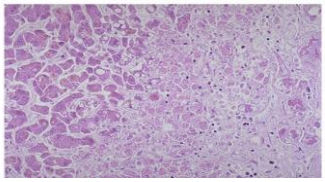
Patho 4: Drug induced liver disease.

Definition	Many drugs can cause injury to the liver, drug induced chronic hepatitis is clinically and histologically indistinguishable from viral/autoimmune hepatitis, that's why we must investigate the underlying cause to initiate the correct treatment. -The injury m.b immediate or take weeks to months.	
Classification of drug reactions	1-Predictable (intrinsic): These reactions are dose and duration dependent, more exposure→ increase likelihood to develop injury, so these patients after wrong administration to a certain drug +for long time (weeks, months, or years after chronic use)→ liver injury that would be resembled by high liver function test. (This applies to most drugs).	Example: Acetaminophen (because its commonly used), Tetracycline. Antineoplastic agents. CCL4, Alcohol (Green: the dr mentioned that they are toxic chemicals)
	2-Unpredictable (idiosyncratic or extrinsic): they are dose independent and cause unpredictable injury to hepatocyte that can sometimes occur after first exposure, they depend on: a- The immune response of the host to the antigenic stimulus Drug can produce changes to the antigenicity of the cells that would cause an immune response. b- The rate at which the host metabolizes the agent.	Example: Chlorpromazine (anti-epileptic agent), Halothane, Sulfonamides, Methyldopa (used in non-curative conditions), Allopurinol.
Mechanism of drug injury	**1-Direct toxic damage** e.g. acetaminophen, CCl4, mushroom toxins **2-Immune-mediated damage** Normal cells in the body have antigens that underwent tolerance and are not recognized as antigens anymore, so they are not attacked by the immune system. However, drugs are known to produce haptens. Haptens are small molecules that bind to cell surface, and may play a role in changing the antigenicity, which would stimulate immune attacks.	
Patterns of injury	1-Hepatocellular necrosis 2-Cholestasis 3-Steatosis 4-Steatohepatitis	

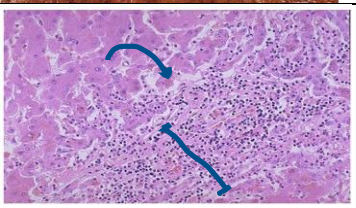
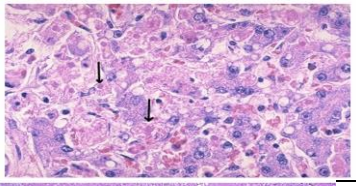
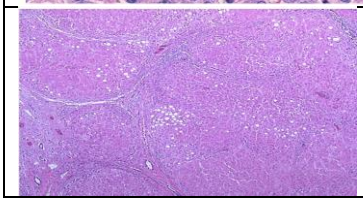
	5-Fibrosis 6-Vascular lesions 7-Granuloma 8-Neoplasms benign & malignant	
Drugs that may cause acute liver failure	1-acetaminophen (taken in large amounts like in suicidal attempts) 2-Halothane (produce necrosis) 3-antituberculosis drugs ([redacted], isoniazid) 4-antidepressant monoamine oxidase inhibitors 5-toxins as CCL4 & mushroom poisoning	
Morphology	Massive necrosis → 500 – 700 gm liver Submassive necrosis Patchy necrosis (focal)	
	As we can see the left side is different from the right side, whereas the left side present preserved hepatocytes, that have preserved outline. The right side, however present a damaged part of the liver (necrosis of cells), the cells on the right side have no outline and most nuclei are lost.	

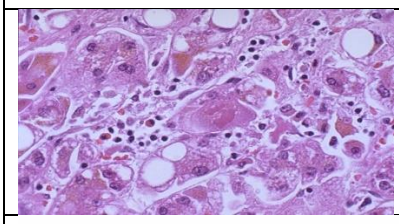
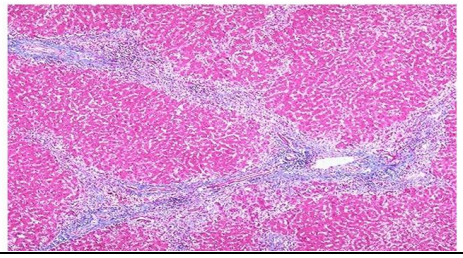
Fulminant hepatitis

Definition	Severe hepatitis is associated with necrosis, Hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy in 2-3 weeks. Sub fulminant (up to 3 months).
Causes	1-viral hepatitis (50-60%) B, C, E HBV x2> HCV +HDV superimposed on HBV. 2-drugs and chemicals (25-50%) 3-Obstruction of hepatic vein 4-Wilson's disease 5-acute f[redacted] change of pregnancy 6-massive tumor infiltration 7-reactivation of chronic hepatitis B 8-acute immune hepatitis
Morphology 	-↓ liver size (500 – 700 gm) -Necrosis of hepatocytes -Collapsed reticulin tissue (fibres seen in liver by a special stain) -Inflammatory infiltrate -Regenerative activity of hepatocytes -Fibrosis
This picture is a gross appearance of fulminant hepatitis, pale areas (yellow – beige) → necrosis and this indicates severe inflammation	

Chronic hepatitis

HALLMARK IN ALL CASES OF CHRONIC HEP → NECROSIS

Definition	Symptomatic, biochemical, or serological evidence of continuing or relapsing hepatic disease for more than 6months with histologically documented inflammation and necrosis. *Progressive (inflammation associated with the parenchyma fibrosis) * non-progressive (inflammation limited to portal areas) depending on the amount of fibrosis. Treatment is taken to delay fibrosis. • HBV, HCV, HBV-HDV At the time of evaluation, we look for the amount of lost hepatocyte, severity, and look for fibrosis.
Morphology	Mild to severe 1.Protal inflammation 2.Lymphoid aggregate 3.Necrosis of hepatocytes-councilman bodies 4.Bile duct damage 5.Steatosis 6.Interface hepatitis 7.Bridging necrosis & fibrosis 8.Fibrosis 9.Ground-glass appearance (characteristic of HBV, which is considered a DNA virus, these viruses will enter and integrate in the DNA and produce this appearance) 10.Sanded nuclei 11.Lobular disarray
	- Normal liver → homogenous - We notice this section is not homogenous → due to fibrosis (chronicity) - Fibrous tissue retracts→ nodularity
	- This slide presents chronic hepatitis, regardless the cause, how did we know? We mentioned that fibrosis is the HALLMARK of CHRONIC HEPATITIS and here we see a white fibrous band involving the parenchyma (black dots → lymphocytes) Eosinophilic granules in the cytoplasm represent Mallory- hyaline bodies (think of alcoholic liver disease!)
	
	Chronic process, due to the presence of fibrous bands and nodules. This is not cirrhosis because in cirrhosis we have full developed fibrous bands around the Parenchyma (this is a pre – cirrhotic phase). Cirrhosis is graded we have 4 levels (level 4 = complete cirrhosis)

	-we can also see the fatty change (significant here)
	-lost arrangement, hepatocytes are pigmented due to cholestasis
	-fibrous bands are prominent

Autoimmune hepatitis

Definition	Chronic hepatitis with immunologic abnormalities -Histologic features are similar to chronic viral hepatitis-Indolent or severe course -Dramatic response to immunosuppressive therapy. Its really important to diagnose autoimmune hepatitis because it has similar presentation as the viral hepatitis, so if a patient was suffering from viral hepatitis and we misdiagnosed him with autoimmune hepatitis and gave him immunosuppressants, this would lead to a massive problem because we need our immune system to fight the virus -Takes years to develop damage, lifelong disease with no cure, treatment is to prevent complications and control the symptoms
Features	1-Female predominance (70%) 2-Negative serology for viral antigens (NOT A VIRAL DISEASE). 3-increase serum Ig (>2.5 g/dl) → AUTOANTIBODIES that attack the cell **note: not all patients have these antibodies, and in these cases it would be more difficult for us to diagnose; because the presence of autoantibodies → HALLMARK 4-High titers of autoantibodies (80% of cases) 5-The presence of other autoimmune diseases as RA, thyroiditis (Graves, Hashimoto thyroiditis), Sjogren syndrome, UC in 60% of the cases
Type of autoantibodies	We can find many types with different titters. 1-Antismooth muscle antibodies (MOST COMMON) (anti actin, anti-troponin, anti-tropomyosin) 2-liver/kidney microsomal Abs (anti cytochrome P-450 components, anti UDP-glucuronosyl transferases) 3-Anti – soluble liver / pancreas antigen
Outcome	Mild to severe chronic hepatitis Full remission is unusual.

	Risk of cirrhosis is 5% which is the main cause of death can also have liver failure due to cirrhosis and its complications.

Non-alcoholic fatty liver disease

Although at first the fatty infiltrate is a reversible but if it progressed it would lead to liver damage

Types	1.Steatosis (Fatty liver) (mild form) 2.Steatohepatitis: (more severe because we have inflammation +fatty change) associated with hepatocyte destruction, parenchymal inflammation, progressive pericellular fibrosis
Predisposing factors	1-Type 2 DM 2-Obesity: body mass index > 30 kg /m2 in Caucasians > 25 kg /m2 in Asians 3-Dyslipidemia (++TG, ++LDL, low HDL) HDL: good proteins
Pathogenesis	. Metabolic syndrome Insulin resistance (type 2 diabetes), Obesity, Dyslipidaemia (can be diagnosed by blood's lipid test)
Mechanism of fatty accumulation	1.Impaired oxidation of fatty acids 2. synthesis & uptake of FFA 3.Decreased hepatic sec. of VLDL, ++increase TNF, IL6, chemokine → liver inflammation & damage
Clinically	All causes that increase the deposition of fat + not due to alcohol is called NAFLD -NAFLD is the most common cause of incidental increase in transaminases. -Most pts. are asymptomatic -Non-specific symptoms: Fatigue, malaise, RUQ discomfort -Severe symptoms (related to liver injury) -Liver Bx (biopsy) is required for dx (confirmatory) -biopsy is to evaluate the presence of fatty infiltration and its degree -NAFLD m.b a significant contributor to cryptogenic cirrhosis

Hemochromatosis

Definition	Excessive accumulation of body iron (liver & pancreas) however, other organs can suffer too, due to iron deposition
Forms	1ry or 2ry (genetic or acquired) usually the primary is called hemochromatosis, but the secondary is referred to as hemosiderosis
Genetic hemochromatosis	Genetic hemochromatosis (4 variants) -The most common form is aut. recessive disease of adult onset caused by mutation in the HFE gene on chr.6, mutation is not the same in all patients? (site of mutation differs)
Acquired hemosiderosis causes	1-multiple transfusions 2-ineffective erythropoiesis (thalassemia) --- these patients survive on repeated blood transfusion, which is overloaded with iron that is directly in the blood with the need to get it absorbed in the intestine, that's why these patients alongside the blood transfusion, receive chelating agents to prevent the deposition of iron 3-increased iron intake in food and drink (Bantu siderosis) 4-chronic liver disease
Features	1-Micronodular cirrhosis (all patients) 2-D.M (because pancreas is damaged) (75 – 80%) 3-skin pigmentation (75-80%) 4-cardiomegaly, joints disease, testicular atrophy (associated with infertility) -Patients are usually not young, symptoms appear in the 5th to 6th decades not before the age of 40,why? Because Iran needs a long time to be accumulated and cause symptoms. -male to female ratio is 5-7:1, why? There is no way the body can excrete iron, so the body works on absorbing it, but women usually shed iron during their menstruation, so the iron deposited amount is less, opposite to men, which technically don't have a way to get the iron out, and present a decade earlier than females.
Pathogenesis	-1ry defect in intestinal absorption of dietary iron. There is no way our body can get rid of iron but it control its levels through absorbtion -Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes, we can also find it in the bone marrow because bone marrow synthesizes RBC which contains iron (specifically heme)) -In disease >50gm Fe accumulated 1/3 in liver

	-In hereditary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 gm/yr -The gene responsible is HFE gene located on chr.6 close to HLA gene complex -HFE gene regulates the level of hepcidin hormone
Hepcidin	hepcidin is a hormone synthesized in the liver it works by preventing excess Iron absorption by controlling the ion channels, and when the person has low iron levels (due to bleeding or anemia) it will lower its levels so the iron can enter the channels. -Hepcidin →(-) Fe. absorption from intestine by increasing the closure of the channels. -Hepcidin is lowered in cases of anaemia for example because the body needs iron -HFE gene deletion → low hepcidin→causes iron overload
Mutations in the HFE gene	1-Mutation at 845 nucleotide→ tyrosine substitution for cystine at AA 282 (C282 Y) 2-aspartate substitution for histidine at AA 63 (H63D) 10% of pts. have other gene mutations -Carrier rate for C282Y is 1/70 -Homozygosity is 1/200 (common) -80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation -10% of pts. are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation
Excessive Fe deposition	Toxicity of the tissues Lipid peroxidation, stimulation for collagen formation (iron is a stimulant for FIBROSIS), DNA damage. **we should notice that fibrosis is possible for both liver and pancreas? Iron is a stimulant→ fibrosis
Morphological changes	1-Deposition of hemosiderin in different organs Liver Pancreas Myocardium Pituitary Adrenal Thyroid & parathyroid Joints Skin 2-Cirrhosis 3-Pancreatic fibrosis -No inflammation -Fibrosis -Cirrhosis -Synovitis -Polyarthritis(pseudogout) -Pigmentation of liver (very dark) -fibrosis of pancreas & myocardium -Atrophy of testes
Clinical presentation	M:F 5 – 7 :1 5 – 6 the decades Hepatomegaly Abdominal pain Skin pigmentation D.M Cardiac dysfunction Atypical arthritis Hypogonadism increase serum Fe ferritin (ferritin is a reflection of iron stores) HCC 200x higher in the risk