Liver diseases II
Hepatitis

Causes:

- **infectious Hepatitis**: viral, Bacterial, Parasitic, and Helminthic
- Autoimmune Hepatitis
- Drug- and Toxin (Alcohol)
- Metabolic
### Table 18-3 The Hepatitis Viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of virus</td>
<td>ssRNA</td>
<td>partially dsDNA</td>
<td>ssRNA</td>
<td>Circular defective ssRNA</td>
<td>ssRNA</td>
</tr>
<tr>
<td>Viral family</td>
<td>Hepatovirus; related to picornavirus</td>
<td>Hepadnavirus</td>
<td>Flaviviridae</td>
<td>Subviral particle in Deltaviridae family</td>
<td>Hepeviridae</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>Fecal-oral (contaminated food or water)</td>
<td>Parenteral, sexual contact, perinatal</td>
<td>Parenteral; intranasal cocaine use is a risk factor</td>
<td>Parenteral</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Mean incubation period</td>
<td>2 to 6 weeks</td>
<td>2 to 26 weeks (mean 8 weeks)</td>
<td>4 to 26 weeks (mean 9 weeks)</td>
<td>Same as HBV</td>
<td>4 to 5 weeks</td>
</tr>
<tr>
<td>Frequency of chronic liver disease</td>
<td>Never</td>
<td>5%-10%</td>
<td>&gt;80%</td>
<td>10% (co-infection); 90%-100% for superinfection</td>
<td>In immunocompromised hosts only</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Detection of serum IgM antibodies</td>
<td>Detection of HBsAg or antibody to HBcAg; PCR for HBV DNA</td>
<td>3rd-generation ELISA for antibody detection; PCR for HCV RNA</td>
<td>Detection of IgM and IgG antibodies; HDV RNA serum; HDAg in liver</td>
<td>Detection of serum IgM and IgG antibodies; PCR for HEV RNA</td>
</tr>
</tbody>
</table>

dsDNA, Double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B core antigen; HBcAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDAg, hepatitis D antigen; HDV, hepatitis D virus; HEV, hepatitis E virus; IV, intravenous; PCR, polymerase chain reaction; ssRNA, single stranded RNA.

• Several clinical syndromes may develop following exposure to hepatitis viruses:

(1) **acute asymptomatic** infection with recovery (serologic evidence only)

(2) **Acute symptomatic** hepatitis with recovery, anicteric or icteric--------incubation period, a symptomatic preicteric phase, a symptomatic icteric phase, and convalescence

(3) **chronic hepatitis**, with or without progression to cirrhosis------HBV, HDV, HCV (m.c)------increased risk for the development of hepatocellular carcinoma.

(4) **acute liver failure/Fulminant hepatitis** with massive to submassive hepatic necrosis------HAV, HBV, or HDV, HEV (pregnant)

(5) **The Carrier State**
Drug- and Toxin-Induced Liver Injury

• As the major drug metabolizing and detoxifying organ in the body, the liver is subject to injury from an enormous array of therapeutic and environmental agents.
• Injury may result from:
  - direct toxicity,
  - through hepatic conversion of a xenobiotic to an active toxin,
  - or be produced by immune mechanisms, such as by the drug or a metabolite acting as a hapten to convert a cellular protein into an immunogen.

Exposure to a toxin or therapeutic agent should always be included in the differential diagnosis of any form of liver disease.
Reactions may be mild to very serious, including acute liver failure or chronic liver disease.
Acetaminophen is the most common hepatotoxin causing acute liver failure.
Alcohol is the most common hepatotoxin causing chronic liver disease.
Drug toxic reactions may be classified as:

**Predictable reactions:** affect all people in a dose dependent fashion------- acetaminophen (suicidal or accidental overdoses of acetoaminophen result in acute liver failure due to effect of toxic metabolite produced by the cytochrome P-450 system)

**Unpredictable reactions:** occurs in rare individuals, depend on idiosyncrasies of the host, particularly the propensity to mount an immune response to the antigenic stimulus or the rate at which the agent can be metabolized -------- halothane

Both classes of injury may be immediate or take weeks to months to develop.
Alcoholic Liver Disease

- Excessive alcohol (ethanol) consumption is the leading cause of liver disease in most Western countries.
- There are three distinctive, albeit overlapping forms of alcoholic liver injury:
  1. hepatocellular steatosis or fatty change,
  2. Alcoholic (or steato-) hepatitis,
  3. Steatofibrosis including cirrhosis in the late stages of disease.
• **Hepatic Steatosis (Fatty Liver):**
  - lipid droplets accumulate in hepatocytes increasing with amount and chronicity of alcohol intake.
  - Fatty change is completely **reversible** if there is abstention from further intake of alcohol.
Figure 18-19 Alcoholic steatosis and steatofibrosis. A mix of small and large fat droplets (seen as clear vacuoles) is most prominent around the central vein and extends outward to the portal tracts. Some fibrosis (stained blue) is present in a characteristic perisinusoidal chicken wire fence pattern. (Masson trichrome stain). (Courtesy Dr. Elizabeth Brunt, Washington University, St. Louis, Mo.)
• Alcoholic (Steato-) Hepatitis:

1. Hepatocyte swelling and necrosis
   (accumulation of fat and water, as well as proteins that are normally exported)

2. Mallory-Denk bodies (intermediate filaments such as keratins 8 and 18 in complex with other proteins such as ubiquitin, characteristic but not specific)

3. Neutrophilic reaction. They may be more or less admixed with mononuclear cells
Figure 18.20  
A, Alcoholic hepatitis with clustered inflammatory cells marking the site of a necrotic hepatocyte. A Mallory Denk body is present in another hepatocyte (arrow).  
B, Alcoholic steatohepatitis with many ballooned hepatocytes (arrowheads). Clusters of inflammatory cells are also present; inset shows immunostaining for keratins 8 and 18 (brown), with most hepatocytes, including those with fat vacuoles, showing normal cytoplasmic staining, but in the ballooned cell (arrow) the ubiquinated keratins are collapsed into the Mallory-Denk body, leaving the cytoplasm "empty." (Courtesy Dr. Elizabeth Brunt, Washington University, St. Louis, MO.)
Alcoholic steatofibrosis:
Alcoholic hepatitis is often accompanied by prominent activation of sinusoidal stellate cells and portal fibroblasts, giving rise to fibrosis. Early stages of scarring can regress with cessation of alcohol use, but the farther along toward cirrhosis the liver gets, the more vascular derangements prevent a full restoration of normal. Complete regression of alcoholic cirrhosis, while reported, is rare.
Figure 18-21. Alcoholic cirrhosis. A, The characteristic diffuse nodularity of the surface is induced by the underlying fibrous scarring. The average nodule size is 3 mm in this close-up view, typical of the "micronodular" cirrhosis of alcoholic liver disease. The greenish tint is caused by cholestasis. B, Microscopically, this cirrhosis is marked by small nodules entrapped in blue-staining fibrous tissue; fatty accumulation is no longer seen in this "burned out" stage. (Masson trichrome stain.)
Figure 18-18 Alcoholic liver disease. The interrelationships among hepatic steatosis, alcoholic hepatitis, and alcoholic cirrhosis are shown, along with depictions of key morphologic features. It should be noted that steatosis, alcoholic hepatitis, and steatofibrosis may also develop independently. In particular, some patients present initially with cirrhosis without any of the other forms of alcoholic liver disease.
Pathogenesis:

- Short-term ingestion of as much as **80 gm** of alcohol over one to several days generally produces mild, reversible hepatic steatosis.
- Daily intake of 80 gm or more of ethanol generates significant risk for severe hepatic injury.
- Daily ingestion of **160 gm** or more for 10 to 20 years is associated more consistently with severe injury.
• Only 10% to 15% of alcoholics, however, develop cirrhosis and it may take 10 to 15 years of drinking for the development of cirrhosis. Thus, other factors must also influence the development and severity of alcoholic liver disease. These include:

- Gender: Women seem to be more susceptible to hepatic injury than men.
- Ethnic and genetic differences: Genetic polymorphisms in detoxifying enzymes and some cytokine promoters may play significant roles and contribute to ethnic differences. ALDH*2, a variant of aldehyde dehydrogenase (ALDH), found in 50% of Asians, has a very low activity. Individuals homozygous for ALDH*2 are unable to oxidize acetaldehyde and do not tolerate alcohol, leading to alcohol intolerance characterized by upper body flushing and, variably, nausea or lethargy.
- Comorbid conditions: Iron overload, HCV and HBV infection------ increased severity of liver disease.
• Exposure to alcohol causes steatosis, dysfunction of mitochondrial and cellular membranes, hypoxia, and oxidative stress.
• **Hepatocellular steatosis** results from
  (1) shunting of normal substrates away from catabolism and toward lipid biosynthesis, as a result of increased generation of reduced NADH by the two major enzymes of alcohol metabolism, alcohol dehydrogenase and acetaldehyde dehydrogenase;  
(2) Impaired assembly and secretion of lipoproteins;  
(3) Increased peripheral catabolism of fat, thus releasing free fatty acids into the circulation.
• **alcoholic hepatitis:**
  - **Acetaldehyde** (the major intermediate metabolite of alcohol) induces lipid peroxidation and acetaldehyde-protein adduct formation, further disrupting cytoskeletal and membrane function.
  - **Cytochrome P-450 metabolism** produces reactive oxygen species (ROS) that react with cellular proteins, damage membranes, and alter hepatocellular function. The induction of cytochrome P-450 enzymes in the liver by alcohol increases alcohol catabolism in the endoplasmic reticulum and enhances the conversion of other drugs (e.g., acetaminophen) to toxic metabolites.
  - Alcohol impairs hepatic metabolism of methionine, which decreases glutathione levels, thereby sensitizing the liver to oxidative injury.
  - Alcohol causes the release of **bacterial endotoxin** from the gut into the portal circulation, inducing inflammatory responses in the liver.
  - Alcohol stimulates the release of endothelins from sinusoidal endothelial cells, causing **vasoconstriction** and contraction of activated myofibroblastic stellate cells, leading to a decrease in hepatic sinusoidal perfusion.
Clinical Features:

- **Hepatic steatosis**: may cause hepatomegaly, with mild elevation of serum bilirubin and alkaline phosphatase levels. Severe hepatic dysfunction is unusual. Alcohol withdrawal and the provision of an adequate diet are sufficient treatment.

- **Alcoholic hepatitis**: tends to appear acutely, usually following a bout of heavy drinking. Symptoms and laboratory manifestations may range from minimal to those that mimic acute liver failure. Between these two extremes are the nonspecific symptoms of malaise, anorexia, weight loss, upper abdominal discomfort, and tender hepatomegaly, and the laboratory findings of hyperbilirubinemia, elevated serum aminotransferases and alkaline phosphatase, and often a neutrophilic leukocytosis.
• With proper nutrition and total cessation of alcohol consumption, the alcoholic hepatitis may clear slowly. However, in some patients, the hepatitis persists, despite abstinence, and progresses to cirrhosis.

• In contrast to other chronic liver diseases where serum ALT tends to be higher than serum AST, **serum AST levels tend to be higher than serum ALT levels in a 2:1 ratio or higher in alcoholic liver disease.** This can be helpful in differential diagnosis of chronic liver injury when adequate history is not available.
The manifestations of **alcoholic cirrhosis** are similar to those of other forms of cirrhosis. Cirrhosis may be clinically silent, discovered only at autopsy or when stress such as infection or trauma tips the balance toward hepatic insufficiency.

In the end-stage alcoholic the proximate causes of death are

1. hepatic coma,
2. massive gastrointestinal hemorrhage,
3. intercurrent infection (to which these patients are predisposed),
4. hepatorenal syndrome following a bout of alcoholic hepatitis,
5. hepatocellular carcinoma (the risk of developing this tumor in alcoholic cirrhosis is 1% to 6% of cases annually).
Metabolic Liver Disease

• either acquired or inherited.
- non-alcoholic fatty liver disease (NAFLD)---- m.c
- hemochromatosis,
- Wilson disease,
- α1-antitrypsin deficiency
- neonatal hepatitis
Nonalcoholic Fatty Liver Disease (NAFLD)

- NAFLD represents a spectrum of disorders that have in common the presence of hepatic steatosis (fatty liver) in individuals who do not consume alcohol or do so in very small quantities (less than 20 g of ethanol/week)—— Pathologic steatosis is defined as involving more than 5% of hepatocytes.
- The term “nonalcoholic steatohepatitis” (NASH) is often used to denote overt clinical features of liver injury, such as elevated serum transaminases, but the designation NAFLD is preferred, with steatohepatitis reserved for histologic features of hepatocyte injury already described in the section on alcoholic liver disease.
- NAFLD are most consistently associated with the metabolic syndrome—— obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension.
- Greater than 90% of previously described “cryptogenic cirrhosis” (i.e., cirrhosis of unknown cause) is now thought to represent such “burned out” NAFLD.
• Pathogenesis:
  - **Insulin resistance** gives rise to hepatic steatosis----- obesity
  - **Hepatocellular oxidative injury** resulting in liver cell necrosis and the inflammatory reactions to it.

In individuals with established insulin resistance and metabolic syndrome, the visceral adipose tissue not only increases, but also becomes dysfunctional, with reduced production of the lipid hormone, adiponectin, and increased production of inflammatory cytokines such as TNF-α and IL-6. These changes in turn promote hepatocyte apoptosis.

Kupffer cell production of TNF-α and TGF-β activate stellate cells directly leading to deposition of scar tissue.
Figure 18-22 Nonalcoholic fatty liver disease. A, Liver with mixed small and large fat droplets. B, Steatosis and steatofibrosis extending along sinusoids in a chicken wire fence pattern in which individual and clustered hepatocytes are surrounded by thin scars (blue fibers). Note the resemblance to alcoholic steatohepatitis depicted in Fig. 18-19. (Masson trichrome stain.)
Clinical features:
- Individuals with simple steatosis are generally asymptomatic. Clinical presentation is often related to other signs and symptoms of the metabolic syndrome, in particular insulin resistance or diabetes mellitus.
- Serum AST and ALT are elevated in about 90% of patients with NASH. Despite the enzyme elevations, patients may be asymptomatic. Others have general symptoms such as fatigue or right-sided abdominal discomfort caused by hepatomegaly.
- The goal of treating individuals with NASH is to reverse the steatosis and prevent cirrhosis by correcting the underlying risk factors, such as obesity and hyperlipidemia, and to treat insulin resistance.
- NASH also increases the risk of hepatocellular carcinoma as do other metabolic diseases.
Figure 18-23  Natural history of NAFLD phenotypes. Isolated fatty liver shows minimal risk for progression to cirrhosis or increased mortality, while non-alcoholic steatohepatitis shows increased overall mortality as well as increased risk for cirrhosis and hepatocellular carcinoma (HCC). DM, Diabetes mellitus.
Hemochromatosis

- Hemochromatosis is caused by excessive iron absorption, most of which is deposited in parenchymal organs such as the liver and pancreas, followed by heart, joints, and endocrine organs.
- Fully developed cases exhibit
  1. micronodular cirrhosis in all patients;
  2. diabetes mellitus in 75% to 80% of patients;
  3. abnormal skin pigmentation in 75% to 80% of patients.

Iron accumulation in hereditary forms is lifelong but the injury caused by excessive iron is slow and progressive; hence **symptoms usually first appear in the fourth to fifth decades of life** in men and later in women since menstrual bleeding counterbalances the accumulation until menopause------hemochromatosis affects more males than females (ratio of 5 to 7 : 1).
• Pathogenesis:
Regulation of intestinal absorption of dietary iron is abnormal, leading to net iron accumulation of 0.5 to 1 gm/year.
The disease manifests itself typically after 20 gm of stored iron have accumulated (the total body iron pool ranges from 2 to 6 gm in normal adults).
• The main regulator of iron absorption is the protein **hepcidin**, encoded by the **HAMP gene** and secreted by the liver. Therefore, hepcidin lowers plasma iron levels. Conversely, a deficiency in hepcidin causes iron overload.

• Transcription of hepcidin is increased by inflammatory cytokines and iron, and decreased by iron deficiency, hypoxia, and ineffective erythropoiesis.

• The adult form of hemochromatosis is almost always caused by mutations of **HFE gene** on Ch 6 (regulate hepcidin level)
• Mutations of HAMP gene cause severe juvenile hemochromatosis.

• Excessive iron appears to be directly toxic to tissues------ inflammation is characteristically absent.
### Table 18-7  Classification of Iron Overload

<table>
<thead>
<tr>
<th>I. Hereditary hemochromatosis</th>
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</thead>
<tbody>
<tr>
<td>Mutations of genes encoding HFE, transferrin receptor 2 (TfR2), or hepcidin</td>
</tr>
<tr>
<td>Mutations of genes encoding HJV (hemojuvelin: juvenile hemochromatosis)</td>
</tr>
<tr>
<td>(Neonatal hemochromatosis)*</td>
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</table>

<table>
<thead>
<tr>
<th>II. Hemosiderosis (secondary hemochromatosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Parenteral iron overload</strong></td>
</tr>
<tr>
<td>Transfusions</td>
</tr>
<tr>
<td>Long-term hemodialysis</td>
</tr>
<tr>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>Leukemias</td>
</tr>
<tr>
<td>Iron-dextran injections</td>
</tr>
<tr>
<td><strong>B. Ineffective erythropoiesis with increased erythroid activity</strong></td>
</tr>
<tr>
<td>β-Thalassemia</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
</tr>
<tr>
<td>Pyruvate kinase deficiency</td>
</tr>
<tr>
<td><strong>C. Increased oral intake of iron</strong></td>
</tr>
<tr>
<td>African iron overload (Bantu siderosis)</td>
</tr>
<tr>
<td><strong>D. Congenital atransferrinemia</strong></td>
</tr>
<tr>
<td><strong>E. Chronic liver disease</strong></td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td><strong>F. Neonatal hemochromatosis</strong></td>
</tr>
</tbody>
</table>

*Neonatal hemochromatosis develops in utero and does not appear to be a hereditary condition.*
Severe hemochromatosis (hereditary or secondary) is characterized principally by
(1) deposition of hemosiderin in the following organs (in decreasing order of severity)
the liver, pancreas, myocardium, pituitary gland, adrenal gland, thyroid and
parathyroid glands, joints, and skin;
(2) cirrhosis;
(3) Pancreatic fibrosis.

Biochemical determination of hepatic tissue iron concentration has been the gold
standard for quantitating hepatic iron content. In normal individuals, the iron content
of liver tissue is less than 1000 μg per gram dry weight of liver. Adult patients with
hereditary hemochromatosis exhibit more than 10,000 μg iron per gram dry weight;
hepatic iron concentrations in excess of 22,000 μg per gram dry weight are associated
with the development of fibrosis and cirrhosis. However, with newly available genetic
testing for these diseases, quantitative assessment of tissue iron content is no longer
necessary for confirmation of a suspected diagnosis.
Clinical Features:
The principal manifestations of classic hemochromatosis include:
- hepatomegaly,
- Abdominal pain,
- abnormal skin pigmentation,
- deranged glucose homeostasis or diabetes mellitus
- cardiac dysfunction (arrhythmias, cardiomyopathy)
- atypical arthritis.
- hypogonadism (e.g., amenorrhea in the female, impotence and loss of libido in the male).

Death may result from cirrhosis or cardiac disease.
A significant cause of death is hepatic cellular carcinoma; the risk is 200-fold greater than in the general population.
Currently most patients with hemochromatosis are diagnosed in the subclinical, precirrhotic stage due to routine serum iron measurements (as part of other diagnostic workup).

Treatment by regular **phlebotomy** steadily depletes tissue iron stores. With treatment, life expectancy is normal.

Screening of family members of probands is important.

Screening involves:
- demonstration of very high levels of serum iron and ferritin,
- exclusion of secondary causes of iron overload,
- liver biopsy if indicated.
Wilson Disease

• Wilson disease is an autosomal recessive disorder caused by mutation of the ATP7B gene on Ch 13, resulting in impaired copper excretion into bile and a failure to incorporate copper into ceruloplasmin and inhibits ceruloplasmin secretion into the blood.

• This disorder is marked by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain, and eye, in addition to decrease in circulating ceruloplasmin. Concomitantly, urinary excretion of copper markedly increases from its normal miniscule levels.
Normally, 40% to 60% of ingested copper (2 to 5 mg/day) is absorbed in the duodenum and proximal small intestine, and is transported to the portal circulation complexed with albumin and histidine.

Free copper dissociates and is taken up by hepatocytes. In the liver copper binds to an α2-globulin (apoceruloplasmin) to form ceruloplasmin, which is secreted into the blood. Ceruloplasmin accounts for 90% to 95% of plasma copper.

Excess copper is transported into the bile.

Circulating ceruloplasmin is eventually endocytosed by the liver, and degraded within lysosomes, after which the released copper is excreted into bile.

This degradation/excretion pathway is the primary route for copper elimination. The estimated total body copper is only 50 to 150 mg.
Morphology:
• Fatty change (steatosis)
• acute, fulminant hepatitis
• Chronic hepatitis
• Steatohepatitis
• Cirrhosis
• chronic obstructive cholestasis
• Toxic injury to the brain primarily affects the basal ganglia, Nearly all patients with neurologic involvement develop eye lesions called Kayser-Fleischer rings, green to brown deposits of copper in Descemet membrane in the limbus of the cornea.

• demonstration of hepatic copper content in excess of 250 μg per gram dry weight is most helpful for making a diagnosis. the vast range of genetic alterations in Wilson disease means that genetic testing is not yet a primary diagnostic modality.
Clinical Features:
- the disorder usually manifests in affected individuals between 6 and 40 years of age.
- acute or chronic liver disease.
- Neurologic involvement presents as movement disorders (tremor, poor coordination) or rigid dystonia (spastic dystonia, mask-like facies, rigidity and gait disturbances); these symptoms may be confused with Parkinsonism.
- psychiatric symptoms such as depression, phobias, compulsive behavior, and labile mood.
- Hemolytic anemia may occur due to toxicity of copper to red cell membranes.
The biochemical diagnosis of Wilson disease is based on:
- a decrease in serum ceruloplasmin,
- an increase in hepatic copper content (the most sensitive and accurate test),
- and increased urinary excretion of copper (the most specific screening test).

Serum copper levels are of no diagnostic value, since they may be low, normal, or elevated, depending on the stage of evolution of the disease.

Early recognition and long term copper chelation therapy (with D penicillamine or Trientine) or zinc-based therapy (which blocks uptake of copper in the gut) has dramatically altered the usual progressive downhill course.
α1-Antitrypsin Deficiency

• α1-Antitrypsin deficiency is an autosomal recessive disorder of protein folding marked by very low levels of circulating α1-Antitrypsin (α1AT). The major function of this protein is the inhibition of proteases, which are normally released from neutrophils at sites of inflammation.
• α1AT deficiency is the most commonly diagnosed inherited hepatic disorder in infants and children.

• α1AT deficiency leads:
  - Pulmonary emphysema
  - Cutaneous panniculitis
  - Liver disease:

  neonatal hepatitis without or with cholestasis and fibrosis
  Childhood cirrhosis
  chronic hepatitis
  steatosis
α1AT is plasma glycoprotein synthesized predominantly by hepatocytes. It is a member of the serine protease inhibitor (Pi) family. The gene, located on chromosome 14.

The most common genotype is PiMM, occurring in 90% of individuals (the “wild-type”).

Some deficiency variants, including:
- the PiS variant, result in a moderate reduction in serum concentrations of α1AT without clinical manifestations.
- PiZZ protein have circulating α1AT levels that are only 10% of normal--- m.c
- PiMZ heterozygotes have intermediate plasma levels of α1AT
- Rare variants termed Pi-null have no detectable serum α1AT.
• With most allelic variants, the protein is synthesized and secreted normally. Deficiency variants show a selective defect in migration of protein from endoplasmic reticulum to Golgi apparatus; this is particularly characteristic of the PiZ polypeptide,

• The mutant polypeptide (α1AT-Z) is abnormally folded (protein misfolding) and polymerized, creating endoplasmic reticulum stress and triggering the unfolded protein response, a signaling cascade that may lead to apoptosis. All individuals with the PiZZ genotype accumulate α1AT-Z in the endoplasmic reticulum of hepatocytes, but only 10% to 15% of PiZZ individuals develop overt clinical liver disease. Other genetic factors or environmental factors are thus posited to play a role in the development of liver disease
Clinical Features.
- Neonatal hepatitis with cholestatic jaundice appears in 10% to 20% of newborns with the deficiency.
- In adolescence, presenting symptoms may be related to hepatitis, cirrhosis or pulmonary disease.
- Alternatively, the disease may remain silent until cirrhosis appears in middle to later life.
- Hepatocellular carcinoma develops in 2% to 3% of PiZZ adults, usually, but not always, in the setting of cirrhosis.

The treatment, indeed the cure, for severe hepatic disease is orthotopic liver transplantation.

Patients with pulmonary disease the single most important preventive measure is avoidance of cigarette smoking, because smoking markedly accelerates emphysema and the destructive lung disease associated with α1AT deficiency.