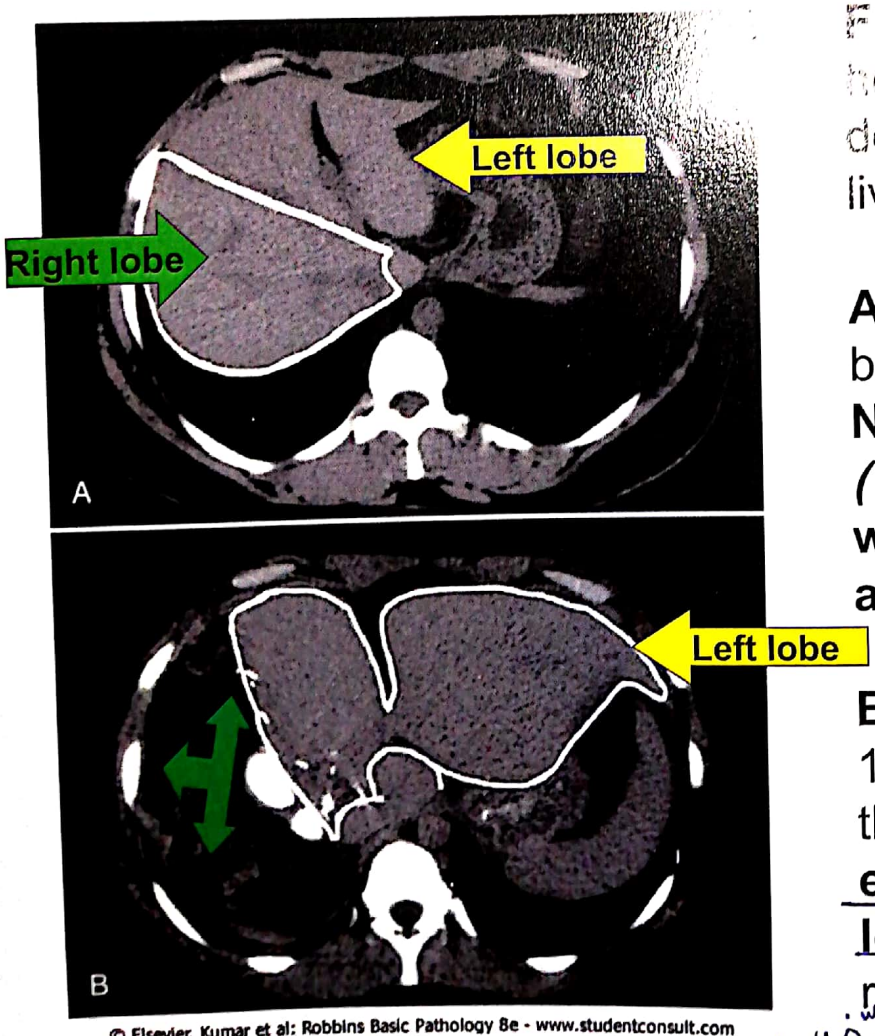
THE LIVER

☺ 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.

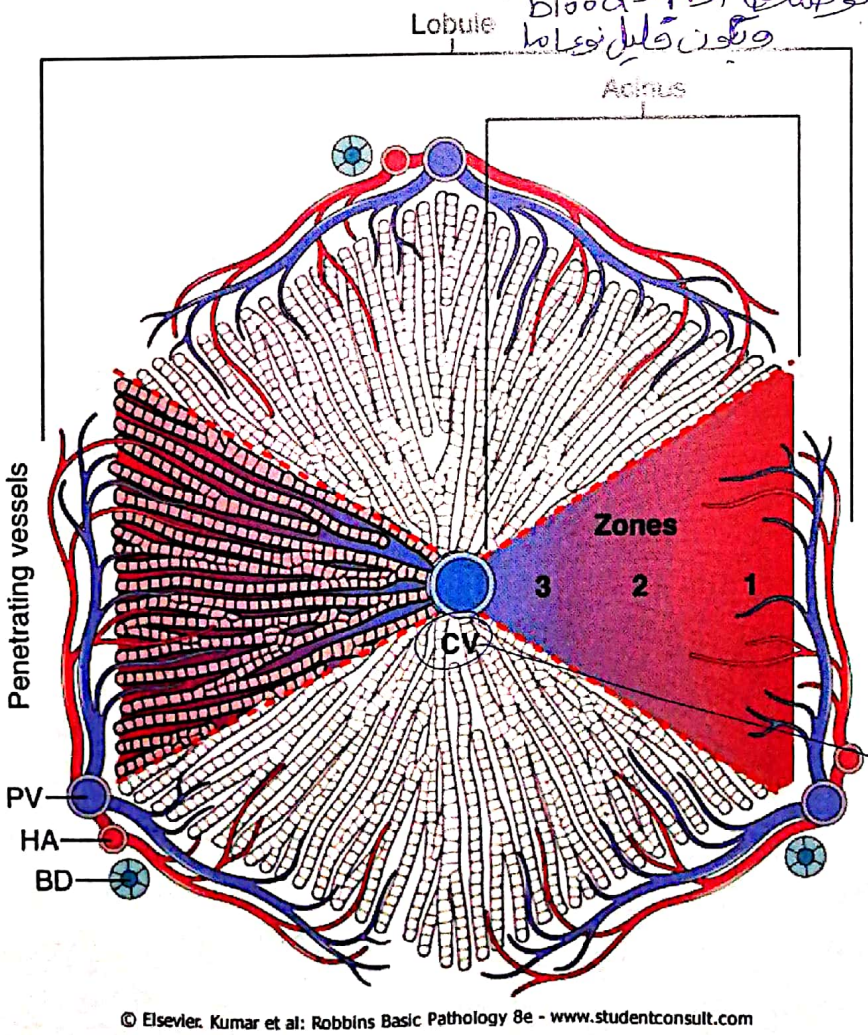
★ ***Intracellular accumulation*** of **fat, iron, copper, & retained biliary** material may occur in H. → hepatocyte.

★ 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.
(الفقاعات تجتمع مع بعض)
عبية، تشحم، تضخم كبير

★ **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)

خراوة.

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.

خراوة

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

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.***

atrophy of testis.

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.

مرضى في 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 الأصل.
hepatorenal syndr. ← الحالات لا ينطبق عليها ال

{Excluded by this definition ... comitant 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
splanchnic vasodilatation & systemic vasoconstrict
في الجوف 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 أمراض 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 ال abcess: ال abcess بعمل fibrosis بمنطقة معينة فقط وليس cirrhosis

Pathogenesis of cirrhosis

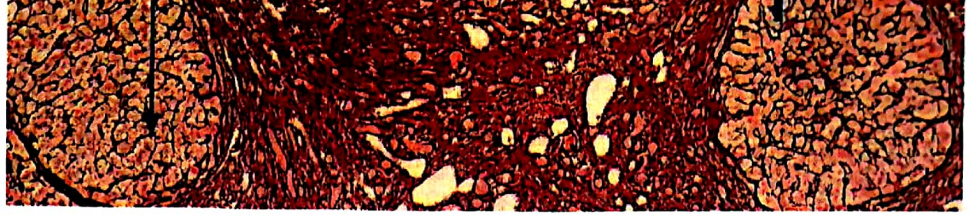
►H death, regeneration, fibrosis, & vascular changes are the **major mechanisms** that combine to create C.

- 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. يعني 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 انهارت رح يصير مباشرة fibrosis

فعلياً ما في قيمة من ال micro or macro لأنه تبدأ micro وبتكمل macro

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.

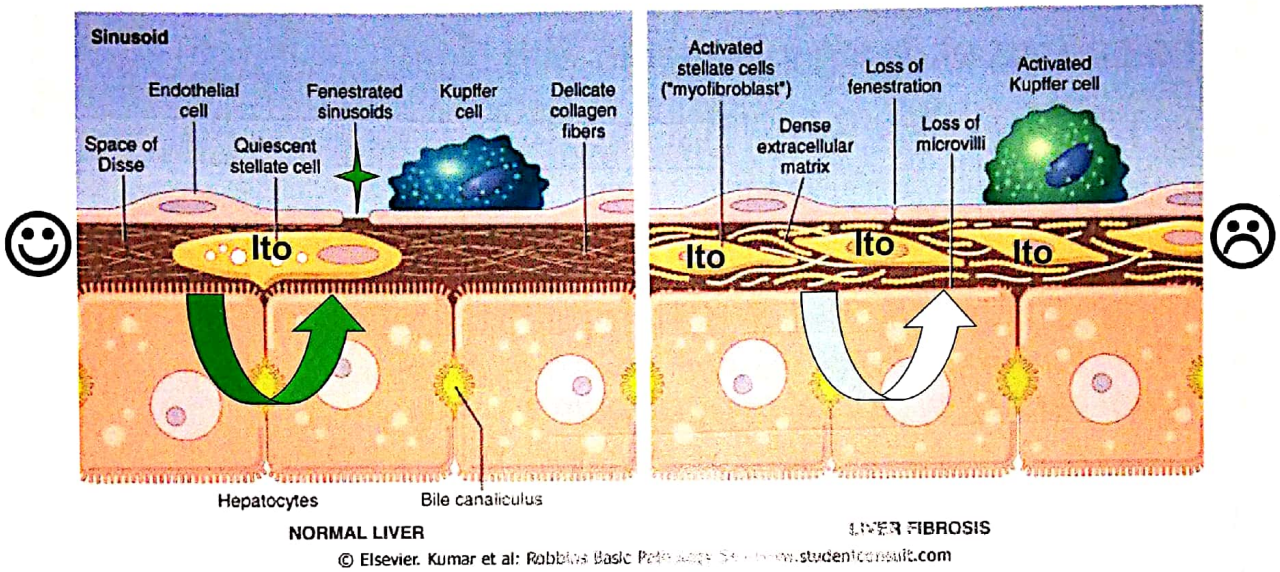
- Vascular changes consisting of the:

(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.

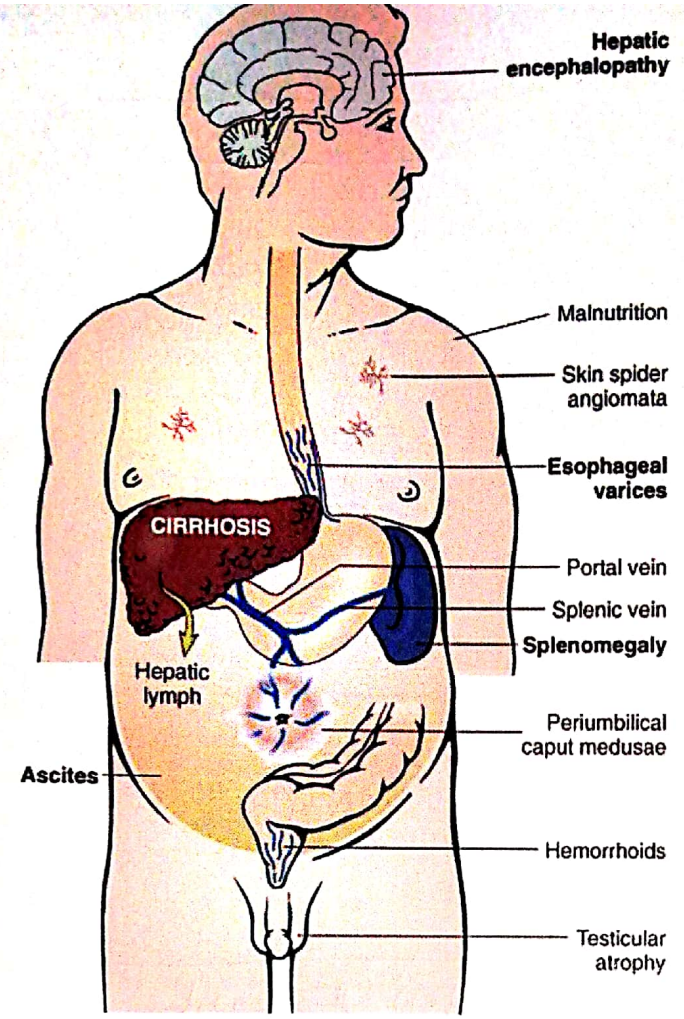
★ *The dominant intrahepatic cause is **cirrhosis,** accounting for most cases of portal hypertension.* أهو عامل يؤدي إلى ارتفاع الضغط.

٪ 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 اعاقة 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: systemic الى البوابي
(1) **Ascites**, (2) Portosystemic venous **Shunts (varices)**, (3) **Splenomegaly** & (4) **Hepatic encephalopathy** (see above).

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.

لـه رأس الحيوان الخرافي في منطقة البطن.

spider nivea لهيف

ارتفاع الـ estrogen أدى الـ

(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.

الـ varices موجودة بالكبد & الـ 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 in systemic circulation and others.

4-3 Varices: oesophagus موجودة بـ 2/3 من المرضى و الـ rupture هو السبب الأول عن قتل 50%.

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 بتصير 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. هنا ح يتأكد 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.. كلهوجود

★ **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 جسور من 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 تشتغل

▼ 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 يسببوا 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,

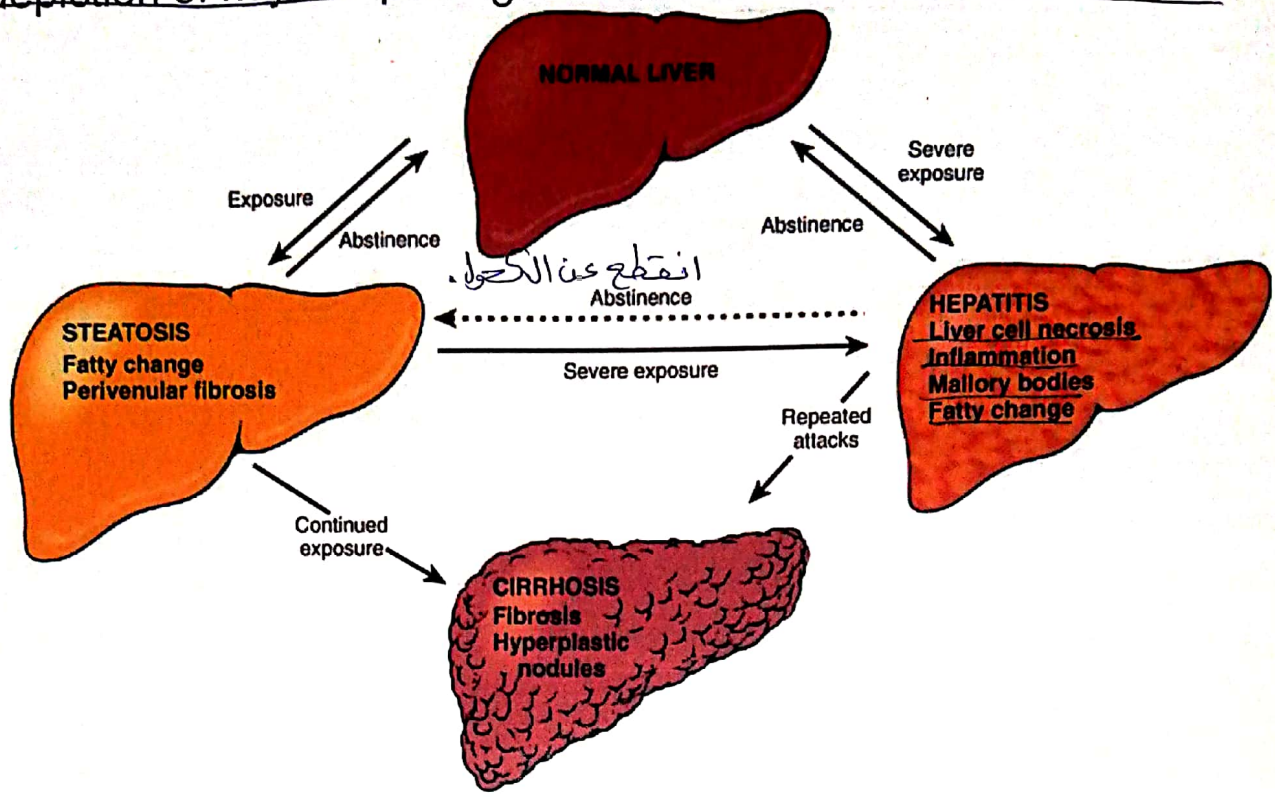
1-IHD 2- cancer 3-CVA 4- COPD 5- Alcoholism.

☠ **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,*
3. *Cirrhosis.* تشحم 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.



يتجمع عند أي شخص يشرب 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.

معظمة
موجودة ~~بس~~ بأمراض أخرى كثيرة.
لا تعتبر pathognomic

★ ***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 ازي متسلق الجبال (الجليدية) ما بستعملها smooth.

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 يضلوا الـ ٣ عام التوالي 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 أعلى من الـ limit طالما انت تحته فبكون 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.

► ***Clinically,*** *Hepatic steatosis* give rise to hepatomegaly 1500g to 4000-6000g.
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. 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).

▼ **In HH, there is deposition of hemosiderin** in the following organs (in decreasing order of severity): **liver** with C {see below}, **pancreas** {with diffused interstitial fibrosis & parenchymal atrophy & consequent DM}, **myocardium** {Cardiomyopathy} pituitary, adrenal, thyroid & parathyroid glands, joints, & **skin** {pigmentation, partially due to hemosiderin deposition in dermal macrophages & from ↑ epidermal melanin production, both renders the skin slate-gray, hence the term Bronze Diabetes}.

★ **In the liver**, first, there is golden-yellow hemosiderin granules in the cytoplasm of **periportal H** which stain blue with the Prussian blue, stain (F16-21 &1-28). Eventually, with ↑ iron load, there is **progressive involvement** of the rest of the lobule, bile duct epithelium & Kupffer cell. **Iron is a direct hepatotoxin, & inflammation is characteristically absent.** Fibrosis develop slowly, leading ultimately to cirrhosis.

► ***Pathogenesis:*** Excessive iron is directly toxic to tissues by the following mechanisms:

(1) Lipid peroxidation by iron-catalyzed free-radical reactions,

(2) Stimulation of collagen formation, &

(3) Direct interactions of iron with DNA. Iron actions may be reversible, with the exception of nonlethal DNA damage.

كلأشي ما عدا تدمير الـ DNA وهذا قد يؤدي reversible وتشويه

cancer of the liver.

► ***Clinically,*** males predominate (M/F ratio of 5 to 7: 1), patients usually present with classic clinical triad of **cirrhosis with hepatomegaly, DM, skin pigmentation**. ☠ Death may result from **cirrhosis, hepatocellular carcinoma, or cardiac disease.** Treatment of iron overload {phlebotomy & the use of iron chelators) does not remove the risk for development of 🕷 **hepatocellular ca** (a **200-fold** higher than normal) because of the iron induced oxidative damage of DNA.

☺ HH can be diagnosed early, before irreversible tissue damage has occurred.

repeated transfusion حتى نقلل نسبة الـ Fe^{+2} في الدم لكن لا يزيل خطورة التعرض للـ cancer.

Wilson Disease

★An autosomal **recessive** disorder of **copper** metabolism, characterized by the accumulation of toxic levels of copper in many tissues & organs, principally the liver, brain, & eye.

★ The responsible genetic defect is a mutation in *ATP7B.*

★ Incidence 1: 30,000; **much less common than HH**.

☺ **Normal copper physiology involves** (1) absorption of ingested copper (2-5 mg/day); (2) plasma transport in complex with albumin; (3) hepatocellular uptake, followed by incorporation into an α_2-globulin to form ceruloplasmin; **(4) secretion of ceruloplasmin into plasma**, where it accounts for 90% to 95% of plasma copper; & (5) hepatic uptake of desialylated, senescent ceruloplasmin from the plasma, followed by lysosomal degradation & **secretion of free copper into bile.**

المستهلك

In Wilson disease, defective function of *ATP7B* inhibit the: **(I)** secretion of ceruloplasmin into the plasma **(Step 4 above)** **&** **(II)** excretion of copper into bile **(Step 5)**, which is *the primary route for copper elimination from the body, resulting in* ➔ **copper accumulation in the liver** causing **toxic** liver injury by: (1) Promoting the formation of **FR**, (free radicals) (2) **Binding to sulfhydryl** groups of cellular proteins, & (3) **Displacing** other metals in hepatic metalloenzymes.

☹ In addition to the liver damage, usually, by the age of 5 years, copper that is not ceruloplasmin bound spills over into the circulation, causing pathologic changes to other sites. يروح على مناطق أخرى.

☹ ➔ The hepatic changes range from minor to massive damage, include **fatty change**, **acute hepatitis**, or **chronic hepatitis** {resembles chronic hepatitis of viral, drug, or alcoholic origin}, progressing to **cirrhosis.** Excess copper deposition can be demonstrated by special stains (eg, rhodamine stain for copper, **orcein stain** for copper-associated protein).

😐 Because **copper** also accumulates in chronic obstructive cholestasis, & because histology cannot reliably distinguish Wilson disease from viral- & drug-induced hepatitis, (demonstration of **hepatic copper content** in excess of 250 µg/gm dry weights is most helpful for making a **diagnosis.**) تحليل صعب لكن مهم.

▼ *The biochemical **diagnosis** of Wilson* disease is based on a: **↓ serum ceruloplasmin**, ***↑ hepatic copper content,*** **&** ***↑ urinary excretion of copper.***

(cornea حلقة خضراء في الـ limbus تحت الـ)

☹ ← ☹ All **patients show eye lesions** called **Kayser-Fleischer rings** (green to brown deposits of copper in Descemet membrane in the limbus of the cornea). In the **brain,** toxic injury primarily affects the putamen of the basal ganglia, which demonstrates atrophy & cavitation. Hence the alternative designation of this disease as **hepatolenticular degeneration**. مهم

liver + in basal ganglia

☺ Early recognition & long-term copper chelation therapy (as with D-penicillamine) have dramatically altered the usual progressive downhill course of the disease.

ياخذ النحاس ويحط بدالو الـ Na^+

HH, Wilson, AAT Deficiency → All are recessive not dominant.

α_1-Antitrypsin (AAT) Deficiency

★ AAT deficiency is an autosomal **recessive** disorder marked by abnormally low serum levels of AAT protease inhibitor.

☺ **The major function of AAT is the inhibition of proteases, particularly neutrophil elastase released at sites of inflammation.** AAT deficiency leads to pulmonary emphysema, because a relative lack of this protein permits the unrestrained activity of tissue-destructive proteases.

★ Homozygotes for the Z allele (*PiZZ* genotype) have circulating AAT levels that are **only 10% of normal levels**.

★ The defect results in misfolding of the nascent polypeptide in the hepatocyte ER, & because it cannot be secreted by the liver cells, it remain accumulated in ER & undergoes excessive lysosomal degradation, & appears as round to oval cytoplasmic **globular inclusions** of retained AAT (F16-22).

☺ Curiously, 100% of individuals with the *PiZZ* genotype **accumulate** AAT in the liver **H**, but only 8% to 20% develop **significant liver damage**. This may be related to a genetic tendency that causes susceptible individuals to be less able to degrade accumulated AAT protein within **H.**

◘H, the **H** in AAT deficiency contain round to oval cytoplasmic **globular inclusions** of retained AAT, which are strongly positive in PAS stain (F16-22). By EM they lie within SER & sometimes RER. The hepatic injury associated with PiZZ homozygosity may range from marked **cholestasis** with **H necrosis** in newborns, to **childhood C.**

►*Clinically,* among newborns with AAT deficiency, 10% to 20% show **cholestasis**. In older children, adolescents, & adults, the presenting symptoms may be related to **chronic hepatitis**, **cirrhosis, or pulmonary disease.**

☺ The **treatment** & cure for the severe hepatic disease is **orthotopic liver transplantation**.

Neonatal Cholestasis

☺ Mild transient elevations in serum **unconjugated** bilirubin are common in normal newborns.

☹ Prolonged **conjugated** hyperbilirubinemia in the newborn, termed ***neonatal cholestasis,*** **affects 1 in 2500 live births.** The major causes are (I) **extrahepatic biliary atresia**, discussed later, & a variety of other disorders collectively referred to as (II) *neonatal hepatitis.*

😐 Neonatal hepatitis is not a specific entity, nor is the disorders necessarily inflammatory. Instead, the finding of "neonatal cholestasis" should evoke a diligent search for recognizable toxic, metabolic, & infectious liver diseases.

Idiopathic neonatal hepatitis **constitutes as many as 50% of cases of neonatal hepatitis!**

► Clinical presentation of infants with any form of neonatal cholestasis is fairly typical, with **jaundice**, **dark urine**, **light or acholic stools, & hepatomegaly.**

➔ **Differentiation** between the two most common causes of neonatal cholestasis (extrahepatic atresia & idiopathic hepatitis) **assumes great importance,** because definitive treatment of biliary **atresia requires surgical** intervention, whereas surgery may **adversely** affect the clinical course of a child with **idiopathic neonatal hepatitis**.

★ Fortunately, discrimination between these diseases can be made in 90% of cases using clinical data and liver biopsy. by needle liver biopsy.

Reye Syndrome

• ***A rare (1 per Million) disease characterized by fatty change in the liver & encephalopathy, can be fatal.***

• It primarily affects **children < 4 years of age**, typically developing 3 to 5 days after a viral illness. The onset is heralded by **pernicious (severe) vomiting, &** is → . نبضات غيبوبة accompanied by **irritability or lethargy & hepatomegaly**. Although most patients recover, about 25% progress to **coma**, accompanied by LF, with elevations in the serum levels of aminotransferases, bilirubin, & particularly ammonia.

الربع بموت .

☠ **Death occurs from coma or liver failure**

•The pathogenesis of Reye syndrome involves a generalized **loss of mitochondrial function**.

• Reye syndrome has been associated with **aspirin administration during viral illnesses,** but there is no evidence that salicylates play a causal role in this disorder.

• Although the case rate for classic **Reye syndrome in the United States is less than 1 per million per year,** this disorder & "Reye-like syndromes" must be considered in the differential diagnosis of postviral disorders in children.

• The key pathologic finding in the **liver** is microvesicular steatosis, & in the **brain,** cerebral edema is usually present.

DISEASES OF THE INTRAHEPATIC BILIARY TRACT

غير معروف السبب مرضين مهمين

Primary Biliary Cirrhosis (PBC)

- **PBC** is chronic, progressive, & often fatal cholestatic (obstructive) liver disease.
- **PBC** characterized by **nonsuppurative destruction** of small & medium-sized intrahepatic bile ducts (BD), **portal inflammation,** scarring with eventual late cirrhosis & LF over years or decades.
- **PBC** is primarily a disease of middle-aged **women**, & peak incidence between 40 & 50 years of age.
- **PBC pathogenesis:** <90% of patients have high titers of **antimitochondrial antibodies (AMA),** غير عن autoimmune hepatitis.
- **PBC is** *almost always* associated with elevated *serum alkaline phosphatase & cholesterol levels, hyperbilirubinemia is a late & usually signifies incipient hepatic failure.*

(immunologically based disease).

- **PBC** associated extrahepatic conditions include Sjögren syndrome, scleroderma, thyroiditis, RA, membranous GN, Raynaud phenomenon, & celiac disease.
- ***Clinically,*** **PBC** onset is insidious, usually presenting as pruritus; jaundice develops late. Over a period of 20 years or more, the individuals develop LF.

◙ In **PBC** precirrhotic stage, there is a dense lymphocyte/plasma cell infiltrate around small BD in portal tracts, + granulomatous lesions may also appear (F 16-24). Interlobular BD are destroyed by inflammation (the **florid duct lesion**),

لـ تدمير القناة النشيط.

▼ The obstruction to intrahepatic bile flow leads to upstream BD **proliferation** (F16-25), inflammation & necrosis of the adjacent periportal hepatic parenchyma, & generalized cholestasis.

☹ In the end stage of **PBC,** interlobular BD are **absent.**

دع تند بالنهاية وتعتبر مختفية.

▼Over years to decades, relentless (progressive) portal tract scarring & bridging fibrosis leads to cirrhosis. The end-stage liver of **PBC (and of PSC)** showing marked yellow-green pigmentation & the liver cut surface is hard, with a finely granular appearance (F16-23).

Primary Sclerosing Cholangitis {PSC}

★ **PSC** is a chronic, obstructive **fibrosing cholangitis** disorder, characterized by progressive destruction & fibrosis of **extrahepatic & large intrahepatic bile ducts.**

intra ليس not small and medium size.

★ Because the changes in the ducts are patchy, **retrograde cholangiography** shows a characteristic **"beading"** of the contrast medium in the affected biliary tree segments.

(constricted جزء dilated جزء المسبحة على شكل Bile duct الـ)

★The large BD show periductal fibrosis that obliterates the lumen, leaving a solid cord scar with few inflammatory cells.

زي قشرة البصل.

★ **PSC** is commonly seen in association with IBD, particularly **chronic UC, UC coexists in 70% of individuals with PSC**. Conversely, the prevalence of **PSC** in persons with UC is about 4%.

* الأرقام مهمة

★ **PSC** cause is **unknown,** but the **association with UC,** linkage with certain *HLA-DR* alleles, & **presence of antinuclear cytoplasmic antibodies with a perinuclear localization in 80% of cases all suggest** that this is an **immunologically mediated disease**

★ **PSC** tends to occur in the 3rd to 5th decades, most often after development of IBD. M/F ratio is 2 : 1. Symptoms include pruritus, & jaundice, & weight loss, ascites, variceal bleeding, & encephalopathy. علامات الـ cirrhosis

(30-50 y)

🕷 **Cholangiocarcinoma** develop in 10% to 15% of **PSC**, with a median time of 5 years from diagnosis. There **is no effective therapy** for **PSC** & the disease has **become an important indication fo** [illegible] **transplantation.**

سرطان القنوات الصفراوية

◙ **PSC** Characteristic feature is a **fibrosing cholangitis** of BD. Specifically, affected portal tracts show concentric periductal **onion-skin fibrosis** & mild lymphocytic infiltrate (F16-26).

▲ Progressive atrophy of the bile duct epithelium leads to obliteration of the lumen, leaving behind a solid, cordlike fibrous scar. In between areas of progressive stricture, bile ducts become ectatic (dilated) & inflamed, presumably the result of down-stream obstruction.

▲ **Ultimately, biliary cirrhosis** develops, much like that seen with primary & secondary biliary cirrhosis.

✱(Remember: **Secondary** biliary cirrhosis to stone, stricture or tumor) is much more common than both PBC & PSC).

primary: أضعاف أضعاف حالات الـ

carcinoma of the head of pancreas → obstruction

TUMORS & HEPATIC NODULES

• The liver & lungs are the most commonly involved organs by **metastatic** cancer secondaries. • Indeed, the *most common hepatic tumors are metastatic carcinomas* (F6-11 & 5-27) *mainly* from colon + lung + breast primaries.

• The main two primary liver cancers are (1) **hepatocellular carcinomas** (HCC), which is the most common *primary hepatic malignancy,* & (2) **cholangiocarcinomas** from bile duct epith.

• Two rare primary liver tumors (not discussed further): **Hepatoblastoma,** a childhood hepatocellular tumor, & **Angiosarcoma** of blood vessels that is associated with exposure to vinylchloride & arsenic, & Thorotrast.

• Clinically, hepatic masses may (1) cause epigastric fullness, (2) be detected by routine physical ex, or (3) be incidental finding during X-ray ex. for other indications. X-Ray for another indication.

Hepatocellular Nodules

★Solitary or multiple benign hepatocellular (H) nodules which may develop in the liver are of 3 types, (I) focal nodular hyperplasia, (II) macroregenerative, &(III) dysplastic nodules.

(I) Focal nodular hyperplasia

- Is **not a tumor**, but a **nodular regeneration.**
- Is a localized, well-demarcated, but poorly encapsulated lesion, consisting of hyperplastic H nodules with a central fibrous scar, may reach up to many cm in ∅.
- Nodules appear in **noncirrhotic** livers.
- Occurs in response to **local vascular injury,** & in about 20% of cases, it coexists with hepatic **cavernous** hemangiomas.
- Occurs usually as an incidental finding, commonly in women of reproductive age, & **does not carry a risk for cancer.**

***(II) Macroregenerative* nodules** (F16-31),

- Appear in cirrhotic livers, larger than surrounding cirrhotic nodules; but **do not display atypical** features.
- Nodules contain more than one portal tract, have an intact reticulin framework, & are **not precursors of cancer.**

"هذا ← only small cell high-grade are precancerous

small **(III) Dysplastic nodules**

- Nodules less than 1 mm in ∅ that appear in cirrhotic liver.
- The H in dysplastic nodules & in smaller lesions called dysplastic foci, are highly proliferative & show low or high grade atypical features, i.e., crowding & pleomorphism.
- ***High-grade dysplastic lesions are considered to be precursors of HCC,*** *are often monoclonal, & may contain chromosome aberrations similar to those present in HCC.*
- Dysplastic nodules are subdivided into small-cell & large-cell dysplastic nodules or foci. • Only **small-cell dysplasias are precursors to HCC;** H in large-cell dysplastic lesions are apparently have reached replicative senescence.

لذلك نعتبرها precanc

Benign Tumors

- ***Cavernous hemangioma*** *is the* commonest BT of the liver.
- Well-circumscribed lesions (F 5.11), consist of EC-lined vascular channels & intervening stroma • Appear as discrete red-blue, subcapsular, soft nodules, less than 2 cm in ∅.

Clinical significance: (A) blind percutaneous needle biopsy may cause severe intra-abdominal **bleeding, &**

(B) importance of not **mistaking** them for metastatic **cancer.**

1- blind percutaneous needle → internal bleeding
2- X-Ray examination → metastatic cancer

F 5.11: **Hemangioma: liver.** Red, hemorrhagic 4cm in ∅

Hepatic Adenoma

- BT of H, usually occurs in women of childbearing age who have used **oral contraceptive** steroids, & it may regress on discontinuance of hormone use. These T may be yellow-tan pale, or bile-stained, well-demarcated nodules found anywhere in the hepatic substance but, often **subscapsular** (F16-32). **They may reach 30 cm in ∅.**

■ H, composed of sheets & cords of cells that resemble normal H. Portal tracts are **absent**; instead, prominent arteries & veins are distributed through the tumor.

Clinically, hepatic adenomas are significant for 3 reasons:

(1) They may be **mistaken for HCC**; metastatic tumor

(2) Subcapsular adenomas are at risk for **rupture,** particularly during pregnancy (under estrogenic stimulation), causing **life-threatening intra-abdominal hemorrhage**; & (acute abdomen)

(3) Although adenomas are not considered precursors of HCC, **adenomas carrying β-catenin mutations carry a risk of developing into cancers.** small size high grade dyp. nodules

Hepatocellular Carcinomas (HCC)

★ ***Epidemiology,*** worldwide, HCC (also known as **liver cell carcinoma** or, erroneously, *hepatoma*) constitutes 5.4% of all cancers, but the incidence varies widely in different areas of the world.

★ More than **85%** of cases occur in countries with high rates of chronic HBV infection. Highest incidences are found in **Asian countries** (Southeast China, Korea,& Taiwan) & **African countries** such as Mozambique, in which HBV is transmitted vertically, & in which carrier state starts in infancy.

★ Moreover, many of these populations are exposed to **aflatoxin, which, combined with HBV** infection, ↑ the risk of HCC development by more than ***200-fold over noninfected, nonexposed populations***.

★ The **peak incidence of HCC in these areas** is between **20 & 40 years of age**, & in almost **50% of cases, the HCC appear in the absence of cirrhosis!**

★ HCC incidence is *rapidly* in the West. **It tripled in the US during the last 25 years**, but it is still much lower (8- to 30-fold) than the incidence in some Asian countries.

★ In the **West,** HCC is rarely present before age 60, & in **90%** of cases, **HCC** develop in persons with **cirrhosis!**

★ There is a marked **male** preponderance of HCC throughout the world; **3:1 in low-incidence** areas & as high as **8:1 in high-incidence areas**. These differences may be related to the greater prevalence of HBV infection, alcoholism, & chronic liver disease among males.

Pathogenesis of HCC

• **3** major etiologic associations have been established: **HBV or HCV infection/ chronic alcoholism/ aflatoxin exposure**.

Other conditions include *hemochromatosis* & *tyrosinemia*. Many variables, including age, gender, chemicals, viruses, hormones, alcohol, & nutrition, interact in the development of HCC, e.g., the disease *most likely to give rise to HCC is, in fact, the extremely rare hereditary* ***tyrosinemia****, in which 40% of patients develop HCC despite dietary control.*

- The development of **cirrhosis seems to be an important,** but not requisite, contributor to the emergence of HCC.

Carcinogenesis is greatly enhanced in the presence of cell injury & replication, as occurs in chronic viral hepatitis.

- In many parts of the world, including **Japan & Central Europe**, **chronic HCV infection is the greatest risk factor in the development of liver cancer.** HCC in patients with hepatitis C occurs almost exclusively in the setting of C.

- In **China & South Africa**, where **HBV** is endemic, there is also high exposure to dietary **aflatoxins** derived from the fungus ***Aspergillus flavus***. These carcinogenic toxins are found in "moldy" grains & peanuts. Aflatoxin can bind covalently with cellular DNA & cause a mutation in *p53*.
- Despite the detailed knowledge about the etiologic agents of HCC, the **pathogenesis of HCC is still uncertain** (3 contributing factors)

► **Origin**: HCC seems to *arise from both* **mature hepatocytes** *& progenitor cells (known as ductular cells or* ***oval cells***). *In most cases, it develops from small-cell, high-grade dysplastic nodules in cirrhotic livers,* these nodules may be monoclonal & may contain chromosomal aberrations similar to those seen in HCC.

► **Distinguishing** high-grade dysplastic nodules from early HCC **is difficult** even in biopsies, because there are **no molecular markers** specific for these stages.

▼ **An important criterion of HCC is tumor nodule vascularization,** visualized by imaging (U/S), which is almost always a clear indication of malignancy.

▼ *An almost* ***universal feature of HCC*** *is the presence of structural & numeric chromosomal abnormalities.* The precise origin of HCC genetic instability is not known.

➔ **Cell death, H replication, & inflammation seen in all forms of chronic hepatitis, are believed to be main contributors to DNA damage.**

▶ Poor regulation of H replication can occur by: (1) point mutations or (2) overexpression of specific cellular genes (such as *β-catenin),* (3) mutations or loss of heterozygosity of tumor suppressor genes (such as *p53*), (4) methylation changes, & (5) constitutive expression of GFs, (6) Defects in DNA repair, particularly those in repair systems for double-stranded DNA breaks, perpetuate DNA damage & may cause chromosome defects.

☺ **Neither HBV nor HCV contains oncogenes**, & the tumorigenic capacity of these viruses probably relates primarily to their capacity to cause continuing cell death, regeneration & chronic inflammation. which will contribute to DNA damage.

★**Morphology:** HCC may appear **grossly** as a (1) **Unifocal**, single massive tumor (F16-33 & F 5-23); (2) **Multifocal,** made of multiple nodules of variable size; or (3) **Diffusely infiltrative** cancer which may involves the entire liver. In the latter two patterns, it may be difficult to distinguish regenerative nodules of cirrhotic liver from cancer nodules of similar size!. Tumor masses are grossly yellow-white, punctuated sometimes by bile staining & areas of hemorrhage or necrosis.

★**Vascular invasion: all HCC have a strong propensity** for invasion of vascular channels, resulting in extensive intrahepatic metastases, & occasionally **snakelike cancer masses** invade the **portal vein** (causing occlusion) or the **inferior vena cava**, extending into the right side of the **heart!**

■ H, HCC range from well-differentiated T that reproduce H arranged in cords, trabeculae or glandular patterns (F16-34), to poorly differentiated T, often composed of large multinucleate anaplastic T giant cells.

In the better differentiated variants,

- **Globules of bile** may be found within the cytoplasm of cells & in pseudocanaliculi between cells, & *acidophilic hyaline* intracytoplasmic inclusions (***Mallory bodies***) may be seen.
- There is **surprisingly *scant stroma*** in most HCC, explaining the soft consistency of these T.

ناعم وليس خشن.

في ال alcohilic hepatitis لكن موجودة في أمراض أخرى منها HHC

- **Fibrolamellar carcinoma** is a distinctive clinicopathologic variant of HCC which occurs in young (20-40 years of age) with equal sex incidence, has **no association with cirrhosis or other risk factors** (F16-35), usually consists of a single large, hard ("scirrhous") tumor with fibrous bands coursing through it, resembling focal nodular hyperplasia.

HBV, HC

scirrhous زي cancer in breast.

  - H, composed of well-differentiated polygonal cells growing in nests or cords & separated by parallel lamellae of dense collagen bundles.

ال stroma تكون قليلة جداً في ال HCC.

Clinical Features

- Although HCC may present with **silent hepatomegaly**, HCC are often **encountered in individuals with cirrhosis** who already have symptoms of it.

☺In cirrhotic persons, a *rapid ↑ in liver* ***size***, *sudden worsening of* ***ascites****, or the appearance of* ***bloody ascites, fever, & pain*** *call attention to the development of HCC.*

cirrhosis → HCC

خلال فترة قصيرة صارت هاي التغيرات هذا يعني انه

Laboratory studies are *helpful but not diagnostic*.

➔ **50% of patients have elevated serum α-fetoprotein.**

However, this T "marker" lacks specificity, because **modest elevations** are also encountered in other conditions, such as cirrhosis,, chronic hepatitis, normal pregnancy, fetal distress or death, & gonadal germ cell T.

Very high levels (>1000 ng/mL), however, are rarely encountered except in HCC. → Alpha-feto prt.

- ***Final diagnosis is by histopathological examination of liver biopsy.***

لأنه ال α-fetoprt. لا يعتبر specific

وفعليا لأنه هاي احسن طريقة tumor

▼**Prognosis of HCC is grim; But** it is significantly better f individuals who have a single tumor less than 2 cm in Ø. diameter & good liver function.

▼The **median survival is 7 months,** with death from:

(1) Profound cachexia

(2) Bleeding esophageal varices

(3) LF with hepatic coma, or rarely

(4) Rupture of the tumor with fatal hemorrhage.

☺ **Early detection** of HCC is **critical** for successful treatme The most effective therapies are **surgical resection of smaller** T detected by U/S screening of persons with chron liver disease, & **liver transplantation** for patients with sma tumors & good liver function.

▼T recurrence rate is greater than 60% at 5 years.

☺ **Best hope** for preventing HCC in regions endemic for HB infection is a comprehensive anti-HBV immunization progra

DISORDERS OF THE GALLBLADDER & EXTRAHEPATIC BILIARY TRACT: GALLBLADDER DISEASES

Cholelithiasis (Gallstones, GS)

★ **GS** afflict 10% to 20% of adult populations in northern hemisphere Western countries. Adult prevalence rates are higher in Latin American countries (20% to 40%) & are low in Asian countries (3% to 4%).

★ **GS are of 2 main types.** *In the West, about 80% are* ***cholesterol GS****, containing crystalline cholesterol monohydrate & 20%* are ***pigment GS*** composed mainly o bilirubin & calcium salts.

Pathogenesis & Risk Factors

• **Bile** is the only pathway for elimination of excess choles (**Ch**) from the body, either as free **Ch** or as bile salts.

☺ **Ch is water insoluble** & is rendered water soluble by aggregation with + **bile salts + lecithins** secreted into bile

➔ **Supersaturation** of the bile with **Ch**,
➔ **Nucleation sites** establishment by microprecipitates of calcium salts,
➔ **Stasis** = Hypomobility of the GB which promotes nucleation
➔ **Mucus hypersecretion** to trap the crystals, enhancing their aggregation into stones.

Table 16-8. Risk Factors for GS

Cholesterol GS

Demography: Northern Europeans, North & South Americans, **{Advancing age, , Female gender}**, Female sex hormones, Oral contraceptives, Pregnancy, Obesity, Rapid weight reduction, GB stasis, inborn disorders of bile acid metabolism, Hyperlipidemia syndromes

Pigment GS

Demography: Asian more than Western, **chronic hemolytic syndromes**, biliary infection, GIT disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency.

☹ However, 80% of individuals with GS have no identifying risk factors other than age & sex. Comment on some factors:

- ***Age & gender.*** The prevalence of GS ↑ throughout life. The prevalence in white women is about **twice** as high as in men.
- ***Ethnic & geographic.*** **Ch** GS prevalence approaches 75% in Native American populations, GS are more prevalent in the West & uncommon in developing societies.
- ***Heredity***, family history alone imparts ↑ risk associated with impaired bile salt synthesis & secretion.

- ***Environment.*** estrogenic influences, like oral contraceptives & pregnancy ↑ hepatic **Ch** uptake & synthesis, leading to excess biliary secretion of **Ch**. Obesity, rapid weight loss, & treatment with the hypocholesterolemic agent clofibrate are also strongly associated with ↑ biliary **Ch** secretion.
- ***Acquired disorders*** Any condition in which GB motility is reduced predisposes to GS, such as pregnancy, rapid weight loss, & spinal cord injury. However, in most cases, GB hypomotility is present without obvious cause.

Morphology of GS

★ **Cholesterol GS** arise only in the GB & consist of 50% to 100% cholesterol. **Pure cholesterol GS** are pale yellow (F5.33); increasing proportions of calcium carbonate, phosphates, & bilirubin impart gray-white to black discoloration (F16-36). They are ovoid & firm; they can occur singly or multiple with faceted surfaces resulting from opposition to one another.

★ **Most** cholesterol **GS** are radiolucent, although as many as **20%** may have sufficient **calcium carbonate to render** them **radiopaque.**

- **Pigment GS** may arise anywhere in the biliary tree (GB or bile ducts) & are either black or brown.
- **Black pigment GS** are found in sterile GB bile, small & present in large number (F16-37; 5-35&36)& crumble easily.
- **Brown GS** are found in infected intrahepatic or extrahepatic ducts, tend to be single or few in number & are soft with a greasy, soaplike consistency that results from the presence of retained fatty acid salts released by the action of bacterial phospholipases on biliary lecithins.

★**Pigment GS** contain **calcium salts of unconjugated bilirubin + mucin glycoproteins +(cholesterol.** Because of calcium carbonates & phosphates, **50% to 75% of black GS are radiopaque.** Brown GS, which contain calcium soaps, are radiolucent.

Clinically, **70% to 80%** of persons with GS **remain asymptomatic** throughout life, the remainder becomes symptomatic at the rate of 1% to 3% per year

➔ The symptoms are striking: **sever pain** either **constant or "colicky" (spasmodic)** from an **obstructed GB** or when small GS move down-stream & lodge in the biliary tree.

☹ **Complications, depending on the site of the GS** include GB empyema, perforation, fistulae; inflammation of the biliary tree, & obstructive jaundice, or pancreatitis.

☺ The larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction; occasionally a large stone may erode directly into an adjacent small bowel loop, causing intestinal obstruction (**"Gallstone ileus"**).

☹ **It is the very small stones, or "gravel," that are more dangerous!**

Cholecystitis

• GB inflammation may be (1) acute, (2) chronic, or (3) acute superimposed on chronic, & **almost** always occurs in association with GS. **In US, cholecystitis is one of the most common indications for abdominal surgery.**

Its epidemiologic distribution closely parallels that of GS.

Mphology

▶ In **acute cholecystitis,** the GB is usually **enlarged** (X 2 to 3 times) & **tense**, & bright **red** or blotchy, violaceous to green-black due to **subserosal hemorrhages**

• The GB serosal covering is frequently covered by **fibrinous exudate** &, in severe cases, by **pus.**

• **In 90% of cases GS are present, often obstructing the neck of the GB or the cystic duct.** The GB lumen is filled with cloudy or turbid bile, that may contain fibrin, blood, & pus. When the contained exudate is virtually **pure pus**, the condition is called **empyema of the GB (F1.7).**

• In **mild** cases the GB wall is thickened, edematous, & hyperemic. In more **severe** cases the GB is transformed into a green-black necrotic organ with multiple abscesses, called **gangrenous cholecystitis (F1.8).**

H, the inflammatory reactions are non-specific & consist of congestion, edema, WBC infiltration, frank abscess formation, or gangrenous necrosis.

► The morphologic changes in **chronic cholecystitis** are extremely variable & sometimes minimal.. وجود الحصوة لحاله الكافي للتشخيص

☺ **The mere presence of stones** within the GB, even in the absence of acute inflammation, is often taken as **sufficient justification for the diagnosis**. The GB may be contracted, of normal size, or enlarged. The submucosa & subserosa are often thickened from fibrosis, with lymphocytic cell infiltration.

Acute Calculous Cholecystitis

وجود حصوة تؤدي إلى إلتهاب

► Acute inflammation of a GB that contains stones is termed ***acute calculous cholecystitis*** & is caused by obstruction of the GB (neck or cystic duct) ***It is the most common major complication of gallstones & the most common reason for emergency cholecystectomy.*** مهم جدا!!

😐 Presentation may be sudden as an acute surgical emergency, or may be mild. Inflammation of the GB wall in the setting of obstruction to bile outflow with consequent acute calculous cholecystitis **results initially from *chemical irritation.*** not bacter مهم ترتيب

(1) The action of **phospholipases** derived from the mucosa hydrolyzes biliary lecithin to lysolecithin, which is toxic to the mucosa. The normally protective glycoprotein mucous layer is disrupted, exposing the mucosal epithelium to the direct detergent action of bile salts. (2) **Distention & ↑ intraluminal pressure** may also compromise blood flow to the mucosa. مهم جدا!!

😐 These events occur in the **absence of bacterial infection**, only later may bacterial contamination develop. مهم

Acute Non-Calculous (Acalculous) Cholecystitis

حالة مهمة في التشخيص مهم جدا!!

Between 5% & 12% of GB removed for acute cholecystitis contain **no GS**. **Most of these cases occur in seriously ill patients:** (1) the **postoperative** state after major, nonbiliary surgery; (2) **severe trauma** (eg RTA); (3) **severe burns;** & (4) **sepsis**. Events thought to contribute to it include: dehydration, GB stasis & sludging, vascular compromise, &, ultimately, bacterial contamination.

GB عدم إنقباض ال ← ↑conc. of bile ← Road traffic accidents.

Chronic Cholecystitis

May be (1) the sequel to **repeated attacks of acute cholecystitis**, but (2) in most instances it develops **without any history of acute attacks**. Like acute cholecystitis it is **almost** always associated with GS; BUT...

☹ **GS do not seem to have a direct role in the initiation of inflammation or the development of pain**, because chronic acalculous cholecystitis causes symptoms & morphologic changes **similar** to those seen in the chronic calculous type.

▶Rather, *supersaturation of bile predisposes to both forms (calculous & acalculous) chronic inflammation & in most instances, to stone formation.* Microorganisms, usually *Escherichia coli* & enterococci, can be cultured from the bile in only about 1/3 of cases.

Symptoms of chronic cholecystitis are similar to that of the acute & range from **biliary colic to indolent abdominal pain** (mild).

Clinical Features

★***Acute calculous cholecystitis*** may present with mild pain or with severe, **steady upper abdominal pain**, often radiating to the right shoulder. When GS are present in the GB neck or in ducts, the pain is **colicky**. Spasm of the abdominal muscles result in **right subcostal tenderness & rigidity, &** occasionally a **tender, distended GB can be palpated**.

Mild attacks may subside spontaneously over 1 to 10 days; but recurrence is common

★***Acute acalculous cholecystitis*** symptoms are usually **obscured by the generally severe clinical condition of the patient.**

☹Diagnosis therefore rests on keeping this possibility in mind.

★***Chronic cholecystitis*** is usually characterized by recurrent attacks of either steady or colicky epigastric or right upper quadrant pain. Nausea, vomiting, **& intolerance for fatty foods** are frequent accompaniments.

★**Diagnosis** of acute & chronic cholecystitis usually rests on the **detection of GSs** or **dilatation of the bile ducts by U/S,** typically accompanied by evidence of a **thickened GB wall.**

☹ **Complications of cholecystitis:**

- Bacterial superinfection with cholangitis or sepsis,
- GB **perforation** → localized peritonitis +abscess formation
- GB **rupture** → diffuse peritonitis,
- **Biliary-enteric fistula**, with drainage of bile into adjacent organs, entry of air & bacteria into the biliary tree, & potentially large sized GS-induced intestinal obstruction
- Aggravation of preexisting medical illness, with cardiac, pulmonary, renal, or liver decompensation.

DISORDERS OF EXTRAHEPATIC BILE DUCTS

Choledocholithiasis & Cholangitis

★ ***Choledocholithiasis*** is the presence of stones within the biliary tree. Almost **all stones** in the West, are derived from the GB; in Asia, there is a much higher incidence of primary ductal & intrahepatic, usually **pigmented** stone formation.

★**Choledocholithiasis** may not immediately obstruct major bile ducts; **asymptomatic stones are found in 10%** of patients at the time of surgical cholecystectomy.

Effects & complications of choledocholithiasis are:
(1) biliary obstruction, (2) pancreatitis, (3) cholangitis, (4) hepatic abscess, (5) chronic liver disease with secondary biliary cirrhosis, or (6) acute calculous cholecystitis (by stone obstructing cystic duct).

★ ***Cholangitis*** is **acute inflammation of the wall of bile ducts**, always caused by bacterial infection of the normally sterile lumen, the bacteria most likely enter the biliary tract through the sphincter of Oddi (ascending infection).

►**Causes:** any lesion obstructing bile flow, **most commonly stones** & also from **surgical reconstruction of the biliary tree**. Uncommon causes include tumors, strictures, indwelling stents or catheters, acute pancreatitis.

* Any obstruction predispose to infection

الصاعد.

★ ***Ascending cholangitis*** refers to the tendency of bacteria, once within the biliary tree, **to ascend & infect intrahepatic biliary ducts.** The usual pathogens are *E. coli, Klebsiella, Clostridium, Bacteroides,* or *Enterobacter;* group D streptococci are also common, & two or more organisms are found in 50% of cases.

★Parasitic cholangitis is a significant in some world populations ***Fasciola hepatica*** or **schistosomiasis** in Latin America & the Near East, ***Clonorchis sinensis*** **or** ***Opisthorchis viverrini*** in the Far East, & cryptosporidiosis in individuals with AIDS.

★ **Clinically,** bacterial cholangitis produces fever,, abdominal pain, chills & jaundice. In the most severe form, **suppurative cholangitis**, purulent bile fills & distends bile ducts, with risk of liver abscesses (F5.39) formation, & because **sepsis** rather than cholestasis is the main **risk** in cholangitic patients, prompt diagnosis & intervention are **imperative.**

septic shock. لأنه ممكن يؤدي ~~ك~~ التشخيص والعلاج السريع ضروري جدا"

Secondary Biliary Cirrhosis

►The **most common** cause of obstruction is extrahepatic **cholelithiasis**. Other causes include **cancers** of the head of the pancreas & biliary tree &, **biliary atresia** & **strictures** resulting from previous surgical procedures. ← in newborns.

▲The **initial** morphologic features of cholestasis (in the liver) are entirely **reversible** with correction of the obstruction, however

▼ **Prolonged obstruction** of the extrahepatic biliary tree **initiates periportal fibrogenesis**, scarring & nodule formation with **secondary inflammation**, generating **secondary biliary cirrhosis**. Subtotal obstruction may promotes ascending cholangitis, which further contributes to the damage. (irreversible).

Biliary atresia

Is complete obstruction of bile flow caused by destruction or absence of part or all of the extrahepatic bile ducts.

It is the most frequent **fatal** liver disease in early childhood & accounts for >50% of children referred for liver transplantation.

(100 per million) obstructive jaundice

★ **Biliary atresia** is a major cause neonatal cholestasis {1/3 of cases} & occurring in 1/10,000 live births. Salient features:
(1) Inflammation & fibrosing stricture of **hepatic BD or CBD**;
(2) Inflammation of major **intrahepatic** bile ducts, with progressive destruction of the intrahepatic biliary tree;
(3) Florid features of biliary obstruction on **liver biopsy** (i.e., marked bile ductular proliferation, portal tract edema & fibrosis, & parenchymal cholestasis); &
(4) Periportal fibrosis & **cirrhosis** in 3 to 6/12 after birth.

علامات تدل على أنه الإنسداد هناك الكبد

high bilirubin

Clinically, Infants present with **neonatal cholestasis & jaundice**. Laboratory findings do not distinguish between biliary atresia & intrahepatic cholestasis,

الأسباب قد تكون متشابهة.

★ **Liver biopsy** provides evidence of bile duct obstruction in 90% of cases & **Liver transplantation remains the definitive treatment.** Without surgical intervention, death usually occurs within 2 years of birth.

Carcinoma of the gall bladder (GB Ca)

★ GB Ca develops from the GB epithelial lining. It is the most frequent cancer of the biliary tract. It is slightly more common in women & occurs mostly in elderly individuals.

☹ **Preoperative** diagnosis is **exceptional,** occurring in <20% of patients. Mean 5-year survival is dismal (sad) **5%,** (**as in pancreatic carcinoma**).

★ **GS** are present in 60% to 90% of cases. Presumably, GB containing **stones** or **infectious** agents develop cancer as a result of **recurrent trauma & chronic inflammation**.

► **Grossly,** GB Ca grows in one of two patterns:

(I) **Infiltrating,** the more common, scirrhous, very firm & appears as an ill-defined area of diffuse thickening & induration of GB wall that may involves part or the entire GB,

(II) **Exophytic,** less common, grows into the lumen as an irregular cauliflower mass, but invading the underlying wall concurrently, (F16-38).

وفيه خلايا surface تفرز mucin.

■ H, most GB Ca are **adenocarcinomas** (F16-39), either well-, moderate-, poorly-, or un-differentiated infiltrating Ca.

- About 5% are SCC or have adenosquamous differentiation.
- A minority are carcinoid tumors.

Stone in GB → irritation → metaplasia → dysplasia → Adenomatous → cancer.

▲**Spread of GB Ca:** when discovered, **most** Ca have **invaded the liver directly** & many have infiltrate the cystic & other adjacent bile ducts & portal hepatic LNs. Distant metastases are less common. Presenting symptoms are insidious & indistinguishable from those associated with cholelithiasis.

العلامات خفيفة

☺ In the event of a very rare discovery of GB Ca at a resectable stage, **the fortunate person either (I)** develops **early obstruction** & acute cholecystitis before T infiltration into other structures or (II) **have cholecystectomy** for coexistent symptomatic GS!

في مرحلة

المحظوظ هو من تُزال له الـ gall bladder.

▼**Preoperative diagnosis** rests on detection of **GS** with **GB wall** abnormalities **documented by imaging studies.**

كمان زيادة الـ thickness تعتبر علامة حيث يدل على المرض.

Cholangiocarcinomas

★ **Cholangioca** are well-differentiated adenocarcinomas, with biliary differentiation, arising from cholangiocytes lining intra- or extra-hepatic bile ducts, with an abundant fibrous stroma {**desmoplasia,** F16-40} explaining their firm, & gritty consistency. **Bile pigment & hyaline inclusions are not** found within the cells. It occur mostly in elderly individuals.

★ **Risk factors** (I) **primary sclerosing cholangitis (PSC),** (II) **fibrocystic diseases of the biliary tree**, (III) **exposure to Thorotrast,** previously used in biliary tree radiography.

★ **2/3** are **extrahepatic T**, develop at the hilum (known as Klatskin T) or more distally in the biliary tree, as far as the peripancreatic portion of the distal CBD.

★ **1/3** are **intrahepatic**, the incidence of which ↑ worldwide, while that of extrahepatic T has ↓. The causes for these changes are **unknown,** but suggest that intra- & extrahepatic cholangioca may have **different pathogenesis**.

عند التشخيص بكون صغيرة وهذا الخلينا نميز بينه وبين ال stone .

Because ► **extrahepatic cholangioca** causes obstructive jaundice early, they tend to be **relatively small at the time of diagnosis,** most appear as firm, gray nodules, some are **papillary** or polypoid, within the bile duct wall; some may be **diffusely infiltrative**, with ill-defined wall thickening.

► **Intrahepatic cholangioca** presented by non-specific symptoms such as weight loss, pain, anorexia, & ascites, & are detected by the presence of liver mass on **X-ray or CT**.

▲**Spread** of Cholangioca occur to regional LN, lungs, bones, & adrenal glands, **Indeed**, Cholangioca have greater tendency for extrahepatic spread than Hepatocellular ca! مهم

مهم ☹ **Prognosis is poor**, because most cholangiocarcinomas are generally **asymptomatic** until they reach an advanced stage & most patients have unresectable tumors.

Surgical resection is the only treatment available, & mean survival is 6 to18 months, regardless of whether aggressive resection or palliative surgery is performed. بعد العملية تعيش لبعد 8-18 months

زي ال GB cancer ما في أعراض .

The exocrine Pancreas (P)

The exocrine P composed of:

(I) ***Acinar cells*** that produce enzymes, mostly as an inert **proenzymes** forms (e.g. trypsinogen); {**amylase & lipase are exceptions & are secreted in an active form**} & store proenzymes in membrane-bound ***zymogen granules***.

➔ When acinar cells are stimulated to secrete, the ***zymogen* granules fuse with the apical plasma membrane** & release their contents into the central acinar lumen.

(II) Ductules & ducts that transport & convey enzymes to the duodenum. The proenzymes remain largely inactive until they reach the duodenum; there, **enteropeptidase** (a brush-border enzyme) cleaves trypsinogen into active trypsin.

➔ Activated trypsin then functions to catalyze the cleavage of the other proenzymes.

اقترب منه بحذر .

☺ **Surgical rule:** ➔ **Don't mess around with the pancreas.**

CONGENITAL ANOMALIES

- **Agenesis:** totally absent P, very rare.
- ***Pancreatic divisum***: is the **most common clinically significant congenital P anomaly** { incidence of 3%-10% }. It occurs when the fetal duct systems of the **P** primordia fail to fuse. As a result, the main **P** duct (Wirsung) is very short & drains only a small portion of the head of the **P**, while the bulk of the **P** drains through the minor sphincter. This predisposes such individuals to chronic pancreatitis.

- ***Annular Pancreas***: uncommon variant of **P** fusion; the outcome is a ring of pancreatic tissue that completely encircles the duodenum, **cause duodenal obstruction.**
- ***Congenital cysts***: result from abnormal duct development. Cysts range from mm to 5 cm in ∅, lack a cell lining or lined by duct cuboidal epithelium & enclosed in a thin fibrous capsule. In ***polycystic disease***, the **kidney, liver, & P** can all contain cysts.
- ☺ **Rule**: unilocular **P** cysts tend to be benign, while multilocular **P** cysts are more often neoplastic & possibly malignant.

- **Ectopic Pancreas:** Abnormally situated, or *ectopic,* **P** tissue occurs in 2% of the population, favored sites are the stomach & duodenum, followed by the jejunum, Meckel diverticulum, & ileum. ● Typically small (mms to cms in ∅) & are located in the submucosa; they are composed of normal **P** acini with occasional islets. Although incidental & asymptomatic, ectopic **P** can cause: ► **pain from localized inflammation**, or rarely ► **mucosal bleeding**, even more rarely an ►**intussusception** (Personal 2 cases),► 2% of **islet cell T** arises in ectopic **P** tissue.

Pancreatitis = inflammation of the pancreas

★By definition, in ***acute pancreatitis*** the **P** can return to normal if the underlying cause of inflammation is removed.

In contrast, *chronic pancreatitis* is defined by the presence of irreversible destruction of exocrine **P** parenchyma.

"البنكرياس" → not a primary bacterial infection.

Acute Pancreatitis (Ac P)

★ **Ac P** is an acute ***autodigestion of the P substance by inappropriately activated P enzymes.*** It ranges from mild, self-limited disease to a ☠ life-threatening

★**Ac P** is a group of **reversible lesions** characterized by inflammation; ranging from focal edema & fat necrosis to widespread parenchymal necrosis with severe hemorrhage.

★ **Ac P** is relatively **common,** with an annual incidence in industrialized world of **100 to 200 cases/million people**.

★ **80% of cases** are attributable to either "الزفت والكحول".

(I) Biliary tract disease (GS are implicated in 35% to 60% of cases, & about 5% of patients with GS develop **Ac P**), &

(2) Alcoholism; excessive alcohol intake as a cause of **Ac P** varies from 65% of cases in the US, to 5% or less in the UK (Table 17-1).

Etiologic Factors in Ac P:

- **Alcoholism & Gallstones (80% of cases)**
- **10% to 20%** of cases are **idiopathic** with no identifiable cause.

Other causes of **Ac P are:**

- **Trauma,** both blunt force **& Iatrogenic injury** (Perioperative or Endoscopic procedures with dye injection). → surgical procedures may lead to Ac P.
- Non-gallstone **obstruction** of pancreatic ducts = periampullary tumors, **P** divisum, biliary "sludge" (thick) & *Ascaris lumbricoides*,
- **Medications**: thiazide furosemide, procainamide, pentamidine azathioprine, estrogens, methyldopa, sulfonamides,,
- **Infections**: Mumps, Coxsackie virus, *Mycoplasma pneumoniae*,
- **Metabolic** disorders: hypertriglyceridemia, hyperparathyroidism, & other hypercalcemic states, (obscure link).
- **Vascular:** Shock, Ischemia due to thrombosis, embolism, vasculitis (eg Polyarteritis nodosa).

• **Genetic:** ***Hereditary pancreatitis*** is an autosomal dominant disease with an 80% penetrance characterized by recurrent attacks of severe pancreatitis usually beginning in childhood. It is caused by **mutations in the *PRSS1* gene** that affect a **site on the trypsinogen** molecule that is essential for the cleavage **(inactivation)** of trypsin by trypsin itself. When this site is mutated, trypsinogen & trypsin become resistant to inactivation, leading to ongoing activation of other digestive proenzymes, & eventually the development of pancreatitis.

▶Basic pathological changes are (1) **edema**, (2) **proteolytic** destruction of pancreatic parenchyma, (3) **fat necrosis** by lipases, (4) an **acute inflammatory** reaction, & (5) BV destruction with **hemorrhage.**

▲ **In mild Ac P** (F17-1A), there are (I) **interstitial edema &** (2) **focal areas of fat necrosis in the pancreatic substance** results from enzymatic destruction of **peripancreatic fat cells**, the released fatty acids combine with calcium to form insoluble salts that precipitate in situ.

▶**In more severe Ac P = acute necrotizing pancreatitis:**
(a) Necrosis of **P** tissue affects acinar, **ductal** as well as the **islets of Langerhans**;
(b) vascular damage causes **hemorrhage** into **P** parenchyma.
☹ Grossly, the **P shows** red-black hemorrhages interspersed with foci of yellow-white, chalky fat necrosis (F 17-1B). Fat necrosis can also occur in extra-pancreatic fat, including the omentum (F1-13 & 5.44), bowel mesentery, & even outside the abdominal cavity e.g., in subcutaneous fat, & peritoneum contains a serous, slightly turbid brown fluid with globules of fat (derived from enzymatically digested adipose tissue).
▼The severest form, **Acute Hemorrhagic pancreatitis** (F5.43) shows extensive **diffuse** hemorrhage & **P** tissue necrosis.

Pathogenesis

★The histologic changes seen in **Ac P** strongly suggest ***autodigestion of the P substance by inappropriately activated P enzymes.*** Zymogen forms of P enzymes must be enzymatically cleaved to be activated by trypsin; therefore ***activation of trypsin is a critical triggering event in* Ac P.**

★If **trypsin** is inappropriately generated from its proenzyme **trypsinogen**, it can **activate elastases & phospholipases** that can cause autodigestion. Trypsin also converts **prekallikrein** to its activated form Kallikrein, activating the kinin system &, by **activation of** Hageman factor **{factor XII}** also sets in motion the **clotting & complement systems.** → will be activated.

☼ Three possible pathways can incite the initial enzyme activation that may lead to **Ac P** (Fig. 17-2).

(1) *Pancreatic duct obstruction*:

➔Impaction of a GS or biliary sludge, or extrinsic compression of the ductal system by a mass blocks ductal flow, ↑ intraductal pressure, & allows accumulation of an enzyme-rich interstitial fluid. كل شي مع بعض

➔ Since **lipase is secreted in an active form**, this can cause **local fat necrosis, with the result that**

➔ injured tissues, periacinar myofibroblasts, & WBCs **release pro-inflammatory cytokines** that promote local inflammation & interstitial edema. **Edema** further compromises local blood flow, causing vascular insufficiency & ischemic injury to acinar cells.

وبالنهاية يؤدي إلى Ac P

★ ***Primary acinar cell injury.*** can incite **Ac P** caused by ischemia, viruses (eg mumps), drugs, & direct trauma to **P.**

★ ***Defective intracellular transport of proenzymes within acinar cells.*** ☺ In normal acinar cells, digestive enzymes intended for **zymogen** granules (& eventually extracellular release) & hydrolytic enzymes destined for **lysosomes** are transported in discrete **(separate) pathways** after synthesis in the ER. However, at least in some animal models of metabolic injury, ☹ **pancreatic proenzymes & lysosomal hydrolases become packaged together.** This results in proenzyme activation, lysosomal rupture (action of phospholipases), & local release of activated enzymes.

☻ ***How alcohol causes* Ac P? *is unknown,*** although: (1) abnormal **proenzyme trafficking** has been implicated. It leads to (2) contraction of the sphincter of **Oddi** (3) direct **toxic** effects on acinar cells, & (4) Alcohol ingestion causes ↑ secretion of protein-rich P fluid, leading to deposition of **inspissated** protein plugs & obstruction of small P ducts.

Clinically, Abdominal pain is cardinal symptom; vary from mild to sudden severe constant pain, often referred to the upper back, with rigid abdomen.

Diagnosis of Ac P depends on markedly elevated serum 😐 **amylase** during the first 24 hours, followed (within 72-96 hours) by rising serum lipase levels. **Hypocalcemia** can result from precipitation of calcium in the extensive areas of fat necrosis. The **enlarged inflamed pancreas** can be visualized by **CT or MRI** & the exclusion of other causes of acute abdominal pain {• acute appendicitis, • acute cholecystitis, • perforated PU ulcer, • intestinal obstruction & bowel infarction, • ruptured ectopic pregnancy}

☹ Severe **Ac P** *manifestations are due to* ***systemic release of*** *digestive enzymes & explosive activation of the inflammatory response.* Patients may show ⇧ vascular permeability, **DIVC, ARDS** (due to alveolar capillary injury), & diffuse fat necrosis.

😐 Management of Ac P is by **supportive therapy.**

➔ ***Shock*** *can rapidly* follows as a result of loss of blood volume & electrolyte disturbances & in 40% - 60% of Ac P the necrotic debris becomes **infected,** usually by gram-negative bacteria from the GIT & may cause endotoxemia.

☺ Most **Ac P** patients eventually recover; **5% (or more) die from ☠ shock.** If the patient survive, a common sequelae is:

★ ***P Pseudocyst (PP)*** forms by: (1) walling off areas of hemorrhagic fat necrosis, & (2) drainage of **P** secretions (from damaged pancreatic ducts) into cyst over months or years cause massive cyst enlargement (2 to **30 cm in** ∅).

★ ***PP*** account for 75% of all pancreatic cysts

★ ***PP*** are **solitary**, **attached to the surface of the** pancreas & involve peripancreatic tissues such as the lesser omental sac or the retroperitoneum between the stomach & transverse colon or liver (F17-3A).

★ ***PP*** contains necrotic debris encased by fibrous granulation tissue lacking an epithelial lining (pseudo)(F17-3B).

★ Many ***PP*** spontaneously resolve, some can become secondarily **infected** & larger ***PP*** can compress or even perforate into adjacent structures.

Chronic Pancreatitis (Ch P)

★ Is longstanding inflammation & fibrosis of the pancreas, with **destruction of the exocrine part**; later, the endocrine part is also lost. Prevalence: 0.04% to 5% of populations.

★ Although Ch P can result from recurrent attacks of acute pancreatitis *the* ***chief distinction between acute & Ch P is the irreversible impairment*** *of pancreatic function in* ***Ch P.***

➤ *The* ***most common*** *cause of* ***Ch P*** *is* ***long-term alcohol abuse***, middle aged men constitute the bulk of the group.

- Less common causes of ***Ch P*** include:

★ Long-standing pancreatic duct ***obstruction*** (pseudocysts, calculi, neoplasms, or pancreas divisum),

★ ***Tropical pancreatitis***, attributed to malnutrition, is a poorly characterized disorder seen in Africa and Asia,

★ ***Hereditary pancreatitis*** due to *PRSS1* mutations, or mutations in the *SPINK1* gene encoding trypsin inhibitor.

★ ***Ch P*** *associated with CFTR gene mutations* **(cystic fibrosis)** in which there is ↓ bicarbonate secretion, thereby promoting protein plugging.

40% of *Ch P cases* have no predisposing factors.

➤ **Grossly**, in ***Ch P,*** the pancreas is **hard,** sometimes with **extremely dilated ducts & visible calcified concretions.**

◙ H, **Acinar cell loss** (reduced number & size) is a constant feature (leading to pancreatic insufficiency & malabsorption),
+ with a chronic inflammatory **cell infiltration** around remaining lobules & ducts
+ severe **parenchymal fibrosis**
+ variable **dilation of the pancreatic ducts** with atrophic, hyperplastic, or squamous metaplasia of ductal epithelium
+ ductal **concretions** (F17-4B).

exocrine → Malabsorption
endo → DM.

Initially, there is **sparing of the islets of Langerhans** (F17-4A), later, they become embedded in the fibrotic tissue & may fuse & appear enlarged; & eventually they disappear ➔ DM.

Pathogenesis: Several hypotheses are proposed;

- ***Ductal obstruction by concretions.*** Many of the inciting agents in ***Ch P*** (e.g., alcohol) ↑ the protein concentration of pancreatic secretions, & forming ductal plugs.

- ***Toxic-metabolic.*** Toxins, including alcohol, can exert a direct toxic effect on acinar cells, leading to lipid accumulation, acinar cell loss, & eventually parenchymal fibrosis.

كلهم مربوطين بالكحول.

- ***Oxidative stress.*** Alcohol-induced oxidative stress may (A) generate FR in acinar cells, leading to membrane lipid oxidation & subsequent chemokine expression that recruits mononuclear inflammatory cells,
(B) promotes abnormal proenzyme **trafficking** with resulting acinar cell necrosis, inflammation, & fibrosis.

- ***Necrosis-fibrosis.*** Acute pancreatitis can cause local perilobular fibrosis, duct distortion, & altered pancreatic secretions. Over time & with multiple episodes, this can lead to loss of pancreatic parenchyma & fibrosis.

Clinically, Ch P can present in **several** different ways:

► Repeated attacks of **jaundice** {with ↑ in serum levels of **alkaline phosphatase**}, vague **indigestion**, persistent or recurrent, severe abdominal & **back pain.** The attacks can be **precipitated** by **overeating** (⇧ demand on pancreatic secretions), **alcohol abuse**, or **opiates** or other drugs that ↑ **the muscle tone** of the sphincter of Oddi.

► **Entirely silent** until one or both of the following develop: (A) Pancreatic insufficiency resulting in **malabsorption** with hypoalbuminemic edema & weight loss, (B) **DM** (islets loss).

★ ***Pancreatic pseudocysts*** develop in **10%** of Ch P.

☹ Individuals with **hereditary pancreatitis** have a **40%** lifetime **risk** of developing pancreatic cancer 🕷.

★ ***Diagnosis*** *of* ***Ch P*** *requires a high degree of suspicion.* A very helpful finding is visualization of **calcifications** within the pancreas by CT or U/S.

EXOCRINE PANCREATIC TUMORS (T)

Cystic *Neoplasms*

➔ **Pancreatic Pseudocyst** account for 75% of all pancreatic cysts.

➔ 5% to 15% of all pancreatic cysts are **neoplastic**; these constitute less than 5% of all pancreatic T. Some, like ★ Serous cystadenoma are **benign**; while

★ Mucinous cystic T& *Intraductal Papillary Mucinous T* can be benign, borderline malignant, or malignant T.

Serous Cystadenomas Neoplasms

- T account for about a 25% of all pancreatic cystic tumors;
- T composed of **glycogen-rich cuboidal cells** lining cysts containing clear, straw-colored fluid (F17-5).
- T typically presents in the 7th decade of life with abdominal pain; M/F ratio is 2: 1.
- T are **entirely benign**, & surgical resection is curative in the vast majority of patients.

Mucinous Cystic Neoplasms

★ Always arise in **women**, in the body or tail of the pancreas,
★ P/A painless, slow-growing masses.
★ The cystic spaces are filled with thick, tenacious mucin, & the cysts are lined by a **columnar mucinous epithelium** with an associated densely cellular stroma (F17-6).

Intraductal Papillary Mucinous Neoplasms

- IPMNs also produce cysts containing mucin; BUT In contrast to mucinous cystic neoplasms,
- IPMNs **arise more frequently in men than in women** &
- more frequently involve the **head** of the pancreas.
- IPMNs arise in the **main pancreatic ducts** & lack the cellular stroma seen in mucinous cystic T (F17-7).

★• Both ***Mucinous Cystic & IPM neoplasms*** can be **benign**, lacks significant cytologic or architectural atypia; **borderline malignant**, showing significant cytologic & architectural atypia but no tissue invasion. **or malignant, which are invasive.**

مش لازم
cancer
of ovary.

Pancreatic Carcinoma (P Ca)

★ **P Ca** is the 4th **leading cause of cancer death in the US**, preceded only by lung, colon, & breast cancers.

★30,000 Americans are diagnosed with P Ca annually & **all will die of it; the 5-year survival rate is dismal <5% (as in GB carcinoma!)** very very aggressive and invasive

Pathogenesis of P Ca (F17- 8).

★There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive lesions in small ducts & ductules, to invasive ca

الورم الأب

★Antecedent lesions are **"pancreatic intraepithelial neoplasias" (PanINs)** (Fig. 17- 8).

Evidence in favor of their precursor relationship to frank ca:

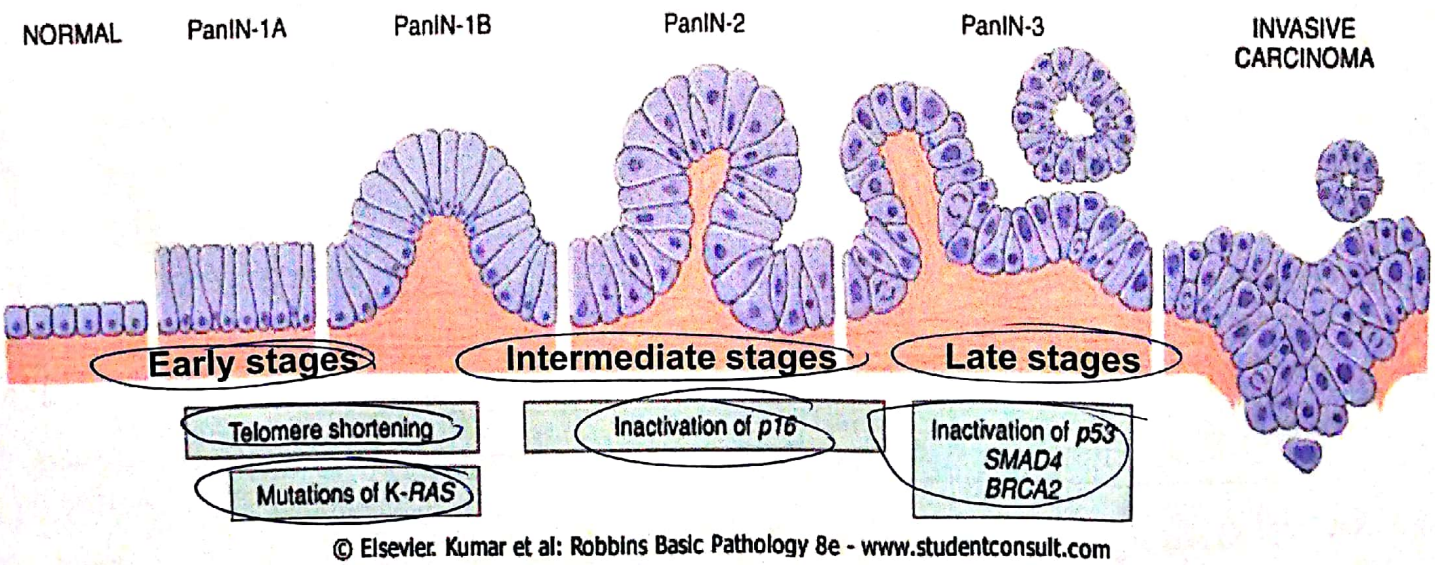
(1) They are often found **adjacent to infiltrating P Ca** &

(2) Share a number of the same **genetic mutations**,

(3) PanINs epithelial cells show dramatic **telomere shortening**, potentially predisposing them to accumulating additional chromosomal abnormalities.

Commonest molecular alterations in pancreatic carcinogenesis:

F17-8: **Model for the development of pancreatic cancer.**



- ***K-RAS*** gene is the most frequently altered oncogene, it is activated by point mutation in up to **90%** of P Ca cases.
- ***p16 (CDKN2A)*** T suppressor gene is inactivated in **95%,**
- ***p 53*** T suppressor gene inactivation occurs in **60%, &**
- ***SMAD4*** T suppressor gene is inactivated in **55%**

😐 What causes these molecular changes? is **unknown.**

- **P Ca** is a disease of elderly, 80% of patients are 60 to 80y,
- **P Ca** is more **common in blacks** than in whites.
- **Smoking**, strongest environmental influence doubles the risk.
- **Chronic pancreatitis & DM** are both associated with an↑ risk of P Ca. BUT it is difficult to sort out whether **chronic pancreatitis is the cause of P Ca or an effect of it ?** since small P Ca can block the pancreatic duct & thereby produce chronic pancreatitis. Similarly, DM can occur as a consequence of P Ca.

- Familial clustering of P Ca has been reported. In particular, **familial pancreatitis** (related to **mutations in the *PRSS1*** **trypsinogen** gene; see above) incurs an X 50- to 80-fold ↑ risk of P Ca.

Morphology (F17-9A).

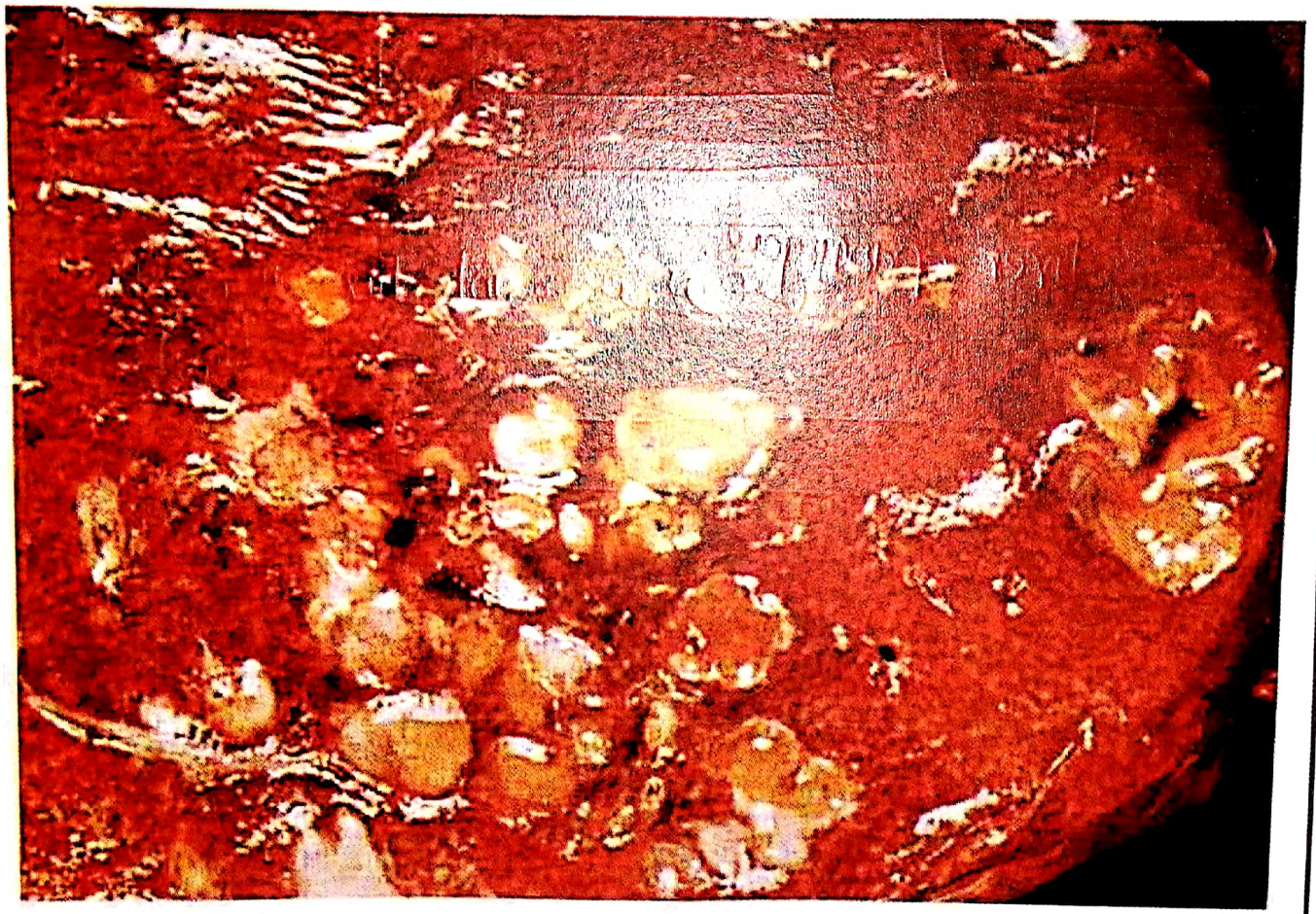
so, most common is head.

- **60%** of P Ca arise in the pancreatic **head**, **15%** in the body, & **5%** in the tail; & **in 20%,** the P Ca involves the entire organ.
- **P Ca** is hard, stellate, gray-white, poorly defined T.
- **P Ca** vast majority are **ductal adenoca**, forming glands & secreting mucin.
- Even **early** invasive **P Ca** is highly & extensively invasive T
- **P Ca** elicits an intense **desmoplastic fibrotic response.**
- In **50%** of cases of **P Ca** of the **head, there is** obstruction of the distal CBD as it courses through the head of the pancreas, resulting in **obstructive jaundice;**

In contrast, • **P Ca of the body & tail** do not impinge on the biliary tract & hence remain **silent.**

obstractive Jaundice.

F 5.39: **Suppurative cholangitis: liver.** The patient had ⇨ca of the head of pancreas obstructing the CBD, followed by ⇨ ascending cholangitis, which lead to the formation of multiple yellow & white ⇨ hepatic abscesses, centered on bile ducts.



5.39 Suppurative cholangitis: liver

- **Spread: P Ca** invade & infiltrate directly the retroperitoneal space, entrapping nerves, & occasionally invading the transverse colon, spleen, adrenals, spine, & stomach.
- Commonly, peripancreatic, gastric, mesenteric, omental, & portahepatic **LNs** are involved, as well as the **liver.** → عن طريق الدم
- Distant metastases occur, mainly to lungs & bones.

* carcinoma usually prefer LN spread.

- H, **P Ca** is usually a **moderately to poorly differentiated adenoca** forming abortive tubules or cell clusters & with deeply infiltrative growth pattern (F17-9B), **dense stromal fibrosis** & a tendency for **lymphatic & perineural invasion**.

غير كاملة التمو

and in carcinoma of prostate.

P Ca less common **variants** include:

- **Acinar cell ca** showing prominent acinar cell differentiation with zymogen granules & exocrine enzyme production;
- **Adenosquamous ca** with focal squamous differentiation in addition to glandular differentiation; Compination of both. like in cancer in uterus.
- **Undifferentiated ca** with osteoclast-like giant cells.

Clinical Features of P Ca

★ **P Ca** typically remains ***silent*** until it infiltrates or spreads.

★ **Pain** is usually the first, but unfortunately, very late symptom,

★ **Obstructive jaundice** occurs in 50% of pancreatic head Ca.

★ **S & S of advanced P Ca** include weight loss, anorexia, malaise & weakness.

★ ***Migratory thrombophlebitis (Trousseau syndrome)*** occurs in about 10% of patients & is due to the elaboration of platelet-aggregating factors & procoagulants from **P ca**.

▼ **<20%** of **P Ca** are **resectable** at the time of diagnosis. Serum levels of many enzymes & antigens (e.g., CEA & CA19-9 Ag) are elevated, but are **neither** specific **nor** sensitive to be used as screening tests. CT & endoscopic U/S are helpful in the diagnosis & in performing percutaneous needle **biopsy**, but are **not** useful as screening tests.

☺ **End of Liver, GB, Biliary Tract & Pancreas= 114W + 61F = 175 PPP (@ 28-10-2019), Lectures prepared by:**

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