Lecture 10 & 11
Liver Cirrhosis

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

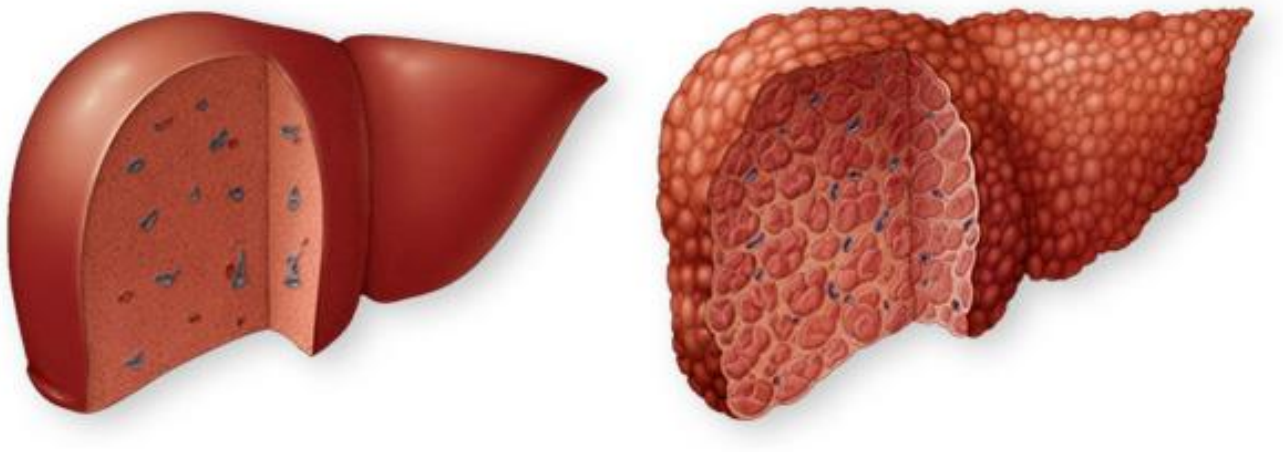
Revised by
هشام الغفيلي & خولة العماري

Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

- Define Cirrhosis.
- Recognize the types of cirrhosis.
- Recognize the major causes and the pathogenetic mechanisms.
- Describe the pathological findings in cirrhotic livers.
- Recognize the major complications of cirrhosis.
- Understand the pathogenetic mechanisms underlying the occurrence of the complications.
- Recognize the clinical features inherent to the above mentioned complications.
- Describe the pathological findings of the different complications.
- Recognize the major complications of cirrhosis.
- Understand the pathogenetic mechanisms underlying the occurrence of the complications.
- Recognize the clinical features inherent to the above mentioned complications.

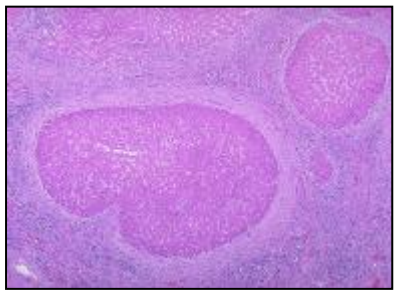
References: Lecture slides, Robbins & First Aid Step 1

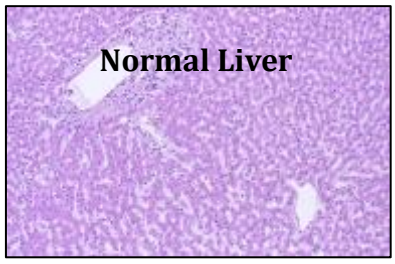


قبل لا تبدأ بدراسة المحاضرة وبعد الاستعانة بالله، ننصح بشدة بمشاهدة هذا الفيديو، يشرح أهم ما في المحاضرة بطريقة ميسرة وبسيطة.

Cirrhosis:

Epidemiology:





- Cirrhosis is among the top 10 causes of death in the Western world.
- The chief worldwide contributors are **alcohol abuse and viral hepatitis**.
- Other causes include biliary disease, and iron overload.
- Cirrhosis is the **end-stage** of chronic liver disease.
- Defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

Cirrhosis is defined by three characteristics:
○ *Fibrosis* in the form of delicate bands or broad scars/septa
○ *Nodules* containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm, micronodules) to large (several centimeters, macronodules)
○ *Disruption* of the architecture of the entire liver

Features of Cirrhosis:

- **Vascular architecture is reorganized** by the parenchymal damage and scarring, with the formation of abnormal **interconnections between vascular inflow and hepatic vein outflow channels.**
- **Fibrosis is the key feature of progressive damage to the liver**. Once cirrhosis has developed, reversal is thought to be rare.

Classification of Cirrhosis:

The classification is based on the underlying etiology.

- Morphological classification based on size of nodules: micronodular and macronodular.
- Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular, but there is a tendency for nodules to increase in size with time.

Classification of Cirrhosis Based On Causes:			
Alcoholic Liver Disease	60% to 70%	**Wilson Disease**	RARE
Viral Hepatitis	10%	**A1-Antitrypsin Deficiency**	RARE
Biliary Diseases	5% to 10%	**Cryptogenic Cirrhosis**	10% TO 15%
Primary Hemochromatosis	5%		

Hepatitis B & C are the most common. Hepatitis A is usually self-limiting

drug-induced cirrhosis.

infants and children with galactosemia and tyrosinosis

Metabolic disorders

Infrequent types of cirrhosis also include

Severe fibrosis can occur in the setting of cardiac disease (sometimes called "cardiac cirrhosis").

In some cases there is no cause and these are referred to as *cryptogenic cirrhosis.*

Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone. يعني اذا صار التليف تقريبا مستحيل تعرف السبب

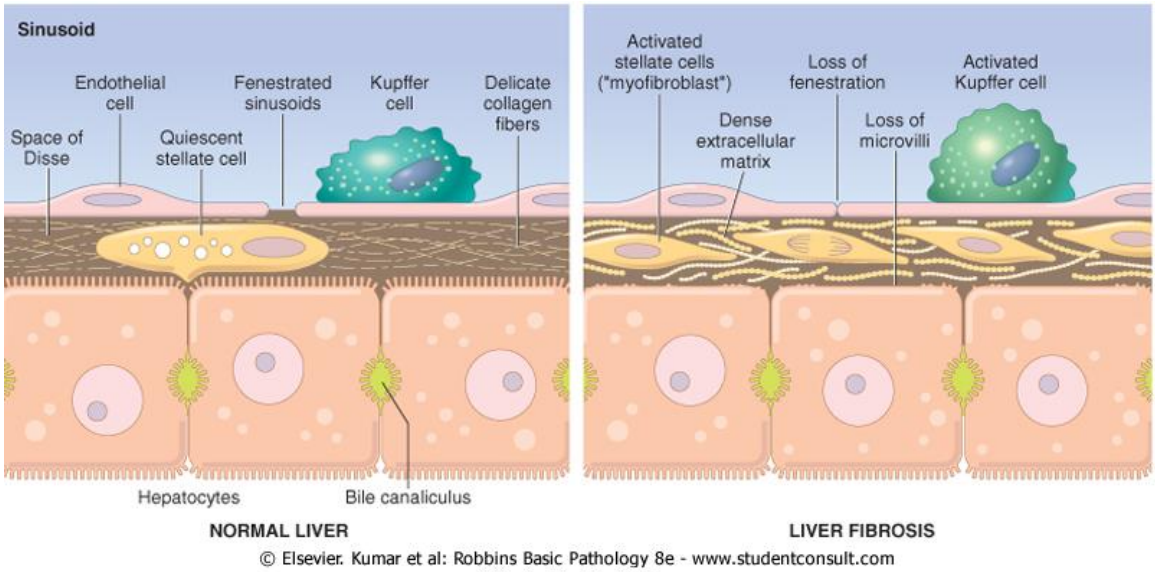
Cirrhosis looks the same no matter the underlying cause, the diagnosis is solely dependent on the history

Pathogenesis:

The pathogenetic processes in cirrhosis are **progressive fibrosis and reorganization of the vascular microarchitecture of the liver.**

Normally	In a normal liver, interstitial collagens (types I and III) are concentrated in portal tracts and around central veins. The type IV collagen(reticulin) is in the space of Disse.
In cirrhosis	When hepatocytes get inflamed they activate **stellate cells** → activated Stellate cells transform into **myofibroblast-like cells** → types I and III collagen are deposited in the perisinusoidal space in the lobule (Fibrosis), creating delicate or broad septal tracts.

- ❖ Kupffer cell activation leads to secretion of multiple cytokines; These cytokines "activate" stellate cells, a major source of collagen in cirrhosis, and acquire a myofibroblastic state.
- ❖ Kupffer cells also are a major source of TNF released into the system's circulation.
- ❖ The fibrosis process leads to loss of fenestrations in the sinusoidal endothelial cells (capillarization of sinusoids, which is the sinusoidal space that comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma).
- ❖ Stellate cells normally function as vitamin A fat-storing cells.



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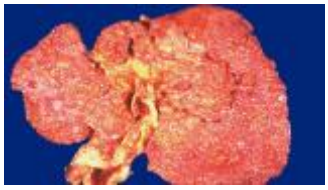
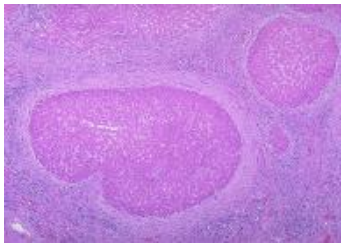
Collagen synthesis is stimulated by:

- Chronic inflammation, with production of inflammatory cytokines.
- Cytokine production by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells).
- Disruption of the normal extracellular matrix.
- Direct stimulation of stellate cells by toxins.

Morphology:

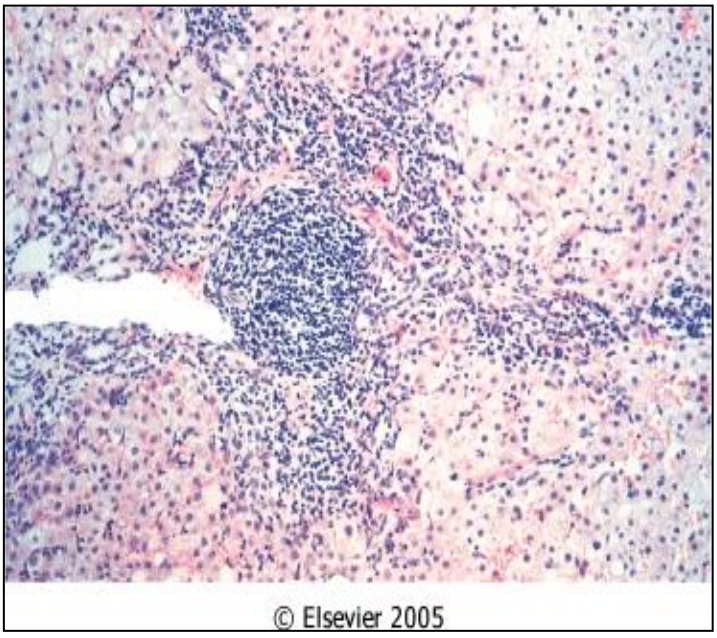
Gross	The nodules seen here are larger than 3 mm and, hence, this is an example of "macronodular" cirrhosis.		Microscopic	
	Micronodular cirrhosis: The regenerative nodules are quite small, averaging less than 3 mm in size. Chronic alcoholism.			Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts. Collagenous tissue, lymphocytes as well as a proliferation of bile ducts.

Clinical Features:

- All forms of cirrhosis may be clinically silent.
- When symptomatic, they lead to nonspecific clinical manifestations: anorexia, weight loss, weakness, osteoporosis, and, in advanced disease, frank debilitation.
- Incipient or overt hepatic failure may develop.
- Jaundice

The ultimate mechanisms of most cirrhotic deaths are

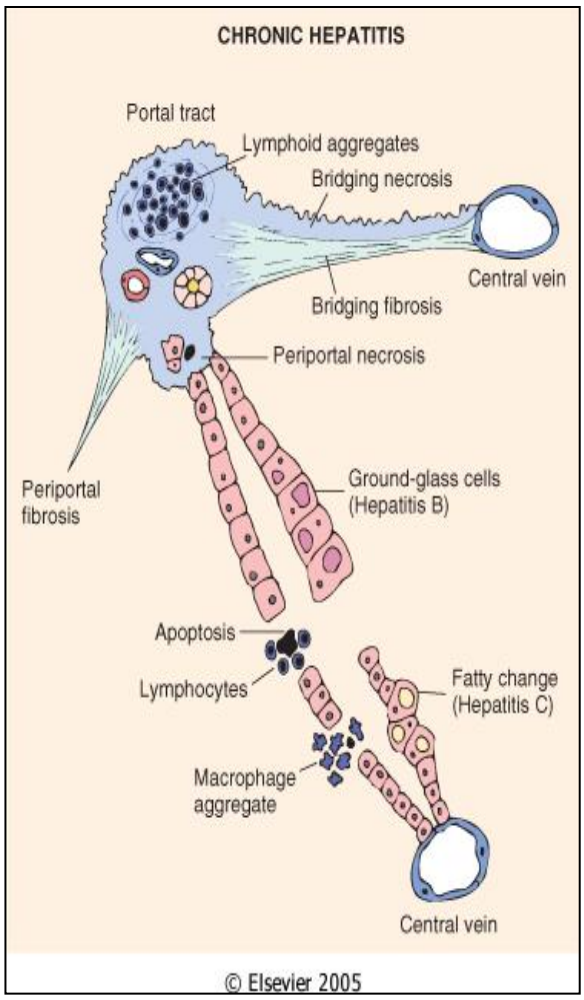
- Progressive liver failure
- The development of hepatocellular carcinoma
- A complication related to portal hypertension

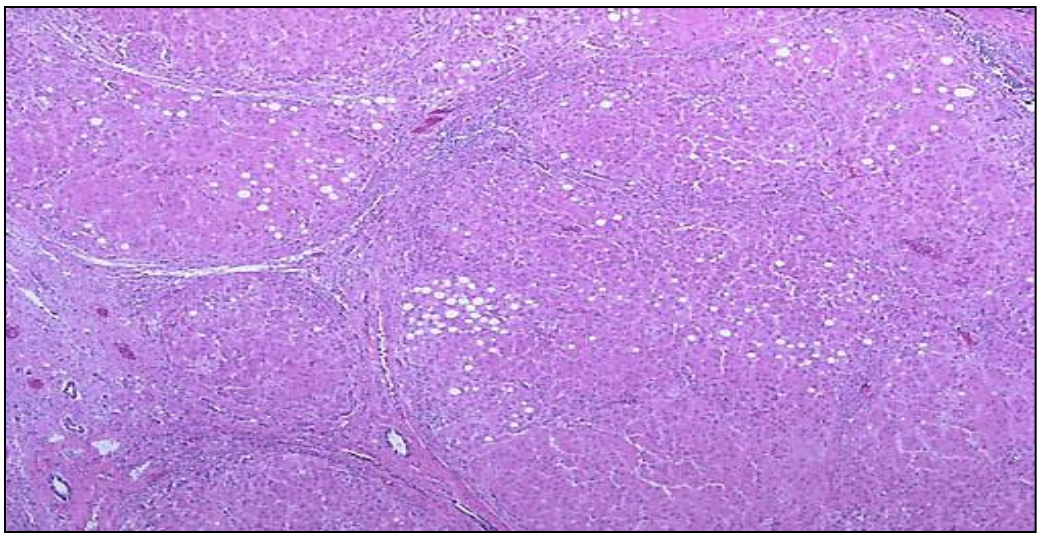


Chronic Hepatitis: Morphology:

Ongoing infection for more than 6 months

Hepatocyte injury, **necrosis**, and regeneration	
Sinusoidal cell reactive changes	
Portal tract Inflammation	Confined to portal tracts
	Spillover into adjacent parenchyma, with necrosis of hepatocytes (interface hepatitis)
	Bridging inflammation and necrosis
Fibrosis	Continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
HBV	"ground-glass" hepatocytes, "sanded" nuclei
HCV	bile duct damage, lymphoid aggregate formation
Cirrhosis	*The end-stage outcome*

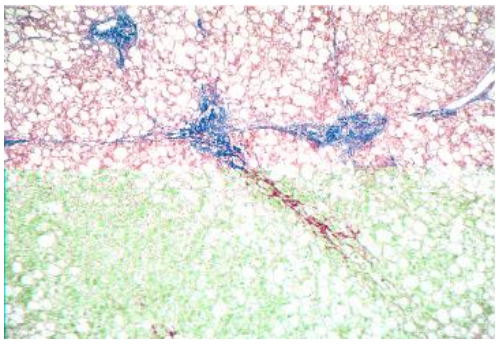
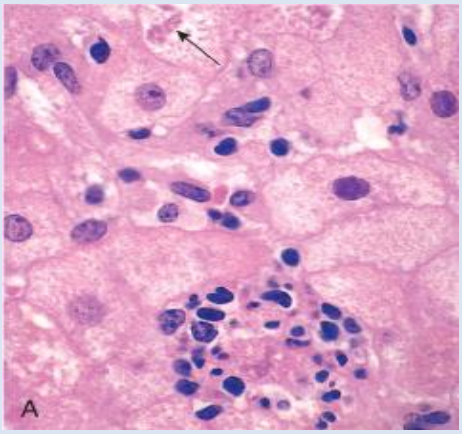
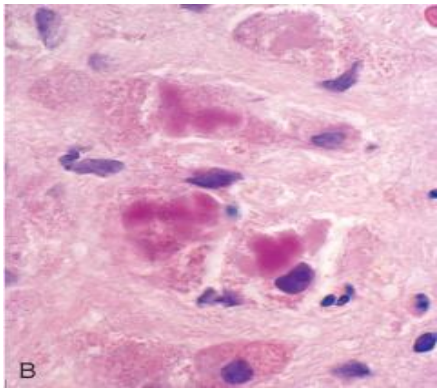
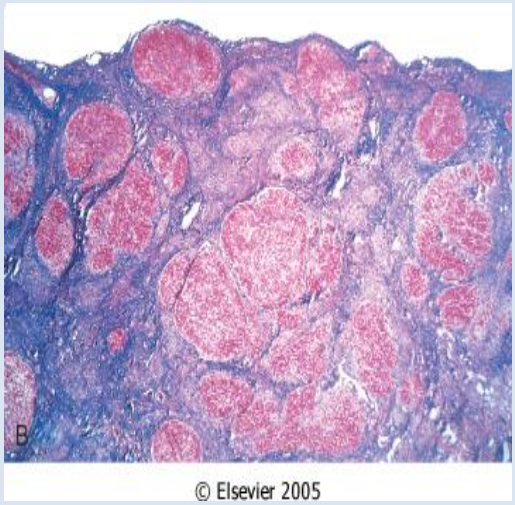




Viral hepatitis C which is at a high stage with extensive fibrosis and progression to macronodular cirrhosis, as evidenced by the large regenerative nodule at the center right.

VHC: Lymphocytes and plasma cells

Alcoholic Liver Disease:

Alcoholic liver disease: macrovesicular steatosis, involving most regions of the hepatic lobule. The intracytoplasmic fat is seen as clear vacuoles. Some early fibrosis (stained blue) is present (**Masson trichrome**).	
Alcoholic hepatitis. *A*, the cluster of inflammatory cells marks the site of a necrotic hepatocyte. A Mallory body is present in a second hepatocyte (*arrow*).	
Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by fibrous tissue (H&E).	
▪ **Diffuse nodularity** of the surface reflects the interplay between nodular regeneration and scarring. ▪ The greenish tint of some nodules is due to bile stasis. ▪ A hepatocellular carcinoma is present as a budding mass at the lower edge of the right lobe (lower left of figure). ▪ Nodules of varying sizes entrapped in blue-staining fibrous tissue. ▪ The liver capsule is at the top (Masson trichrome).	

Complications of liver cirrhosis:

(20 mins video but very helpful)

Most cases of ultimately fatal cirrhosis involve one of the following mechanisms:

Cirrhosis

Liver failure

Hepatocellular carcinoma

Portal hypertension

Resistance to blood flow

Portosystemic venous shunts

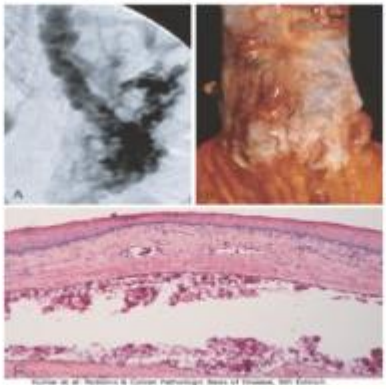
wherever the systemic and portal circulations share capillary beds

Rectum

Hemorrhoids

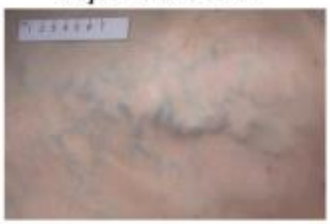
Cardioesophageal junction

Esophagogastric varices



Abdominal wall

caput medusae



Liver failure

Metabolism catabolosim excretory

Bilirubin

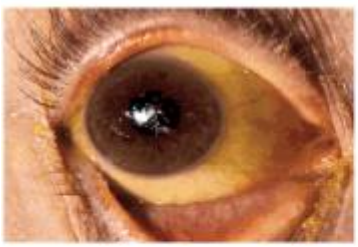
Ammonia

estrogens

Hyperammonemia

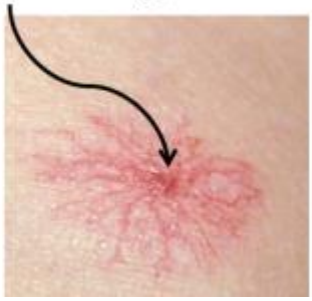
Hepatic encephalopathy

Jaundice



Hyperestrogenemia

spider angiomas & *hypogonadism gynecomastia*



Synthesis

Albumin

clotting factors

Hypoalbuminemia

Peripheral edema

Ascites

Coagulopathy and bleeding

Prothrombin time

1. Portal hypertension:

Portal hypertension is amazingly explained in this video

- Resistance to blood flow.
- It can be prehepatic, intrahepatic, or posthepatic (eg. Cardiac cirrhosis).
- The dominant intrahepatic cause is **cirrhosis**, accounting for most cases of portal hypertension.
- Can we see noncirrhotic forms of portal hypertension?
  Yes, examples are: schistosomiasis, massive fatty change, diffuse granulomatous diseases (e.g., sarcoidosis, miliary tuberculosis), and diseases affecting the portal microcirculation, exemplified by nodular regenerative hyperplasia.

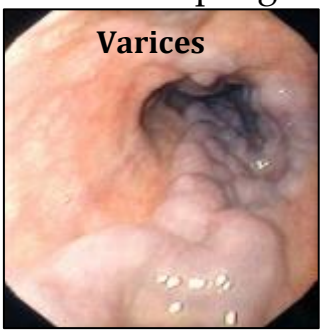
Resistance due to what?
Prehepatic: thrombosis of portal vein before enter the liver.
Posthepatic: thrombosis in the hepatic vein which is going to the heart. Such as heart failure. (Cardiac Cirrhosis)

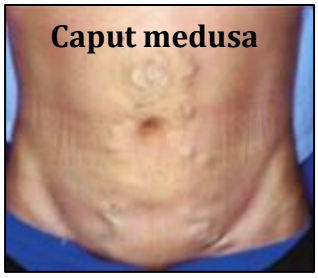
Pathogenesis:

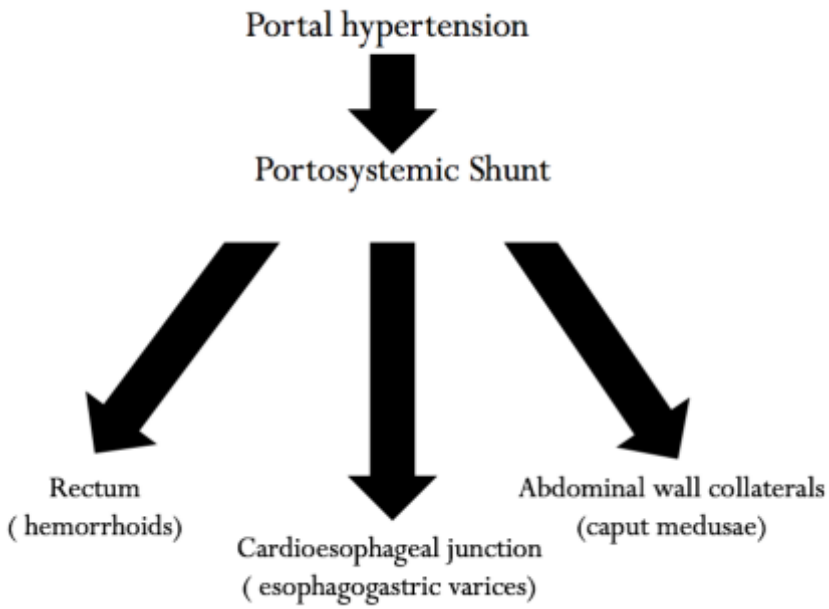
- ↑ resistance to portal flow by fibrosis and expanded parenchymal nodules.
- **Anastomoses** between the arterial and portal systems in the fibrous bands impose arterial pressure on the normally low-pressure portal venous system (imbalance).
- Could result from a hyperdynamic circulation. Caused by arterial vasodilation in the splanchnic circulation, from increased production of nitric oxide (NO)[1]

Portal hypertension leads to portosystemic venous shunts formation:

- Rectum → hemorrhoids.
- Abdominal wall → caput medusa.
- Cardioesophageal junction → **esophagogastric varices.**







[1] This occurs in response to reduced clearance of bacterial DNA absorbed from the gut that bypasses the Kupffer cells due to intrahepatic shunting of blood from portal to systemic circulation. Bacterial DNA causes increased production of NO.

Esophageal Varices:

Varices are congested subepithelial and submucosal venous plexus within the distal esophagus.

- Normally, instead of returning directly to the heart, **venous blood** from the GI tract is delivered to the liver via the **portal vein** before reaching the **inferior vena cava.**
- This circulatory pattern is responsible for the ***first-pass effect*** in which drugs and other materials absorbed in the intestines are processed by the liver before entering the systemic circulation.

Varices = bleeding: Bleeding might kill the patient because of previous decreased coagulability
Varices can go from asymptomatic to rupture. Anything that may increase pressure will give you a risk of bleeding
First pass effect: instead of going into the liver it won't (bypass it) and won't be metabolized.

Epidemiology:

- Diseases that impede this flow cause portal hypertension and can lead to the development of **esophageal varices,** an important cause of esophageal bleeding (Variceal bleeding).
- 90% of cirrhotic patients, most commonly in association with **alcoholic liver disease**. Worldwide, hepatic schistosomiasis is the second most common cause of varices.
- **Half of patients die** from the first bleeding episode either as a direct consequence of hemorrhage (variceal rupture) or following hepatic coma triggered by **hypovolemic shock.**
- Additional 50% within 1 year.

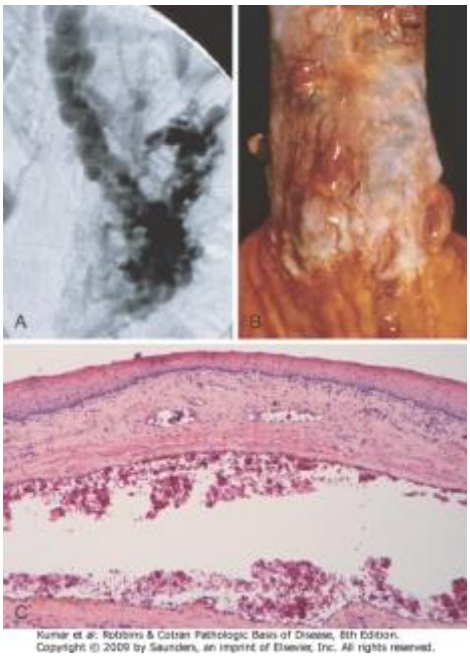
50% of the patients die from bleeding on the first time, if they survived, 25% of the first 50% will die from the second bleeding.

Pathogenesis:

Portal hypertension → induce the development of collateral channels at sites where the portal and caval systems communicate → these collateral veins enlarge the subepithelial and submucosal venous plexi within the distal esophagus → these vessels are termed varices.

Although these collateral (reorganization) veins allow some drainage to occur, they lead to the development of **varices.**

Portal hypertension will give you collateral channels that allow some drainage leading to the development of congested subepithelial or submucosal venous plexus
If someone still hasn't gotten cirrhosis you still might see this



Morphology:

- Varices can be detected by **venogram**[2] **as: tortuous** dilated veins lying primarily within the **submucosa** of the distal esophagus and proximal stomach.
- Venous channels directly beneath the esophageal epithelium may also become massively dilated.
- Varices may not be grossly obvious in surgical or postmortem specimens, because they collapse in the absence of blood flow.
- Variceal rupture results in **hemorrhage** into the lumen or esophageal wall, in which case the overlying mucosa appears **ulcerated and necrotic**.
- If rupture has occurred in the past, venous thrombosis, inflammation, and evidence of prior therapy may also be present.

Clinical features:

Asymptomatic but if it ruptures → massive hematemesis and death.

Portal HTN due to increase resistance in the liver will lead to varices which will lead to hematemesis (why? Tension in the varicose veins & low coagulability due to low (bad) vitamin k function)

Factors that lead to rupture: (not well defined)

- **Inflammatory erosion of thinned overlying mucosa.**
- **Increased tension** in progressively dilated veins.
- **Increased vascular hydrostatic pressure** associated with vomiting.

In any case, hemorrhage due to variceal rupture is a medical emergency which is treated by any of several methods:

- Sclerotherapy by endoscopic injection of thrombotic agents.
- Endoscopic balloon tamponade.
- Endoscopic rubber band ligation.

- Venogram: If we have a section of the esophagus:

  Stratified squamous epithelium, we see very large dilated veins, once I take it outside of the body they collapse when we don't have the blood flow. Why? Because the pressure of the blood flow is no longer there. (When a patient is alive it will be pink, if the patient is dead &/ or taking a biopsy (which we don't usually do because of low coagulability) they will collapse)
- They might give them sclerotherapy which is:

  Usually for females that have varicose veins in the legs the plastic surgeon will inject sclerotic material into the veins which will dry it out, and make thrombosis.
- Endoscopic band rubber ligation- closing the base of varicotic veins.

2 Radiography of a vein after injection of a radiopaque fluid.

Ascites:

- It is the accumulation of excess fluid in the **peritoneal cavity** 85%.
- Usually becomes clinically detectable when at least 500 mL have accumulated.
- Generally, it is a **Serous fluid** containing less than 3 gm/dL of protein (largely albumin).

Ascites can be detected by ultrasound. Ascites may be complicated by peritonitis

Pathogenesis:

Involves one of the following three mechanisms or more of them:

- Sinusoidal hypertension and **hypoalbuminemia** → drives fluid into the extravascular space of Disse.
- Leakage of hepatic lymph into the peritoneal cavity (approaches 20 L/day, thus, it exceeds the thoracic duct capacity) → protein-rich fluid (Hepatic lymph is rich in protein & low in triglycerides).
- Could also be due to sodium and water retention due to secondary hyperaldosteronism.

They can get infection (spontaneous bacterial infection) because the liver is not working properly (It's a part of our immune system) so all the cells in the body don't work properly & the bacteria will kill the patient as it gets to the peritoneum so it will make a very severe infection, and we cannot give antibiotics because it is metabolized in the liver and even other antibiotics that aren't necessarily metabolized in the liver will lead to some liver injury.
Loss of protein (albumin) so there is fluid = ascites due to portal hypertension.

Splenomegaly (hypersplenism):

- Long-standing congestion (portal HTN & portosystemic shunts) may cause congestive splenomegaly (1000 gm or less).
- Massive splenomegaly may induce Hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia or pancytopenia.

  Thrombocytopenia + decreased vitamin K (because of liver insufficiency) → bleeding into the tissues, bruising, and slow blood clotting.

Pulmonary hypertension & Hepatopulmonary syndrome:

Pulmonary arterial hypertension associated with liver disease or portal hypertension.

- Causes of liver injury may also damage the lungs (e.g., α1-antitrypsin deficiency leading to both cirrhosis and emphysema).
- **Causes:**
  - Portal hypertension of any cause and excessive pulmonary vasoconstriction and vascular remodeling, which eventually lead to right-sided heart failure.
  - Changes in pulmonary blood flow occurring **secondary to hepatic failure.**
- **Clinical features:** the most common clinical manifestations are **dyspnea on exertion and clubbing of the fingers**, followed by palpitations and chest pain.

Hepatic Damage (liver failure):

Jaundice and icterus:

- Jaundice, a yellow discoloration of skin and sclerae (icterus), occurs when systemic retention of bilirubin produces serum levels above 2.0 mg/dL (the normal level in adults is below 1.2 mg/dL).
- Jaundice occurs when the equilibrium between bilirubin production and clearance is disrupted.
- **Causes of Jaundice:** Bilirubin overproduction**,** hepatitis (alter the conjugation process of bilirubin), **obstruction** of the flow of bile and **hemolytic anemia.**

Cholestasis:

Defined as systemic **retention** of bilirubin and other solutes which are eliminated in bile. (particularly bile salts and cholesterol).

- Results from impaired bile flow due to hepatocellular dysfunction or intrahepatic or extrahepatic biliary obstruction.
- May manifest as jaundice.
- **Clinical symptoms:**
  - Sometimes **pruritus** is the presenting symptom.
  - *Skin xanthomas* (focal accumulations of cholesterol) sometimes appear, the result of hyperlipidemia and impaired excretion of cholesterol.
  - **Laboratory finding:** *elevated serum alkaline phosphatase,* an enzyme present in bile duct epithelium and in the canalicular membrane of hepatocytes.

Jaun= in French means yellow. Starts with the sclera. Due to systemic reduction in bilirubin, liver cells are not working well and its contents (bilirubin & things derived from it) overflow into the blood causing jaundice because they are not eliminated well.

Spider angiomas, hypogonadism, gynecomastia → Hyperestrogenemia.

Hepatic encephalopathy:

Spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to deep coma and death.

- There are only **minor morphologic changes** in the brain, such as edema and an astrocytic reaction.
- In acute setting → **elevated** blood ammonia levels (important sign of hepatitis), which impair neuronal function and promote generalized brain edema.
- In chronic setting → deranged neurotransmitter production → neuronal dysfunction.
- Reversible if the underlying hepatic condition can be **corrected**.

the most important cause is elevated blood ammonia level

Clinical features:

- Rigidity, hyperreflexia, nonspecific electroencephalographic changes, and, rarely, seizures.
- Particularly characteristic is asterixis[3] (also called flapping tremor).

Hepatorenal syndrome:

- Appearance of renal failure in individuals with **severe chronic liver disease without** any primary abnormalities of the kidneys themselves.
- Kidney function improves if hepatic failure is reversed.
- There will be **no intrinsic morphologic or functional causes** for the renal failure.
- The cause of failure is decreased renal perfusion pressure due to **systemic vasodilation** and activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles (systemic vasodilatation and renal vasoconstriction).
- Increased synthesis of **renal vasoactive mediators** will **decrease glomerular filtration**.
- The incidence of this syndrome is about 8% per year among patients who have cirrhosis and ascites.
- The syndrome is heralded[4] by:
    - ↓ urine output.
    - ↑ blood urea nitrogen and creatinine values.
- The ability to concentrate urine is retained, producing a hyperosmolar urine low in sodium.

Liver failure will lead to kidney failure & on the long run will develop hepatocellular carcinoma.
A kind of a mystery, under the microscope you don't see anything pathological, so we still don't understand it very well. And we don't know why the kidneys stop working (8% risk every year to develop kidney failure)
Why is this kidney that has nothing pathological is not working properly? (Theory)

- Renal perfusion pressure is decreased.
- Increase in vasoactive mediators' secretion = Decrease glomerular filtration.
- Activation of the renal sympathetic system.
    - Sympathetic nervous system = vasoconstriction so no enough blood in kidneys.

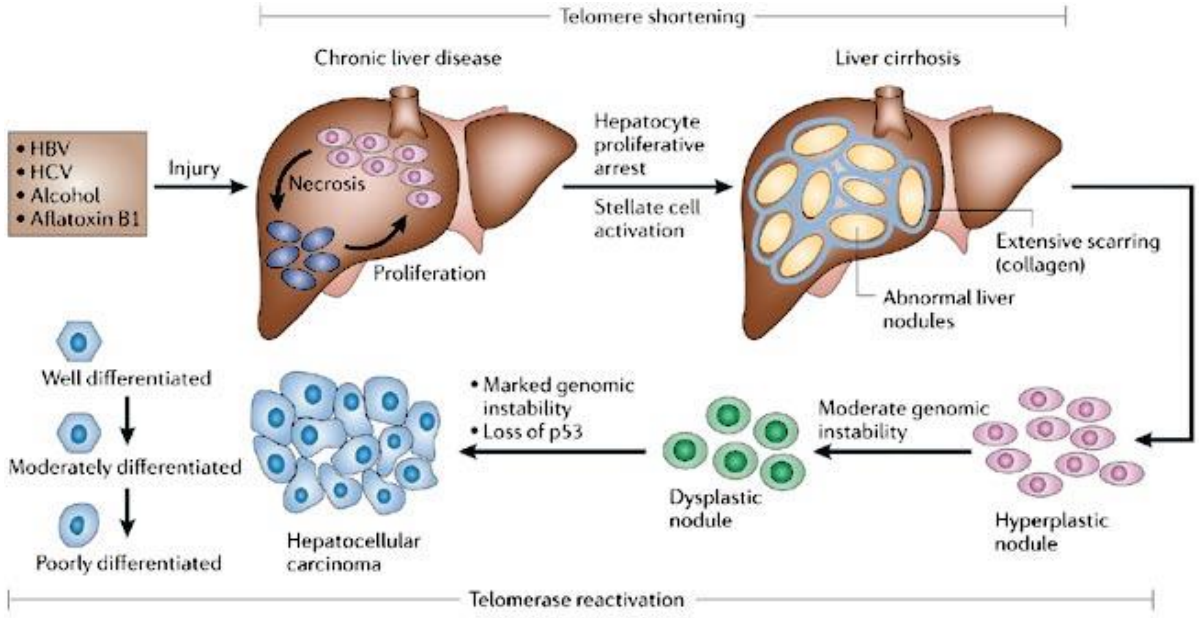
[3] A pattern of nonrhythmic, rapid extension-flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists.
[4] Signaled, be a sign that something is about to happen.

Hepatocellular carcinoma:

Most common 1° malignant tumor of liver in adults A . Associated with HBV (+/− cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and non-alcoholic fatty liver disease, autoimmune disease, hemochromatosis, α1-antitrypsin deficiency, Wilson disease) and specific carcinogens (e.g., aflatoxin from Aspergillus). May lead to Budd-Chiari syndrome.

Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously. Diagnosis: α-fetoprotein; ultrasound or contrast CT/MRI B , biopsy.

Background of cirrhosis because its inflammation so it might lead to it. If they are benign mesothelial cells or hepatocellular cells from the carcinoma shedding into the ascites



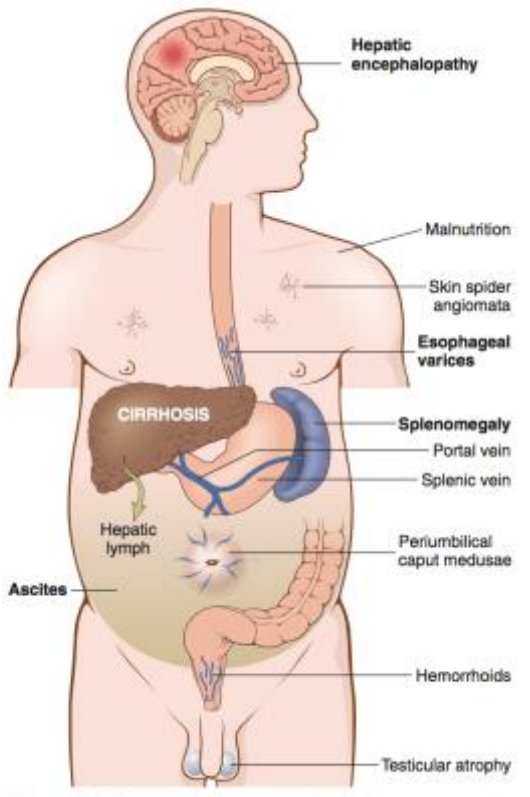
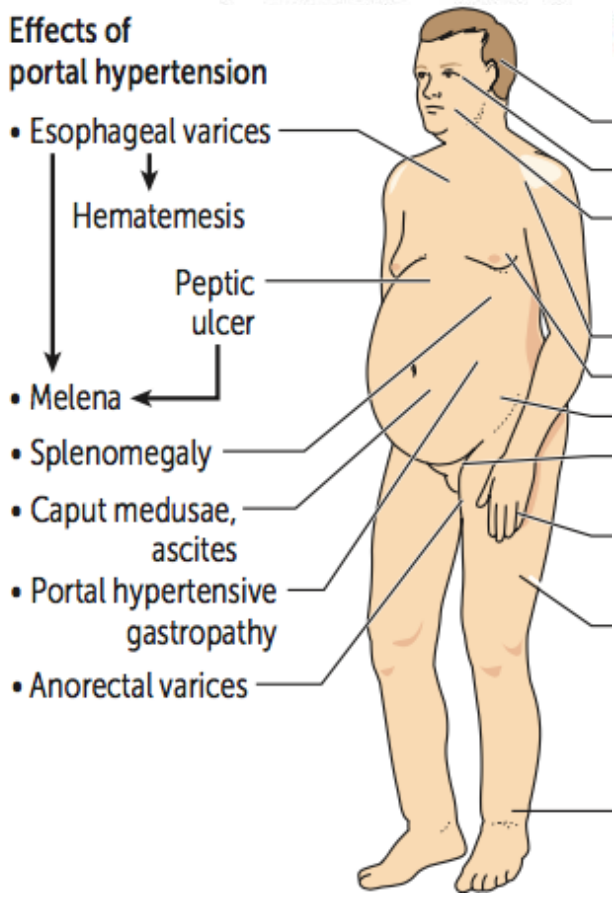


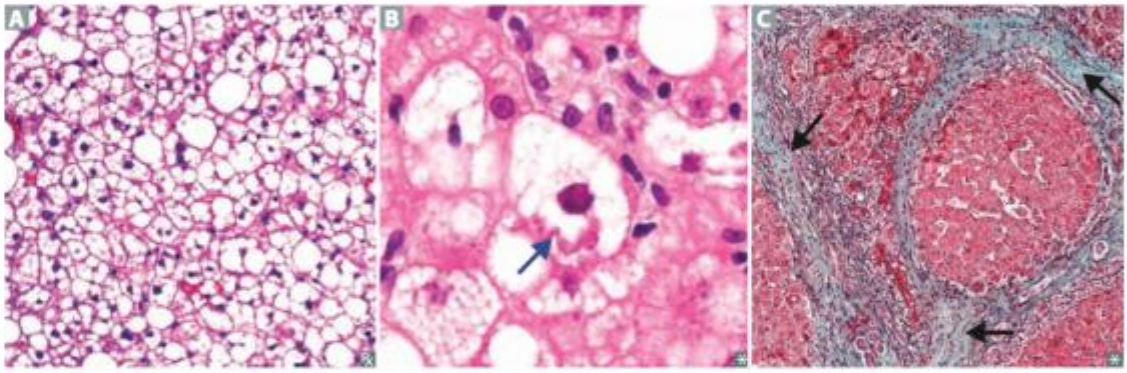
Figure 15–3 Some clinical consequences of portal hypertension in the setting of cirrhosis. The most important manifestations are in **bold** type.



Quick summary for some of the diseases that we mentioned

Alcoholic liver disease

Hepatic steatosis	Macrovesicular fatty change A that may be reversible with alcohol cessation.	
Alcoholic hepatitis	Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies B (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).	Make a toAST with alcohol: AST > ALT (ratio usually > 1.5).
Alcoholic cirrhosis	Final and irreversible form. Micronodular, irregularly shrunken liver with "hobnail" appearance. Sclerosis (arrows in C) around central vein (zone III). Manifestations of chronic liver disease (e.g., jaundice, hypoalbuminemia).	



Non-alcoholic fatty liver disease	Metabolic syndrome (insulin resistance) → fatty infiltration of hepatocytes → cellular "ballooning" and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.	ALT > AST (Lipids)
Hepatic encephalopathy	Cirrhosis → portosystemic shunts → ↓ NH_3 metabolism → neuropsychiatric dysfunction. Spectrum from disorientation/asterixis (mild) to difficult arousal or coma (severe). Triggers: ▪ ↑ NH_3 production and absorption (due to dietary protein, GI bleed, constipation, infection). ▪ ↓ NH_3 removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS). Treatment: lactulose (↑ NH_4^+ generation) and rifaximin.	

Check Your Understanding

MCQs:

1. **Which of the following terms is used to describe a chronic liver disease in which scar tissue surrounds the portal areas?**
   A- Alcoholic cirrhosis
   B- Postnecrotic cirrhosis
   C- Biliary cirrhosis
   D- Compensated cirrhosis
2. **The main characteristics of cirrhosis are?**
   A- Involvement of most or all the liver
   B- Bridging fibrous septa
   C- Parenchymal nodules containing a mix of senescent and replicating ones
   D- A + B
   E- A + B + C

3.What is the most common cause of hepatic cirrhosis in Saudi Arabia?

A- Hepatitis B and C
B- Hemolytic anemia
C- Drugs
D- Schistosoma

4. **A male client with a history of cirrhosis and alcoholism is admitted with severe dyspnea as a result of ascites. The nurse should be aware that the ascites is most likely the result of increased ….?**
   A- Production of serum albumin
   B- Secretion of bile salts
   C- Pressure in portal vein
   D- Interstitial osmotic pressure
5. **A 62-year-old man is brought to the emergency room in a disoriented state. Physical examination reveals signs of poor hygiene and an odor of alcohol, as well as jaundice, splenomegaly, and ascites. The patient has a coarse flapping tremor of the hands, palmar erythema, and diffuse spider angiomata. The abdomen displays dilated paraumbilical veins. Serum levels of ALT, AST, alkaline phosphatase, and bilirubin are all mildly elevated. Soon after admission, the patient vomits a large amount of blood. Which of the following is the most likely underlying cause of hematemesis in this patient?**
   A- Acute alcoholic hepatitis
   B- Acute gastritis
   C- Cirrhosis
   D- Hepatic steatosis

6. **A telltale sign of liver disease is?**
   A- Hair loss
   B- Increased urination
   C- Insomnia
   D- Jaundice

7. **Which one of the following complications is associated with high mortality rate in severe advanced hepatic cirrhosis?**
   A- Esophageal varices
   B- Peliosis hepatis
   C- Budd-Chiari syndrome
   D- Splenomegaly

8. **Which of the following results in impaired coagulation and consequent bleeding?**
   A- Vitamin D deficiency
   B- Vitamin C deficiency
   C- Vitamin K deficiency
   D- Vitamin E deficiency

1:A 2:E 3:A 4:C 5:C 6:D 7:A 8:C

Contact us: Pathology435@gmail.com

Team Members:

فهد العبداللطيف نوف التويجري

محمد الدغيثر	أثير النشوان	فاطمة الدين
معاذ باعشن	الجوهرة المزروع	فتون الصالح
عبدالناصر الوابل	إلهام الزهراني	كوثر الموسى
عبدالرحمن الزامل	بدور جليدان	لميس آل تميم
محمد الزاحم	خولة العماري	لولوه الصغيّر
عبدالعزيز الزيدان	دانيا الهنداوي	مريم سعيدان
عبدالله الفريح	دانة عمله	منيرة العيوني
ماجد العسبلي	ديما الفارس	مي العقيل
عبدالله العليوي	رزان السبتي	نورة الخراز
عبدالرحمن الناصر	رغد المنصور	نورة الطويل
محمد الفضل	سارة القحطاني	نوف الرشيد
	شما السهيلي	نوف العبدالكريم

قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
