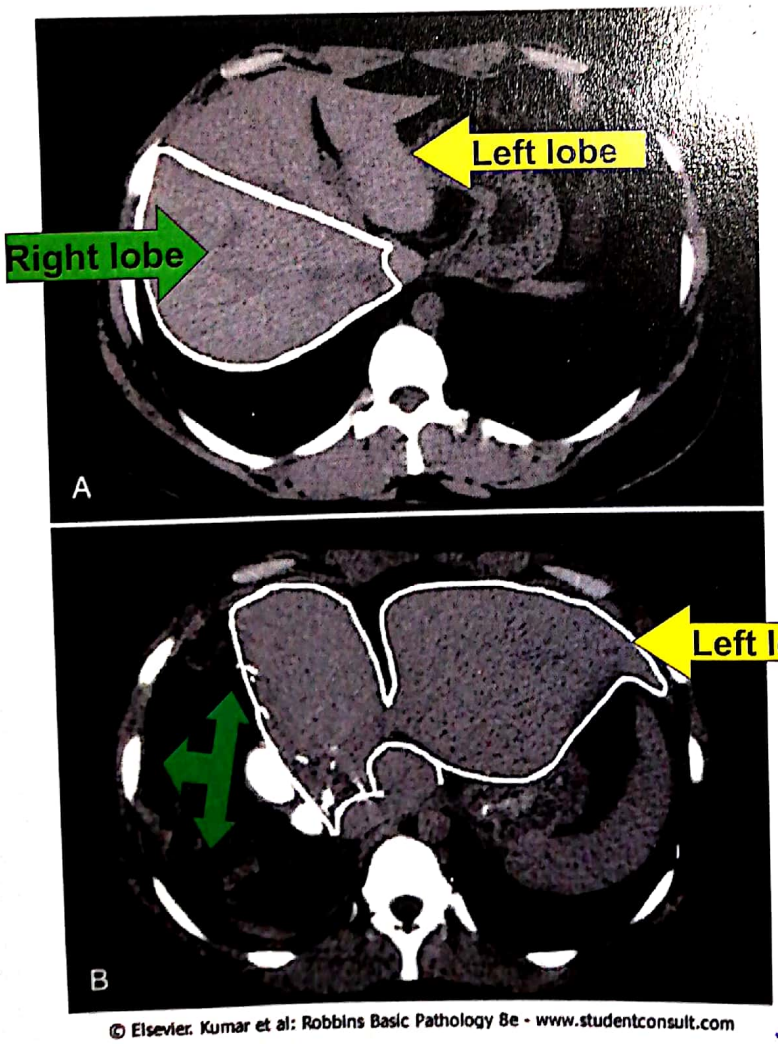
THE LIVER

☺ The liver maintains the body's metabolic homeostasis. This includes the processing of dietary carbohydrates, lipids, & vitamins; synthesis of serum proteins; & detoxification & excretion into bile of endogenous waste products & xenobiotics. Thus, it is vulnerable to a wide variety of toxic (including **Drugs**), **Viruses**, circulatory & metabolic insults.

القدرة على التعويض.

★The liver has enormous **functional regeneration reserve:**
☺ **Surgical removal of 60% of the liver of a normal person (F 3-10) produces minimal & transient hepatic impairment** & regeneration restores most of the liver mass within 4 to 6 weeks.

☺ In persons with **massive hepatocellular necrosis that has not destroyed the hepatic reticulin framework,** perfect restoration may occur if the individual can survive the metabolic insult of liver failure. واذا صار موت في الخلايا مع بقاء الـframework هو الاساس بقدر يرجع ينمو الخلايا مرة ثانية.



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F 3-10: Regeneration of human liver. CTS of the donor liver in living-donor liver transplantation

A, The liver of the donor before the operation. **Note the right lobe *(white outline),* which will be resected & used as a transplant.**

B, Scan of the same liver 1 week after resection of the right lobe; note the **enlargement of the left lobe *(outline)*** without regrowth of the right lobe.

الـ left هو اللي بتعوض.

PATTERNS OF HEPATIC INJURY & RESPONSES (F 16-1).

★ ***Degeneration*** للاستحالات

Moderate **cell swelling** caused by toxic or immunologic insults is **reversible**. More serious damage cause enlargement *of* hepatocytes (H) {***ballooning degeneration***} with irregularly clumped cytoplasm showing large, clear spaces.

تنتفخ في الخلية.

★ ***Intracellular accumulation*** of **fat, iron, copper, & retained biliary** material may occur in H. → hepatocyte.

★ Accumulation of fat droplets within H is known as ***steatosis*** *or* ***fatty change***. Multiple tiny droplets that do not displace the nucleus are known as ***microvesicular steatosis*** & appear in alcoholic liver disease, Reye syndrome, & acute fatty liver of pregnancy.

الكبد الشحمي

★ A single large fat droplet that displaces the nucleus, known as ***macrovesicular steatosis***, may be seen in alcoholic liver disease or in the livers of obese or diabetic individuals.

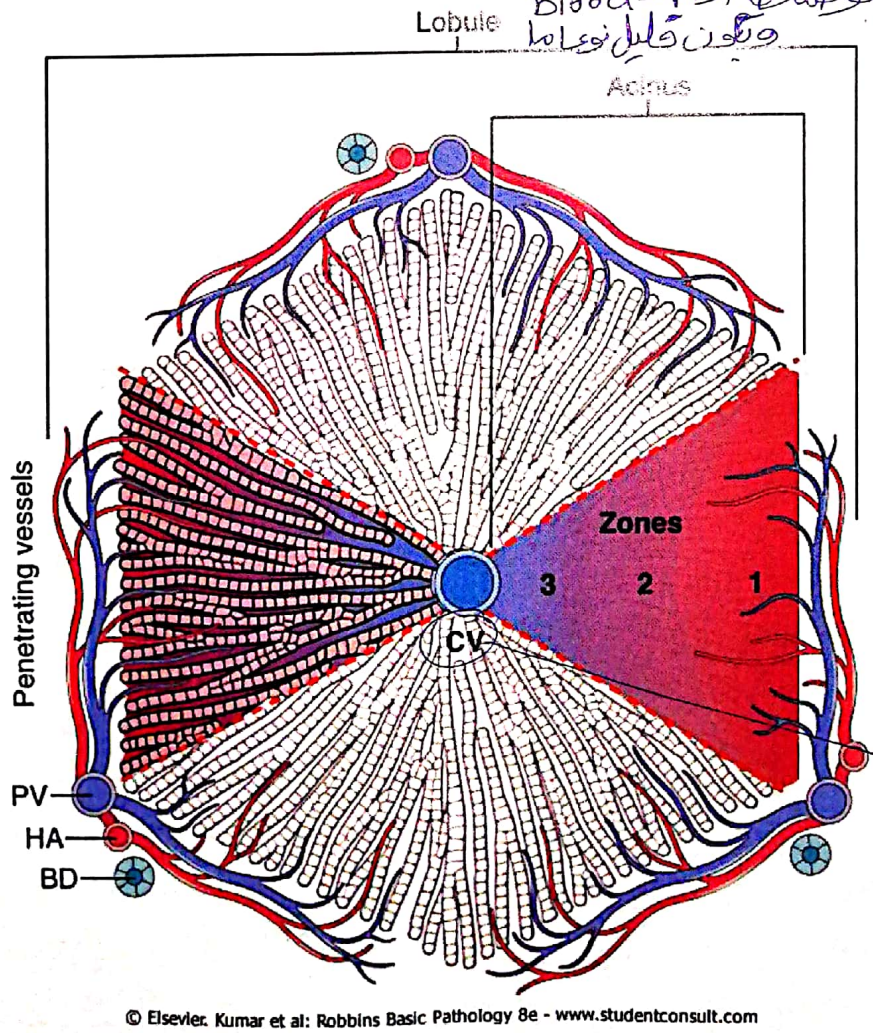
كمية الشحوم صبحت كبيرة

الفقاعات تجمعت مع بعض

★ **Retained biliary material cause** diffuse, foamy, swollen of H (**feathery degeneration**).

ريشي

★ أكثر منطقة معرضة للإصابة هي ال central
لأنه هي آخر منطقة توصلها ال blood supply
وتكون قليل نوعاما



F16-1:
Microscopic architecture of the liver parenchyma.

→ central vein.

PV :- Portal vein
HA :- Hepatic Artery
BD :- Bile duct

★ *Necrosis & apoptosis.*

★Any insult to the liver may cause H destruction. Poorly stained (mummified) H seen in **coagulative necrosis**, while in **apoptosis,** isolated H are shrunken, pyknotic, & intensely eosinophilic. (death without insults)

★ In ischemia & several drug & toxic reactions, H necrosis is **(centrilobular)**, distributed immediately around the central vein extending into the midzonal area. with variable mixture of inflammation & H death encountered.

{Pure midzonal & periportal necrosis is rare},

necrosis in central part (حول الـ CV)

★ **Necrosis & apoptosis** may be limited to (1) **scattered cells** within the lobule, or to the **interface** between the periportal parenchyma & inflamed portal tracts (2) **(interface hepatitis)**. → necrosis in portal tract and periportal area

★ With more severe inflammatory or toxic injury, apoptosis or necrosis of contiguous H may span adjacent lobules in a **portal-to-portal, portal-to-central, or central-to-central** fashion (3) **(bridging necrosis)**. → التنخر الجسري

★ Destruction of entire lobules (4) **(submassive necrosis)** or most of the liver parenchyma (5) **(massive necrosis)** is usually accompanied by hepatic failure.

★ *Regeneration.*

Cell death or tissue resection (such as in living-donor transplantation) triggers H replication, to compensate for the cell or tissue loss. (I) **Hepatocyte proliferation is recognized by the presence of mitoses.** (II) The cells of the **bile canals of Hering (oval cells),** constitute a reserve compartment of progenitor cells for H & bile duct cells proliferate when the H are unable to replicate or have exhausted their replicative capacity.

★ *Inflammation*

=**hepatitis** referred to ➔ injury to H associated with an influx of acute or chronic inflammatory cells. → neutrophils, monocytes ---

Although H necrosis may precede the onset of inflammation, the converse is also **true**. Lysis of antigen-expressing liver cells by sensitized T cells is the cause of liver damage in some forms of viral hepatitis.

★Inflammation may be limited to **portal tracts** or may spill over into the **parenchyma.** Foreign bodies, organisms, & a variety of drugs may incite a **granulomatous reaction.**

★ *Fibrosis.*

☹ Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver, with long lasting effects on hepatic blood flow & perfusion of H.

In the **initial stages, fibrosis** may develop within or around portal tracts (1) ***portal or periportal fibrosis)*** or **around** the **central vein (2) (perivenular)**, or deposited directly within the sinusoids around single or multiple H, (3) ***(pericellular fibrosis).*** With time, fibrous strands link regions of the liver (portal-to-portal, portal-to-central, central-to-central), a process called (4) ***bridging fibrosis.***

★ *Cirrhosis (C)*

☹ With progressive parenchymal injury & fibrosis,

(1) the liver develops **nodules** of regenerating H,
(2) Surrounded by **bands of scar tissue**. In this process, the
(3) normal liver architecture is **destroyed**, & the condition called cirrhosis, **which is the end-stage of liver disease.**

Depending on the size of the nodules **(smaller or larger than 3 mm), C** can be classified as being **micronodular or macronodular**. This classification has **little significance.**

☹ C ↑ the risk of liver malignancy.

Ductular reaction. In biliary & other forms of liver disease, the number of intrahepatic bile ducts & canals of Hering may ↑. This is **known as a ductular reaction or proliferation**, & it is usually associated with fibrosis & inflammation. Ductular reaction has gained much interest recently, because some of the proliferating (Oval) cells originating from the canals of Hering can function as progenitor cells for hepatocytes & bile ducts.

CLINICAL SYNDROMES

The major clinical syndromes of liver disease are **hepatic failure, cirrhosis, portal hypertension, & cholestasis.** having characteristic clinical manifestations, & a battery of laboratory tests are used to diagnose these disorders (Table 16-2). These conditions are discussed next.

Table 16-1. Clinical Consequences of Liver Disease

★ Severe Hepatic Dysfunction, Characteristic Signs:

Jaundice & cholestasis + Hypoalbuminemia + Hyperammonemia + Hypoglycemia + Palmar erythema + Spider angiomas + Hypogonadism + Gynecomastia + Weight loss + Muscle wasting.

★ **Portal Hypertension** Associated with

Ascites + Splenomegaly + Esophageal varices, Hemorrhoids, Caput medusae of abdominal skin.

★ **Complications of Hepatic Failure:** Coagulopathy + Hepatic encephalopathy + Hepatorenal syndrome

disturbance in clotting system?

عجز في الكلية والكبد.

Table 16-2. Laboratory Evaluation of Liver Disease

Test Category & Serum Measurement*

Hepatocyte integrity: Cytosolic hepatocellular enzymes† *Serum aspartate aminotransferase* (AST), *Serum alanine aminotransferase* (ALT), Serum lactate dehydrogenase (LDH)

خراب.

Biliary excretory function: Substances secreted in bile†

Serum bilirubin - *Total:* unconjugated plus conjugated, *Direct:* conjugated only, *Delta:* covalently linked to albumin, Urine bilirubin, Serum bile acids.

خراب

Plasma membrane enzymes† (from damage to bile canaliculus): *Serum alkaline phosphatase*, Serum γ-glutamyl transpeptidase, Serum 5'-nucleotidase

خراب

Hepatocyte function: Proteins secreted into the blood, *Serum albumin*‡, *Prothrombin time*† (factors V, VII, X, prothrombin, fibrinogen),

Hepatocyte metabolism

Serum ammonia†, Aminopyrine breath test (hepatic demethylation), Galactose elimination (intravenous injection).

*Most common tests are in italics.

†An elevation implicates liver disease.

‡A decrease implicates liver disease.

Hepatic or Liver Failure (LF)

☹ The severest clinical consequence of liver disease is LF. It generally develops as the **end point** of progressive damage to the liver, either by (1) slow insidious destruction of H or (2) by repetitive discrete waves of parenchymal damage (3) Less commonly, LF is the result of sudden & massive destruction of hepatic tissue.

زي الـ paracetamol

▼**80% to 90% of hepatic function must be lost before hepatic failure develop.** In many cases, the balance is tipped toward decompensation by intercurrent diseases that place demands on the liver, including systemic **infections, electrolyte disturbances**, stress (**major surgery**, heart failure), & **GIT bleeding**.

▼Alterations cause LF fall into 3 categories:

1. Acute LF with massive hepatic necrosis.

- *The histologic correlate of which is massive hepatic necrosis.*
- Mostly ***caused by drugs or fulminant viral hepatitis.***
- Acute LF means clinical hepatic insufficiency that **progresses from onset of symptoms to encephalopathy within 3 weeks,** if the course extends for **3 months**, it is called **subacute LF**. It is an uncommon life-threatening condition that often **requires liver transplantation**.

2. Chronic LF This is the **most common route to hepatic failure** & is the end point of **cirrhosis.**

3. Hepatic dysfunction [illegible] necrosis.

H may be viable but unable to perform normal metabolic function, as in **acute fatty liver of pregnancy** (which can lead to acute liver failure a few days after onset), **tetracycline toxicity**, & **Reye** syndrome (a rare syndrome of one per Million, of **fatty liver & encephalopathy** in children, associated with aspirin intake & virus infection).

***Clinical Features* of LF**

★***Jaundice*** **{always present},** acute LF may P/W jaundice or encephalopathy. Impaired hepatic synthesis & secretion of albumin leads to ★***Hypoalbuminemia,*** predisposes to peripheral edema. ★***Hyperammonemia*** due to defective hepatic urea cycle function. Impaired estrogen metabolism & consequent ★***Hyperestrogenemia*** causes : ***palmar erythema*** (local vasodilatation) & ***spider naevus*** **(F14.18)** *of* skin, & in male it leads to ***hypogonadism*** **&** ***gynecomastia.***

Prognosis: ☠ LF is life-threatening, due to the accumulation of toxic metabolites, & patients are **highly susceptible to multi-organ failure.** Thus, ▼ **Respiratory failure** with pneumonia & sepsis combines with ▼**Renal failure** {see below) cause death of many patients with LF.

▼**Coagulopathy** from impaired hepatic synthesis of blood clotting factors results in **bleeding tendency** which may lead to massive GIT bleeding. Intestinal absorption of blood places a metabolic load on the liver that ↑ the severity of LF.

☠ **The outlook of full-blown LF is particularly grave** for persons with chronic liver disease. A rapid downhill course is usual, with death occurring within weeks to a few months in about 80% of cases. About 40% of individuals with **acute liver failure** may recover spontaneously. The others either die without transplantation (30%) or receive a liver transplant.

☠ Two serous complications of LF are hepatic encephalopathy & hepatorenal syndrome.

مرضاني الدماغ

☠ Hepatic Encephalopathy

☠ Hepatic encephalopathy is a feared complication of LF
• Two factors are important in the genesis of this disorder
(1) Severe loss of hepatocellular function &
(2) Shunting of blood from portal to systemic circulat
resulting in an **elevation of blood ammonia**, which impa
neuronal function **& promotes generalized brain edema**
Patients show a spectrum of disturbances in brain functio
ranging from subtle ➔ **behavioral abnormalities to ma**
➔ **confusion & stupor, to ➔ deep coma & death.**
• These changes may progress over hours or days as, e
fulminant hepatic failure or, more insidiously, in someone
with marginal hepatic function from chronic liver disease.
• In the brain, there are only minor morphologic change
including edema & an astrocytic reaction.

☠ Hepatorenal Syndrome

مهمة
▼Appears in individuals with LF, consists of **developme**
renal failure without primary abnormalities of the
kidneys themselves.
الكلية ماعندها مشاكل
من التعريف.
hepatorenal syndr. ي الحالات لا ينطبق عليها ال

{Excluded by this definition ... concomitant damage to
liver & kidney, as may occur with exposure to ➔ carbon
tetrachloride & certain ➔ mycotoxins, the ➔ copper tox
of Wilson disease, & ➔ LF in which circulatory collapse
leads to acute tubular necrosis & renal failure.

► Pathogenesis: **unknown**, but evidence points to
في الكبد **splanchnic vasodilatation & systemic vasoconstrict**
leading to severe reduction of renal blood flow, particula
to the cortex, with oligurea & uraemia.

▲ Kidney function promptly improves if hepatic failure is
reversed.

النهاية لكل امراض الكبد ← **Cirrhosis (c)**

★ C is among the top 10 causes of death in the West.
مهمة ★ The most common causes of C are ✱**chronic alcoh**
& ✱**chronic hepatitis B & C, followed by ✱ biliary**
diseases & ✱hemochromatosis (10% of C...

(1) Bridging fibrous septa in the form of delicate bands or broad scars around multiple adjacent lobules. Long-standing fibrosis is irreversible (F 5-19 & ◙11.28).

***(2)* Parenchymal nodules**, contain proliferating hepatocytes varying from very small (<3 mm in ∅, micronodules) to large (>3 mm in ∅, macronodules), encircled by fibrotic bands.

(3) Disruption of the architecture of the entire liver. The parenchymal cell injury & fibrosis are diffuse, extending throughout the liver; **focal injury** with scarring (eg abscess) does **not constitute cirrhosis**.

مثلاً "من الـ abscess: منطقة محنية فقط fibrosis بعمل abscess الـ ولكن cirrhosis

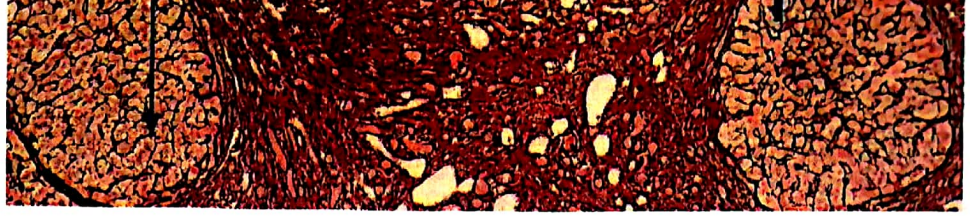
Pathogenesis of cirrhosis

►H death, regeneration, fibrosis, & vascular changes are the **major mechanisms** that combine to create C.

- Hepatocellular death causes are numerous, mostly due to **toxins & viruses**. The development of C requires that cell death &fibrosis occur over long periods of time. تعني مش بسرعة
- Regeneration is the compensatory response to cell death.
- Fibrosis, when the injury involves the **parenchyma** and **the supporting connective tissue, then, fibrosis** is the wound-healing reaction that progresses to scar formation

"هي الهيكل" إذا انضربت ع بعيد مباشرة fibrosis
وغالباً "ماني قيمة من الـ macro or micro لأنه تتبدل macro micro وبتكمل

F 5-19: **Macronodular cirrhosis: liver.** The entire ☺ normal



basement membrane ما في بل في
delicate دقيقة membrane تفصل الخلية عن الي حولها.

extracellular matrix.

☺ In the **normal liver**, ECM consisting of interstitial collagens (fibril-forming collagens types **I, III, V, & XI)** is present only in the liver **capsule**, in **portal tracts**, & **around central veins**.

☺ The **normal** liver has no true basement membrane; instead, a delicate framework containing **type IV collagen** lies in the **space of Disse,** between sinusoidal EC & hepatocytes

☹ By contrast, **in cirrhosis, types I & III collagen** & other ECM components are deposited in the space of Disse (F16-2).

➔In advanced fibrosis & C, fibrous bands separate nodules of hepatocytes throughout the liver.

في كل الكبد وليس منطقة محددة.

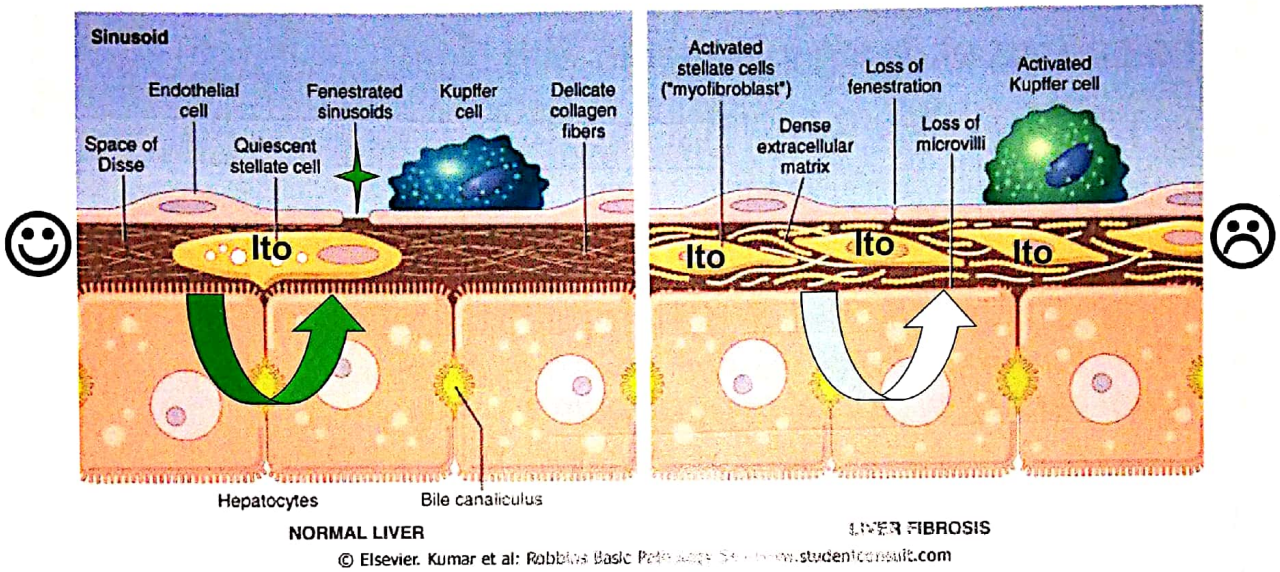
- Vascular changes consisting of the:

(I) loss of sinusoidal EC fenestrations &
(II) the development of portal vein-hepatic vein & hepatic artery-portal vein **vascular shunts** contribute to defects in liver function.

☹ Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma & H to higher pressure, **fast-flowing vascular channels** without such solute exchange.

الدم تتحرك بسرعة وبالتالي ما بتقدر ال hepatocyte تعمل exchange

F16-2: ☺ **In the normal liver**, the perisinusoidal space of Disse contains a delicate framework of ECM components.
☹ **In liver fibrosis,** Ito stellate cells are activated to produce a dense layer of ECM that is deposited in the space. Collagen deposition blocks the EC fenestrations & prevents the free exchange of materials from the blood . Kuppfer cells activation produce cytokines that involved in fibrosis.



☹ In particular, the movement of proteins (e.g., albumin, clotting factors, & lipoproteins) between H & the plasma is markedly impaired. These functional changes are aggravated by the loss of microvilli from the H surface, which diminishes the transport capacity of the cell.

☹ **The major source of excess collagen in C are the perisinusoidal stellate cells (Ito cells or fat-storing cells), which lie in the space of Disse,** which are ☺ normally function as storage cells for vitamin A & **fat**, but during the development of fibrosis they become ☹ **activated, & transform into myofibroblast-like cells,** which express smooth muscle α-actin & glial fibrillary acidic protein.

▶ The **stimuli for the activation of stellate cells** & production of collagen are: **ROS, GFs, & cytokines {TNF, IL-1}, & lymphotoxins,** which can be produced by damaged H or by stimulated Kupffer cells & sinusoidal EC. (Activated **Ito** stellate cells produce GFs, chemokines & cytokines that cause their further proliferation & collagen synthesis) **TGF-β** is the main fibrogenic agent for Ito cells.

damage to H → stimulate Ito → ↑ ROS, GFS →

Clinical Features of cirrhosis

★ All forms of C may be clinically **silent.**

★ When symptomatic, they lead to nonspecific manifestations: anorexia, weight loss, weakness, &, in advanced disease, frank debilitation. → (جلد وعظم) مُهلك

★ **Progression or improvement in cirrhosis** depends to a large extent on the **activity** of the disease responsible for the C. Incipient or overt LF may develop, usually precipitated by imposition of a **metabolic load** on the liver, as from **systemic infection or a GIT hemorrhage.**

LF هو أصلاً "يا دوب ماشي ولكن اصابة زيادة على الطين ٥ هذا يؤدي إلى

★The causes of death in patients with C is:
(1) Progressive **LF**, (2) Rupture of esophageal **varices** due to portal hypertension, or (3) Development of liver **carcinoma.**

from GIT to liver (الدم يتصفى في Sinusoids الدورة البوابية)

Portal Hypertension

★ ↑ resistance to portal blood flow may develop from prehepatic, intrahepatic, & posthepatic causes.

★ *The dominant intrahepatic cause is **cirrhosis,** accounting for most cases of portal hypertension.* أهو عامل يؤدي إلى إرتفاع الضغط.

٩٠٪ الـ cirrhosis هي التي تؤدي إلى portal hypertension.

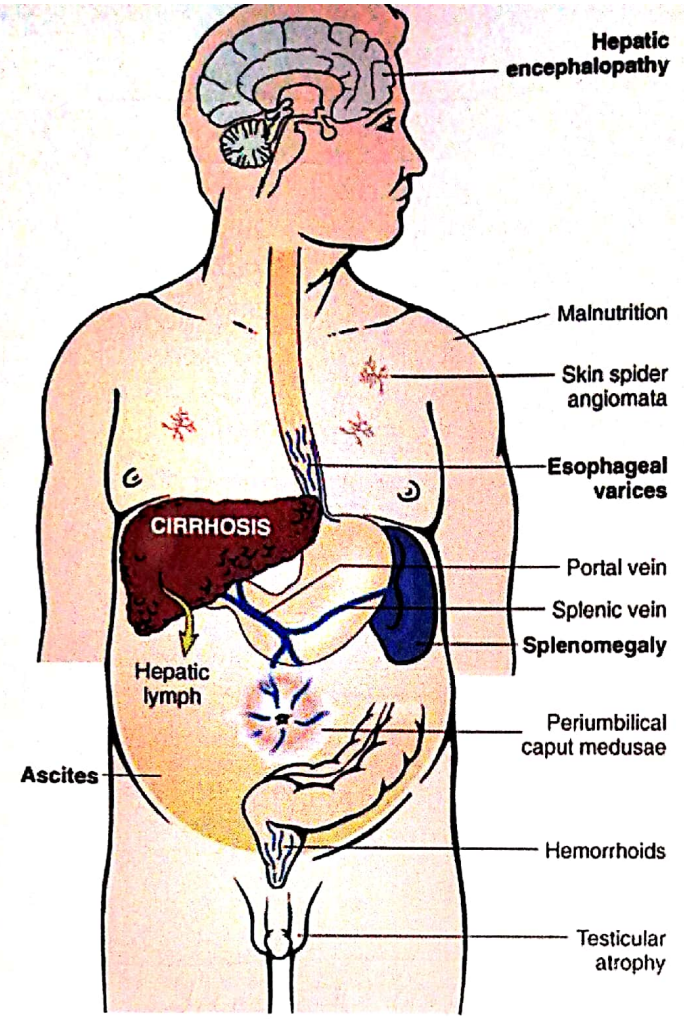
Rare causes include **schistosomiasis**, **massive fatty change,** diffuse granulomatous diseases, diseases affecting the portal microcirculation, eg nodular regenerative hyperplasia. leads to hepatic fibrosis.

Portal hypertension in C results from:
(1) ↑ **resistance to portal flow** at the level of the sinusoids & compression of central veins by **perivenular fibrosis** & expanded parenchymal nodules, & يعني في إعاقة في مرور الدم.
(2) **Anastomoses** between the arterial & portal systems in the fibrous bands by imposing arterial pressure on the normally low-pressure portal venous system. الضغط رح ينتقل من

★ 4 major clinical consequences of portal hypertension in the setting of C are described next (Fig. 16-3), including: (1) **Ascites**, (2) Portosystemic venous **Shunts** (**varices**), (3) **Splenomegaly** & (4) **Hepatic encephalopathy** (see above). systemic إلى البوابي

Ascites استسقاء البطن (البطن منتفخة)

★Is collection of excess fluid in the peritoneal cavity, becomes clinically detectable when **at least 500 mL have accumulated,** but many **liters** may collect & cause massive abdominal distention.



F16-3: Some clinical **consequences of portal hypertension** in the setting of cirrhosis.

★ The most important manifestations are shown in **boldface** type.

★It is generally a **serous** fluid having as much as **3 gm/dL of protein (largely albumin),** may contain scant number of mesothelial cells & mononuclear leukocytes.

★ Influx of **neutrophils** suggests **secondary infection**, whereas **red cells** point to possible disseminated intra-abdominal **cancer.** neutrophil إذا حسناها السائل فيكون فيه RBC أو

★ With long-standing ascites, **seepage** of peritoneal fluid through **transdiaphragmatic lymphatics** may produce **hydrothorax**, more often on the right side.

hydrothorax may follow ascites? yes.

►**Pathogenesis** of ascites is complex, involving one or more of the following mechanisms: (الترتيب) مهم

(1) ***Sinusoidal hypertension*** **(↑ hydrostatic pressure)** alters Starling forces & drives fluid into the space of Disse, which is then removed by **hepatic lymphatics**; this movement of fluid is also promoted by **hypoalbuminemia.**

(2) Renal retention of sodium & water due to **secondary hyperaldosteronism.**

albumin → ↓

(2) Leakage of hepatic lymph **into the peritoneal cavity**:
☺ **normal thoracic duct lymph flow** approximates **1L/day**.
☹ With C, **hepatic lymphatic flow may approach 20 L/day,** exceeding thoracic duct capacity. Hepatic lymph is rich in proteins & low in triglycerides, as reflected in the protein-rich ascitic fluid.

Portosystemic Shunt

▶With ↑portal venous pressure, bypasses develop wherever there is porto-systemic anastomoses circulations share capillary beds. Principal sites are:

(1) Veins within & around the rectum (manifest as **hemorrhoids**), & although hemorrhoidal bleeding may occur, it is rarely massive or life threatening.

(2) The retroperitoneum & the falciform ligament of the liver (involving periumbilical & abdominal wall collaterals, which appear as dilated subcutaneous veins extending outward from the umbilicus ***(caput medusae)*** & an important clinical hallmark of portal hypertension.

ارتفاع ال estrogen أدى ال spider nivea (عنكبوت)

له رأس الحيوان الخرافي في منطقة البطن.

(3) The cardioesophageal junction (producing the much more **important esophagogastric varices, F 4.3), that appear in about 65% of those with advanced cirrhosis of the liver, rupture** of which cause massive hematemesis & death in about half of cirrhotic patients.

← الأخطر والأهم

ال varices موجودة بالتالي ال rupture مسؤول عن القتل 50% من المرضى.

Splenomegaly

Long-standing congestion may cause congestive splenomegaly. The degree of enlargement varies widely (usually **≤1Kg**, ☺ Normal spleen 150g). Massive splenomegaly may secondarily induce hypersplenism.

(150g - 1Kg)

Jaundice & Cholestasis

★***Jaundice is*** **yellow discoloration of skin & sclerae** ***(icterus)*** occurs when serum bilirubin levels are elevated **above 2.0 mg/dL** (the ☺ normal in the adult is <1.2 mg/dL).

★ ***Cholestasis*** is defined as systemic retention of bilirubin & other solutes eliminated in bile (bile salts & cholesterol).

↑ bilirubin and others in systemic circulation.

4-3 Varices: oesophagus موجودة بـ 2/3 من المرضى و الـ rupture هو سبب الموت عند 50% من قبل.

Pathogenesis & Clinical Features of jaundice

☺ In the normal adult the rate of bilirubin (B) production is equal to the rates of hepatic uptake, conjugation, & biliary excretion. Jaundice occurs (bilirubin levels may reach 30-40 mg/dL in severe disease) when the equilibrium between bilirubin production & clearance is disturbed by one or more of the following mechanisms (Table 16-3):

(1) ↑ production of bilirubin,
(2) ↓ hepatic uptake,
(3) Impaired conjugation, these 3 mechanisms…
★ Produce **unconjugated** hyperbilirubinemia,
(4) ↓ hepatocellular excretion, & conjugation لكن مش قادر يخرجها للخلية.
(5) Impaired bile flow (both intrahepatic & extrahepatic)
★ Produce predominantly **conjugated** hyperbilirubinemia.
★ ★ More than one mechanism may operate to produce jaundice, especially in **hepatitis**, which may produce conjugated & unconjugated hyperbilirubinemia.
★ In general, however, one mechanism predominates.

Table 16-3. Main Causes of Jaundice

Predominantly Unconjugated Hyperbilirubinemia أهم وحدة

Excess production of bilirubin, **Hemolytic anemias**, Resorption of blood from internal hemorrhage (e.g., GIT bleeding, hematomas), **Ineffective erythropoiesis syndromes** (e.g., pernicious anemia, thalassemia), Reduced hepatic uptake, Drug interference with membrane carrier systems, Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis), Impaired bilirubin conjugation, **Physiologic jaundice of the newborn.**

Predominantly Conjugated Hyperbilirubinemia:

Decreased hepatocellular excretion, Deficiency in canalicular membrane transporters, Drug-induced canalicular membrane dysfunction (e.g., oral contraceptives, cycloporine), Hepatocellular damage or toxicity (e.g., **viral or drug-induced hepatitis,** total parenteral nutrition, systemic infection), **Impaired intra- or extra-hepatic bile flow**, Inflammatory destruction of intrahepatic bile ducts (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, graft-versus-host disease, liver transplantation).

يشتغل بالشيت

Of the various causes of jaundice listed in Table 16-3, the **most common** are (1) **hepatitis**, (2) **obstruction** to the flow of bile, & (3) **hemolytic** anemia.

😐 Because the hepatic machinery for conjugating & excreting bilirubin does not fully mature until about 2 weeks of age, almost every newborn develops transient & mild unconjugated hyperbilirubinemia, termed ***neonatal jaundice*** **or physiologic jaundice of the newborn.**

يعني كل الأطفال يتصير عندهم unconjugated انتبه

Jaundice may result from inborn errors of metabolisms, including:

physiological لأن

★ ***Gilbert syndrome*** is a relatively common, benign, condition presenting as **mild, fluctuating unconjugated** hyperbilirubinemia. The primary cause is ↓ hepatic levels of glucuronosyltransferase. Affecting up to 7% of the population, the hyperbilirubinemia may go undiscovered for years & *does not have associated morbidity.*

undiscovered حالة بسيطة وشائعة وهي بالعادة

★ ***Dubin-Johnson syndrome*** results from an autosomal recessive defect in the transport protein responsible for hepatocellular excretion of bilirubin glucuronides across the canalicular membrane. These patients exhibit **conjugated hyperbilirubinemia.** Other than having hepatomegaly, patients are otherwise without functional problems.

Obstructive cholestasis

►Results from:- (1) impaired bile flow due to hepatocellular dysfunction or (2) biliary obstruction (intrahepatic or extrahepatic), may present as

- **Jaundice,** however, sometimes
- ***Pruritus*** is the presenting symptom, presumably related to the **elevation in plasma bile acids & their deposition in peripheral tissues, particularly skin.**
- ***Skin xanthomas*** **(focal accumulations of cholesterol)** sometimes appear the result of hyperlipidemia & impaired excretion of cholesterol.

- **Obstructive cholestasis** other manifestations relate to intestinal **malabsorption**, including inadequate absorption of the fat-soluble vitamins A, D, & K.

- **Obstructive cholestasis** *characteristic laboratory finding is* ***elevated serum alkaline phosphatase,*** an enzyme present in bile duct epithelium & in the canalicular membrane of H. (An isozyme is normally present in many other tissues such as bone, therefore, the ↑ levels must be verified as being hepatic in origin). لازم نعرف انه هل هو جاي من الكبد ولا من العظم ؟.

▲ **Extrahepatic biliary obstruction is frequently amenable to surgical alleviation**, in contrast to

▼ ***Intrahepatic cholestasis*** caused by both (1) diseases of the intrahepatic biliary tree or (2) hepatocellular secretory failure, which cannot be benefited by surgery (short of transplantation), & the patient's condition may be worsened by an operative procedure. حتى ح يتأذى من العملية.

☺ **Thus,** ***there is urgency in making a correct diagnosis of the cause of jaundice & cholestasis.***

★ *The most common primary liver infection is **viral hepatitis.***
★ Less common is a condition called *autoimmune hepatitis.*

Systemic viral infections that can involve the liver include
(1) Infectious mononucleosis (Epstein-Barr virus);
(2) Cytomegalovirus or herpesvirus infections, particularly in the newborn or immunosuppressed; &
(3) Yellow fever, which has been a major & serious cause of hepatitis in tropical countries.

★ ***The term viral hepatitis is reserved for infection of the liver caused by a small group of viruses having a particular affinity for the liver.*** The etiologic agents of viral hepatitis are hepatitis viruses A (HAV), B (HBV), C (HCV), D (HDV), & E (HEV). Table 16-4 summarizes some of the features of the hepatitis viruses.

☺ **Because other infectious or noninfectious causes, specially drugs & toxins, can lead to essentially identical syndromes, serologic studies are critical for the diagnosis of viral hepatitis & identification of virus types.**

Clinical Features & Outcomes of Viral Hepatitis

The clinical syndromes which may develop after exposure to hepatitis viruses include:

1. • **Asymptomatic acute infection**: serologic evidence only
2. • **Acute hepatitis**: with/without jaundice
3. • **Chronic hepatitis**: with/without progression to cirrhosis
4. • **Chronic carrier** state: asymptomatic
5. • **Fulminant hepatitis**: submassive to massive hepatic necrosis with acute liver failure

•HAV, HCV, & HEV do **not** generate a **carrier** state.
•HAV & HEV infections do **not** progress to **chronic** hepatitis.

◘ **Morphologic** features of acute & chronic viral hepatitis are listed in Table 16-5. Examples are presented in F16-10 & 16-11. The morphologic changes in acute & chronic viral hepatitis are shared among the hepatotropic viruses & can be mimicked by **drug** reactions.

• With **acute hepatitis**, there is **ballooning degeneration** of H. An inconstant finding is **cholestasis**.
Fatty change is mild & is unusual except with HCV infection.

• Whether acute or chronic, HBV infection may generate **"ground-glass"** H (F16-12): a finely granular, eosinophilic cytoplasm shown by EM to contain massive quantities of **HBsAg** in the form of spheres & tubules. Other HBV-infected H may have **"sanded" nuclei,** resulting from abundant intranuclear **HBcAg**.

■ Two patterns of **hepatocyte death** are seen.

(I) **Cytolysis** from cell membranes rupture leads to "dropped out" necrotic cells with collapse of the sinusoidal collagen reticulin framework where the cells have disappeared; scavenger **macrophage aggregates mark sites** of dropout.

(II) **Apoptosis**, apoptotic H is shrink, intensely eosinophilic, & have fragmented nuclei; & effector **T cells present in the immediate vicinity**. Apoptotic H are phagocytosed within hours by macrophages & hence may be difficult to find despite extensive ongoing apoptosis of H.

▼ **Bridging necrosis** connecting portal-to-portal, central-to-central, or portal-to-central regions of adjacent lobules, signifying a more severe form of acute hepatitis.

• H swelling, necrosis, & regeneration produce compression of the vascular sinusoids & loss of the normal radial array of the parenchyma (**lobular disarray**). يعمل تشوه في normal architecture.

★Inflammation is prominent in acute hepatitis. **The portal tracts are infiltrated with a mixed** inflammatory cells, which may spill over into the parenchyma to cause necrosis of periportal hepatocytes (**interface hepatitis**), & **Kupffer cells undergo hypertrophy & hyperplasia,** & are laden with lipofuscin pigment caused by phagocytosis of H debris. لأنها قاعدة تزيل اشلاء الخلايا الميتة.

★Finally, **bile duct epithelium** may become reactive & even proliferate, particularly in cases of HCV hepatitis, forming poorly defined ductular structures in the midst of the portal tract inflammation. Bile duct destruction does not occur.

Mangene liver biopsy مهمة

* تأخذ biopsy عن طريق needlebiopsy من البطن وبأخذ عينة وهذه العينة بنأخذها للتشخيص.

◘ The histologic features of **chronic hepatitis** range from exceedingly mild to severe.

★**Scattered** H necrosis throughout the lobule may occur in all forms of chronic hepatitis. Continued **periportal necrosis (piece-meal necrosis)** & **bridging necrosis** are harbingers of progressive liver damage. زي لما تاكل رغيف الخبز علامات تشوه م.

★ In the mildest forms, significant inflammation is **limited to portal tracts** & consists of lymphocytes, macrophages, occasional plasma cells, & rare neutrophils or eosinophils. **Lymphoid aggregates** in the portal tract are often seen in HCV infection. الهيكل, الخطة.. كله موجود

★ **Liver architecture is usually well preserved.** ما وصلنا على الـ cirrhosis يعني.

►**The hallmark** of serious liver damage is the deposition of fibrous tissue, (1) At **first**, there is **only portal tracts fibrosis**, but with time (2) **periportal fibrosis** occurs,& (3) followed by **bridging fibrosis.** fibrous tissue يعمل جسر مع الـ

▼**Continued loss of hepatocytes & fibrosis results in C,** with large, irregular nodules separated by broad scars {**macronodular cirrhosis** (F16-13)}.

Autoimmune Hepatitis (rare).

Is a syndrome of mild or severe chronic hepatitis, which **responds dramatically to immunosuppressive therapy.**

- It is indistinguishable from chronic viral hepatitis. Features:
  - Absence of serologic markers of a viral infection, . ماف virus
  - Female predominance (70%) & only 30% are men.
  - Elevated (>2.5 g/dL), serum IgG
  - High titers of autoantibodies in 80% of cases {most patients have circulating **antinuclear Abs**, **anti-smooth muscle Abs**, **liver kidney microsomal Ab**, & **anti-soluble liver/pancreas Ag**}. These Abs can be detected by immunofluorescence or enzyme linked immunosorbent assays.

- The main effectors of cell damage in autoimmune hepatitis are CD4+ helper cells.

- Presence of other autoimmune diseases is seen in up to 60% of patients, like RA, UC, thyroiditis, Sjögren syndrome

- The overall risk of C, the main cause of death, is 5%.

autoimmune gastritis

5% فقط بعد development

ALCOHOL- AND DRUG-INDUCED LIVER DISEASE

The liver is the major drug metabolizing & detoxifying organ in the body, thus, it is subjected to injury from an enormous therapeutic & environmental chemicals. **Injury** may result :

(1) From **direct toxicity**, سام مباشر للكبد زي الكحول.
(2) Hepatic **conversion** of a xenobiotic to an active toxin, or be
(3) Produced by immune mechanisms, usually by the drug, or a metabolite acting as a **hapten** to convert a cellular protein into an immunogen.
toxin إلى cellular prtn وتحول hapten كـ drug الـ يشتغل

▼ A diagnosis of drug-induced liver disease may be made on (1) the basis of an **association of liver damage following drug administration** &, it is hoped, recovery on removal of the drug, with (2) exclusion of other potential causes.
مثل بباراسيتامول Paracetamol بكميات كبيرة.

★ Exposure to a toxin or **therapeutic agent** should always be included in the **differential diagnosis of any form of liver disease.**
أهو شيئ قد يسبب الأمراض بالكبد drug or viruses

★ By far, the most important agent that produces toxic liver injury is **alcohol**.

Alcoholic Liver Disease
methanol من

Excessive **ethanol** consumption causes more than 60% of chronic liver disease in the West & accounts for 50% of deaths due to C.

- **More than 10 million Americans are alcoholics; &** in USA,

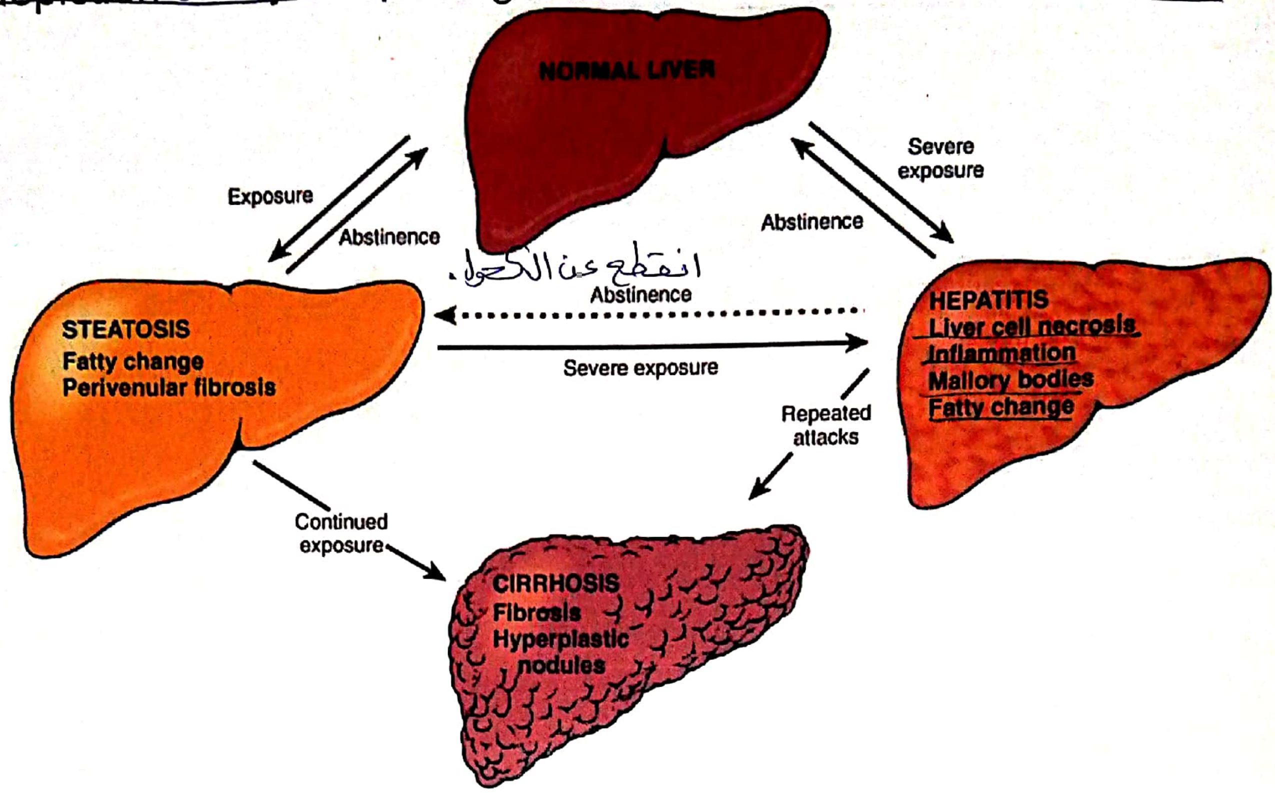
1-IHD 2- cancer 3-CVA 4- COPD 5- Alcoholism.

☠ **Alcohol** abuse: is the 5th **leading cause of death** (after IHD, Cancer, CVA, & COPD);
☠ **it** causes 100,000 to 200,000 deaths annually. Of these deaths, 20,000 are attributable directly to end-stage cirrhosis; many more are the result of automobile accidents (Road Traffic Accidents, RTA).

The 3 distinctive, albeit overlapping forms, *collectively referred to as* ***alcoholic liver disease*** (F16-14) are:
1. *Hepatic steatosis (fatty liver), 2. Alcoholic hepatitis* (1/3)
3. *Cirrhosis.* تشمع الكبد

- **90% to 100%** of heavy drinkers develop **fatty liver, &**
- **10% to 35%** develop **alcoholic hepatitis. However,**
- **8% to 20%** of chronic alcoholics **develop cirrhosis**.

F16-14: **Alcoholic liver disease**. The interrelationships among hepatic steatosis, hepatitis, & cirrhosis are shown, along with a depiction of key morphologic features at the microscopic level.



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بتصير عند أي شخص بشرب كحول.

☹ **(1) Hepatic Steatosis (Fatty Liver)**

◘ After even moderate intake of alcohol, → **microvesicular** lipid droplets accumulate in H. → with chronic intake of alcohol, lipid accumulates becomes **macrovesicular**, → initially centrilobular but in severe cases it may involve the → entire lobule (F16-15 & 5.4).

Grossly, the liver is large (≤4-6 kg, ☺ Normal 1.5Kg), soft, yellow, & greasy. ☺The **fatty** change is completely **reversible** if there is abstention from further alcohol intake.

امتناع

☹ **(2) Alcoholic Hepatitis:** This is characterized by:

★ ***Hepatocyte Swelling & Necrosis:*** Single or scattered foci of H undergo balloon **swelling** {resulting from accumulation of fat, water & proteins that normally are exported} & **necrosis.**

★ ***Mallory Bodies.*** Scattered H accumulate tangled skeins of intermediate filaments, visible as eosinophilic cytoplasmic inclusions in degenerating H (F16-16), which are a **characteristic but not specific feature of alcoholic liver disease**, because they are also seen in PBC, hepatocellular tumors, Wilson disease, & chronic cholestatic syndromes.

مهمة

لا تعتبر pathognomic موجودة بأمراض أخرى كثيرة.

Scanned with CamScanner

★ ***Neutrophil Infiltration.*** Neutrophils infiltrate the lobule & accumulate around degenerating H, particularly those containing Mallory bodies. Lymphocytes & macrophages also enter portal tracts & spill into the parenchyma.

★ ***Fibrosis.*** Alcoholic hepatitis is almost always accompanied by a brisk **sinusoidal & perivenular fibrosis**; occasionally **periportal** fibrosis may predominate, particularly with repeated bouts of heavy alcohol intake.
In some cases there is cholestasis & mild deposition of hemosiderin (iron) in hepatocytes & Kupffer cells.
Grossly, the liver is mottled red with bile-stained areas

☹ **(3) Alcoholic Cirrhosis.**
This is the **final & irreversible** form of alcoholic liver disease, usually develops slowly; {but may develop more rapidly, within 1 to 2 years, in the setting of alcoholic hepatitis}.
At first the C liver is yellow-tan, fatty, & enlarged, usually weighing over 2 kg. Within years it is transformed into a brown, nonfatty, shrunken liver, weighing less than 1 kg.

▶Initially the developing fibrous septa are delicate & extend through sinusoids from central vein to portal regions as well as from portal tract to portal tract. (bridging fibrosis)

▼ Regenerative activity of entrapped parenchymal hepatocytes generates (**micronodular C** vs. the macronodular C described for viral hepatitis), but The nodularity eventually becomes more prominent; scattered larger nodules create a **"hobnail" appearance** on the surface of the liver (F16-17), & eventually, the C is converted into a mixed micronodular & macronodular pattern (F16-18). Bile stasis often develops; Mallory bodies are only rarely evident at this stage.

▶ multiple nodule ما بستعمل هاد smooth ازي متسلق الجبال (الجليدية)

مهم ▲Thus, **end-stage alcoholic cirrhosis eventually comes to resemble**, both macroscopically & microscopically, the cirrhosis developing from **viral, autoimmune hepatitis** and **other causes.**

صعب نميز بينهم.

Pathogenesis

- Short-term ingestion of as much as 80 gm of ethanol per day (8 beers) produces mild, reversible hepatic **fatty liver**.
- Chronic intake of 60 gm/day is considered a borderline risk for severe injury. **Women seem to be more susceptible to hepatic injury than are men.**

شرب كميات كبيرة بوقت قصير.

- **Binge (party) drinking causes more liver injury** (note that beer binge drinking is, unfortunately, the preferred modality of drinking in college student parties).

يعني مش شرط يصيروا الـ ٣ عالتوالي ممكن الـ cirrhosis

- Steatosis & alcoholic hepatitis may develop **independently**, & thus, they do not necessarily represent a continuum of changes. There is an **inconstant relationship** between hepatic steatosis & alcoholic hepatitis as precursors to cirrhosis, which may develop without antecedent evidence of steatosis or alcoholic hepatitis!
- In the absence of a clear understanding of the pathogenetic factors influencing liver damage, **no "safe" upper limit for alcohol consumption can be proposed.**

لا يمكن اعطاء حد آمن من الـ limit طالما انت تحته فيكون آمن.

☹ The causes of ***Hepatocellular steatosis*** results from:
(1) the shunting of normal substrates away from catabolism & toward lipid biosynthesis,
(2) Impaired assembly & secretion of lipoproteins; &
(3) ↑ peripheral catabolism of fat.

☹ The causes of ***alcoholic hepatitis*** are uncertain, but the following alterations caused by alcohol are important:
(1) Acetaldehyde (the major intermediate metabolite of alcohol en route to acetate production) induces **lipid peroxidation** & acetaldehyde-protein adduct formation, which may disrupt cytoskeletal & membrane function,

(2) Alcohol directly **affects microtubule organization** (as illustrated by the detection of Mallory's hyaline), **mitochondrial function**, & membrane fluidity,

(3) **ROS** are generated during oxidation of ethanol by the microsomal ethanol oxidizing system; in addition, the **ROS** are also produced by neutrophils, which infiltrate areas of H necrosis. These **ROS** reacts with membranes & proteins. The **ROS** are the main stimuli for **the production** of cytokines in alcoholic liver disease (**TNF**, IL-6, IL-8, & IL-18), This abnormal cytokine regulation is a major feature of alcoholic hepatitis & alcoholic liver disease in general, & the TNF is considered to be the main effector of injury.
Concurrent viral hepatitis, particularly hepatitis C, is a major accelerater of liver disease in alcoholics, prevalence of hepatitis C in individuals with alcoholic disease is about 30%.
▷ Viral + alcohol consumption.

1500g to 4000 - 6000g.

► ***Clinically,*** *Hepatic steatosis* give rise to hepatomegaly

It is estimated that 15 to 20 years of excessive drinking are necessary to develop *alcoholic hepatitis*, which appear relatively acutely, usually after a bout of heavy drinking. The outlook is unpredictable; each bout of hepatitis carries about a 10% to 20% risk of death.

• With repeated bouts, C appears in about 1/3 of patients within a few years; alcoholic hepatitis may be superimposed on C.

• With proper nutrition & total cessation of alcohol consumption, alcoholic hepatitis may clear slowly, however, in some the hepatitis may persists despite abstinence & progresses to C.
• ***Alcoholic C*** manifestations are similar to other forms of C, presented earlier, including complications of **portal hypertension (varices)** or hepatic **encephalopathy.**

C can be completely clinically silent.
• **Finally, C may be clinically silent, discovered only at autopsy** or when stress such as infection or trauma tips the balance toward hepatic insufficiency.

☺ **The most important aspect of treatment is abstinence from alcohol.**

☠ In the end-stage alcoholic, the immediate causes of death are (1) **LF**, (2) **Massive GIT** hemorrhage, (3) an intercurrent **Infection**, (4) **Hepatorenal syndrome** after a bout of alcoholic hepatitis, & (5) **Liver cell ca** (3%-6% of cases).

Drug-induced liver disease

1-Alcohol 2-Virus 3-drug

• Common condition that may present as a **mild reaction** or, much more seriously, as **acute LF**. A large number of drugs & chemicals can produce liver injury (Table 16-6).

• Drug reactions may be classified as **predictable (intrinsic) reactions or unpredictable (idiosyncratic) ones.**

• **Predictable** drug reactions may occur in anyone who accumulates a sufficient dose. e.g. paracetamol

• **Unpredictable** reactions depend on idiosyncrasies of the host, particularly the host's propensity to mount an immune response to the antigenic stimulus, & the rate at which the host metabolizes the agent. The injury may be immediate or take weeks to months to develop.

☺ **Rule: *Drug-induced chronic hepatitis*** *is histologically & clinically* ***indistinguishable from chronic viral hepatitis*** *or* ***autoimmune hepatitis,*** *& hence serologic markers of viral infection are critical for making the distinction.*

serology Alcohol → by history autoimmune → IgG

متوقع انه يصير.

• Among the hepatotoxic agents, **predictable** drug reactions are ascribed to acetaminophen (Paracetamol), tetracycline, antineoplastic agents, *Amanita phalloides* toxin, carbon tetrachloride (CCl_4) كان تستعمل لفصل الملابس. (toxin mushroom). غير متوقع.

• Examples of drugs that can cause **idiosyncratic reactions** include **chlorpromazine**, **halothane** anesthetic (which can cause a fatal immune-mediated hepatitis), **sulfonamides**, **α-methyldopa**, & **allopurinol**.

• The mechanism of liver injury may be direct toxic damage to hepatocytes (e.g., acetaminophen, CCl_4, & mushroom toxins) but also involves a variable combination of toxicity & inflammation with immune-mediated hepatocyte destruction.

• Depending on the drug, the patterns of drug-induced liver injury may include one or more of the following: Steatosis/ steatohepatitis/ hepatocellular necrosis/ cholestasis/ fibrosis/ & vascular lesions. لزلك العقار والـ pattern بختلف.

(وما انشرح بالفيديو)

☠ Among drugs that may cause acute liver failure are acetaminophen, halothane, anti TB drugs (rifampin, isoniazid), antidepressant monoamine oxidase inhibitors, CCl_4 & *Amanita phalloides* toxin poisoning.

☠ 46% of cases of acute LF caused by **acetaminophen intoxication**, & 60% of these are accidental overdosage.

► With massive H necrosis (F16-19 & 5.17), **the entire liver is involved, &** ◘ M, **complete destruction of H** leaves only a collapsed reticulin framework & preserved portal tracts, with surprisingly little inflammatory reaction (F16-20). However, with survival for several days there is a massive influx of inflammatory cells to begin the clean-up process.

☺ Patient **survival** for more than a **week** permits regeneration of surviving H, & if the parenchymal framework is preserved, regeneration is complete & normal liver architecture is restored. More massive destruction regeneration yield C.

METABOLIC & INHERITED LIVER DISEASE

The most common metabolic liver disease is:
(1) *nonalcoholic fatty liver disease* (NAFLD), other metabolic diseases attributable to inborn errors of metabolism include: (2) hemochromatosis (3) Wilson disease (4) α_1-antitrypsin deficiency.

Nonalcoholic Fatty Liver Disease

★ **NAFLD** is a common condition, which was first recognized in 1980. It is a condition in which **fatty liver & liver disease develop in individuals who do not drink alcohol.**

★ It may present as (I) steatosis or as (II) *nonalcoholic steatohepatitis (NASH)* similar to alcoholic hepatitis & involves H destruction, inflammation with neutrophils & mononuclear cells, & progressive pericellular fibrosis.

★ NAFLD & NASH are most consistently associated with:

- **Insulin resistance**. Other key associated variables are:
- **Type 2 diabetes** (or family history)
- **Obesity** (BMI >25 kg/m^2 in Asians)
- **Dyslipidemia** (hypertriglyceridemia, low high-density lipoprotein Ch, high low-density lipoprotein Ch)

Inherited Diseases: Hereditary Hemochromatosis (HH)

☺ **Normal adults** total body iron pool is **2 to 6 gm,** about 0.5 gm is stored in the liver. ☹ In HH, the total body iron may exceed **50 gm**, over 1/3 of which is in the liver!

☹ ***HH*** is an autosomal **recessive** disease of adult onset {first appear in the 5th to 6th decades} caused by ► *mutations* in the *HFE* gene, leading to ►↑ *intestinal absorption* of dietary iron, net 0.5 to 1.0 gm/year iron *accumulation* & ► *deposition* in different organs such as liver, pancreas, & skin.
☹ Fully developed HH show **cirrhosis** {100% of cases}, **DM** & **skin pigmentation** (80% in each = **Bronze Diabetes**).

pancreas نتيجة تدميرال and heart

★ **Acquired forms of iron accumulation** from known sources called **Hemosiderosis** or ***secondary iron overload, e.g.,*** multiple transfusions, ineffective erythropoiesis {Sideroblastic anemia & β-thalassemia} &↑ iron intake {Bantu siderosis}.

(شربوا Beer بيرا ميل من الحديد لقبائل في افريقيا).