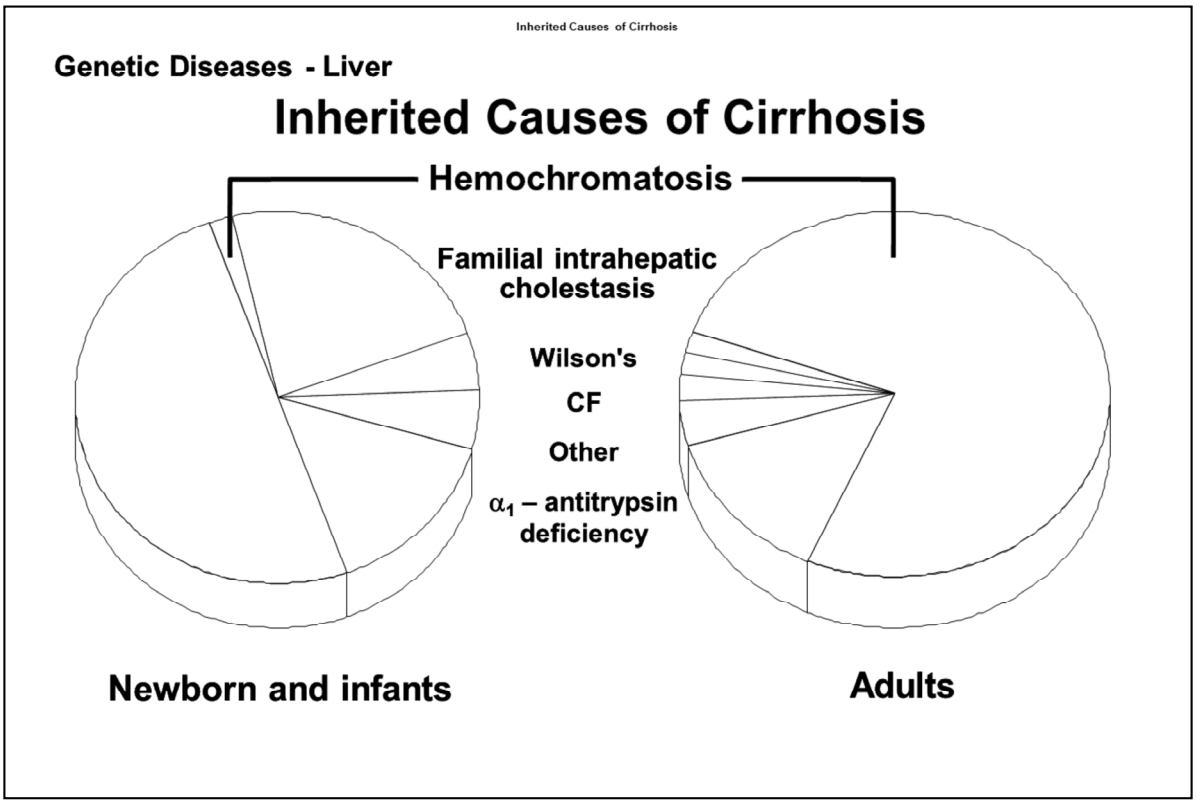


Inherited Causes of Cirrhosis

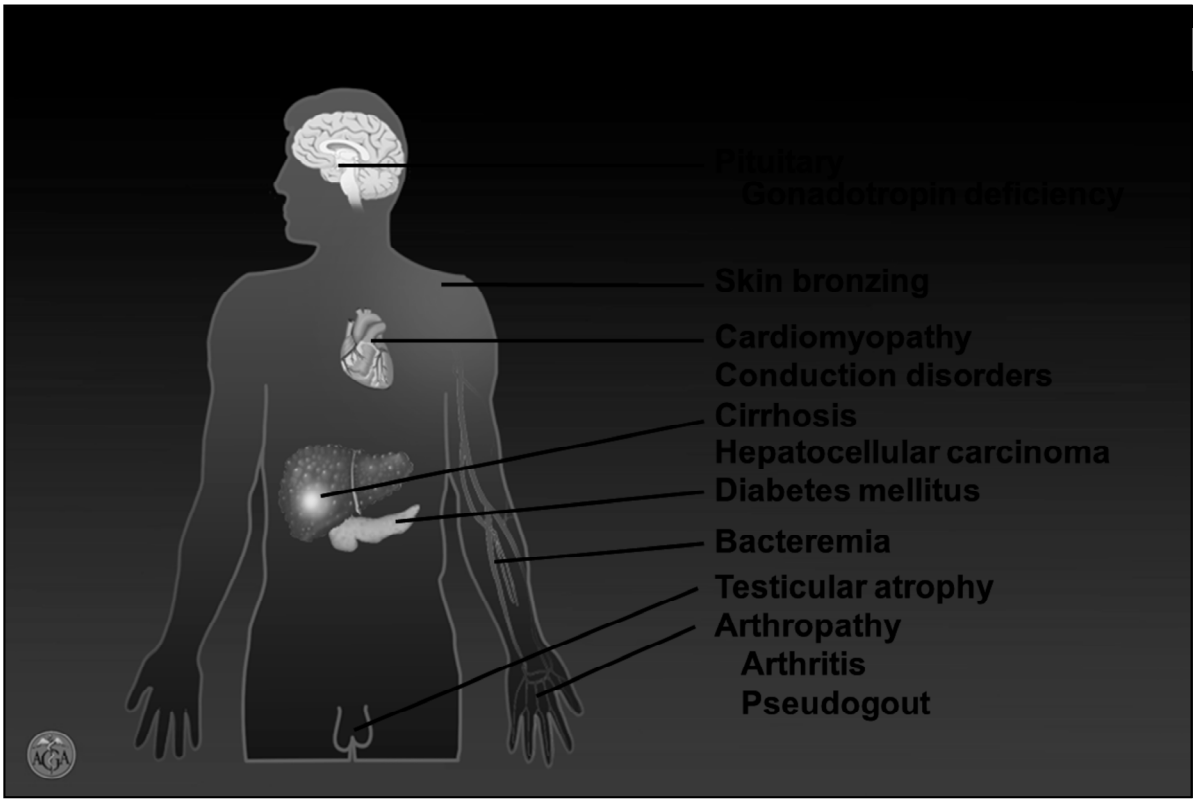
Cirrhosis due to an inherited disease can present at any age. Certain disorders are more likely to result in disease in infants, others in adults. For example, α_1-antitrypsin deficiency with the homozygous Z phenotype is the most common cause of the syndrome of neonatal hepatitis. Severely ill infants require liver transplantation or will die in childhood. Infants who are less severely affected may have resolution of their jaundice, to be followed by signs of portal hypertension later in childhood or in adolescence. In adulthood, an abnormal α_1-antitrypsin phenotype is less likely to be the cause of cirrhosis. In this age group, α_1-antitrypsin associated disease presents primarily as cryptogenic cirrhosis or hepatocellular carcinoma. On the other hand, hemochromatosis is a more frequent cause of cirrhosis in adulthood, but does not cause cirrhosis in infancy and childhood. Wilson's disease presents after the age of six and should be considered as a possible cause of liver disease in any adolescent or young adult. Cases presenting as late as the fifth decade are well-documented. Cystic fibrosis usually presents in childhood, but rarely may be first diagnosed in early adulthood. The familial intrahepatic cholestatic syndromes, including Alagille's syndrome, Byler's syndrome or progressive intrahepatic cholestasis, Norwegian cholestasis, and North American Indian cholestasis, almost invariably present in infancy or childhood. Rare cases may survive, however, into adulthood, and benign recurrent intrahepatic cholestasis and cholestasis of pregnancy, which may be members of this family of disorders,

occur in adults. In infants and children, other causes of cirrhosis include tyrosinemia, galactosemia, and glycogen storage disease. These are much less common in adults.

Leonis MA, Balistreri WF. In Sleisenger & Fordtran's Gastrointerestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. 2002; 65: 1240-1260.

Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointerestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. 2002; 66: 1261-1268.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointerestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. 2002; 67: 1269-1277.



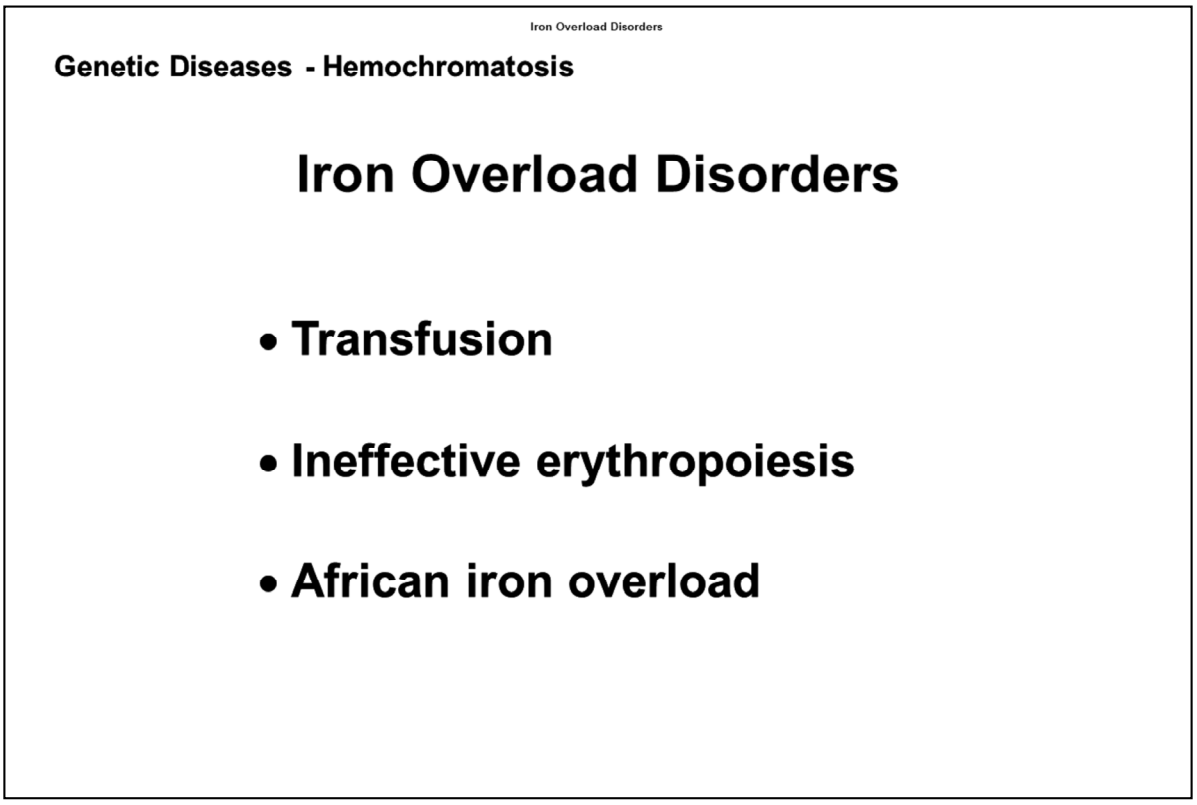
Clinical Manifestations

Most patients having symptomatic disease are diagnosed at age 40 to 50 years. The iron overload of hemochromatosis results in iron deposition in multiple organs. The total body iron stores are increased by a factor of 5 to 8, resulting in a total body iron of 20 to 40 gm. Excessive skin melanin, together with iron deposition in the skin, leads to bronzing of the skin. Excess iron in heart tissue can result in a dilated cardiomyopathy and congestive heart failure and/or in conduction disturbances and arrhythmias. The iron overload in the liver often causes insidious damage with mild serum aminotransferase elevations, progressing to cirrhosis if not treated. The incidence of hepatocellular carcinoma is high, over 200 times that of the normal population, and this complication is reported to occur in as many as 20 to 40% of affected patients. Iron is also deposited in the pancreas and diabetes mellitus is a common result. The arthropathy associated with hemochromatosis involves primarily the metacarpophalangeal and proximal interphalangeal joints. Affected patients also have chondrocalcinosis. Patients with hemochromatosis are also at increased risk for infection with unusual pathogens, such as *Vibrio vulnificus, Listeria monocytogenes, Yersinia enterocolitica* and *Yersinia pseudotuberculosis*.

The figure illustrated here is a man, as hemochromatosis becomes clinically manifest earlier in men, usually in the late 40's to early 50's. Women are partially

protected by blood loss during the menstrual cycle, and present later in life, usually in their 60's.

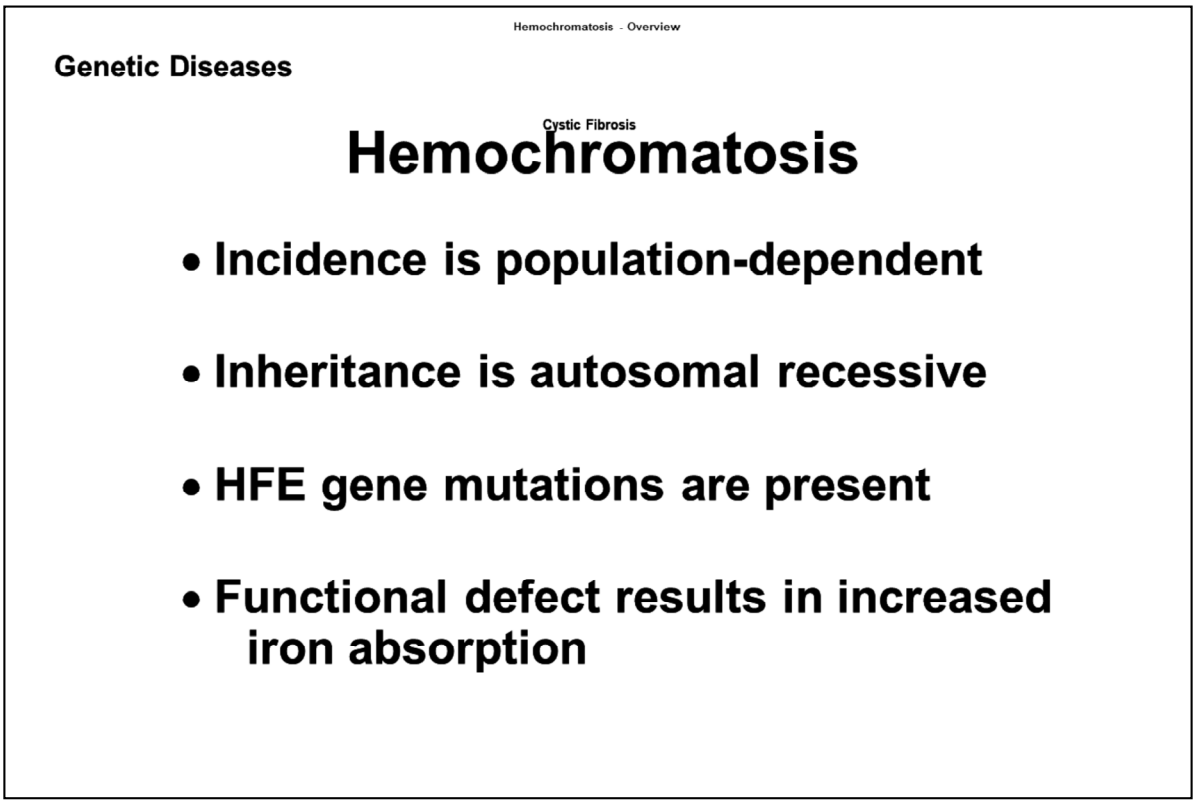
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointerestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. 2002; 66: 1261-1268.



Iron Overload Disorders

Iron overload can be either primary, due to an inherited defect in iron homeostasis, or secondary. The typical primary iron overload disorder is hemochromatosis, which is inherited as an autosomal recessive trait due to a defective gene carried on the short arm of chromosome 6. The causes of secondary iron overload are exogenous administration of excess iron due to transfusions or diet (i.e. patients being frequently transfused or excess iron administration). Secondary overload may also result from hyperabsorption of iron in response to chronic anemia or ineffective erythropoiesis, such as sideroblastic anemia or thalassemia.

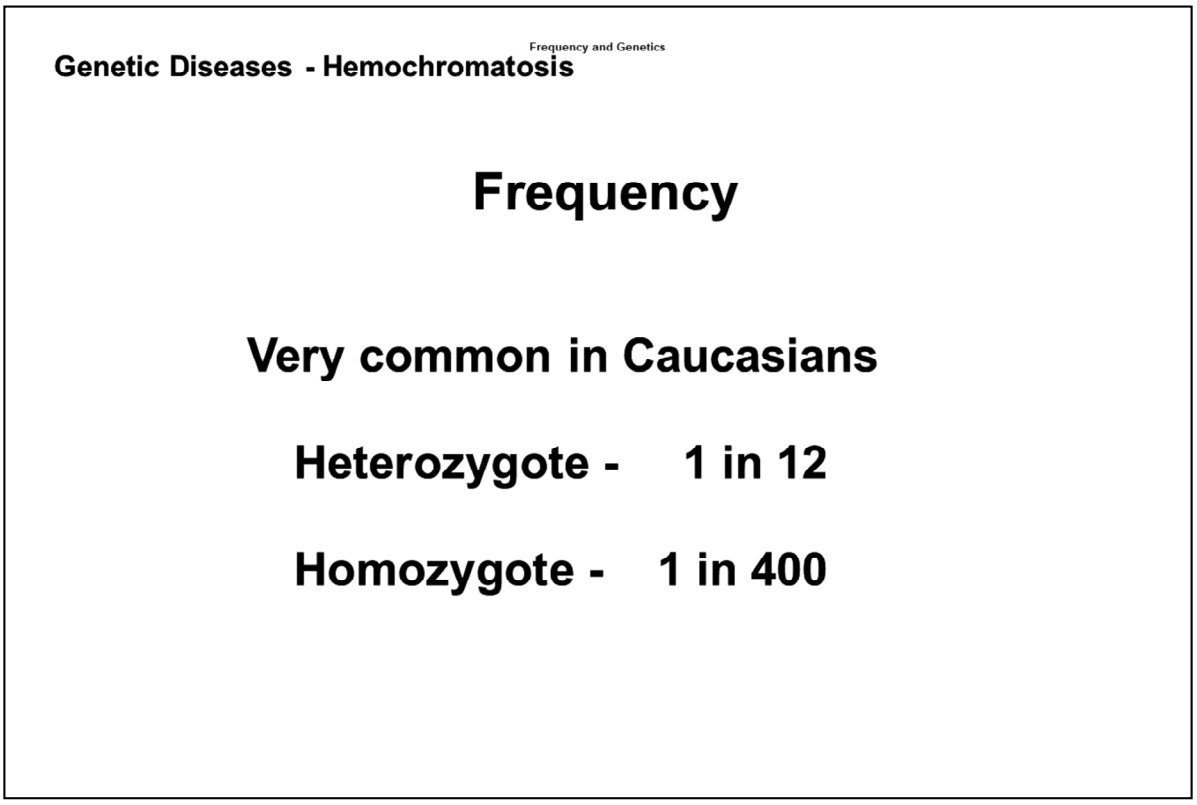
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Hemochromatosis - Overview

Hemochromatosis incidence varies by population (i.e. high incidence in northern European countries and low incidence in Asia, Africa, Middle East, Australia); inheritance is autosomal recessive and due to specific genetic mutations in HFE located on the short arm of chromosome 6. This mutation results in increased iron absorption resulting in excess iron content in tissues with resulting tissue injury and organ failure if not identified and treated. The expression of the disease phenotype is variable and dependent on dietary iron intake and iron loss.

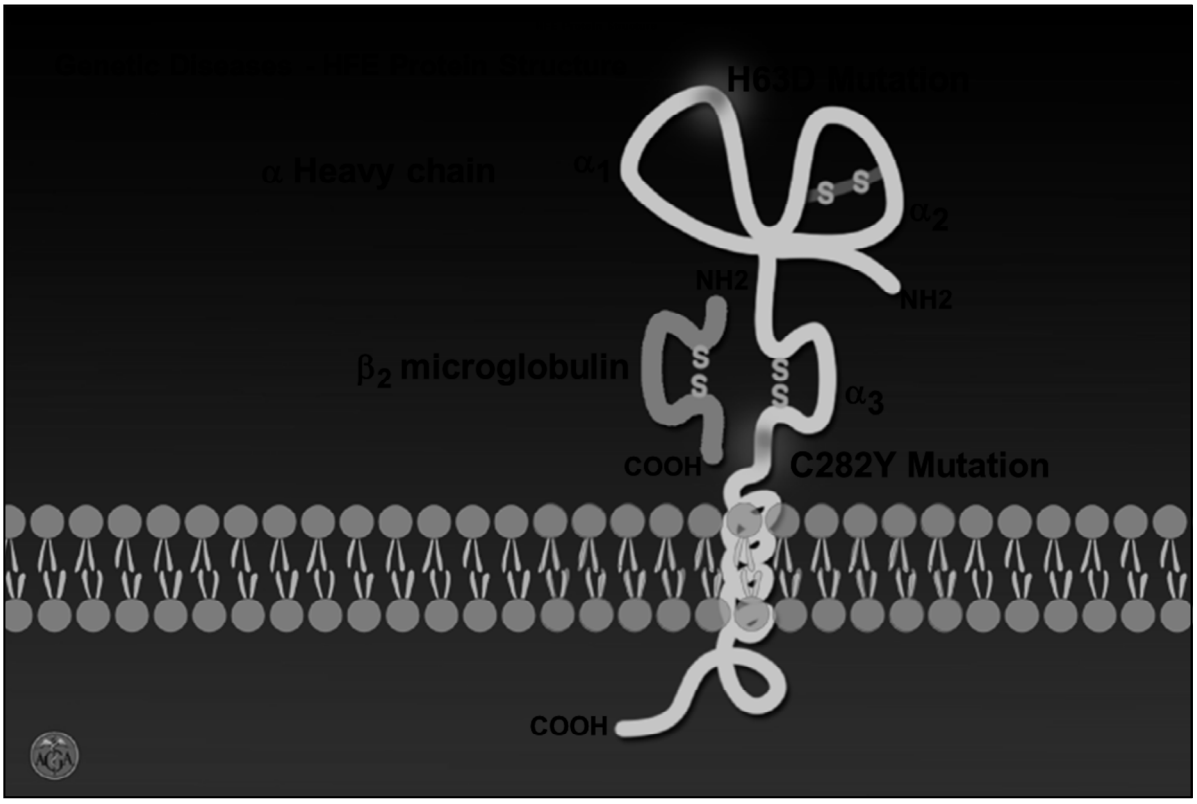
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Frequency and Genetics

Hemochromatosis is inherited as an autosomal recessive trait and is very common in Caucasians: 1 in 400 individuals are homozygotes and 1 in 10-20 are heterozygotes. The frequency varies widely between populations. The defective gene is on the short arm of chromosome 6 and has been identified as HFE.

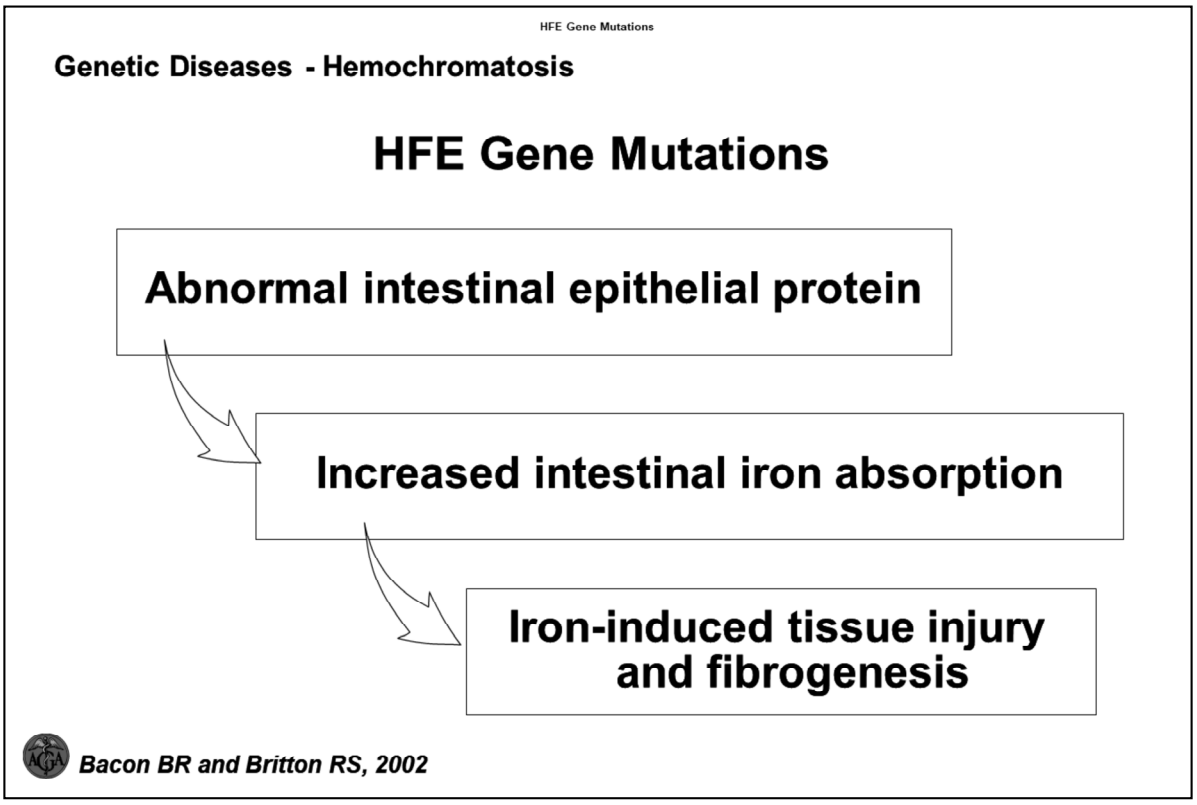
Bacon BR, Powell LW, Adams PC Kresina TF, Hoofnagle JH. Gastroenterology 1999; 116: 193-207.



HFE Protein Structure

The slide demonstrates a hypothetical model for HFE based on its homology with MHC molecules. Of note, there are three alpha domains, one of which binds to Beta2 microglobulin. The model shows the location of the two major HFE mutations, H63D and C282Y.

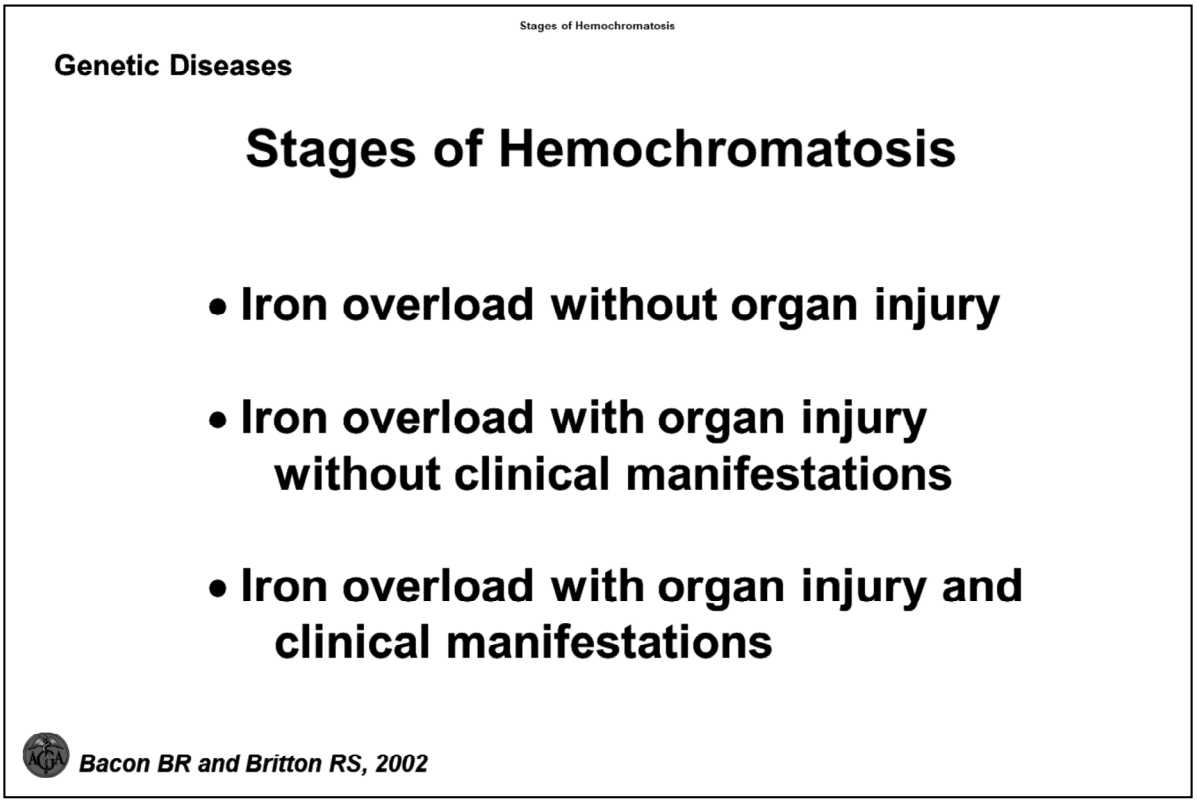
Bacon BR, Powell LW, Adams PC Kresina TF, Hoofnagle JH. Gastroenterology 1999; 116: 193-207.



HFE Gene Mutations

The slide demonstrates the sequence of events in subjects with genotypic hemochromatosis. Over time, patients have an inexorably increasing total body iron load. This begins at birth, due to mutations in HFE which lead to increased iron absorption. By age 10 the serum iron is elevated above the normal range, and by adolescence the hepatic iron is increased. Tissue injury due to the accumulated iron begins by the mid 30's in males, and organ dysfunction, including cirrhosis, diabetes, and cardiac disease, presents in the mid 40's or later.

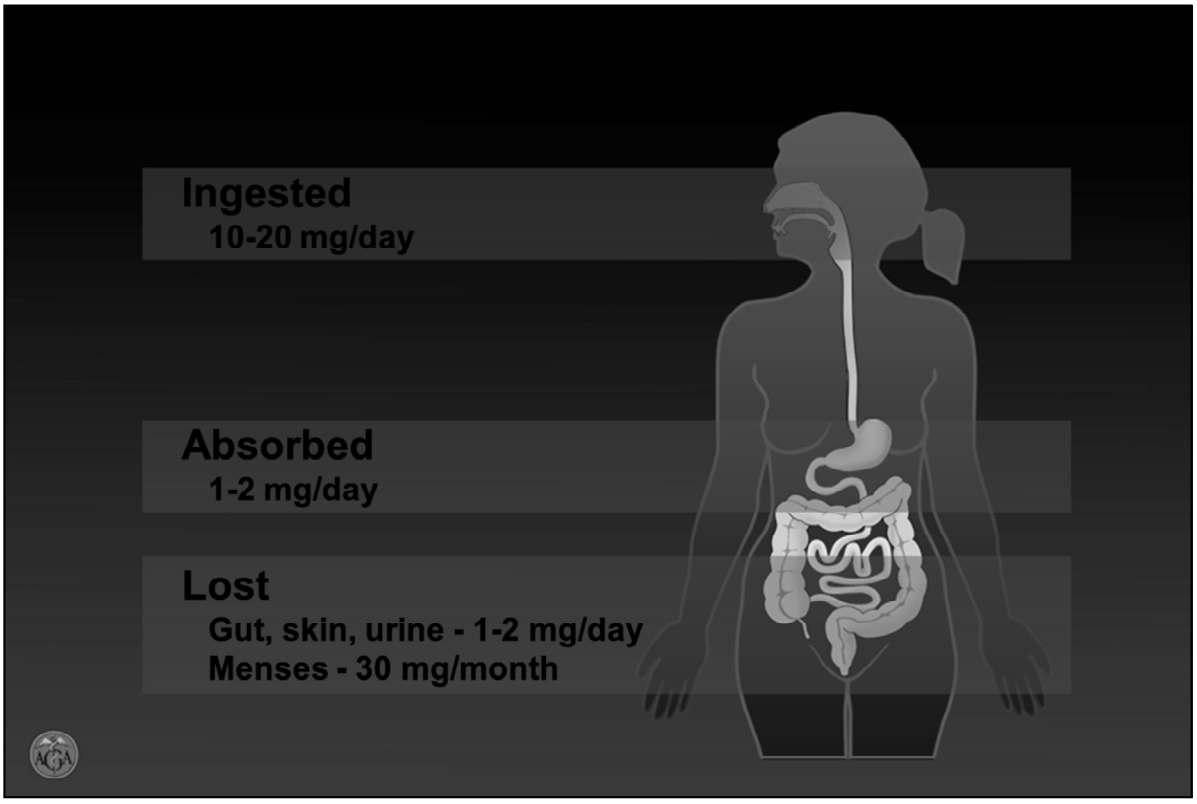
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Stages of Hemochromatosis

The slide demonstrates the sequence of events in subjects with genotypic hemochromatosis. Over time, patients have an inexorably increasing total body iron load. This begins at birth, due to mutations in HFE which lead to increased iron absorption. By age 10 the serum iron is elevated above the normal range, and by adolescence the hepatic iron is increased. Tissue injury due to the accumulated iron begins by the mid 30's in males, and organ dysfunction, including cirrhosis, diabetes, and cardiac disease, presents in the mid 40's or later.

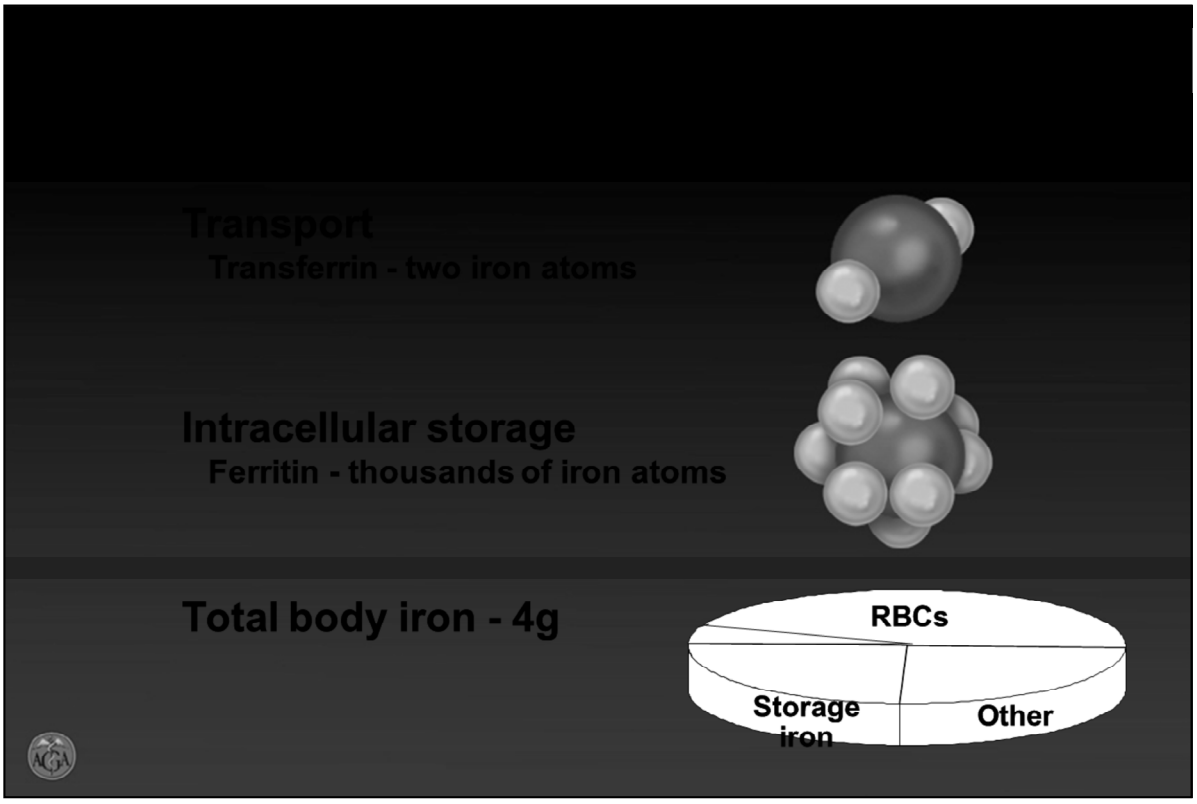
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Normal Iron Balance

Approximately 10 to 20 mg of iron are ingested each day from the diet. The intestinal mucosa forms an effective barrier to iron, however, and only one tenth of ingested iron (1 to 2 mg) is absorbed from the duodenum and upper jejunum into portal blood. Once absorbed, there are few routes for disposing of iron; 1 to 2 mg per day is shed via excretion in bile, cells sloughed by skin and gastrointestinal tract, and in the urine. Women lose approximately 30 mg per menstrual cycle.

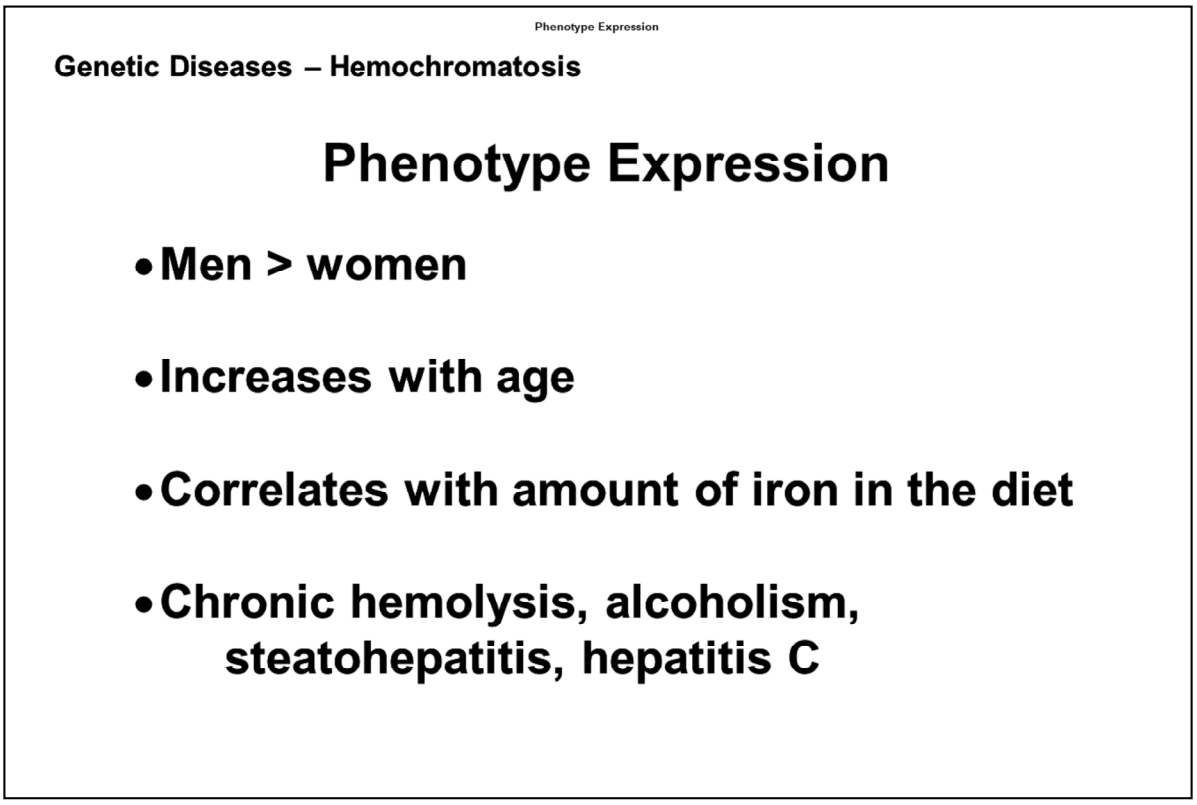
Andrews NC.New Engl J Med. 1999; 341:1986-1995.



Iron Transport and Storage

Iron is transported from its site of absorption to the liver bound to transferrin, which binds 2 atoms per molecule. In the liver iron is taken up by ferritin, a storage form of iron capable of holding thousands of atoms per molecule. The normal total body pool of iron is approximately 4 gm. Hemoglobin in red blood cells makes up half of total body iron stores. One unit of blood (500 ml) contains 250 mg of iron. Iron is also found in muscle as myoglobin and in heme-containing enzymes in the liver and elsewhere. The remainder of the body iron is in storage form, as ferritin or hemosiderin, in liver and reticuloendothelial cells.

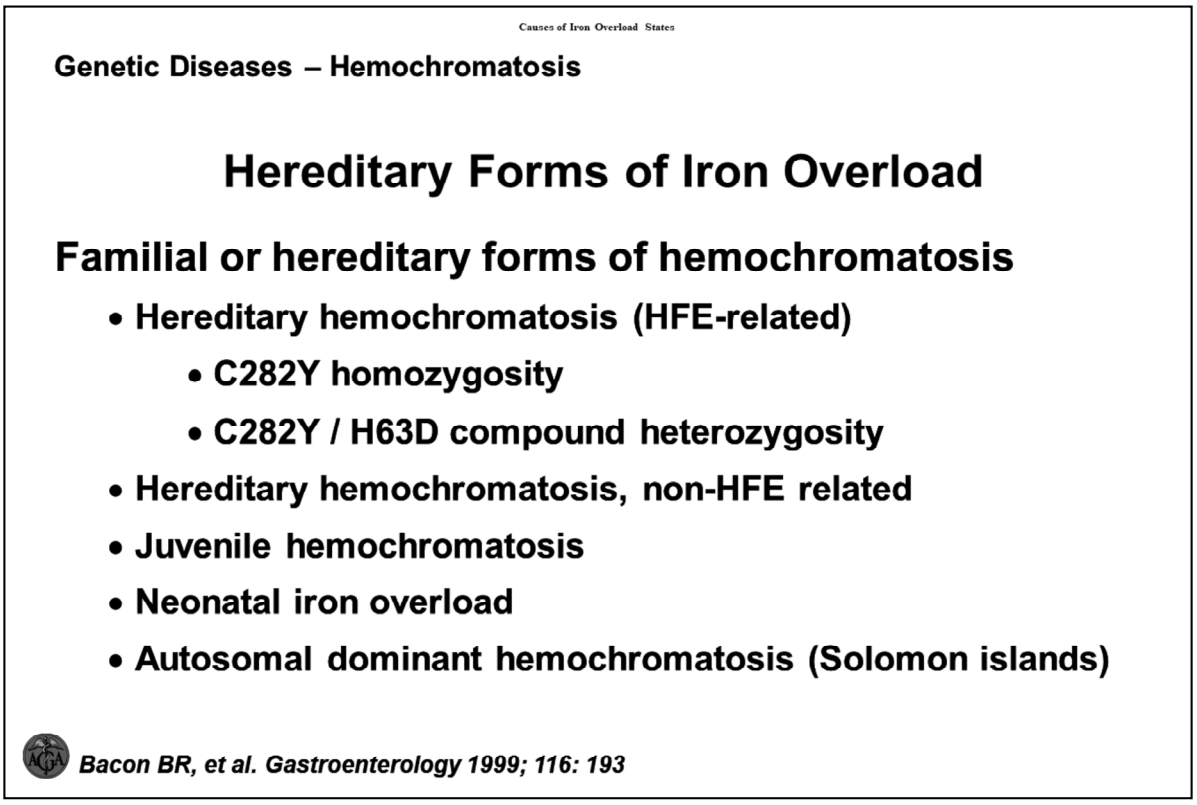
Andrews NC.New Engl J Med. 1999; 341:1986-1995.



Phenotype Expression

This slide points out that phenotypic expression does not correlate directly with presence of genetic mutations. The list above indicates variable phenotypic expression. For example, although the genetic defect is equally distributed between males and females, clinical series indicate that males are more commonly affected with ratios ranging from 8:1 to 2:1 (men:women). The reason for this difference is most likely due to greater amounts of iron loss in women due to menses and childbirth. As indicated in other slides the clinical expression of the disease is also a function of age and iron intake. Finally, iron overload is exacerbated by disorders such as chronic hemolysis; and liver injury is exacerbated by alcoholism, steatohepatitis and hepatitis C.

Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Causes of Iron Overload States

This and the subsequent slide list the causes of iron overload states, both hereditary and acquired, that need to be considered in the differential diagnosis. For the hereditary forms the genetic defect is known only for HFE-related hereditary hemochromatosis. Of those with HFE mutations 95% are homozygous for C282Y and 5% compound heterozygous for C282Y and H63D.

Bacon BR, Powell LW, Adams PC Kresina TF, Hoofnagle JH. Gastroenterology 1999; 116: 193-207.

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

Acquired Causes of Iron Overload

This slide lists the acquired causes of iron overload that should be distinguished from the hereditary causes of iron overload. The contribution of HFE mutations to conditions associated with acquired iron overload states is not established.

Bacon BR, Powell LW, Adams PC Kresina TF, Hoofnagle JH. Gastroenterology 1999; 116: 193-207.

Iron Measurements

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

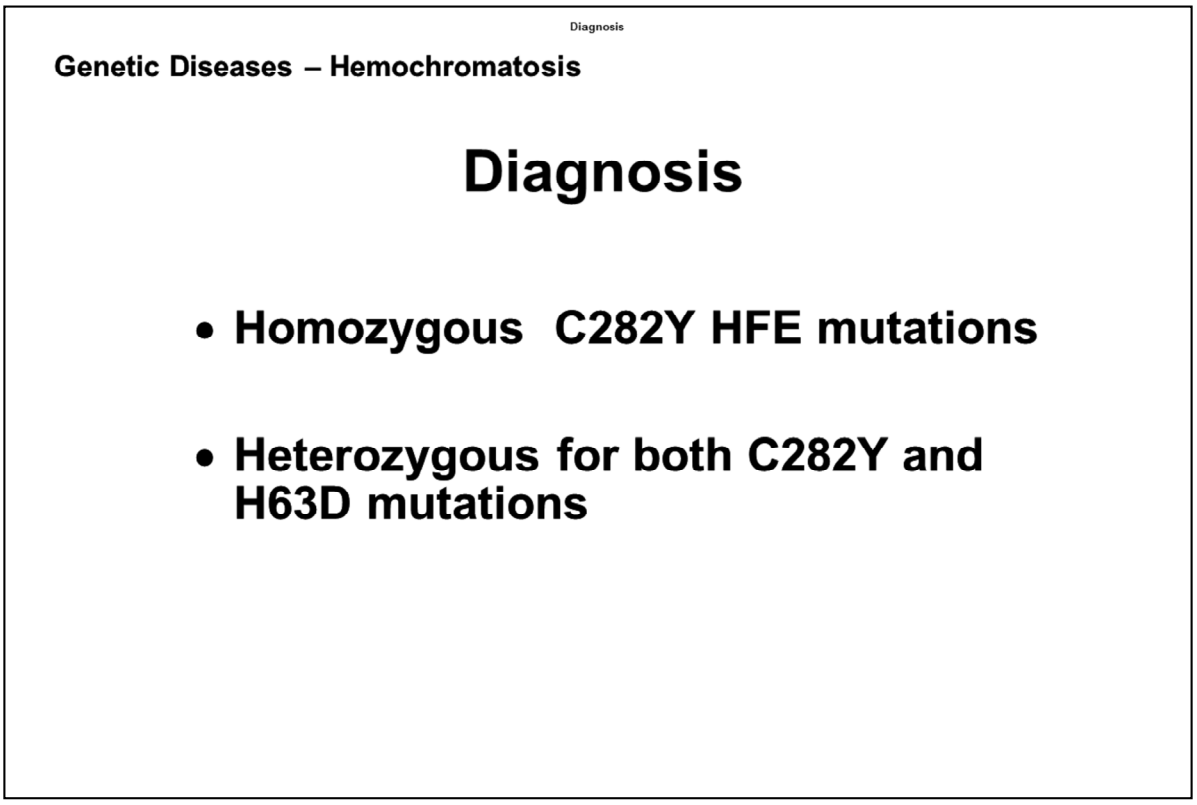
Iron Measurements

This slide lists the usual range for iron studies in normal individuals and patients with hereditary hemochromatosis. In hemochromatosis these studies are abnormal, showing an increase in serum iron with a relatively low total iron binding capacity, to give a percent saturation of transferrin of greater than 50 to 60%. The serum ferritin is increased in hereditary hemochromatosis, reflecting the increased total body stores of iron. When gene analysis for diagnosis of hereditary hemochromatosis does not confirm the diagnosis and the possibility of non-HFE cause of iron overload is under consideration, quantitation of the iron concentration in the liver by iron stains or mass measurement may be useful. For the measurement of iron concentration, a portion of the liver biopsy (0.5 to 1.0 cm from a needle specimen) is saved and placed in a trace metal free tube. The sample need not be stored on ice but is simply transferred dry to the reference lab for measurement. The usual values in μmole or μg per g of dry liver weight are given on the slide. The atomic weight of iron is 56 gm/mole, so that the hepatic iron content in μmole is equal to the value in μg divided by 56.

Bassett ML, Halliday JW, Powell LW. Hepatology 1986;6:24-9.

Summers KM, Halliday JW, Powell LW. Hepatology 1990;12:20-5.

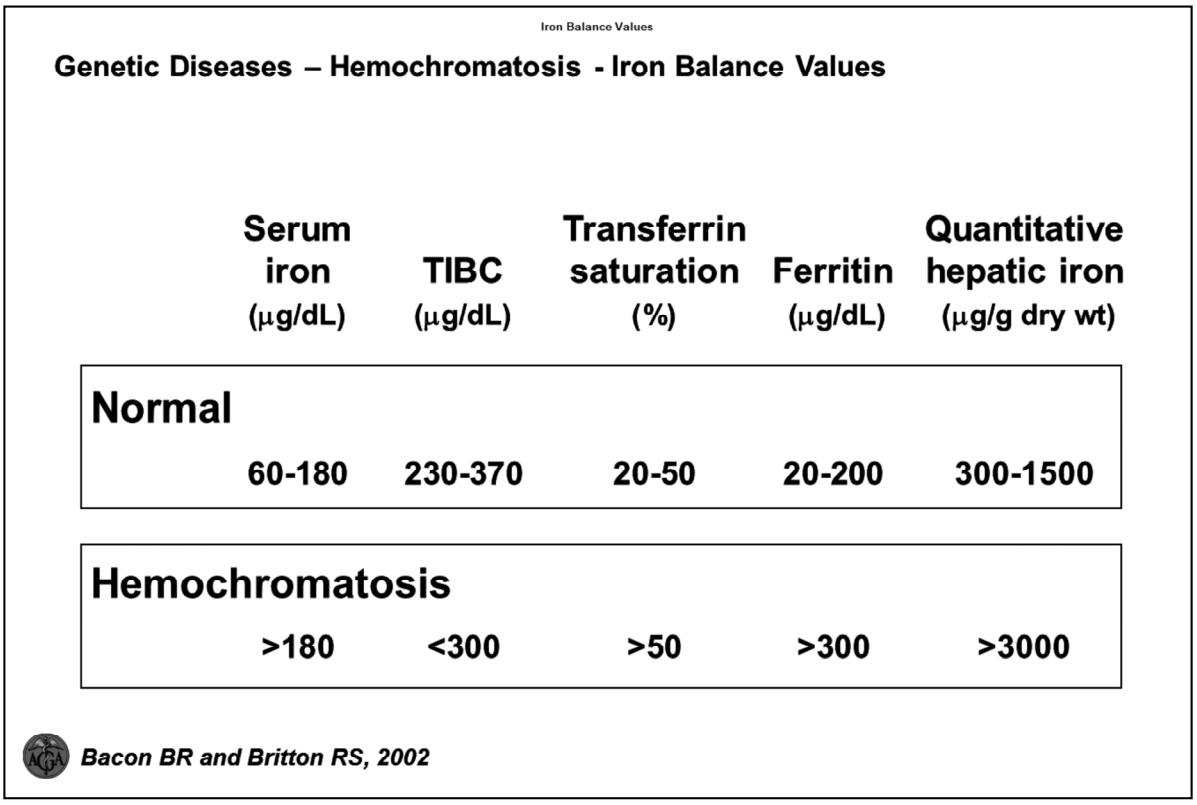
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Diagnosis

Now the diagnosis of hereditary hemochromatosis can be established confidently based on genetic testing with results showing one of the two mutation identities listed in the slide especially in a patient with a family history of hemochromatosis or a patient with abnormal ferritin levels and transferrin saturation.

Bacon BR, Powell LW, Adams PC Kresina TF, Hoofnagle JH. Gastroenterology 1999; 116: 193-207



Iron Balance Values

This slide lists the usual range for iron studies in normal individuals and patients with hereditary hemochromatosis. In hemochromatosis these studies are abnormal, showing an increase in serum iron with a relatively low total iron binding capacity, to give a percent saturation of transferrin of greater than 50 to 60%. The serum ferritin is increased in hereditary hemochromatosis, reflecting the increased total body stores of iron. When gene analysis for diagnosis of hereditary hemochromatosis does not confirm the diagnosis and the possibility of non HFE cause of iron overload is under consideration, quantitation of the iron concentration in the liver by iron stains or mass measurement may be useful diagnostically. For the measurement of iron concentration, a portion of the liver biopsy (0.5 to 1.0 cm from a needle specimen) is saved and placed in a trace metal free tube. The sample need not be stored on ice but is simply transferred dry to the reference lab for measurement. The usual values in μmole or μg per g of dry liver weight are given on the slide. The atomic weight of iron is 56 gm/mole, so that the hepatic iron content in μmole is equal to the value in μg divided by 56.

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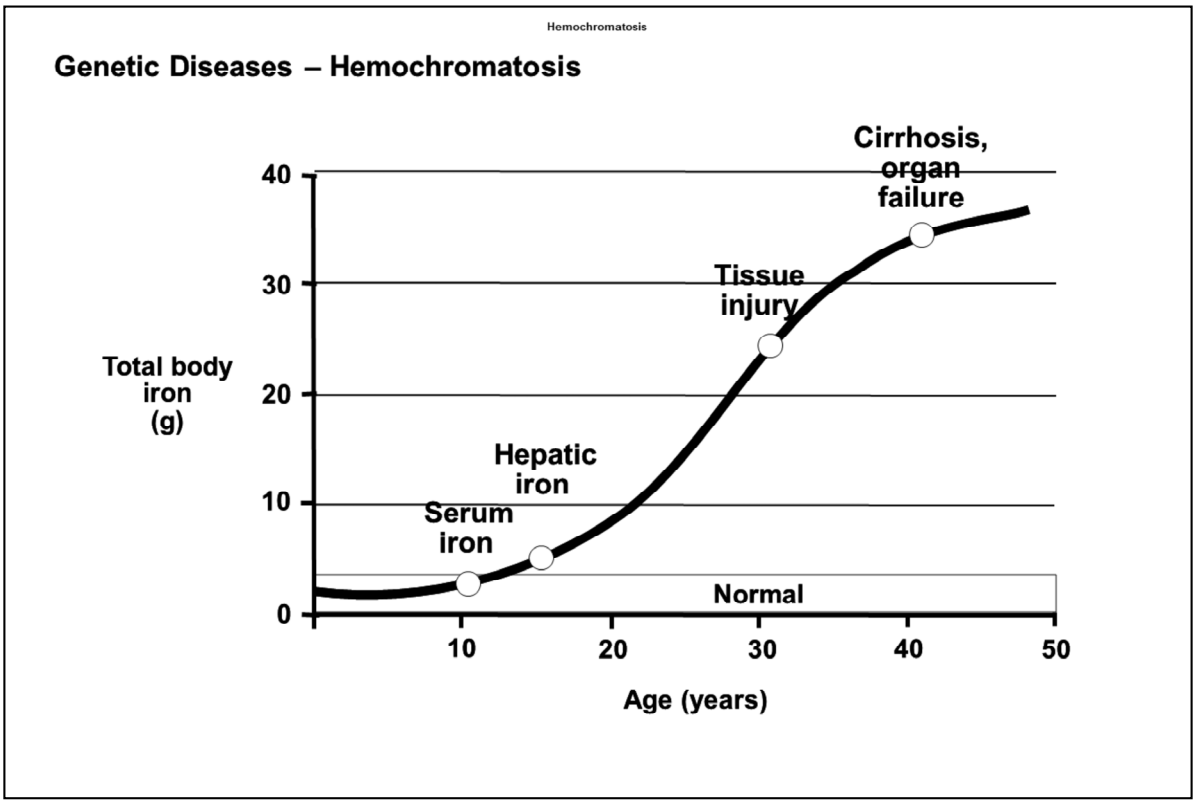
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.

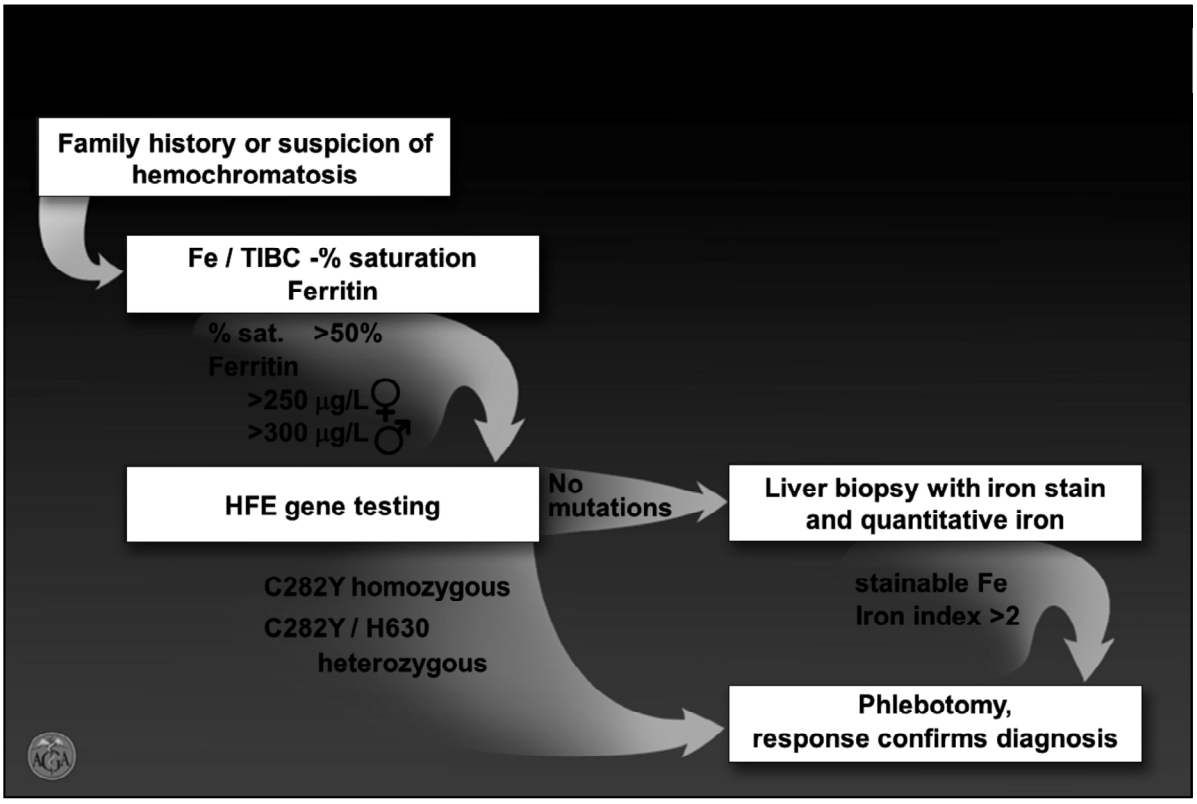


Hemochromatosis

Over time, patients with hereditary hemochromatosis have rapidly increasing total body iron load. This begins at birth and is due to increased iron absorption. By age 10 the serum iron is elevated above the normal range, and by adolescence the hepatic iron is increased. Tissue injury due to the accumulated iron begins by the mid 30's in males, and organ dysfunction, including cirrhosis, diabetes, and cardiac disease, presents in the mid 40's or later.

Adams PC, Halliday JW, Powell, LW. Adv Intern Med 1989;34:111-126.

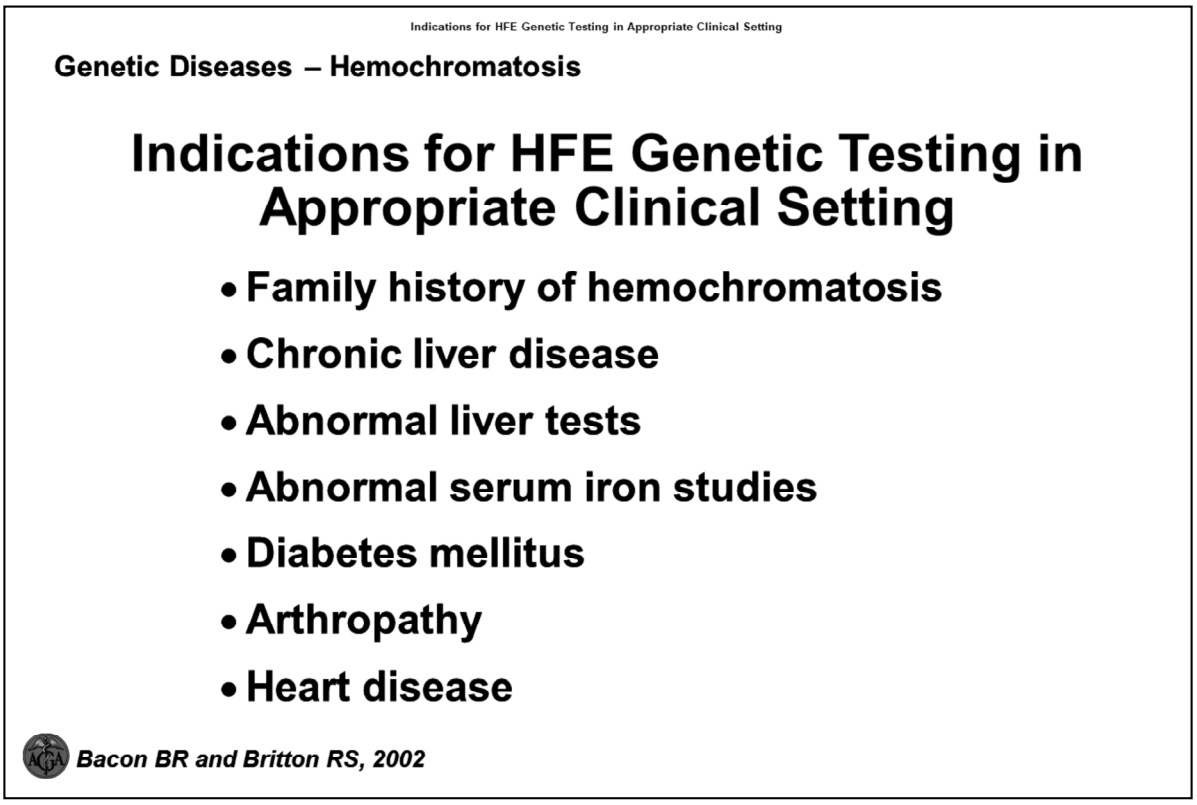
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Diagnostic Testing

In patients with the consideration of hemochromatosis, evaluation should begin with measurements of Fe/TIBC and ferritin. In patients with results consistent with hemochromatosis, genetic testing of HFE should be performed. If the results of genetic testing demonstrate either homozygous C282Y or combined compound heterozygous C282Y/H63D, the diagnosis of hereditary hemochromatosis is established and appropriate therapy should begin. When gene analysis for diagnosis of hereditary hemochromatosis does not confirm the diagnosis and the possibility of non-HFE cause of iron overload is under consideration, quantitation of the iron concentration in the liver by iron stains or mass measurement may be useful. Response to phlebotomy confirms the diagnosis.

Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



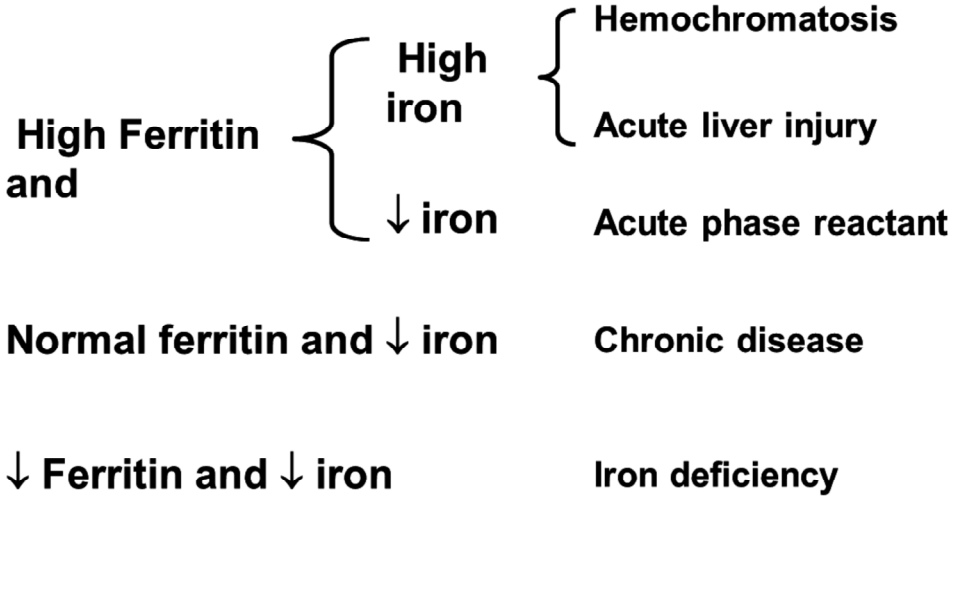
Indications for HFE Genetic Testing in Appropriate Clinical Setting

Hemochromatosis is very common in Caucasians, and should be ruled out in any patient older than 30 years referred for evaluation of abnormal liver tests. It should also be excluded in any patient with liver disease of unknown etiology, including hepatomegaly, hepatitis, cirrhosis and the complications of portal hypertension, or hepatic mass lesions. This common disorder should also be considered in evaluating patients with diabetes mellitus; arthritis or arthropathy, particularly involving the M-P joints of the hands; heart disease, particularly cardiomyopathy and rhythm disturbances in the absence of coronary artery disease; increased skin pigmentation (not a usual complaint); and impotence. All family members should be screened, including siblings, parents and children of an affected individual.

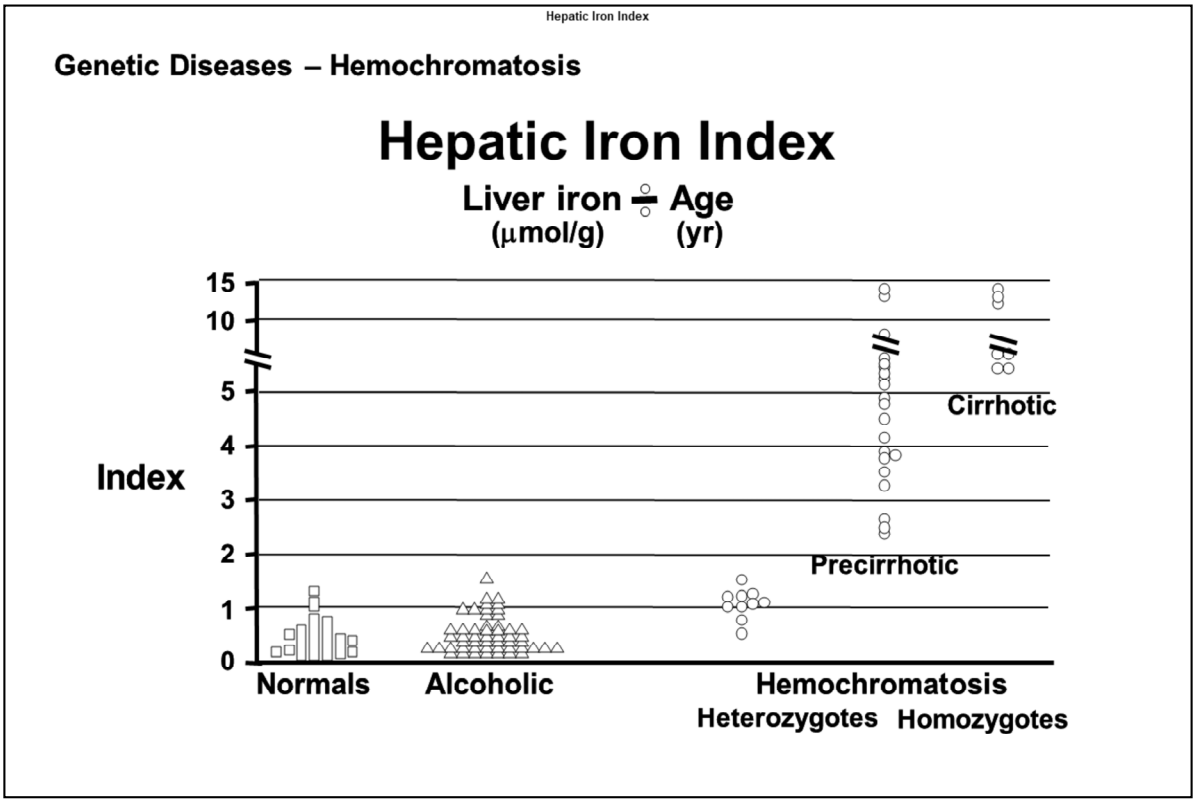
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.

Genetic Diseases – Hemochromatosis

Interpretation of Ferritin Levels



Interpretation of Ferritin Levels



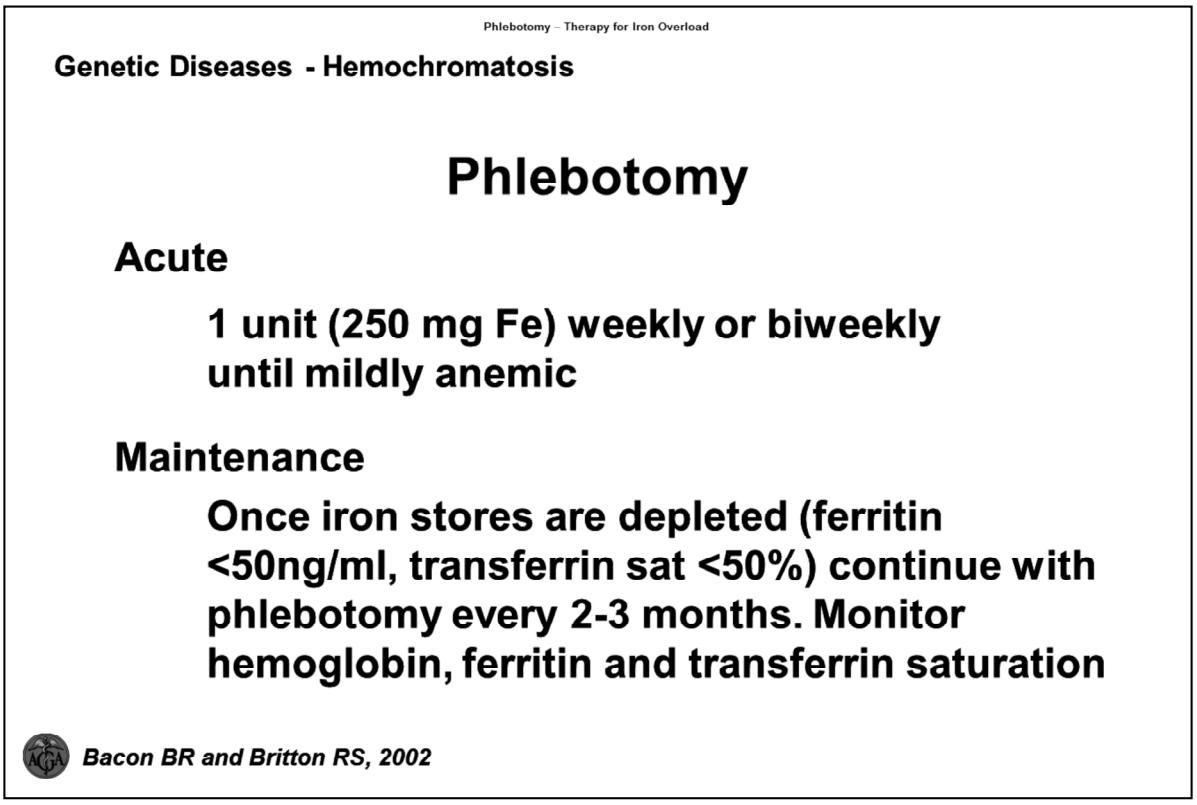
Hepatic Iron Index

Iron levels rise with age in normal individuals as well as in patients with hemochromatosis. Thus, greater specificity can be given to the hepatic iron quantitation by using the hepatic index, defined as the quantitative hepatic iron value, in μmoles per gm dry liver weight, divided by the patient's age in years. This slide shows that the hepatic iron index serves to clearly differentiate patients with alcoholic liver disease from those who are homozygous for hemochromatosis.

Bassett ML, Halliday JW, Powell LW. Hepatology 1986;6:24-29

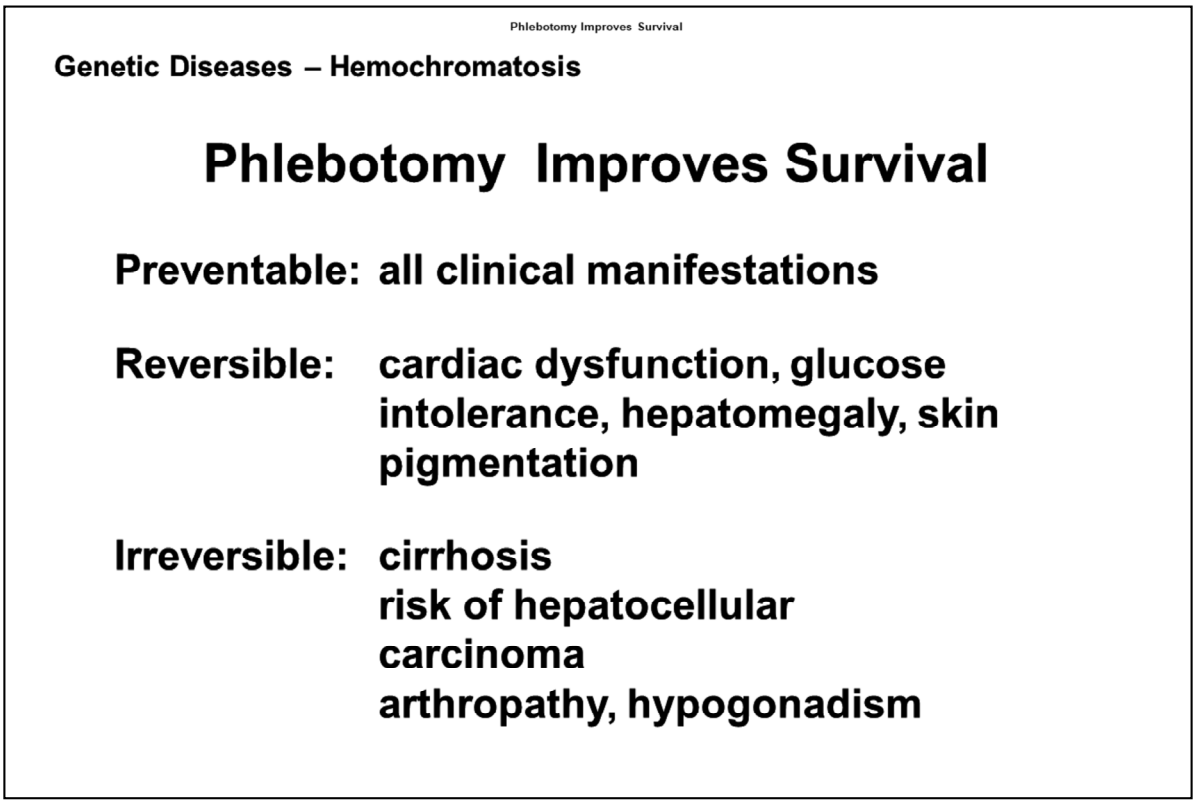
Summers KM, Halliday JW, Powell LW. Hepatology 1990;12:20-25

Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Phlebotomy – Therapy for Iron Overload

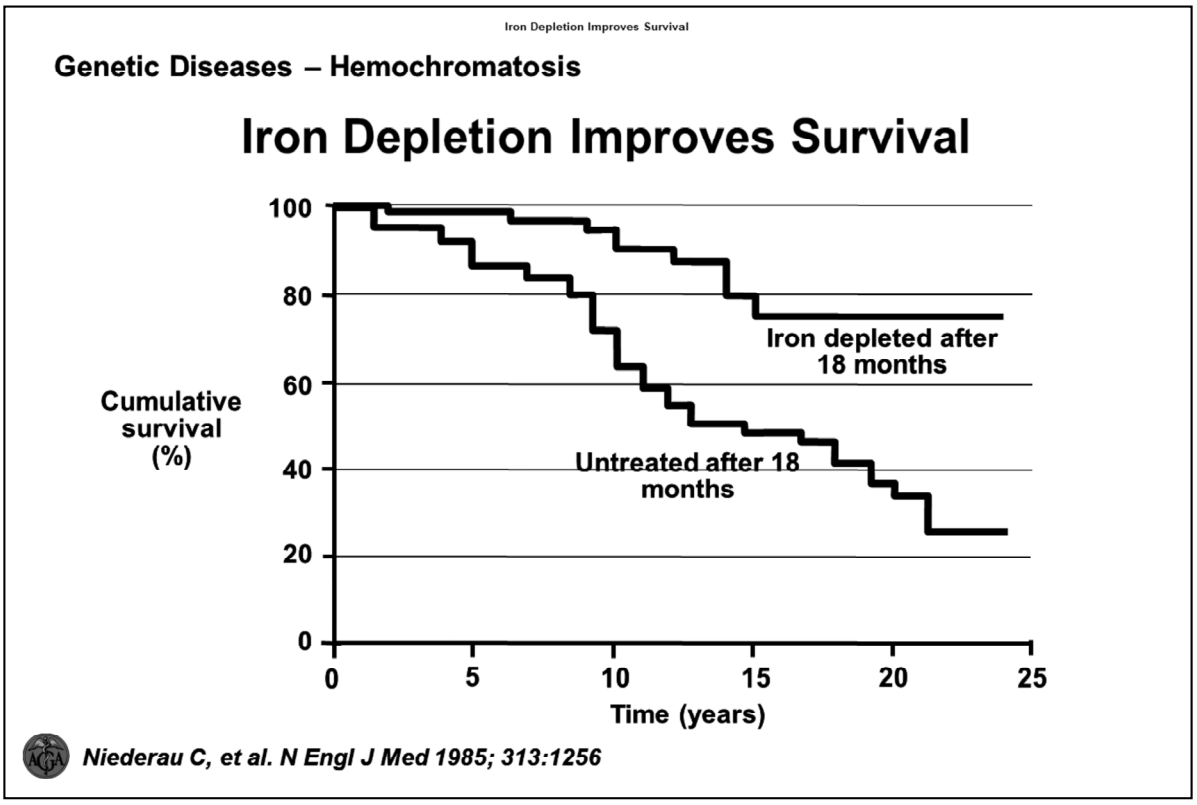
Bacon BR, Britton RS. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 66: 1261-1268.



Phlebotomy Improves Survival

When begun early, for example in an asymptomatic family member detected by screening, phlebotomy therapy prevents all clinical manifestations. Patients with hemochromatosis in whom therapy is begun before the development of cirrhosis have a life span not different from controls. Phlebotomy therapy of affected patients, when successful in depleting the iron overload, results in an improvement in hepatomegaly and liver function, along with an improved survival rate. Also improved are cardiac function, glucose tolerance and insulin requirement, and skin pigmentation. In established hemochromatosis, phlebotomy therapy does not reverse the cirrhosis or lower the risk of hepatocellular carcinoma. The arthropathy and hypogonadism are also not improved by phlebotomy therapy.

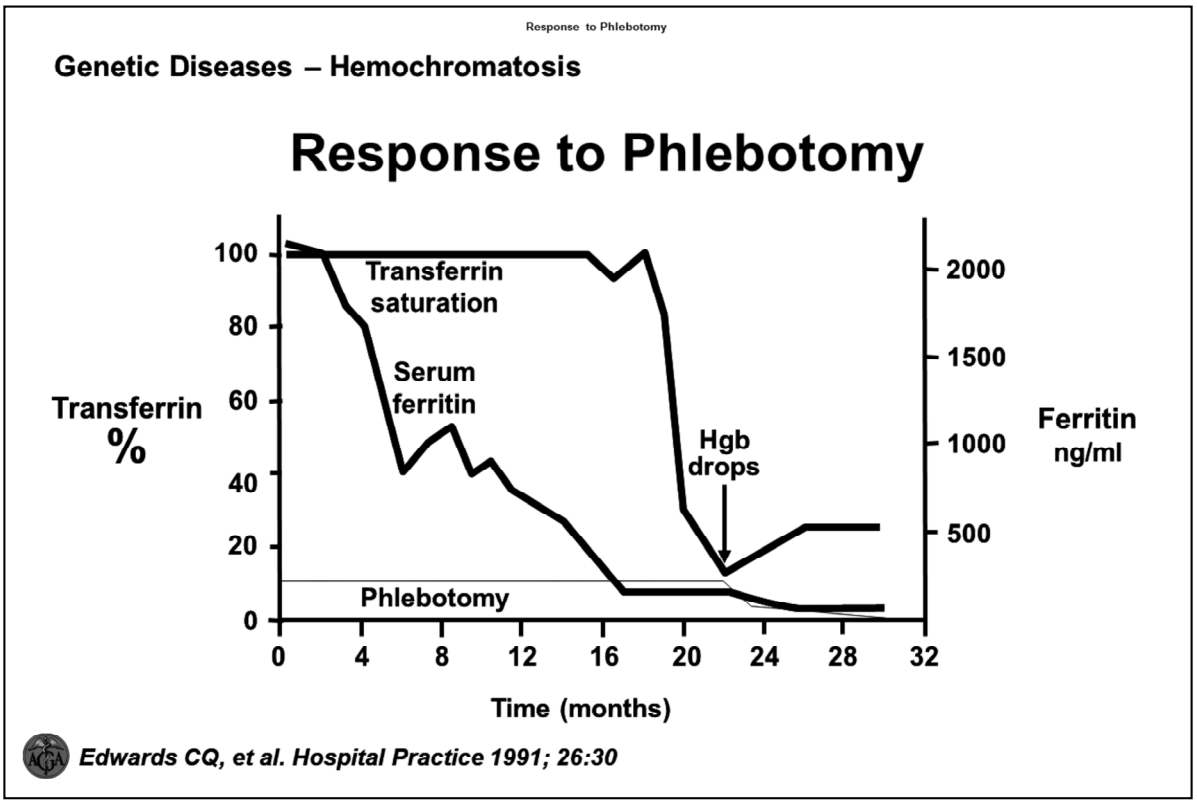
Niederau C, Fischer R, Sonnenberg A, et al. N Engl J Med 1985; 313:1256-1262.



Iron Depletion Improves Survival

The graph comes from the publication listed below indicating that phlebotomy to cause iron depletion in patients with hemochromatosis improves survival.

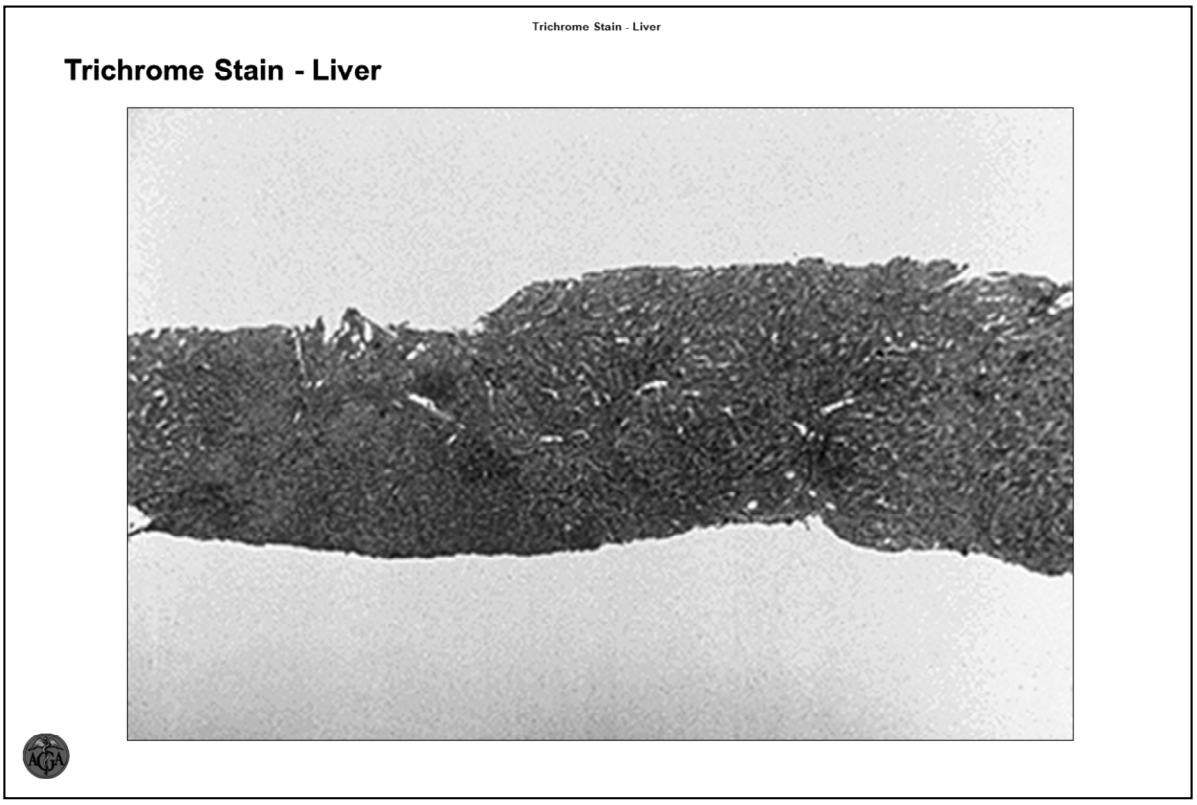
Niederau C, Fischer R, Sonnenberg A, et al. N Engl J Med 1985; 313:1256-1262.



Response to Phlebotomy

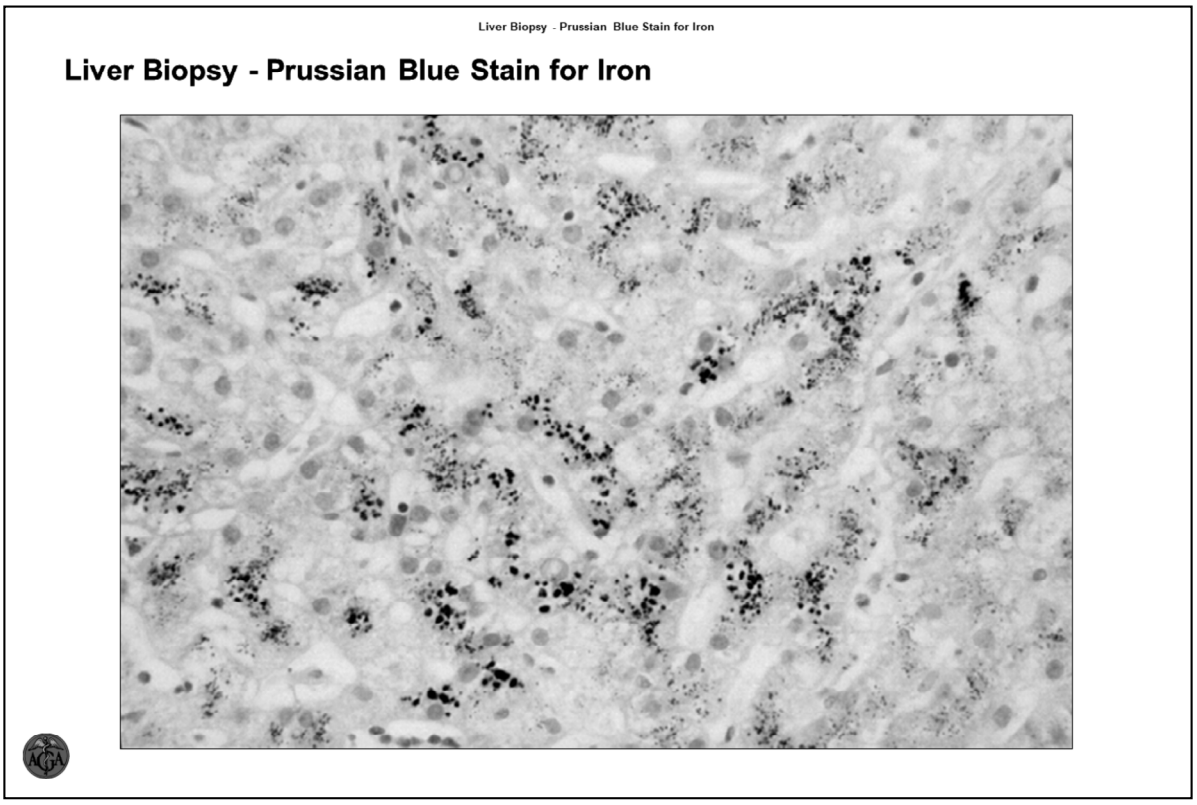
Phlebotomy therapy removing 1 unit of blood per week or on alternate weeks results in predictable changes. The hemoglobin/hematocrit stays stable for many months, and falls only when the body iron stores have been depleted and the patient rendered iron deficient. When the hemoglobin level can no longer be maintained within the low normal range, the phlebotomies are done less frequently, as indicated, keeping ferritin levels at 20 ng/ml or lower. The transferrin saturation remains high (blue line) until the iron stores are depleted. In contrast, the ferritin (yellow line) falls gradually. Decisions about continuing phlebotomy depend on the hemoglobin and ferritin values.

Edwards CQ, Griffen LM, Kushner JP. Disorders of excess iron. Hospital Practice 1991;26:30-6.



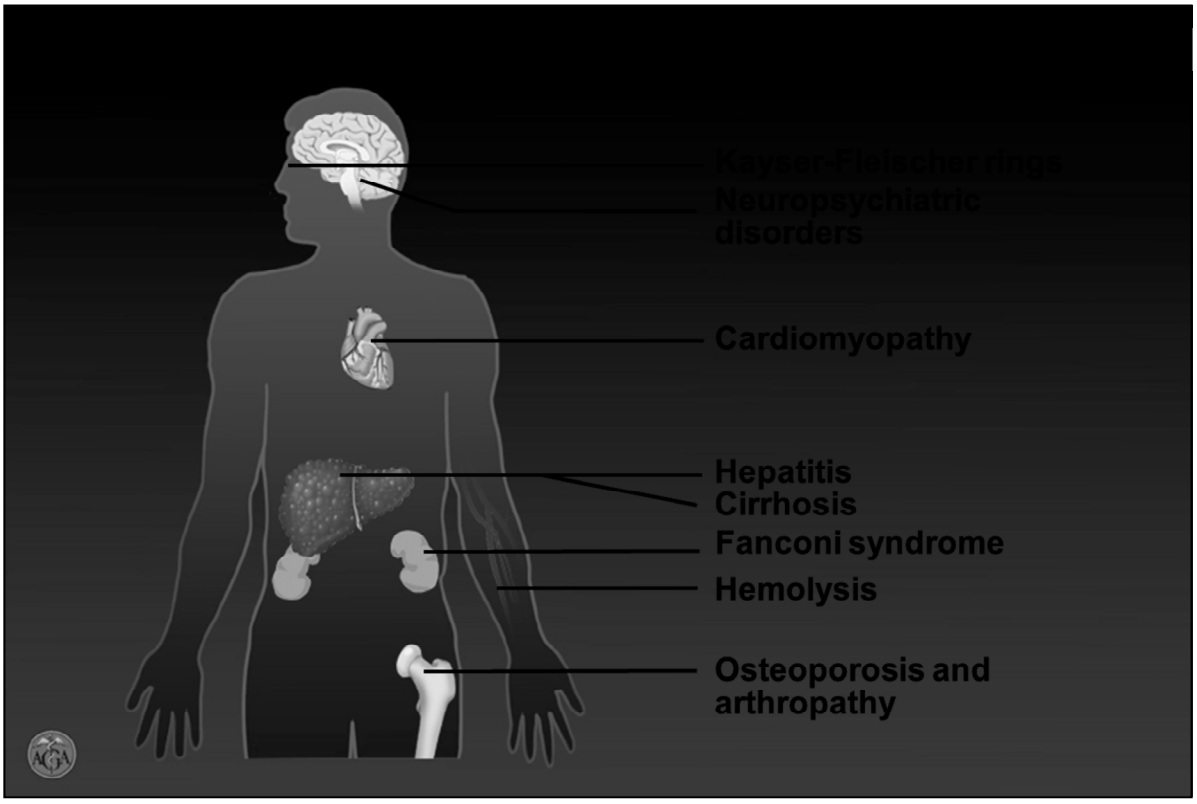
Trichrome Stain – Liver

Liver biopsy with Masson trichrome stain demonstrates bands of fibrosis partially outlining nodules of regenerating hepatocytes observed with lower power microscopy. It should be emphasized that liver biopsy may not be necessary when the diagnosis of hereditary hemochromatosis is confirmed by genetic testing.



Liver Biopsy - Prussian Blue Stain for Iron

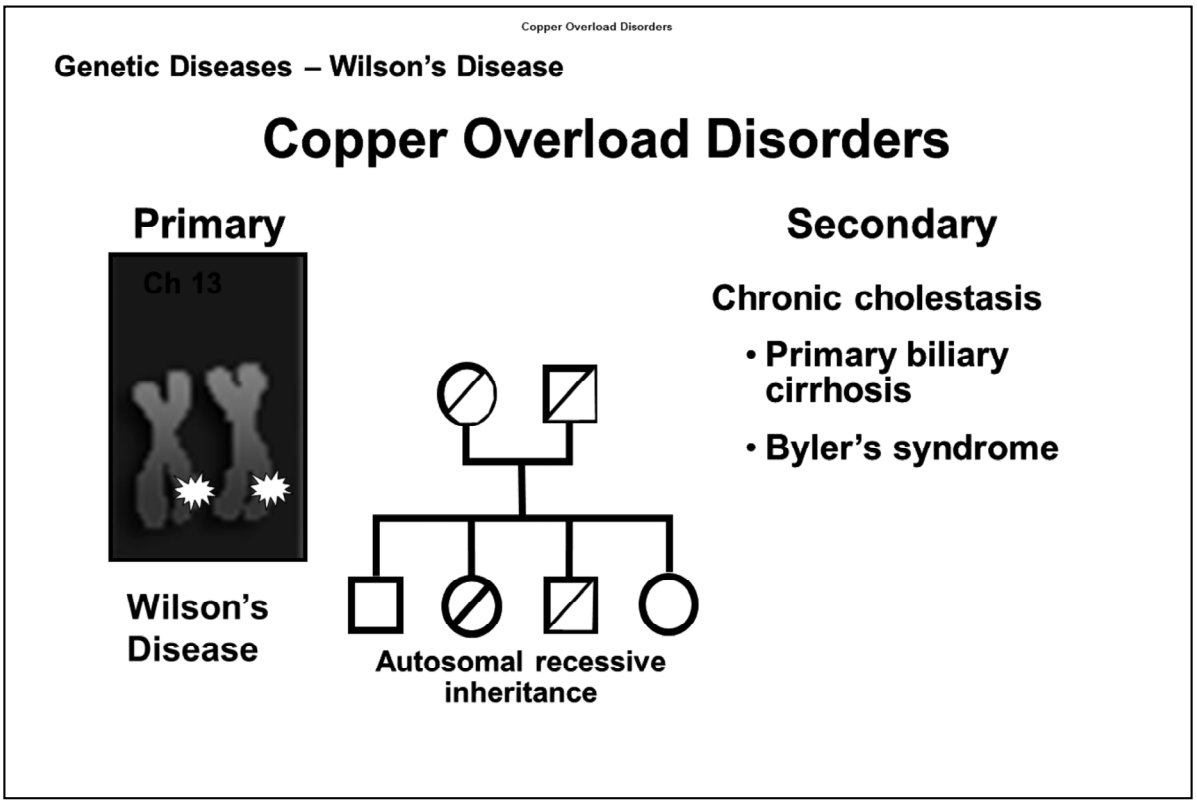
In this photomicrograft, the iron is in lysosomes which are adjacent to the canaliculi, which can be seen in a "chicken wire" pattern outlined by the iron.



Wilson's Disease

Wilson's disease leads to deposition of copper in many organ systems, with resultant clinical manifestations. There is copper deposition in the basal ganglia of the brain, resulting in the neuropsychiatric disorders seen in some affected individuals. Copper deposition in the eye is seen as Kayser-Fleischer rings, a golden brown deposit in Descemet's membrane seen at the limbus. Cardiomyopathy may very rarely be associated with Wilson's disease. The liver is the site of the defect in Wilson's disease, and is affected in all patients, with injury ranging from fatty liver through acute hepatitis to cryptogenic cirrhosis. Copper deposition in the renal tubule causes a Fanconi syndrome, with aminoaciduria, glycosuria, and wasting of uric acid. This may lead to osteopenia, which in some patients can be severe. High circulating levels of non-ceruloplasmin bound copper result in hemolysis.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

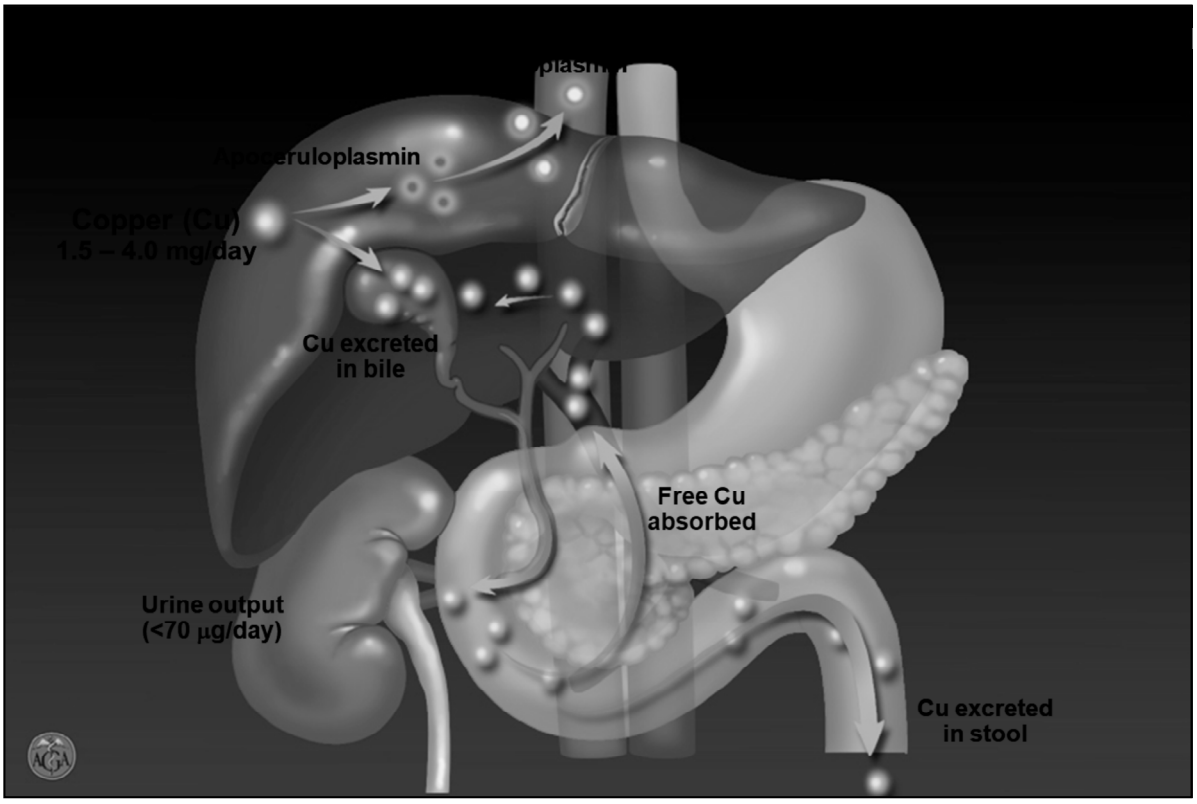


Copper Overload Disorders

Copper overload can be either primary, due to an inherited defect in copper homeostasis, or secondary, seen as an epiphenomenon in any disorder which results in prolonged cholestasis, with a resultant decrease in biliary copper excretion. A typical primary copper overload disorder is Wilson's disease, which is inherited as an autosomal recessive disease due to a defective gene on the long arm of chromosome 13. This disorder was described in detail by Wilson in 1912, although previous reports had appeared. Chronic cholestatic syndromes, such as primary biliary cirrhosis can lead to secondary copper overload. Other examples of cholestatic diseases resulting in copper overload include primary sclerosing cholangitis and Byler's syndrome.

Wilson SAK. Brain 1912; 34:295-507.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

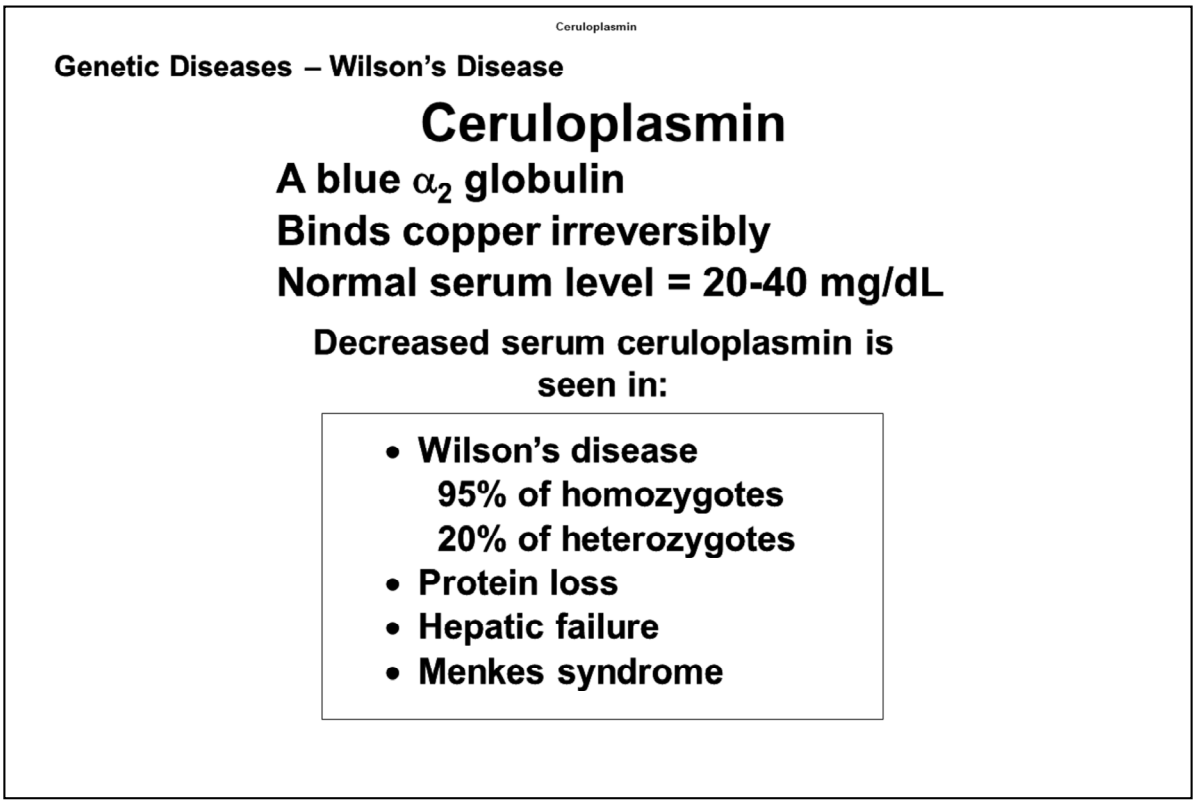


Normal Copper Balance

Copper is ingested with the diet. Many foods are rich in copper, including shellfish, chocolate, nuts, and mushrooms. Once ingested, copper is absorbed in the upper intestine and travels in portal blood to the liver. It is taken up from the sinusoidal blood into the hepatocyte where it binds to a copper-containing enzyme, ceruloplasmin. The bulk of the copper is transported across the hepatocyte and excreted via the lysosomes into the canaliculi. In bile, copper is bound to proteins which prevent its reabsorption, and favor excretion in stool. Very little copper circulates in the free state, and there is very little copper present in urine.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

Cox DW. Am J Hum Genet 1995; 56: 828.

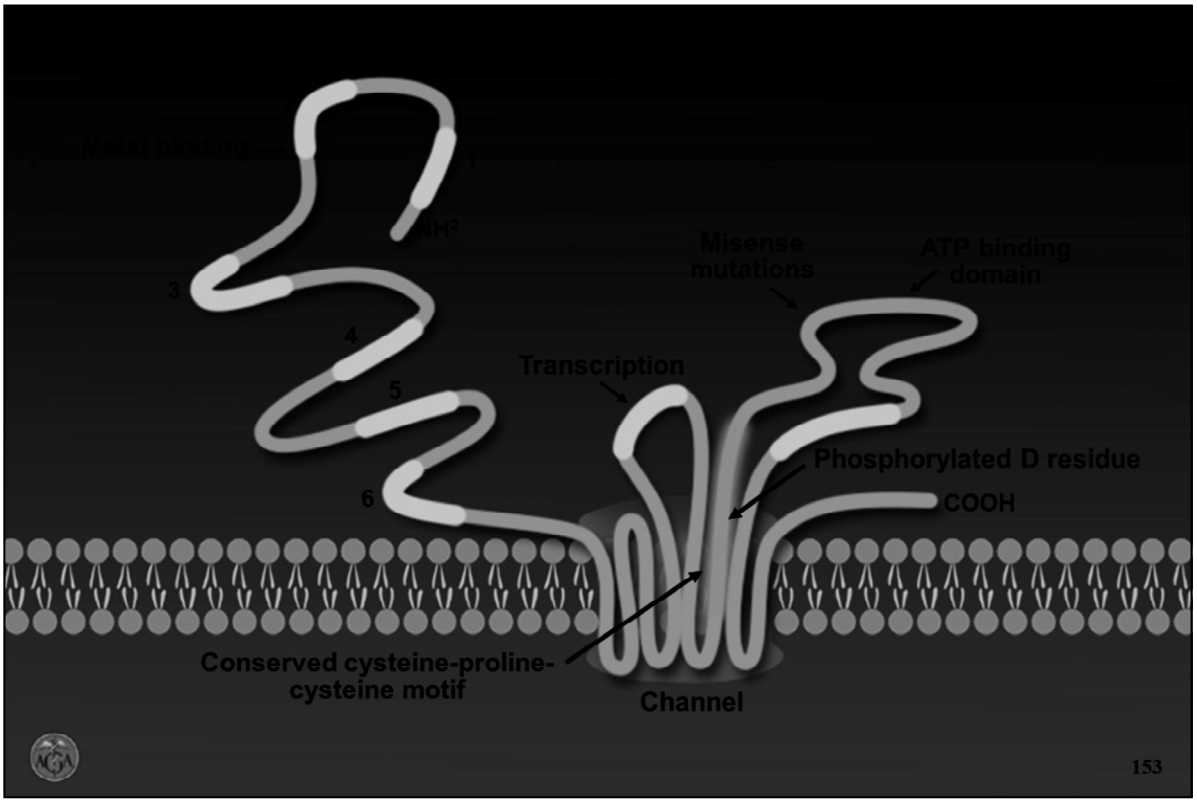


Ceruloplasmin

Ceruloplasmin is an α2 - globulin produced by the liver, and hence decreased in amount in the serum of patients with hepatic insufficiency who have decreased levels of other proteins such as albumin or the coagulation factors. The copper in ceruloplasmin is bound irreversibly.

Serum ceruloplasmin levels can be altered in various states. Protein loss, as in the nephrotic syndrome, or synthetic failure, as in hepatic insufficiency, result in low levels. Patients with Menkes syndrome have low levels. As an α2 - globulin, ceruloplasmin levels rise as do other acute phase reactants in response to pregnancy, estrogen therapy, or the stress of acute inflammation, such as hepatitis. Thus, 5% of patients with Wilson's disease have a ceruloplasmin level in the normal range.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

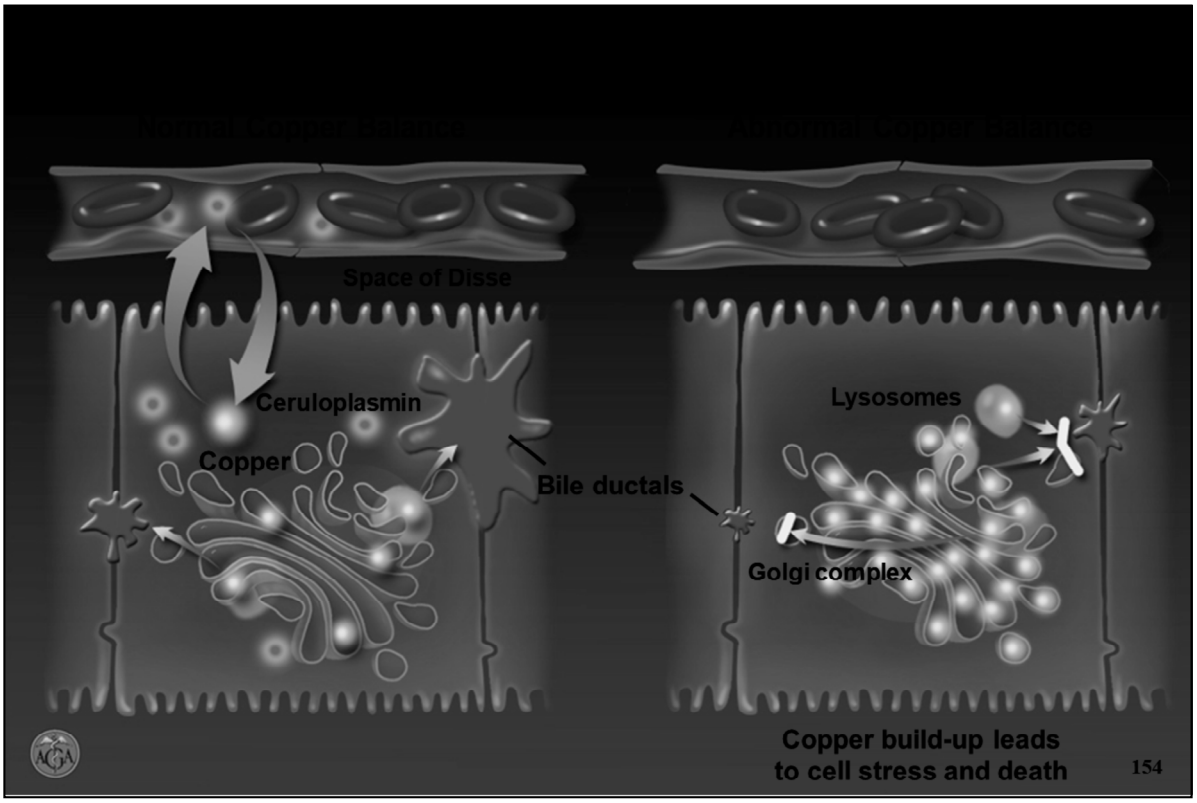


Wilson's Disease Molecular Defect

This model represents the predicted product of the Wilson's disease gene based on information about functional domains in the closely related Menkes disease gene, a rare and related disorder of copper metabolism. The functional domains shared are indicated in the brown colored sequences. The Wilson gene product is a p-type ATPase. The area of the two common missense mutations found in Wilson's disease is indicated-H1069Q and R778L.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

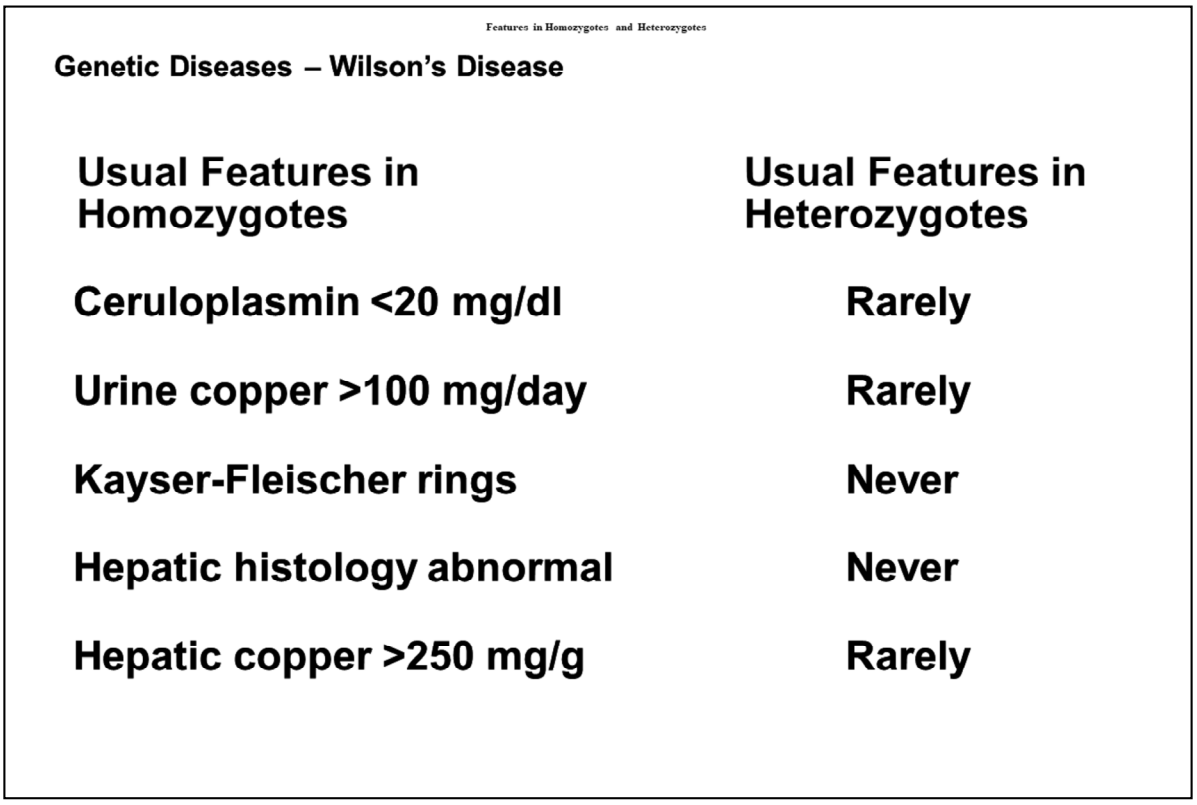
Camakaris J, Voskoboinik I, Mercer JF. Biochem Biophys Res Comm 1999; 261: 225-232.



Wilson's Disease: Copper Transport

This model represents the effect of the abnormal Wilson's disease gene on hepatic copper transport. The p-type ATPase is located both on the bile cannalicular surface and in pericannalicular vesicles. The ATPase is proposed to facilitate copper transport into the bile. With mutation, there is a block in copper transport and accumulation of copper in the hepatocyte as well as ceruloplasmin.

Schaefer M, Roelofsen H, Wolters H et al. Gastroenterology 1999; 117:1380-1385.



Features in Homozygotes and Heterozygotes

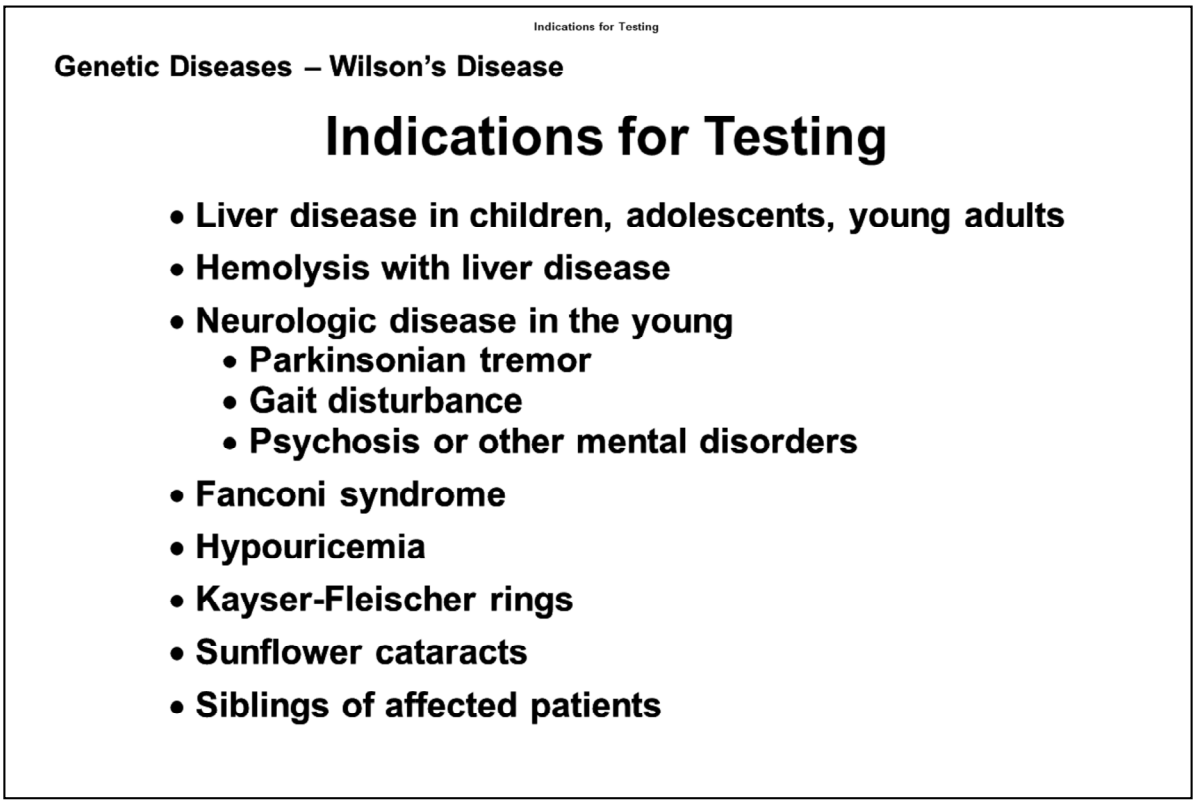
The diagnosis of Wilson's disease rests on assessment of various epiphenomena of the disorder, and is thereby imprecise. Diagnostic strategies will improve with genetic testing although over 200 different mutations in the Wilson's gene have been identified. Heterozygotes for the defect may share findings with affected homozygotes, but these abnormalities are less severe, and heterozygote carriers do not develop the disease. Serum ceruloplasmin levels are usually, but not invariably, low, below 20 mg/dl, in homozygotes. This protein is produced by the liver, and its level can vary in response to stress or hepatic dysfunction. Ceruloplasmin levels are usually normal in heterozygotes, although 20% may have low levels.

Urinary excretion of copper is elevated in homozygote patients, but may be elevated in patients with chronic cholestasis and secondary copper overload. All individuals will have an increase in urine copper in response to infusion of the chelator D-penicillamine, and thus this is not a reliable differential point.

Kayser-Fleischer rings are usually present in affected homozygote patients, and are always present if there is attendant neurologic disease. They are absent in heterozygotes, but may rarely be found in patients with secondary copper overload. Liver disease is usually present when Kayser-Fleischer rings are evident.

Hepatic histology is abnormal in homozygotes and never abnormal in heterozygotes. Hepatic copper concentration is abnormally elevated in homozygotes, and may be elevated at lower levels in heterozygotes.

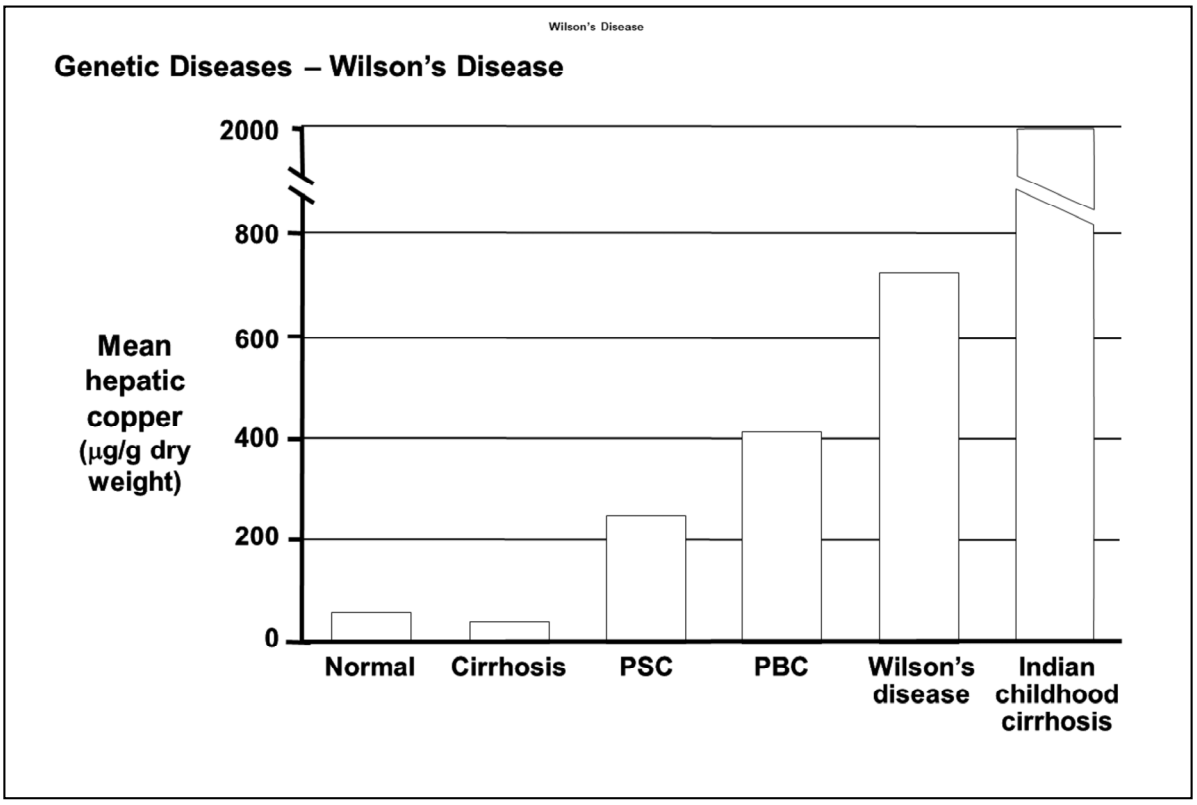
Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277



Indications for Testing

For the clinician, the best approach to Wilson's disease is to maintain a high index of suspicion for this treatable disorder. Wilson's disease should be considered in the differential diagnosis, and excluded by conducting the appropriate tests, in patients with the following disorders: liver disease of unexplained etiology in children over the age of 5, any adolescent with liver disease, and young adults up to the age of 40 (and perhaps 50). Any individual with hemolysis coincident with liver disease should be suspected of having Wilson's disease. Neurologic disorders in the young, such as Parkinson tremor, gait disturbances, personality changes, adolescent-adjustment problems, and psychosis, should prompt a search for Wilson's disease. Patients with Fanconi syndrome, hypouricemia, and the ophthalmologic findings of Kayser-Fleischer rings or sunflower cataracts should be evaluated for Wilson's disease. Finally, family members of an affected individual should be evaluated.

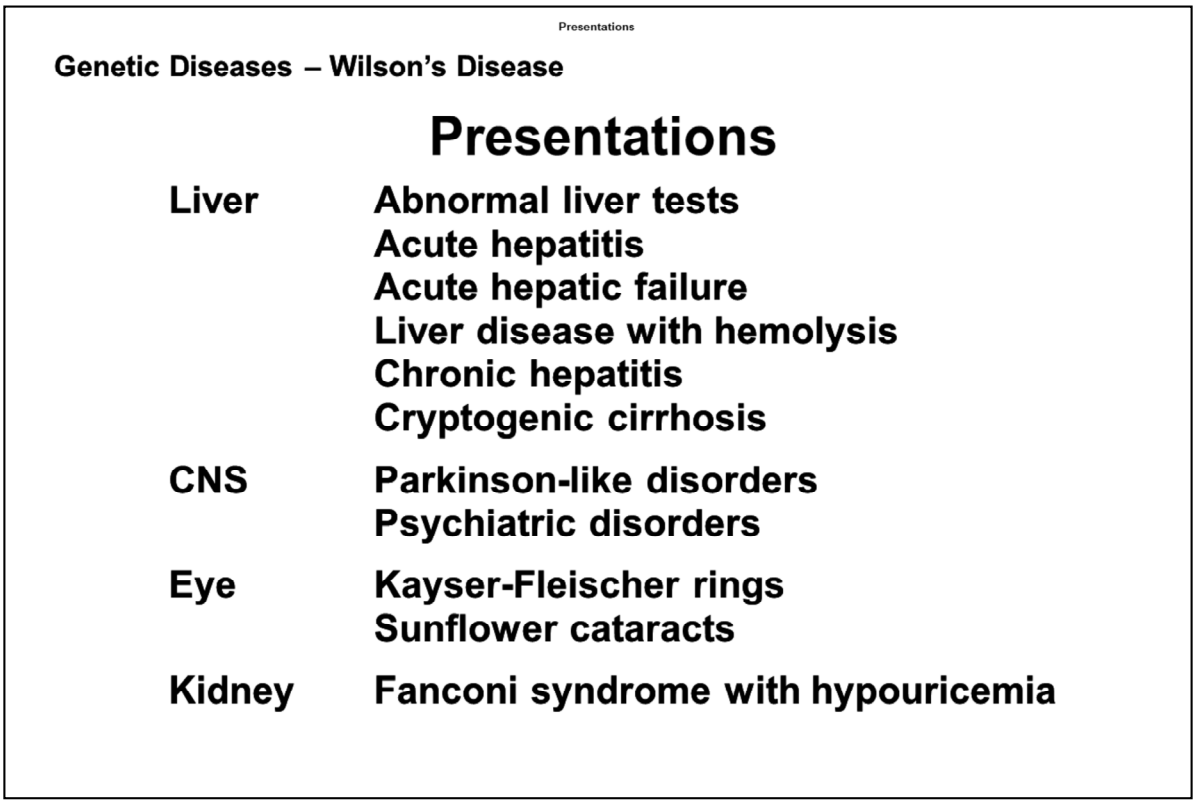
Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277



Wilson's Disease: Hepatic Copper

Determination of the concentration of copper in the liver is very useful in the evaluation for Wilson's disease. This is done by reserving a portion (1 cm or more from a needle biopsy specimen) of liver in a dry, trace metal-free tube for submission to the reference laboratory. The determination is done by drying the specimen, weighing it, and measuring copper by spectrophotometric analysis yielding a result in μg per g dry liver weight. As seen on the left of the slide, the highest levels of hepatic copper are found in patients with Indian childhood cirrhosis, a rare disorder seen in children of Asian Indian extraction. Patients homozygous for Wilson's disease have high values for quantitative hepatic copper. Lower but clearly elevated values are found in patients with prolonged cholestasis, such as primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). The level is normal in other forms of liver disease.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

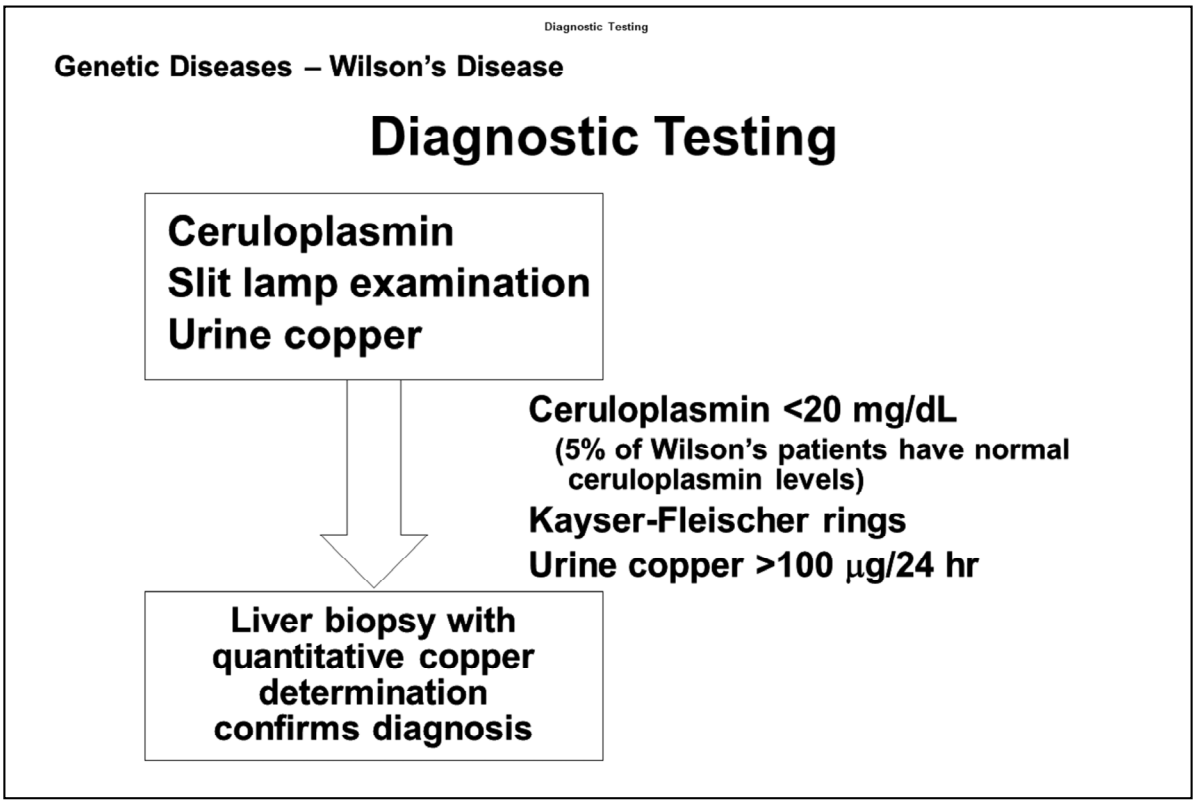


Presentations

Because of its multiorgan involvement, Wilson's disease is a great imitator which can present in a variety of widely divergent ways. Gastroenterologists are most likely to see a liver presentation, which is the initial complaint in approximately 40 % of affected patients. This can vary from an asymptomatic patient who presents for evaluation of abnormal "liver function tests", to a patient with fulminant hepatic failure, or a patient with acute "hepatitis" and hemolysis, or chronic active hepatitis on biopsy, or cryptogenic cirrhosis. Affected patients may present with central nervous system involvement, either Parkinson-like tremor, gait disturbance, or difficulty with handwriting, or psychiatric disturbance. The ophthalmologist may be the first physician to consider the diagnosis in a patient found to have Kayser-Fleischer rings or a sunflower cataract. The renal manifestations, with a Fanconi syndrome, may be the presenting complaint.

Stremmel W, Meyerrose K-W, Niederau C, et al. Ann Intern Med 1991;115:720-726.

Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277

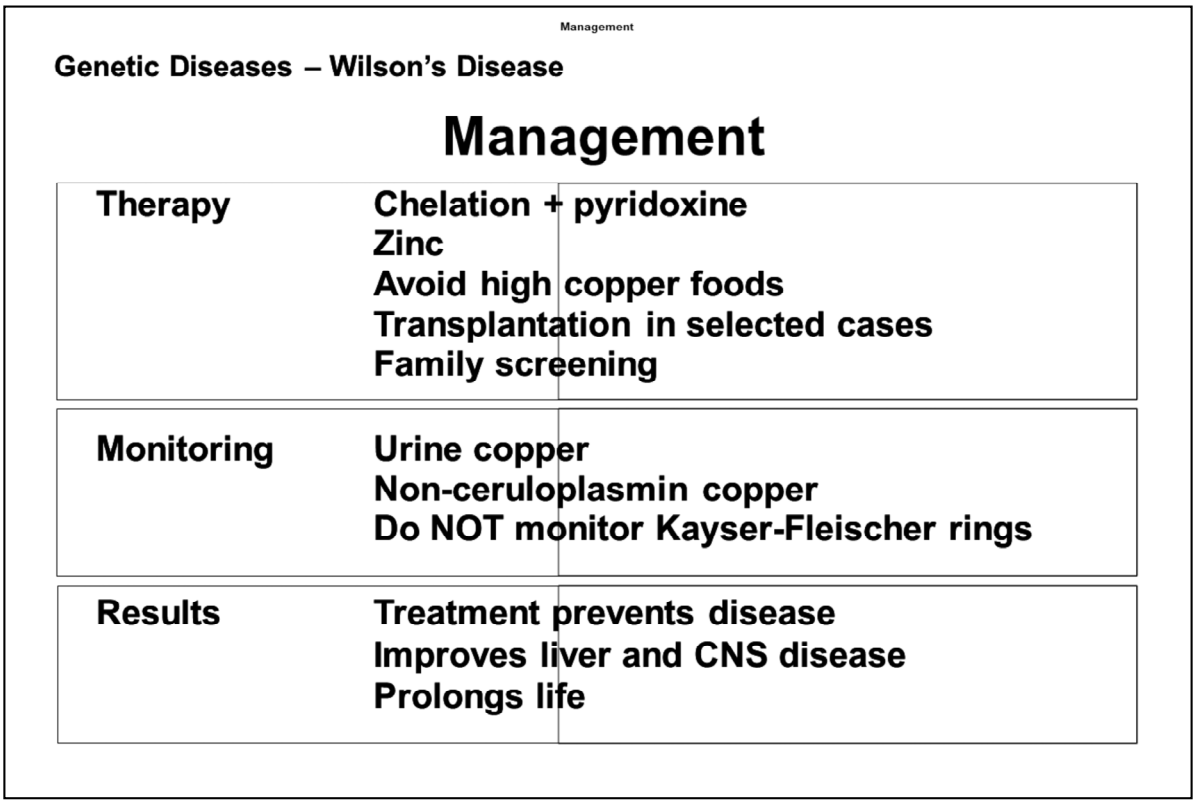


Diagnostic Testing

Initial evaluation for Wilson's disease should include determination of the serum ceruloplasmin level, a slit lamp examination by an ophthalmologist in search of Kayser-Fleischer rings, and determination of urine copper excretion done on a 24-hour urine collected in a trace metal-free container. A ceruloplasmin value of less than 20 mg/dl is suggestive of the diagnosis in an appropriate setting, as are the presence of Kayser-Fleischer rings and a 24-hour urine copper of greater than 100 μg. The diagnosis should be confirmed in most patients by doing a liver biopsy with quantitative liver copper determination.

The ceruloplasmin value may be misleading in rare patients. Kayser-Fleischer rings and elevated levels of urinary copper may be found in rare patients with severe cholestasis. Cholestasis is not a symptom of Wilson's disease, however, and the

quantitative liver copper will differentiate secondary overload, with low level elevation, from the high levels seen in Wilson's disease. In rare patients, for example a symptomatic patient with typical Wilson's disease and Kayser-Fleischer rings, liver biopsy is not necessary to confirm the diagnosis. On the other hand, it is useful to confirm the diagnosis in asymptomatic individuals whose only sign of disease is the presence of Kayser-Fleischer rings, as these will fade over time with treatment.



Management

The cornerstone of treatment in Wilson's disease is removal of excess circulating copper by chelation. Currently, the drug of choice is D-penicillamine, which is given in a dose of 250 - 500 mg QID before meals. Some patients do not tolerate the side effects of D-penicillamine, which include minor problems such as a skin rash and more major difficulties such as a lupus-like syndrome of arthralgias and proteinuria. Trientine (triethylene tetramine) is an alternate chelator which is well tolerated, if somewhat less effective. The patients must take concurrent pyridoxine to counteract the weak antipyridoxine effect of D-penicillamine.

Oral zinc diminishes copper absorption, and may be useful in maintenance therapy of patients with Wilson's disease. Patients should be instructed on which foods are high in copper, and asked to avoid them. Adequately chelated patients who are

compliant with their therapy do not need a restricted diet.

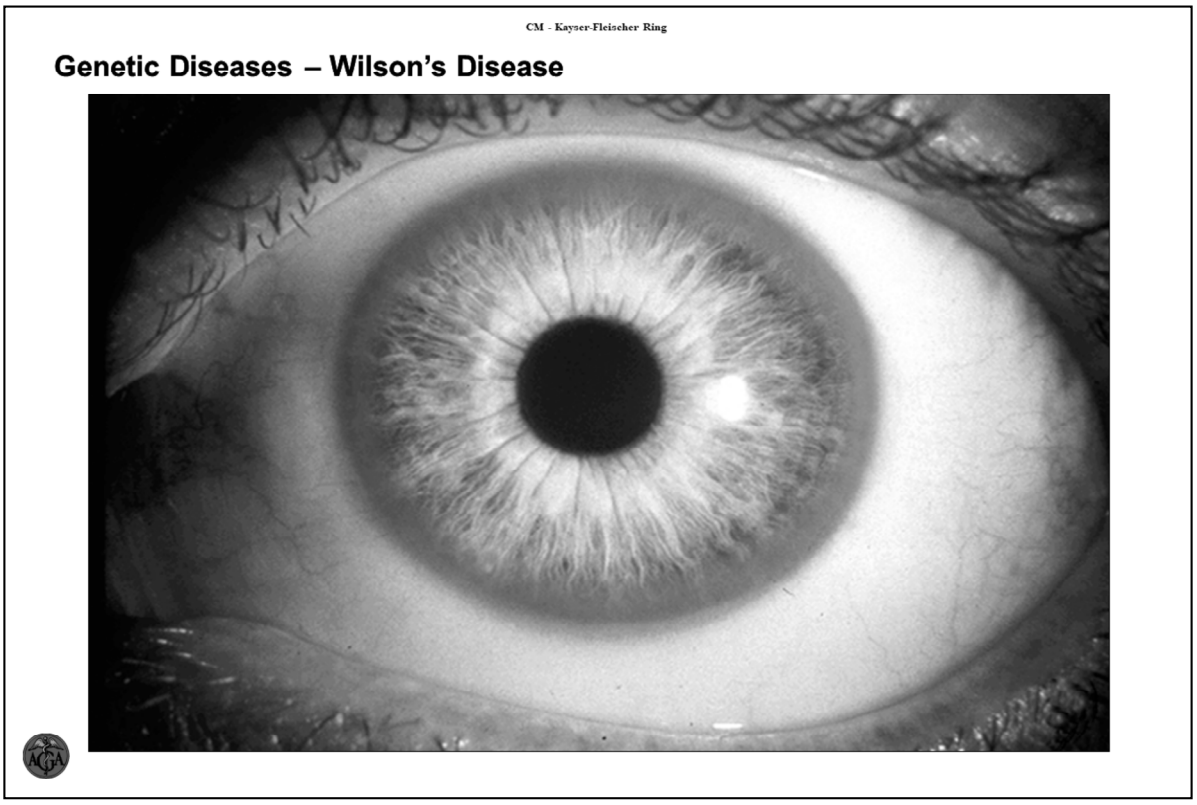
Compliance with therapy is difficult to monitor. In patients with Kayser-Fleischer rings, therapy is associated with a progressive loss in the rings when followed serially by an ophthalmologist. Over time, the urinary excretion of copper decreases, as the patient's copper load decreases. Also of use in follow-up is the serum level of non-ceruloplasmin copper (the total serum copper - the ceruloplasmin bound copper), which should fall with therapy. Compliance is important, as interrupting therapy may be associated with fulminant hepatic failure and death.

The results of treatment of Wilson's disease are very good. Life is prolonged, and the liver and CNS disease may be improved by therapy. When started early in presymptomatic siblings of known patients, therapy prevents the onset of the multiorgan injury of Wilson's disease. Thus, family screening is essential.

Stremmel W, Meyerrose K-W, Niederau C, et al Ann Intern Med 1991;115:720-726.

Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V. J Lab Clin Med 1991;118:466-470.

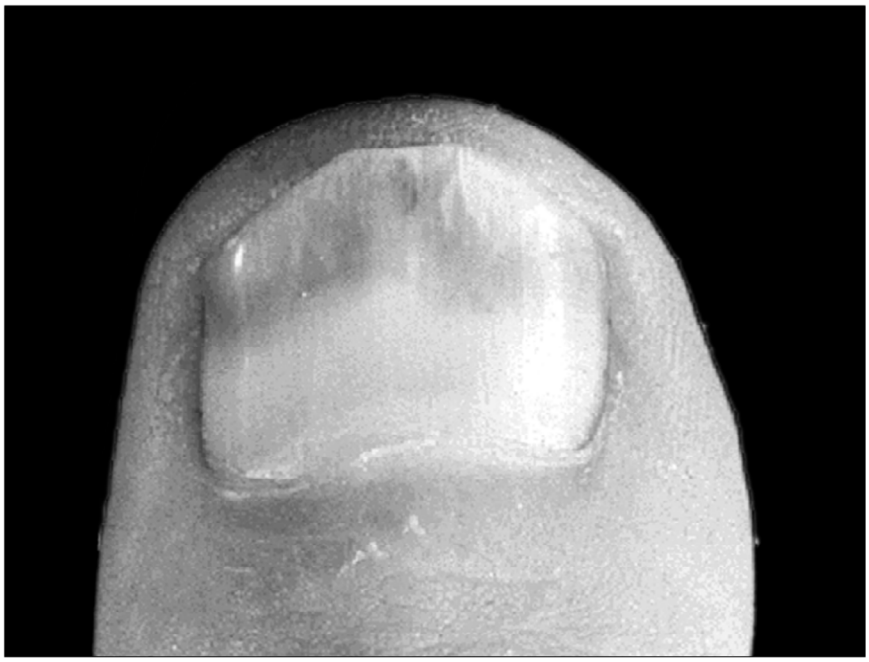
Cox DW, Roberts EA. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis and Management. Edited by M Feldman, LS Friedman, MH Sleisenger. Saunders, Philadelphia 2002; 67: 1269-1277



CM: Kayser-Fleischer Ring

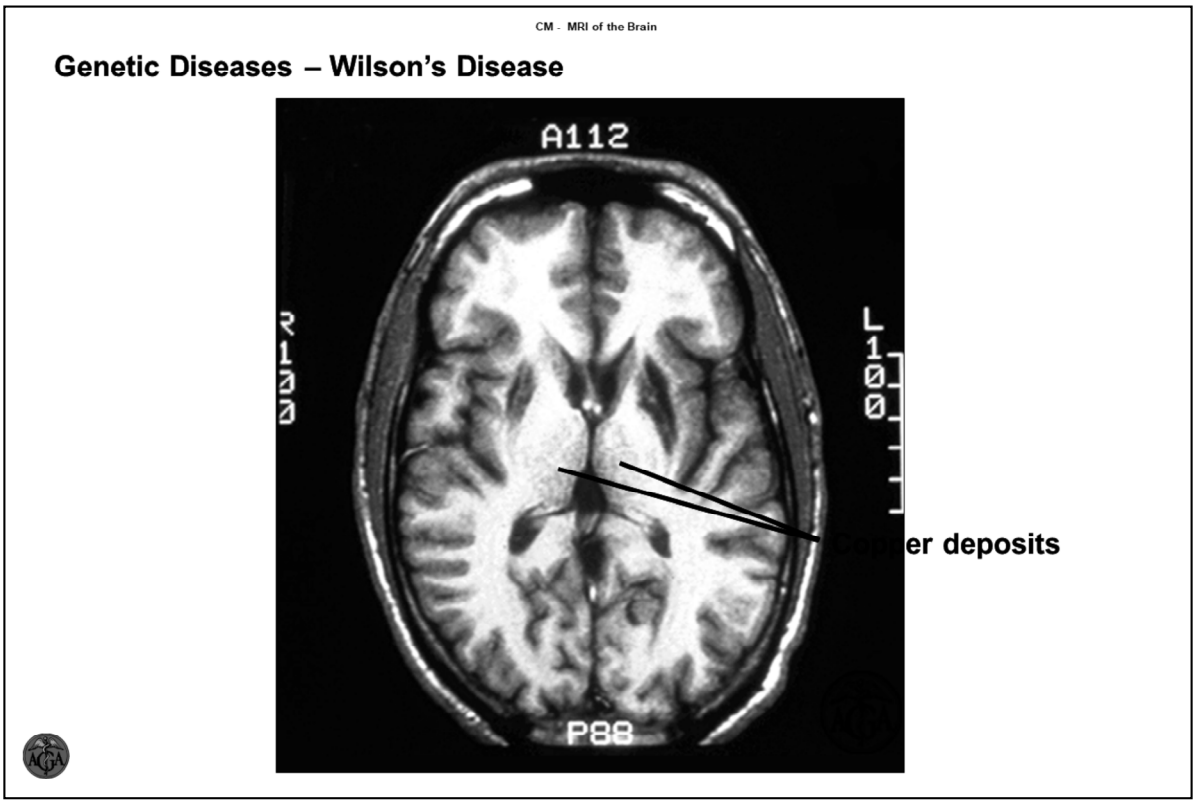
Copper deposition in the eye is seen as Kayser-Fleischer rings, a golden brown deposit in Descemet's membrane seen at the limbus, initially most prominent at 6 and 12 o'clock and later as a concentric ring.

Genetic Diseases – Wilson's Disease



Wilson's Disease

The bluish discoloration of the nails, or azure lunulae, is an unusual manifestation of Wilson's disease. This 43 year old male presented with neurologic symptoms, had Kayser-Fleischer rings and cirrhosis on liver biopsy.



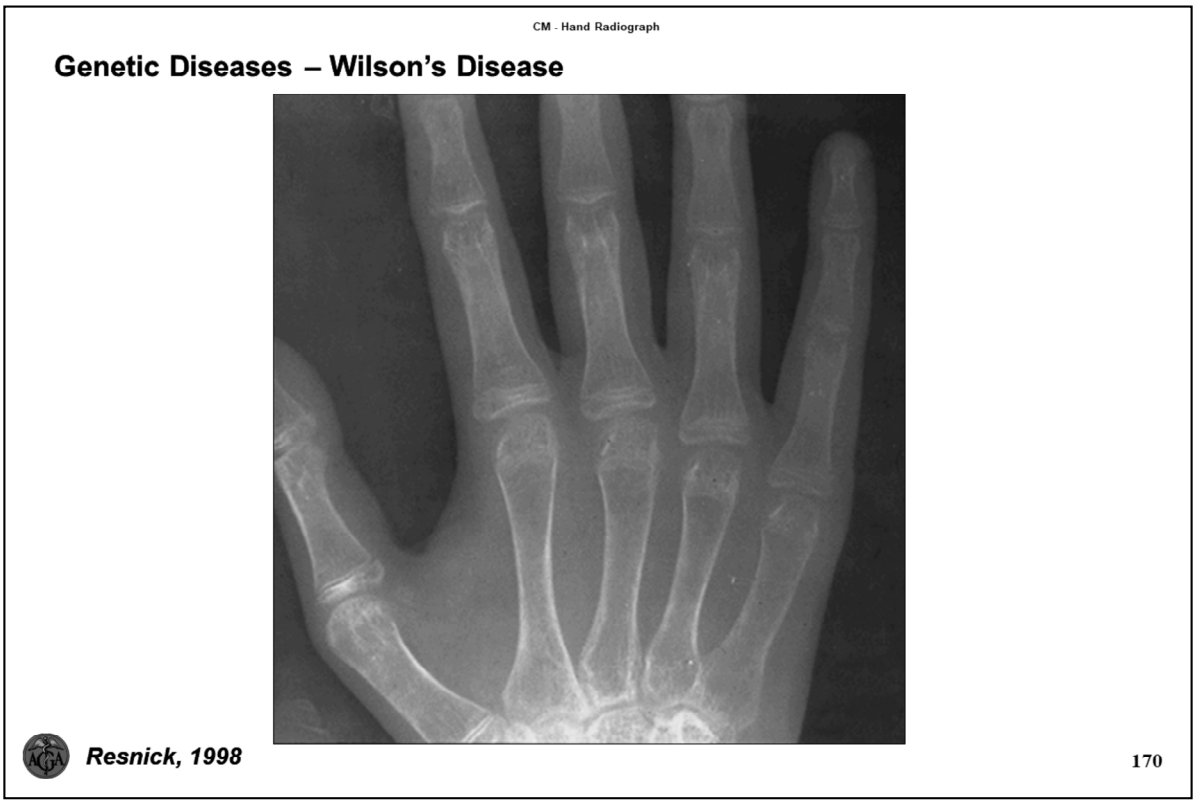
CM - MRI of the Brain

A T1 weighted image on MRI of the brain in this patient with Wilson's Disease shows marked degenerative changes of the basal ganglia bilaterally with greater involvement on the left side. The involvement of lenticular nucleus is typical hence the term hepatolenticular degeneration.

On neurological imaging the typical sites of involvement are the deep gray matter and white matter. Gray matter nuclei involvement is more common and is usually bilaterally symmetrical with variable involvement of the putamen, caudate, thalamus and globus pallidus. White matter lesions are usually asymmetric and located in the subcortical region. The lesions are hypodense on CT, hypointense on short TR MR sequences and variably hyperintense, hypointense or both on long TR sequences. Pathological gliosis, edema and variable necrosis with cavitation occur due to toxicity with copper and/or secondary to ischemia. These changes described likely account for the hypointensity on the short TR image shown.

The cerebral MR images correlate well with the neurologic defects noted. Most patients without neurologic symptoms have normal MR scans while most patients with neurologic symptoms have abnormal studies. Bradykinesia and dystonia correlate with putamen lesions, dysarthria with both caudate and putamen lesions

and distractibility of gaze fixation with frontal lobe involvement.



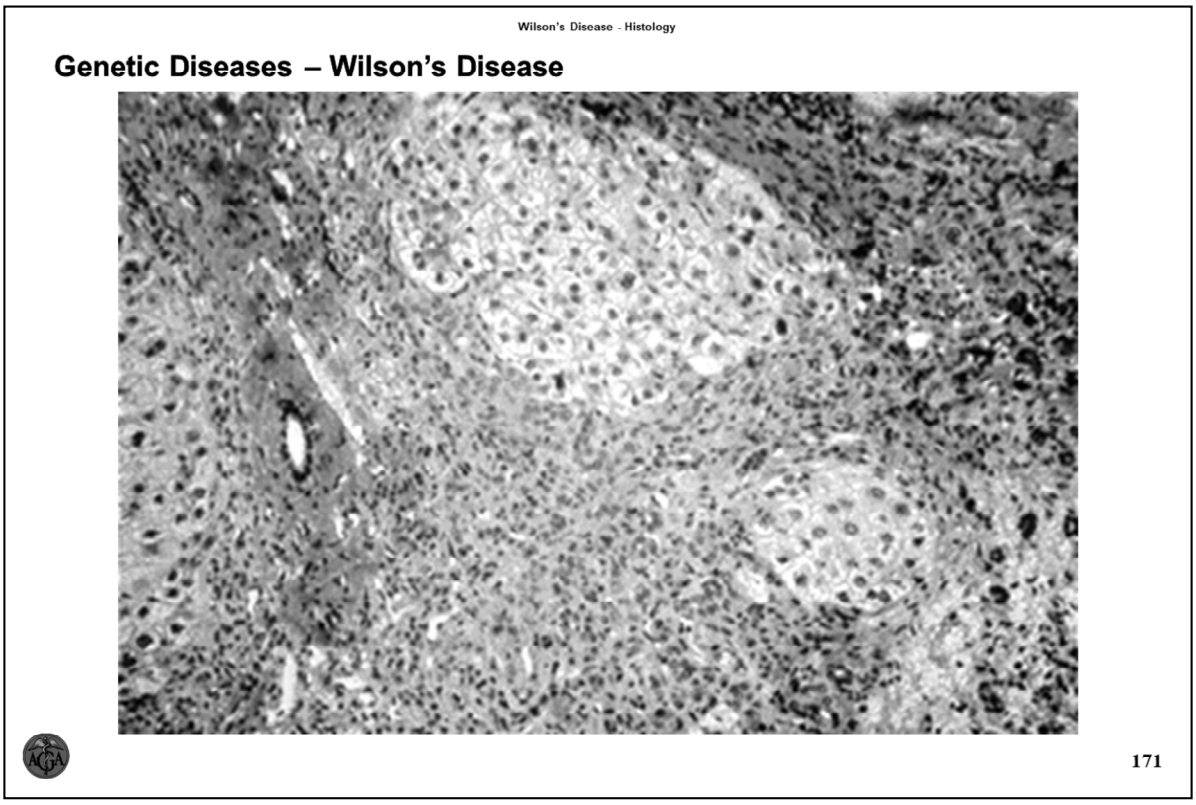
CM - Hand Radiograph

There is a generalized loss of bone density consistent with osteoporosis and osteopenia in this patient with Wilson's disease. There are several radiographic features seen in Wilson's disease. 1) Osteopenia is seen in up to 50% of patients with Wilson's Disease and most apparent in the hands, feet and spine. It may be associated with a high frequency of fractures. The decrease in bone density is presumably a result of loss of calcium and phosphorous ind urine. 2) Chondrocalcinosis is rare in this condition. 3) Articular abnormalities collectively included under arthropathy may be apparent in up to 50% with patients with Wilson's Disease. These include subchrondral bone fragmentation along with cyst formation, cortical irregularities and sclerosis. 4) Miscellaneous abnormalities seen in patients with Wilson's Disease include changes and irregularity of contour of the vertebral bodies which may be wedge shaped and simulate juvenile kyphosis or squared and simulate ankylosing spondylitis.

The pathogenesis of the articular abnormalities in Wilson's Disease remains unknown. The arthropathy most resembles idiopathic CPPD crystal deposition disease and hemochromatosis. The distribution of articular alterations is similar in these three conditions. In Wilson's Disease the distinctive findings include multiple small ossicles and poor definition of the subarticular bone whereas in

hemochromatosis these abnormalities are not apparent and joint space loss throughout the wrist may be seen. In idiopathic CPPD crystal deposition disease larger cysts and more extensive fragmentation are characteristic.

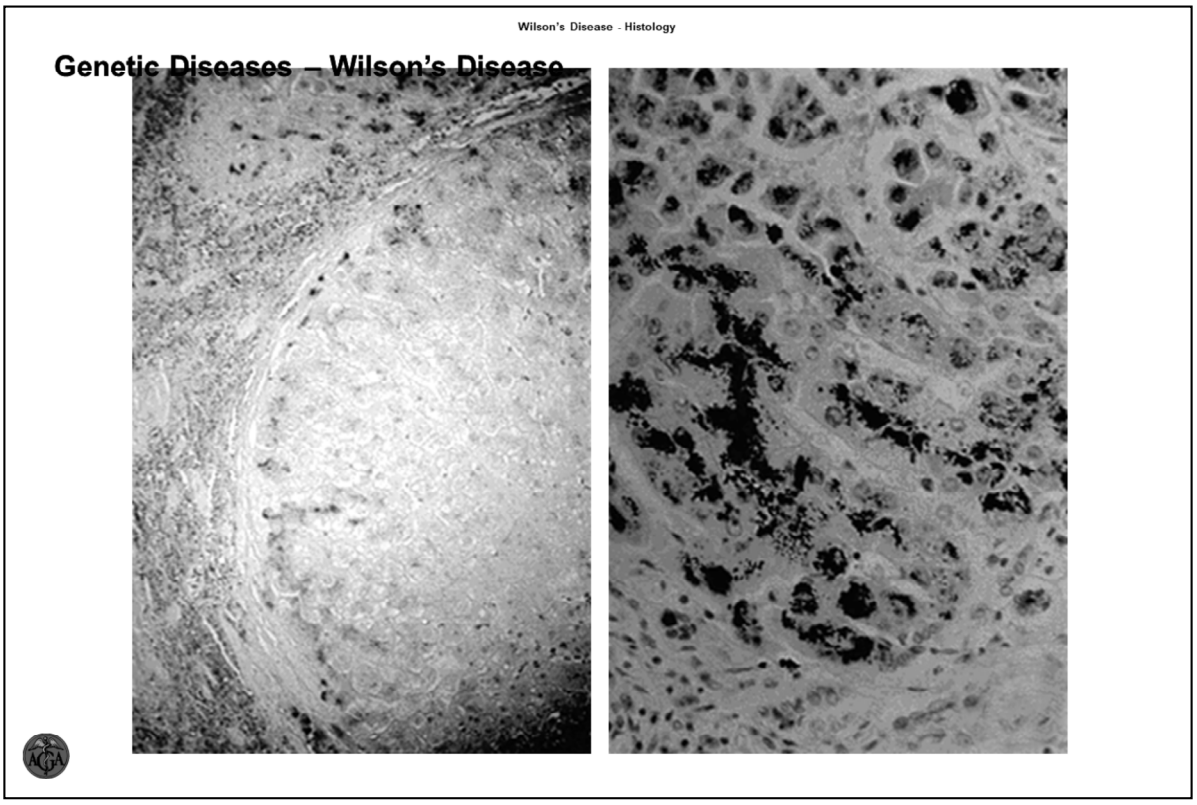
Resnick D. In: Diagnosis of Bone and Joint Disorders, Second Edition, Resnick and Niwayama, eds., Vol 3 Chapter 50. W B Saunders and Company, Philadelphia, 1988, pp 1755-1786.



Wilson's Disease - Histology

Wilson's disease results in a chronic hepatitis which leads to cirrhosis.

This photomicrograph shows cirrhosis, with nodules of regenerating hepatocytes outlined by fibrous septae containing a mononuclear infiltrate (Masson's trichrome stain).



Wilson's Disease - Histology

Copper stains of liver in patients with Wilson's disease may yield positive results, such as those pictured here, but also may be misleading. Copper overload, with positive staining, can be seen in chronic cholestatic syndromes. And the copper staining in patients with Wilson's disease may be spotty, and can be missed in a needle biopsy specimen. The Rubeanic acid stain, left panel, shows copper most densely deposited in the periportal, or periseptal, hepatocytes. The rhodanine stain, right panel, is also markedly positive, confirming deposition of copper in periportal hepatocytes.