	+++	0.3–0.8 μmol (20–50 μg)	Normal to 1.3 μmol (80 μg)	>1.6 μmol (>100 μg) in symptomatic patients; 0.9 to >1.6 μmol (60 to >100 μg) in presymptomatic patients
Liver copper	++++	0.3–0.8 μmol/g (20–50 μg/g of tissue)	Normal to 2.0 μmol (125 μg)	>3.1 μmol (>200 μg) (Obstructive liver disease can cause false-positive results.)
Haplotype analysis	++++ (siblings only)	0 matches	1 match	2 matches

[a]Usefulness range: + (somewhat useful) to ++++ (very useful).

For patients with hepatitis or cirrhosis but without evidence of hepatic decompensation or neurologic/psychiatric symptoms, zinc is the therapy of choice although some experts advocate therapy with trientine. Zinc has proven efficacy in Wilson's disease and is essentially nontoxic. It produces a negative copper balance by blocking intestinal absorption of copper, and it induces hepatic metallothionein synthesis, thereby sequestering additional toxic copper. All presymptomatic patients should be treated prophylactically because the disease is close to 100% penetrant.

The first step in evaluating patients presenting with hepatic decompensation is to establish disease severity, which can be estimated with the Nazer prognostic index **(Table 429-3)**. Patients with scores <7 can usually be managed with medical therapy. Patients with scores >9 should be considered immediately for liver transplantation. For patients with scores between 7 and 9, clinical judgment is required in deciding whether to recommend transplantation or medical therapy. A combination of trientine and zinc has been used to treat patients with Nazer scores as high as 9, but such patients should be watched carefully for indications of hepatic deterioration, which mandates transplantation.

For initial medical treatment of patients with hepatic decompensation, the recommended regimen is a chelator (preferably trientine) plus zinc (Table 429-2). Zinc should not, however, be ingested simultaneously with trientine, which chelates zinc and forms therapeutically ineffective complexes. Administration of the two drugs should be separated by at least 1 h.

For initial neurologic therapy, tetrathiomolybdate is emerging as the drug of choice because of its rapid control of free copper, preservation of neurologic function, and low toxicity. Penicillamine and trientine should be avoided because both have a high risk of worsening the neurologic condition. Until tetrathiomolybdate is commercially available, zinc therapy is recommended. Although it is relatively slow-acting, zinc itself does not exacerbate neurologic abnormalities. Although hepatic transplantation may alleviate neurologic symptoms, it does so only by copper removal, which can be done more safely and inexpensively with anticopper drugs. Pregnant patients should be treated with zinc or trientine throughout pregnancy but without tight copper control because copper deficiency can be teratogenic.

Anticopper therapy must be lifelong. With treatment, liver function usually recovers after about a year although residual liver damage is usually present. Neurologic and psychiatric symptoms usually improve after 6–24 months of treatment.

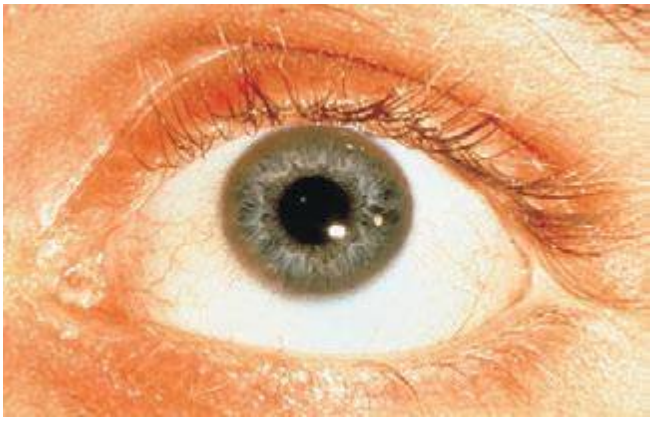

FIGURE 429-1 A Kayser-Fleischer ring. Although in this case, the brownish ring rimming the cornea is clearly visible to the naked eye, confirmation is usually made by slit-lamp examination.

MONITORING ANTICOPPER THERAPY

When trientine or penicillamine is first used, it is necessary to monitor for drug toxicity, particularly bone marrow suppression and proteinuria. Complete blood counts, standard biochemical profiles, and a urinalysis should be performed at weekly intervals for 1 month, then at twice-weekly intervals for 2 or 3 months, then at monthly intervals for 3 or 4 months, and at 4- to 6-month intervals thereafter.

The anticopper effects of trientine and penicillamine can be monitored by following 24-h "free" serum copper levels. Changes in urine copper levels are more difficult to interpret because excretion reflects the effect of the drug as well as body loading with copper. Free serum copper is calculated by subtracting the ceruloplasmin copper from

TABLE 429-2 RECOMMENDED ANTICOPPER DRUGS FOR WILSON'S DISEASE

Disease Status	First Choice	Second Choice
Initial hepatic		
Hepatitis or cirrhosis without decompensation	Zinc[a]	Trientine
Hepatic decompensation		
Mild	Trientine[b] and zinc	Penicillamine[b] and zinc
Moderate	Trientine and zinc	Hepatic transplantation
Severe	Hepatic transplantation	Trientine and zinc
Initial neurologic/ psychiatric	Tetrathiomolybdate[c] and zinc	Zinc
Maintenance	Zinc	Trientine
Presymptomatic	Zinc	Trientine
Pediatric	Zinc	Trientine
Pregnant	Zinc	Trientine

[a]Zinc acetate is supplied as Galzin, manufactured by Gate Pharmaceutical. The recommended adult dose for all the above indications is 50 mg of elemental zinc three times daily, with each dose separated by at least 1 h from consumption of food and beverages other than water as well as from trientine or penicillamine doses. [b]Trientine is supplied as Syprine and penicillamine as Cuprimine, both manufactured by Merck. The recommended adult dosage for both drugs is 500 mg twice daily, with each dose at least 0.5 h before or 2 h after meals and separated by at least 1 h from zinc administration. [c]Tetrathiomolybdate is being studied in clinical trials.