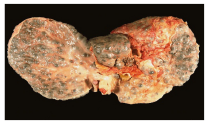
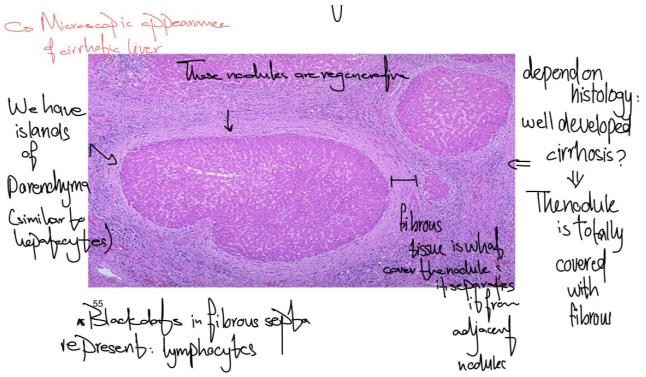
Patho 3

Causes of death in alcoholic liver disease:

Hepatic failure, massive GI bleeding, infections, hepatorenal syndrome, HCC in 3-6% of cases.

Cirrhosis

Definition	Chronic, DIFFUSE (INVOLVE WHOLE LIVER), characterized by fibrosis and the conversion of liver parenchyma into nodules	
Main characteristics	bridging fibrous septa, parenchymal nodules circled by fibrotic bands, diffuse architecture disruption. (that's why when we take small biopsies the whole nodule may not be presented, so we need to ask the radiologist to make sure it is DIFFUSE)	
Types (depending on sizes)	Micronodules < 3mm in diameter Macronodules> 3mm in diameter Notes: there is no difference between these nodules in term of complications or prognosis however we differentiate in their sizes because it may help us to detect the initial cause	Micronodular cirrhosis  Macronodular cirrhosis 
Causes -Differential diagnosis should be based on the patient history and conditions - patients may come to clinic with full developed cirrhosis	1-chronic alcoholism (main cause in developed countries), 2-chronic viral infection like HBV and HCV (main cause in places where these viruses are common), 3-biliary disease. -if we excluded the causes up, we must look for metabolic diseases although they are not common:4- hemochromatosis (most common metabolic cause), 5-autoimmune hepatitis, 6-Wilson disease, 7-A1 antitrypsin deficiency. 8-RARE CAUSES: Inherited causes related to enzyme deficiencies (Galactosemia, tyrosinosis, Glycogen storage diseases III/IV (LEAD TO GLYCOGEN DEPOSITION IN LIVER),Lipid storage disease, Hereditary fructose intolerance (we have to break this disaccharide into monosaccharide or it will be accumulated)) or because of a drug like methyldopa 9-10./. of cases are because of cryptogenic cirrhosis. Cryptogenic cirrhosis is cirrhosis with no known underlying cause, it happens for example when a patient present for the first time with cirrhosis, we cannot detect clearly the features of primary disease and there is no serological test that confirms his case. SO this patient absolutely have an underlying cause BUT we cant detect it. Before 20 years, non-alcoholic fatty liver was not listed among the causes of cirrhosis so that many of them thought they have cryptogenic cirrhosis but now, its clear that non-alcoholic fatty liver is a cause of cirrhosis	

## Pathogenesis In order to say this patient has cirrhosis, you have to see these changes: 1-Hepatocellular death. 2- regeneration (to compensate the loss) 3- progressive fibrosis 4-vascular changes (hallmark of cirrhosis and clinical presentation of cirrhosis)	Here we will talk about each point 1+3-Hepatocellular death (initial step): occur due to many things and when it occurs over a long period of time →accompanied by fibrosis (progressive fibrosis) Why is fibrosis important in the progression of cirrhosis? In normal liver, amount of fibrous tissue is 1-minimal 2-localized in capsule (always filled with fibrous tissue), portal tracts (area), and surrounding central area (very minimal amount) BUT note that the parenchyma itself don't have fibrous tissue in its structure except for collagen in its basement membrane (IV) and ECM types (I, III, V, XI) Why is the basement membrane of hepatocytes important? The BM is what lies between the hepatocyte and endothelial cells of sinusoids, and this thin arrangement allow flow of blood to give nutrients and take back waste, but if this space was fibrous due to any kind of stimulus → thickening of BM, exchange process is going to be affected and the function of the liver would show sub-normality. From where the fibrous tissue synthesis result? The major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of DISSE, Perisinusoidal stellate cells act normally as storage cells for vitamin A and fat upon stimulation due to diseases→ myofibroblast like cells produce TGFB→ stimulate cells to synthesize collagen and deposit it. What are the stimuli that cause deposition of collagen? The stimuli for the activation of stellate cells and production of collagen are 1-reactive oxygen species (when there is cell damage or inflammation) (ROS can cause damage themselves) 2-growth factors (TGFB) 3-cytokines like TNF, IL 1, lymphotoxins After stimulation and deposition of collagen→ fibrosis of liver 4-Vascular changes: result of presence of fibrous tissue in parenchyma → increase the pressure on the walls of delicate BV→ increase resistance of blood flow and it tries to find other ways → 1-Lots of sinusoidal endothelial cells fenestration 2-development of vascular shunts such as: portal vein hepatic vein,, hepatic artery portal vein → which would eventually lead to defect and liver function 3-loss of microvilli from hepatocytes which are directed toward sinusoids) →decrease the transport capacity of cells because of decrease in surface area All of this will affect the function because the blood needs to flow in a certain way to get nutrients and waste exchanged, collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to a higher pressure fast flowing vascular changes without such solute exchange,, the movement of proteins like(albumin clotting factors lipoproteins) between hepatocytes and the plasma is markedly impaired,, these functional changes are aggravated by the loss of microvilli from the hepatocyte surface which diminishes the transport capacity of cell.
## Clinical features of cirrhosis	as we know cirrhosis is a chronic process that takes years to develop clinical features can be; 1-silent (asymptomatic) 2-anorexia weight loss and weakness (non-specific) patients can also represent with complications like, and this is the most common form, because other symptoms are generalized: 1-progressive hepatic failure (hepatocytes can carry out at a minimal level but when there is a high demand it may fail) ,, many patients present for the first time with hepatic failure if they had infection or bleeding 2-portal hypertension 3-hepatocellular carcinoma (conventional type of liver cancer has a background of cirrhosis)
## Cirrhosis vs fibrosis	Cirrhosis: well-developed organized nodules Fibrosis: step before cirrhosis, fibrous tissue is present but nodules are not completely surrounded by fibrous tissue

Portal hypertension

-In normal situations, portal blood pressure is very low, that's why any change can make a difference.

-High resistance to portal blood flow at the level of sinusoids and compression of central veins by perivascular fibrosis and parenchymal nodules

-Arterial-portal anastomosis develops in fibrous bands→ increase in blood pressure in portal venous system

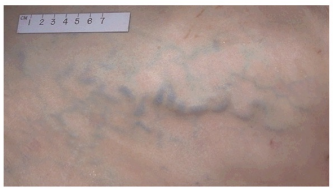
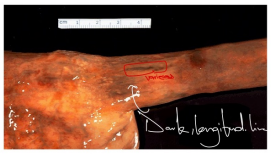
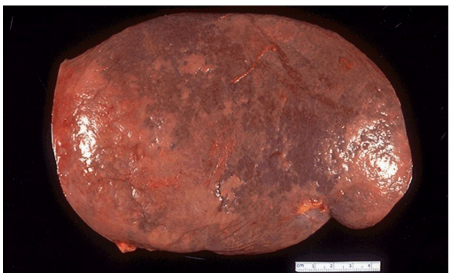
So in summary increase in resistance resulting from the surrounding→ high portal blood pressure →it would lead to anastomosis of channels, anastomoses between arterial and portal system in the fibrous bands also contributes to portal hypertension by imposing arterial pressure on the normally low pressure portal venous system. (high arterial pressure leads to high venous pressure)

Causes of portal hypertension:

Prehepatic (BEFORE LIVER)	1-portal vein thrombosis 2-massive splenomegaly	Problem affects the vein for e.g. before reaching the liver or there is spleen lymphoma (liver and spleen share circulation, that's why any problem can be reflected)
Post hepatic (AFTER THEY LEAVE LIVER)	1-severe right sided heart failure 2-constrictive pericarditis (heart contraction problem) 3-hepatic vein outflow obstruction (problem outside like a tumor)	Problems in heart and IVC. Heart failure indicate abnormal blood flow that will cause pressure on portal veins.
Hepatic	1-cirrhosis (MOST IMP AND MOST COMMON) 2-shistosomiasis (bilharzia) 3-massive fatty change 4-diffuse granulomatosis as sarcoidosis, TB 5-disease of portal microcirculation as nodular regenerative hyperplasia	-bilharzia is known to cause FIBROUSIS not 100./. cirrhosis.

Clinical consequences of portal hypertension: FOR DIAGNOSIS AND FOLLOW UP

Ascites	collection of excess fluids in INTRA ABDOMINAL cavity, it becomes clinically detectable when at least 500 ml have accumulated and they have distended abdomen (we should know the normal amount of fluid is minimal but here →we have litres) This fluid is serous fluid. Patients should be aspirated for relief (palliative treatment) and diagnosis and prevent superimposed infections like peritonitis	features: 1-serious fluids (loss of proteins) 2-contains as much as 3 g/ml of protein(albumin) 3-it has the same concentration as lot of glucose and K+ 4-Asctic fluid usually contains no cells but we may see mesothelial cells (which are sense lining the cavity) and lymphocytes 5-neutrophils = infection 6-RBC= disseminated cancer	Pathogenesis: fluid will be pushed out of the sinusoids and fluid accumulate on the surface of the liver and because it's an intraabdominal organ the fluid→ accumulate in the intraabdominal cavity. 1-sinusoidal high blood pressure 2-hypoalbuminemia which means edema because of low osmotic pressure 3-leakage of hepatic lymph into the peritoneal cavity Thoracic duct lymph flow is 800—1000ML/D interosseous it may approach 20 L/day --to sum up: thoracic duct is near the liver and when circulation increases, the likelihood of fluid lost from vessel wall is increased 4-renal retention of Na+ and water due to secondary hyperaldosteronism At the end increase fluid in circulation → increase BV → increase hydrostatic pressure → fluid is pushed outside (with low osmotic pressure more fluid gets pushed)
Portosystemic shunts	because of high portal venous pressure bypasses develop wherever	Sites:	

	the system became portal circulation share capillary beds (connection between portal +systemic vessels, these connections are already present but collapsed → no need, but in case of liver cirrhosis the flow of blood is against increased pressure so it will find another places with less resistance leading to opening the shunts	1-around and within the rectum (hemorrhoids) (not all patients with hem. Have cirrhosis) 2-gastroesophageal junction (varices) *dilated tortious submucosal blood vessels this is really important because they tend to bleed (opposite to hemorrhoids) Bleeding is extremely imp sign in cirrhotic patients, why? It can precipitate the complications ** gastroesophageal varices appear in 65% of patients with advanced cirrhosis and cause death in 50% then due to UGI bleeding 3-reteroperitoneum (we don't see this normally + bleeding is uncommon) 4-Anterior abdominal wall :falciform ligament of the liver (peri umbilical and abdominal wall collaterals)→caput medusa radiating from umbilical area to all directions	Caput medusae-abdominal skin  Esophageal varicies 
Splenomegaly	Deviation of blood due to resistance of liver to spleen, usually 500-1000 g (N<300 g) which lead to enlarged spleen full of blood (can be seen in cirrhosis) -not necessarily correlated with other features of portal increased blood pressure -may result in hypersplenism: as we know the spleen function in removing death blood cells like RBC's and WBC, in hypersplenism develop pancytopenia → no. of blood cells gets destructed more often → so RBC / WBC/ PLATELET levels drop WBC decrease → susceptible to inflammation Platelet decrease→ susceptible to bleeding		Splenomegaly 
Hepatic encephalopathy	Depending on the amount of toxins produced they develop this case -It is a complication of acute and chronic hepatic failure (both associated with increased levels of toxic sub.) -disturbance in brain function ranging from behavioral changes to marked confusion and stupor to deep coma and death -these changes may progress over hours or days	Neurological signs: DEPEND ON WHICH PART OF BRAIN IS AFFECTED Rigidity hyper reflexia nonspecific EEG seizures Asterixis (none rhythmic rapid extension flexion movements of head and extremities) green chose edema and astrocytic reaction. -if I look at the brain, I don't expect to see inflammation it is just because of toxic ammonia and edema -postmortal examination with patient with cirrhosis→ swollen edematous brain with no more gross changes	Pathogenesis: -Physiologic factors important in development of hepatic encephalopathy: 1-Severe loss of hepatocellular function 2-Shunting of blood around damaged liver with no detoxification ↓↓ -Exposure of Brain to toxic metabolic products like ammonia which passes BBB -Acute insult : ↑ NH3 level in blood → generalized brain edema impaired neuronal function -Chronic insult: alteration in central nervous system AA metabolism