Section 22

LECTURE

Pathology of the Liver

Morphologic Basis of Liver Disease

Normal Architecture

The Adult liver weighs 1400 to 1600 gm, and rests under the diaphragm, largely protected by the rib cage. Although divided into lobes (right, left, caudate, quadrate) based on external contour and distribution of major branches of the portal vein and hepatic artery, hepatic function is based solely on the microscopic architecture of the liver (Figure 1).

A. Lobule: Central (terminal) vein (THV) in center, portal triad (portal vein, hepatic artery, interlobular bile duct) at periphery

B. Acinus

zone 1 (nearest the blood supply and in the vicinity of the terminal vascular branches of the portal vein and hepatic artery),

zone 2 ("mid-zonal")

zone 3 (furthest from incoming blood, surrounding the terminal hepatic vein and extending towards the portal tracts).

C. Cellular constituents (Figure 2)

1) **hepatocytes:** anastomosing cords or "plates".
"limiting plate"- cells at rim of portal tracts

2) **Sinusoids:** fenestrated **endothelial cells**
Kupffer cells, **Ito cells** present on lumenal side.

3) **Biliary system**
Bile excreted into bile canaliculi.
Bile traverses a short cylinder of cuboidal cells (the canal of Hering or a cholangiole) to join the **"interlobular" bile ducts** within portal tracts, which anastomose sequentially to form the main hepatic bile ducts.

2. Patterns of Damage

a. Response to Injury:

1. Necrosis:
Coagulative necrosis (e.g., infarction); rounding up of isolated hepatocytes with eosinophilia (apoptosis, eosinophilic degeneration; e.g. viral hepatitis); or degeneration with swelling (ballooning degeneration; e.g., toxic damage). Necrosis may be randomly scattered throughout the lobule, or zonal in distribution (periportal, mid-zonal, pericentral). It may range from minimal to massive.

2. Degeneration:
In addition to overt liver cell necrosis, signs of injury include alteration in cellular architecture with edema (ballooning), clumping of cytoskeletal elements (**Mallory's hyaline**), and/or storage of excess material (e.g. iron, copper, lipid, glycogen in metabolic disorders)

3. Steatosis: Lipid accumulation within cytoplasm of hepatocytes. Can be macrovesicular or

microvesicular. Secondary to some combination of decreased fatty acid oxidation, decreased lipoprotein secretion, and increased lipid synthesis. Most characteristic of alcoholic liver disease, but also seen in a variety of disorders affecting lipid metabolism, including diabetes, obesity, protein malnutrition, and certain drug toxicities (e.g. methotrexate, salicylates).

4. Regeneration:
   Hepatocytes and bile ducts have a remarkable capacity to proliferate in response to injury. In the absence of inflammation and scarring, there can be complete restoration of liver architecture and function following an insult causing liver cell necrosis. The presence of fibrous scarring promotes the replacement of normal hepatic parenchyma with abnormal nodules of regenerating hepatocytes.

5. Inflammation:
   Influx of inflammatory cells in response to toxic tissue damage or the expression of abnormal antigens in the liver tissue (hepatitis). This may be limited to the portal tracts, or spill over into the parenchyma. May be composed of lymphocytes (e.g., chronic viral hepatitis), neutrophils (e.g., alcoholic hepatitis), together with varying amounts of plasma cells and eosinophils. Foreign bodies and many organisms induce the formation of granulomas - these may also occur in drug reactions and autoimmune conditions such as Primary Biliary Cirrhosis.

6. Fibrosis:
   Deposition of collagen in response to injury, extending out from portal tracts or the terminal hepatic vein depending on the etiology, and eventually subdividing the liver tissue to create Cirrhosis, a diffuse process of fibrosis with conversion of normal architecture into structurally abnormal nodules.

b. Topology of Liver Damage

Injury to the liver affects portions of the liver acinus in characteristic patterns: identification of hepatic microarchitecture in tissue sections is thus essential:

1. Diffuse parenchymal damage ("pan-acinar"), as in fulminant hepatic injury, fulminant acute viral hepatitis or severe hepatotoxic drug reaction.

2. Periportal damage (e.g., inflammation of the portal tracts extending into the surrounding parenchyma); piecemeal necrosis denotes necrosis of periportal hepatocytes in the setting of inflammatory activity (seen in chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis)

3. Pericentral damage: around the terminal hepatic vein (zone 3; also termed "centrilobular"); seen in chemical toxicity, ischemia.

NON-INFECTIOUS HEPATOCELLULAR DAMAGE

1. **Alcohol**: The prototype of hepatotoxins

a. Alcoholic Steatosis (Fatty Liver): Occurs within a few days of alcohol consumption, and is completely reversible with cessation of alcohol intake. Usually macrovesicular. Grossly, the liver becomes enlarged with a soft greasy yellow cut surface.
b. alcoholic hepatitis: Although potentially reversible, this lesion may smolder on long after cessation of alcohol intake. Mostly neutrophils, with admixed lymphocytes, macrophages.
c. liver cell necrosis, often with Mallory bodies, which appear as coarse eosinophilic skeins of protein, typically found in ballooned hepatocytes.
d. Fibrosis and Cirrhosis: Predominant fibrosis is in zone 3 (centrilobular), often with a component of sinusoidal fibrosis. Resulting cirrhosis is usually micronodular (nodules less than 3 mm). Bile stasis may lend a yellow-green hue to the parenchymal nodules.

2. **Drug-related Injury**: Adverse drug reactions induce an astonishing array of hepatic changes that virtually recapitulate all types of hepatic disease, summarized elsewhere in this lecture. Therefore, adverse drug reactions should be considered in the differential diagnosis of all forms of hepatic disease. Many drugs cause more than one pattern of injury.

a. **Pathogenesis of drug-related injury**: see Dr. Chung's lecture.
b. **Major hepatic drug reactions and some implicated agents**: A complete listing of hepatic drug reactions is beyond the scope of this lecture and is covered elsewhere in the course. However, a few classic examples will be mentioned.

Microvesicular fat: tetracycline, salicylates.
Cholestasis (with or without hepatocellular injury): chlorpromazine, sex steroids, including oral contraceptives
Centrilobular necrosis: acetaminophen, carbon tetrachoride
Hepatitis, acute to chronic: isoniazid, alpha-methyldopa, nitrofurantoin, phenytoin
Fibrosis-cirrhosis: ethanol, methotrexate, amiodarone, cinchophen
Granuloma formation: sulfonamides, alpha-methyldopa, quinidine, phenylbutazone, hydralazine, allopurinol, isoniazid, nitrofurantoin, penicillin
Veno-occlusive disease: cytotoxic drugs, pyrrolidine alkaloids
Hepatic or venous thrombosis: estrogens, including oral contraceptives
Peliosis hepatis: anabolic steroids, thorotrast

3. **Reye's Syndrome**:

Clinical: An acute postviral illness, largely of children, characterized by progressive hepatic failure and encephalopathy. Pathogenesis poorly understood, but may be related to hyperammonemia, elevated serum free fatty acids, and salicylate toxicity and/or synergism. While fatality is 10-40% in reported series, recovery is usually complete.

Pathology: Microvesicular fatty change of the liver (first 3- 5 days of illness); Concomitant disruption of mitochondrial ultrastructure with pleomorphic enlargement, distortion of cristae, formation of electron-lucent matrices. Similar changes in skeletal muscle, kidneys and heart.

4. **Liver Disease in Pregnancy**: In any pregnant woman with evidence of hepatic compromise (e.g., hypoalbuminemia, jaundice, elevated serum liver enzymes), these three lesions must be ruled out:

   a. **Acute fatty liver of pregnancy**: Accumulation of microvesicular fat in hepatocytes, associated with potentially rapid onset of liver failure and death. Etiology is unclear. Treatment: termination of pregnancy. Diagnosis is usually made on an emergency basis, using frozen sections stained for fat.

   b. **Recurrent cholestasis of preganancy**: A benign disease, with pure cholestasis, probably on the basis of steroid-induced hepatocellular damage. While not life-threatening, the pruritus can drive a woman to distraction. Treatment: termination of pregnancy.

   c. **Eclampsia:** Disseminated intravascular coagulation causing necrosis of hepatic parenchyma. Potentially fatal if untreated secondary to hemorrhage and circulatory collapse.

INFECTIONS OF THE LIVER - NON-VIRAL

1. **Liver Abscesses**:

   a. Developing countries: Common; most represent parasitic infections, e.g., amebic, echinococcal, and (less commonly) other protozoal or helminthic organisms.
   b. Developed countries: Uncommon; usually bacterial or in origin, typically is a complication of infection elsewhere.
   c. Mechanism of spread: Organisms reach the liver via the portal vein (e.g., intra-abdominal infection), arterial supply (systemic infection), biliary tree (e.g., ascending cholangitis), or direct invasion from adjacent structures, or by a penetrating injury.
   d. Histologic features: Usually non-specific, although parasitic fragments may be identifiable in tissue sections.

2. **Diffuse parenchymal infection, non-viral**: Often in Kupffer cells. Formation of granulomas is common.

   a. **Fungi:** Histoplasmosis, Candida
   b. **Protozoa:** Toxoplasmosis, leishmaniasis
   c. **Malaria** and the liver: deposition of malarial pigment (hemozoin) in Kupffer cells, or sinusoidal lymphocytosis with impairment of sinusoidal blood flow (*Tropical Splenomegaly Syndrome*).

3. **Parasites**: Hepatic disease other than abscess formation includes:

   a. **Schistosomiasis**:Deposition of ova within hepatic parenchyma, inducing a brisk eosinophilic inflammatory response, granuloma formation, and progressive portal-based fibrosis, which causes obliteration of branches of the portal vein, resulting in non-cirrhotic portal hypertension.
   b. **Clonorchiasis, Fascioliasis**:Liver flukes migrate up the biliary tree and inhabit the major intrahepatic bile ducts.
   c. **Other reported parasites:** Ascariasis, toxocariasis, capillariasis.

VIRAL HEPATITIS

1. **Systemic viral infections** that may involve the liver include:

   a. *Infectious Mononucleosis (Epstein-Barr virus):* generally mild hepatic involvement with sinusoidal lymphocytosis, may cause lymphoma in the immunocompromised
   b. *Cytomegalovirus:* diffuse parenchymal infection. Viral cytopathic changes visible.
   c. *Herpes virus:* In overwhelming systemic infection, rarely as an isolated event. Usually causes bland (i.e. without inflammation) necrosis of hepatic parenchyma.
   d. In children, rarely: *rubella, adenovirus, enterovirus*

2. **The Hepatotropic Viruses**-account for most viral infections of the liver. All produce similar patterns of clinical and morphological acute hepatitis, but vary in their potential to induce chronic or fulminant disease or the carrier state.

CLINICAL FEATURES

a. Hepatitis A Virus (HAV)

- self-limited disease, fecal-oral spread, incubation period 14-45 days
- accounts for 20-25% of acute hepatitis in developing world
- Does not cause chronic disease or carrier state, fulminant hepatitis is rare.

b. Hepatitis B Virus (HBV)

-The most versatile hepatitis virus, producing:

- aymptomatic carrier state
- acute hepatitis with complete recovery
- chronic hepatitis, either indolent or progressive
- fulminant hepatitis with massive liver necrosis
- risk factor for hepatocellular carcinoma

-Spread mainly by parenteral routes (transfusion, blood products and body fluids, needle-stick accidents and shared needles, during parturition, sexual activity)

c. Hepatitis C Virus (HCV):

- Identified in 1989, accounts for >90% of post-transfusion hepatitis that was previously designated "Non-A, Non-B". Anti-HCV present in a considerable proportion of patients with other chronic liver diseases.

-Also a "versatile" virus, with similar spectrum of disease to HBV. However, progression of chronic liver disease appears to be more frequent than for HBV.

d. Delta Hepatitis Virus (HDV)

-A small, defective RNA virus that can replicate and cause infection only when it is encapsulated by HBsAg. Hence, HDV can develop only when there is concomitant HBV infection, either acute coninfection or superinfection of HBV carrier.

- May cause anything from mild to fulminant acute hepatitis.

e. Hepatitis E Virus (HEV)

- Enterically transmitted, water-borne infection.
- Occurs primarily in young-to-middle aged adults in epidemic form.
- Generally mild, but fatality may approach 20% in pregnant women.
- Average incubation time is 6 weeks following exposure.

f. Other Hepatotropic viruses (? F,G . . .)

3. Pathobiology of Viral Hepatitis:

a. *The Carrier State:* An individual without manifest symptoms who harbors and therefore can transmit an organism. Most HCV, some HBV (especially congenitally infected children), no HAV-infected individuals.

Pathology: normal liver architecture and hepatocytes. In HBV infection, isolated - cells or clusters may show a finely granular, eosinophilic cytoplasm ("ground glass"), staining positive with orcein, aldehyde fuchsin, or HBVsAg immunoperoxidase stains. By EM: tubules and spheres of HBsAg in the cytoplasm. In some HBV carriers, there may be evidence of chronic disease (see below).

b. *Acute Hepatitis* (similar for all hepatitis viruses): divided into incubation period, symptomatic pre- icteric phase, symptomatic icteric phase, and convalescence.
Pathology (can be mimicked by drug reactions):
1) Necrotic hepatocytes with balooning or with eosinophilic cytoplasm (Councilman bodies).
2) Mononuclear inflammation, consisting primarily of lymphocytes. Necrotic foci are associated with clusters of macrophages
3) In more severe cases, the necrosis may extend across the entire lobule ("bridging necrosis") or even involved the entire liver ("massive necrosis")

c. *Chronic Hepatitis:* Symptomatic, biochemical or serological evidence of continuing inflammatory hepatic disease for more than six months without steady improvement. Occurs commonly with HCV and with HBV (particularly with HDV superinfection).

1. Portal tract chronic inflammation: Portal tracts are expanded by an inflammatory infiltrate of lymphocytes, macrophages, occasional plasma cells and rare segmented leukocytes. In mild cases, the infiltrate is limited to the portal tracts and does not spill out into the hepatic parenchyma.

2. More severe chronic (i.e. chronic active) hepatitis:
1) Portal inflammatory infiltrate extends into the surrounding lobule.
2) *Piecemeal necrosis* (inflammatory cells in direct contact with liver cells undergoing degeneration and fragmentation, lending a "moth-eaten" appearance to the limiting plate);
3) Necrosis of hepatocytes, which may range in severity from single cells to bridging necrosis with collapse of the reticulin framework.
4) *Progressive fibrosis* extending from the portal tracts into the hepatic parenchyma, leading in many cases to a fully developed cirrhosis.

b. Differentiating features:

HBV, HDV and, hopefully, HCV can be identified by immunocytochemical or in situ hybridization methods. Ground-glass cells may be present in HBV infection. HCV hepatitis frequently exhibits mild steatosis, lymphoid follicle formation in portal tracts and sinusoidal lymphocytosis, and mononuclear inflammation of bile ducts (bile ducts are not destroyed).

There are also many non-viral causes of chronic hepatitis, including drugs, metabolic disorders such as Wilson's disease, autoimmune hepatitis, and primary biliary cirrhosis. Distinguishing histologic features among these possibilities are for the most part absent. An increased proportion of eosinophils and neutrophils is suggestive of a drug reaction.

d. *Massive Necrosis (Fulminant Hepatitis):* Defined as hepatic insufficiency progressing from onset to death (or hepatic transplantation) within 2-3 weeks. Viral hepatitis accounts for 50-65% of cases, but may also result from drugs, poisoning (e.g., Amanita phalloides), and many other causes.

Pathology: The entire liver may be involved or only portions. Microscopically, entire lobules or portions thereof may be necrotic, with liquefaction of hepatocytes and collapse of the reticulin framework, with surprisingly little inflammatory reaction. If the patient survives for more than a week, secondary changes develop, including marked regeneration of hepatocytes, which take on the appearance of proliferating ductules, and hypertrophy and hyperplasia of surviving Kupffer cells, which become laden with lipofuscin and cellular debris.

CIRCULATORY DISORDERS

1. **Impairment of vascular inflow**
Infraction is rare, due to the double blood supply of the liver. Nevertheless, significant vascular impairment may occur.

a. **Liver infarcts**: Thrombosis or compression of an intrahepatic branch of the hepatic artery by polyarteritis nodosa, embolism, neoplasia, or sepsis may result in a localized infarction.

b. **Portal vein obstruction and thrombosis**: Extrahepatic causes include malignancy in abdominal organs, peritoneal sepsis with portal vein pylephlebitis (this may also occur with hepatic abscess), pancreatitis with splenic vein thrombosis propogating into the portal system, and postsurgical thrombosis. Intrahepatic causes are most frequently cirrhosis (see below).

c. **Low-flow states with Shock or Left Ventricular Failure**: Ischemic necrosis of zone 3 hepatocytes (those furthest from the blood supply), also termed centrilobular necrosis.

d. **Sinusoidal occlusion**: Sickle Cell Disease and Disseminated Intravascular Coagulation may cause direct occlusion of sinusoidal channels by sickled erythrocytes and fibrin thrombi, respectively.

2. **Impairment of Vascular Outflow:** Common histologic features:
Acute: centrilobular congestion, may result in hemorrhagic necrosis
Chronic: Atrophy of centrilobular hepatocytes, and pericentral fibrosis.

a. **Acute and Chronic Passive Congestion and Central Hemorrhagic Necrosis**:
Usually cardiac (particularly right-sided) failure (this is commonplace at autopsy, the result of preterminal circulatory failure). Macroscopically, the congestion and subtle depression of the centrilobular areas have been termed nutmeg liver.

b. **Hepatic Vein Thrombosis (Budd-Chiari Syndrome)**: systemic thrombotic disorders.

c. **Hepatic Veno-occlusive Disease (VOD)**: Associated with hepatotoxic alkaloids found in herbal teas (Jamaican "bush tea"), antineoplastic drugs, immunosuppressants, and hepatic irradiation, VOD is of primary concern in patients post-bone marrow transplant with hepatic dysfunction. The terminal hepatic vein exhibits focal subendothelial deposition of a delicate collagen network, with ultimate obliteration of the smaller veins of the liver. Thrombosis may propogate into the major veins, mimicking Budd-Chiari syndrome.

JAUNDICE AND CHOLESTASIS

Jaundice (also termed icterus) is the clinical indicator of hyperbilirubinemia. Cholestasis refers to cessation of bile flow with accumulation of biliary substances in blood, including bile salts, bilirubin and biliary proteins (e.g., alkaline phosphatase). Morphologically, cholestasis is evident as accumulation of pigmented material in tissue sections:

-ballooned hepatocytes with wispy cytoplasm ("feathery degeneration")
-dilated canaliculi with green-brown plugs of bile ("canalicular cholestasis"), typically around terminal hepatic vein.
Bile may rupture into the extravascular space and be phagocytosed by Kupffer cells, or may for bile lakes in the parenchyma.

A. **Extrahepatic biliary obstruction. (e.g., gallstones, tumor, extrinsic compression)** Specific histologic features in the portal tracts include:
-Portal tract edema and bile duct distension, and periductular inflammation ("cholangiolitis"), particularly neutrophils.
-Proliferation of bile ductular structures in the portal tract and at the junction of the portal tract and hepatic parenchyma.
-Superimposed bacterial infection of the biliary tree results in neutrophils entering the bile ductular lumen in great numbers ("cholangitis").

B. **Cholestatic drug reactions** (see above).

C. **Primary biliary tract diseases**
There is a specific set of diseases that involve direct destruction of bile ducts, each with a characteristic morphology. Unfortunately, characteristic features are not always present, and so differentiating these diseases from one another and from secondary biliary obstruction and chronic active hepatitis is frequently problematical.

1. Primary Biliary Cirrhosis (PBC): Thought to be an autoimmune disorder focused on inter-lobular bile ducts and cholangioles, this disease causes chronic inflammation of intrahepatic bile ducts leading to their destruction and, in time, cirrhosis. Primarily affects women (F:M ratio 9:1), with average age of clinical onset 50-55 years (range 20-80 years).

a. **Pathology**: Histological damage is irregular and may vary in severity within a given liver. Assessment of disease progression by biopsy is thus somewhat unreliable. Nevertheless, four histological stages have been described which are helpful in monitoring disease status.

1. **Stage I: Florid Duct Lesion**: dense portal infiltrate of lymphocytes, plasma cells and scattered other inflammatory cells, granulomas around bile ducts with lymphocytic infiltration of bile ductular. Parenchymal cholestasis may be present.
2. **Stage II: Ductular Proliferation**: The portal inflammation remains, and may spill over into

the parenchyma, resembling chronic active viral hepatitis.
3. **Stage III: Fibrosis**: Fibrous septa may interconnect portal areas and create nodules. Bile ducts are markedly reduced, inflammation is less marked, granulomas are infrequent, and cholestasis may be prominent.
4. **Stage IV: Cirrhosis**: Fibrous septa subdivide the liver into overt micronodules.

2. Primary Sclerosing Cholangitis (PSC): An uncommon cholestatic condition with hyperbilirubinemia and elevated serum alkaline phosphatase, and frequently associated with chronic ulcerative colitis.

Pathology: Segmental, random and uneven chronic fibrosing inflammatory reaction involving single or multiple combinations of intra- and extrahepatic bile ducts, leading to focal fibrous stricture or obliteration of the biliary tree. A milder variant (pericholangitis) with mild periductular inflammation without sclerosis is seen in many patients with ulcerative colitis undergoing liver biopsy.

3. Graft-versus-Host Disease (GVHD): A serious complication of allogeneic bone marrow transplantation. Hepatic involvement with this disease reflects attack of the donor immune system on antigens expressed on the biliary epithelium

Pathology: Portal tracts show lymphocytic infiltration and necrosis of bile ducts. Cholestasis is prominent. Particularly characteristic is endothelialitis, in which lymphocytes attach to and infiltrate the endothelium of the terminal hepatic vein and/or portal vein, lifting the endothelium off the basement membrane. Over time bile ducts decrease in number, and fibrosis may develop around the portal tract.

4. Paucity of Bile Duct Syndromes: Diminished or absent intrahepatic bile ducts, ranging from inflammatory to syndromatic conditions. Of primary concern is **Biliary Atresia**, which is inflammatory loss of bile ducts in the weeks following birth, requiring surgical intervention for survival.

CIRRHOSIS

Cirrhosis has been mentioned several times above (see the discussions of alcohol, viral hepatitis, and biliary tract diseases), but merits separate emphasis. Cirrhosis is the generic term for hepatic disease of varied etiology having the following characteristics:

1) Interconnecting fibrous scars formed in response to hepatocytic injury and loss which obliterate the normal hepatic architecture.
2) Nodules of regenerative hepatocytes, varying from micronodules (less than 3 mm in diameter) to macronodules (3 mm to several centimeters in diameter).
3) Abnormal arteriovenous interconnections.
Once cirrhosis is established, determining the etiology may be quite difficult. Such features as loss of bile ducts, accumulation of iron or copper (see below), or ground glass cells may permit identification of the underlying disease process.

- **Alcoholic Cirrhosis** (60-70% of cirrhotic livers in the Western World): Typically micronodular; only with long-standing regeneration do larger macronodules develop. Fibrous bands are usually central-portal.

- **Biliary Cirrhosis** (5-10%): With long-standing mechanical obstruction of the biliary tree **(Secondary Biliary Cirrhosis),** fibrous bands usually link portal tracts. This appearance together with bile ductular proliferation and cholestasis suggest an obstructive etiology.
- **Post-necrotic Cirrhosis** (10%): Macronodular. Most commonly postviral, but may also result from repeated (rarely single) doses of a hepatotoxic drug
- **Pigment Cirrhosis** (5%); as in primary or secondary hemochromatosis, see below): macronodular cirrhosis. Inflammation is largely absent, so that the presence of inflammation suggests a second cause of cirrhosis (e.g. viral).
- **Cirrhosis associated with Storage Disorders** (rare): Wilson's Disease and other storage disorders such as Galactosemia, Tyrosinemia and Alpha-1-antitrypsin deficiency. Demonstration of abnormal substances or characteristic ultrastructural changes is helpful in sorting out etiology.
- **Cryptogenic Cirrhosis** (10-15%): Frequently incidental or presenting as end-stage liver disease, there are no pathologic or clinical features that permit determination of the causative process.

INBORN ERRORS OF METABOLISM

The histological features of these disorders frequently overlap with the patterns of damage described for acquired diseases, and it is important to keep them in mind during work-up of any liver disease. Although a multitude of inherited metabolic disorders affect the liver, only specific examples will be addressed.

1. **Primary Hemochromatosis**: An autosomal recessive disorder with massive accumulation of iron in visceral organs and skin. Prior to modern diagnostic techniques, diagnosis was based on the classic triad of micronodular cirrhosis, diabetes mellitus, and skin pigmentation (giving rise to the term "bronze diabetes"). Now diagnosed on the basis of elevated serum indices of circulating iron and quantitation of hepatic iron content in liver biopsies. Successful treatment requires a regular program of phlebotomy.

Pathogenesis
- Postulated mechanisms includes a defect in regulation of iron absorption by the duodenum and jejunum, a defect in the immediate post-absorptive excretion of iron, and a genetic inability of phagocytes to take up iron.
- The excess cytoplasmic iron may generate free radicals generation leading to cell damage, or to lysosomal disruption.
- The hemochromatosis "gene" is linked to HLA-A3, and is arguably the most prevalent allele for inherited metabolic disease, with a frequency of 1:200. Heterozygotes have low to intermediate accumulation of iron, which may be exacerbated by alcoholism.

Pathology
-Excessive deposits of iron (mainly ferritin and hemosiderin) in the liver, pancreas, myocardium, joint linings, endocrine glands and skin
-Micronodular cirrhosis of the liver with minimal inflammation
-Iron deposition is at first in periportal hepatocytes and eventually involves the whole lobule. With severe iron deposition, Kupffer cells also become loaded. Quantitative iron determination may reveal upwards of 2 mg iron per g liver dry weight. With long-term treatment, the iron is effectively removed, and much of the fibrous tissue may be resorbed.

Secondary hemochromatosis (due to ineffective erythropoiesis, as in erythrogenesis imperfecta; or transfusion iron overload, as in thalassemics and hemodialysis patients) exhibits a more even

distribution of iron between Kupfer cells and hepatocytes - clinical history usually allows easy distinction from primary hemochromatosis.

2. Wilson's Disease (Hepatolenticular Degeneration)
An autosomal recessive disorder of copper metabolism marked by accumulation of toxic levels of copper in the liver, brain and eye. Defect may involve defective mobilization of copper from hepatocellular lysosomes for excretion into bile. Clinical indices are: decreased serum ceruloplasmin, increased hepatic copper content, increased urinary excretion of copper, and "Kayser-Fleischer rings" in the cornea (green-brown deposits of copper in Descemet's membrane).

Pathology: May range from minor to severe.
-Fatty change, with occasional hepatocyte necrosis.
-Acute hepatitis, resembling viral hepatitis, with fatty change and some stainable copper
-Chronic active hepatitis, resembling viral, but with Mallory bodies, fatty change and copper accumulation
-Cirrhosis, micronodular to macronodular, with features of the above CAH
-Massive liver necrosis, fortunately rare

3. Alpha-1-Antitrypsin deficiency (A1AT)
An autosomal allelic (codominant) condition marked by abnormally low serum levels of this protease inhibitor, due to impaired hepatic secretion of defective protein. The resultant deficiency permits proteolytic enzymes to run amok, with particular damage to the basilar lobes of the lungs.

Pathology: Accumulation of globular protein within hepatocytes (within the endoplasmic reticulum by electron microscopy), stainable by PAS and immunoperoxidase. The mechanism of hepatocellular damage is not known.
-Associated with neonatal hepatitis, and with cirrhosis in children and adults.

BENIGN PROLIFERATIONS AND TUMORS

1. Cavernous Hemangioma (common): Frequently beneath the liver capsule, these discrete red-blue, soft nodules are made of cavernous endothelium-lined, blood-filled channels.
2. Cysts: Occuring singly or multiply, they have been subdivided into:
Simple cysts: Lined by flattened biliary epithelium, up to several cm in
siameter, occuring singly or in clusters (microhamartomas).
Congenital Intrahepatic Dilations of biliary tree, occuring in Caroli's Disease and Polycystic Liver Disease
Choledochal cysts: usually in extrahepatic biliary tree

3. Focal Nodular Hyperplasia: Well-demarcated but poorly-encapsulated nodules up to several cm in diameter, marked by prominent central stellate scarring on cut section. Microscopically composed of normal-appearing parenchyma between prominent fibrous septa containing proliferated bile ductules and an intense lymphocytic infiltrate. Evidence for association with oral contraceptives is controversial.

4. Adenoma
Bile Duct Adenoma: Firm, pale, discrete nodule rarely over 1 cm in diameter.
Composed of epithelium-lined channels or ducts separated by scant-to-abundant connective tissue.
Generally considered to be hamartomas, usually an incidental finding.
Hepatocellular Adenoma: Well-demarcated soft, pale yellow-tan and frequently bile stained nodule

ranging from several cm to up to 30 cm in size. Sheets and cords of cells resembling normal hepatocytes or with more variation in cell and nuclear size. Typically marked by abnormally arrayed blood vessels with no portal tracts or bile ducts evident. Strongly associated with use of oral contraceptives, also with pregnancy and use of anabolic steroids.

MALIGNANT TUMORS

1. **Hepatocellular Carcinoma (HCC;** unfortunately, also called "hepatoma"): Accounts for 90% of primary liver cancers, arising typically in the mid-to-late decades of life with a male:female ratio of 3-4:1. Accounts for 40% of all cancers in high-incidence locales (Africa, Southeast Asia). In U.S. and Western Europe, HCC represents 2-3% of all cancers.

a. Etiology: Strongly associated with protracted HBV infection, particularly when acquired early in life;cirrhosis from other causes (alcoholism, primary hemochromatosis, Tyrosinemia); environmental carcinogens (aflatoxin B_1 from Aspergillus flavus); and iatrogenic carcinogens (Thorotrast).

b. Gross: unifocal, usually large mass; as multifocal nodules; or diffusely infiltrative

c. Microscopic: may range from well-differentiated to highly anaplastic undifferentiated lesions. In well-differentiated tumors, tumor cells resemble hepatocytes and are arranged in trabecular (sinusoidal) or acinar (tubular or pseudoglandular) patterns. Features helpful in determining hepatocellular origin are bile formation in canaliculi (by light microscopy; uncommon in poorly differentiated tumors), cytoplasmic inclusions resembling Mallory bodies, and immunoperoxidase staining for alpha-fetoprotein.

d. Prognosis: Usually grave, but dependent upon tumor stage and coexisting cirrhosis.

Fibrolamellar variant of HCC: Arising in the absence of identifiable risk factors or underlying liver disease in children, adolescents and young adults, it is more often resectable, with 60% survival at 5 years. Usually a single, sometimes encapsulated multinodular mass, this variant contains prominent fibrous bands separating trabeculae of large, eosinophilic polygonal hepatocytes. Hyalin globules and PAS-positive inclusions may be present in the cytoplasm of tumor cells.

2. **Cholangiocarcinoma**: Arising from elements of the intrahepatic biliary tree.

a .Etiology: Thorotrast, protracted infection of the biliary tree with clinorchis, other parasites.

b. Gross: unifocal large mass, multifocal, or diffusely infiltrative.

c. Microscopic: neoplastic glands and tubules, and may closely resemble adenocarcinomas elsewhere. Dense fibrous stroma, vascular invasion common.

d. Prognosis: Dismal, as these tumors are rarely resectable at the time of detection.

3. **Mixed HCC-cholangiocarcinoma** variants occur rarely.
4. **Angiosarcoma**: A highly aggressive neoplasm resembling those occuring elsewhere, associated with exposure to vinyl chloride, arsenic and Thorotrast - the latent period has ranged up to several decades.
5. **Hepatoblastoma**: A rare tumor of infancy recapitulating development of the liver in utero, capable of metastasis (and thus lethal) but sometimes resectable. May be either **epithelial** (small, compact dark embryonal or fetal hepatocytes) or **mixed** type (composed of the above cells mixed with those having greater differentiation, and interspersed with foci of mesenchymal differentiation).
6. **Metastatic tumors**: overwhelming majority of hepatic malignancies. Most commonly from carcinomas of the breast, lung and colon. Typically, multiple implants are present, with massive enlargement of the liver (up to several kg) in advanced cases.

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