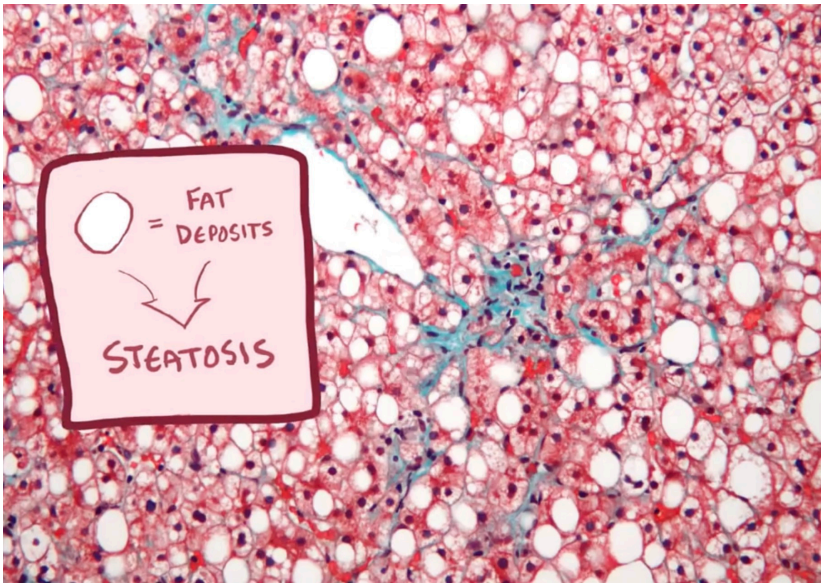
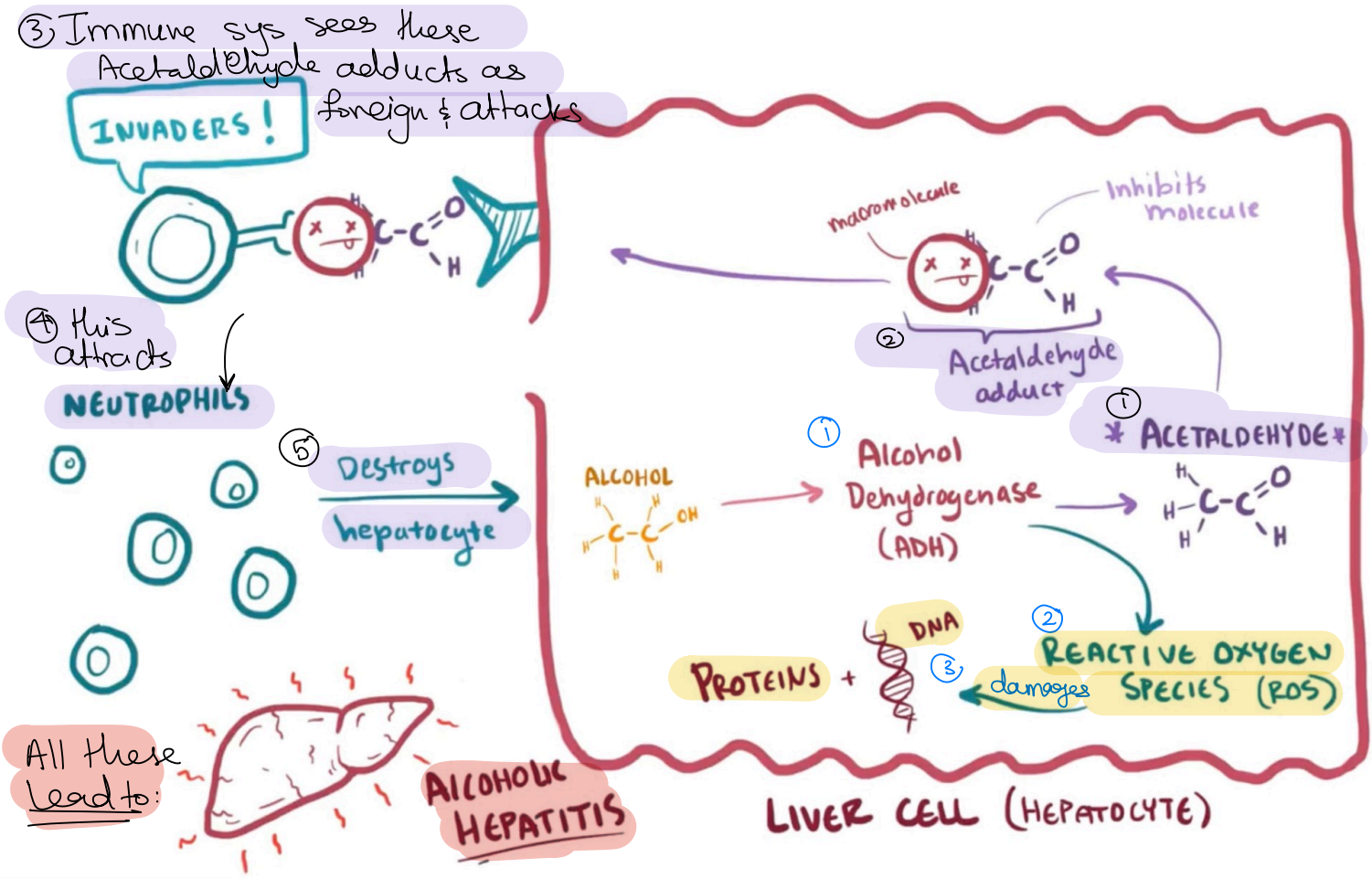
* Alcoholic liver disease - Lec 2

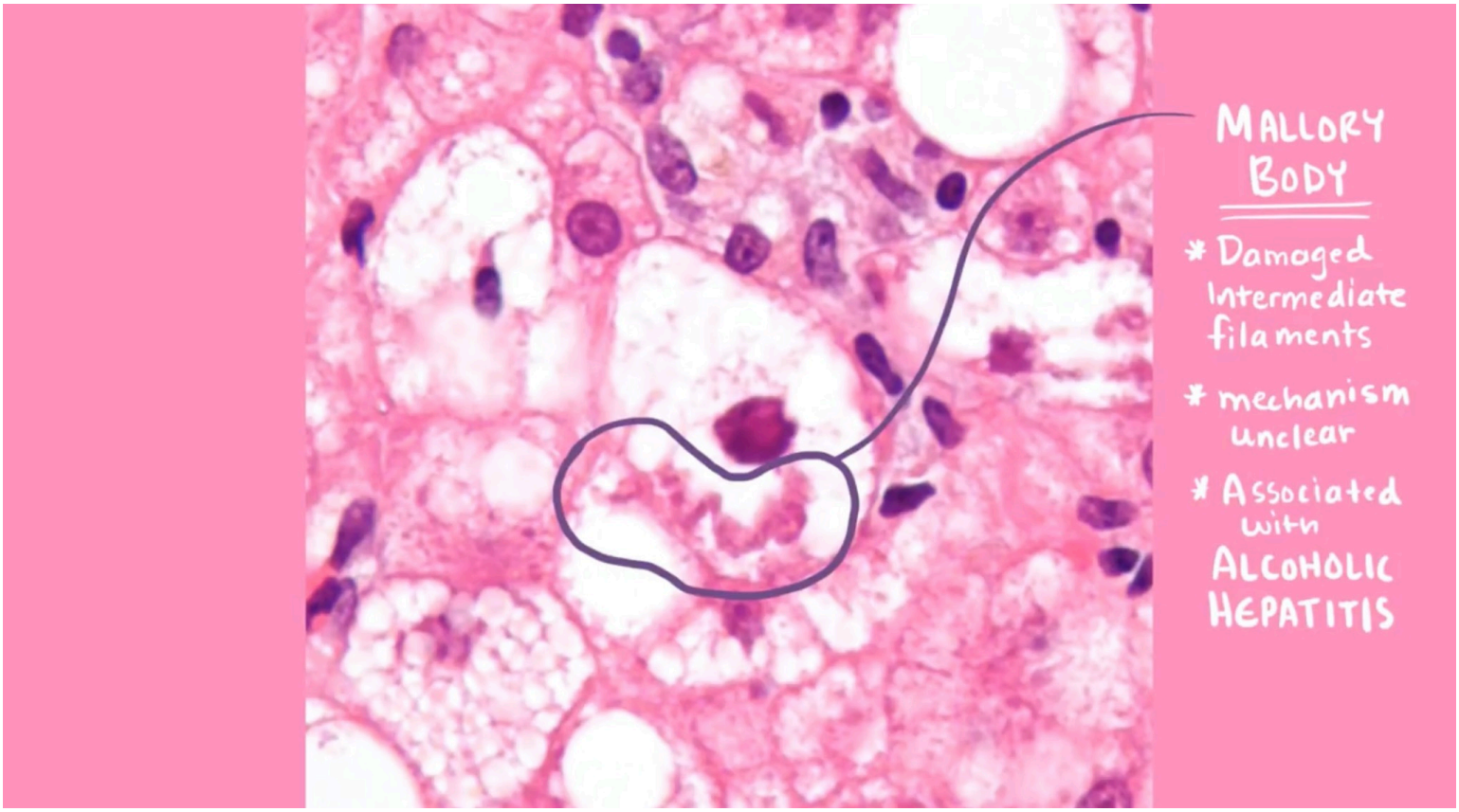
① Early on, ↑↑ NADH & ↓↓ NAD^+ will lead to fatty change (Steatosis)

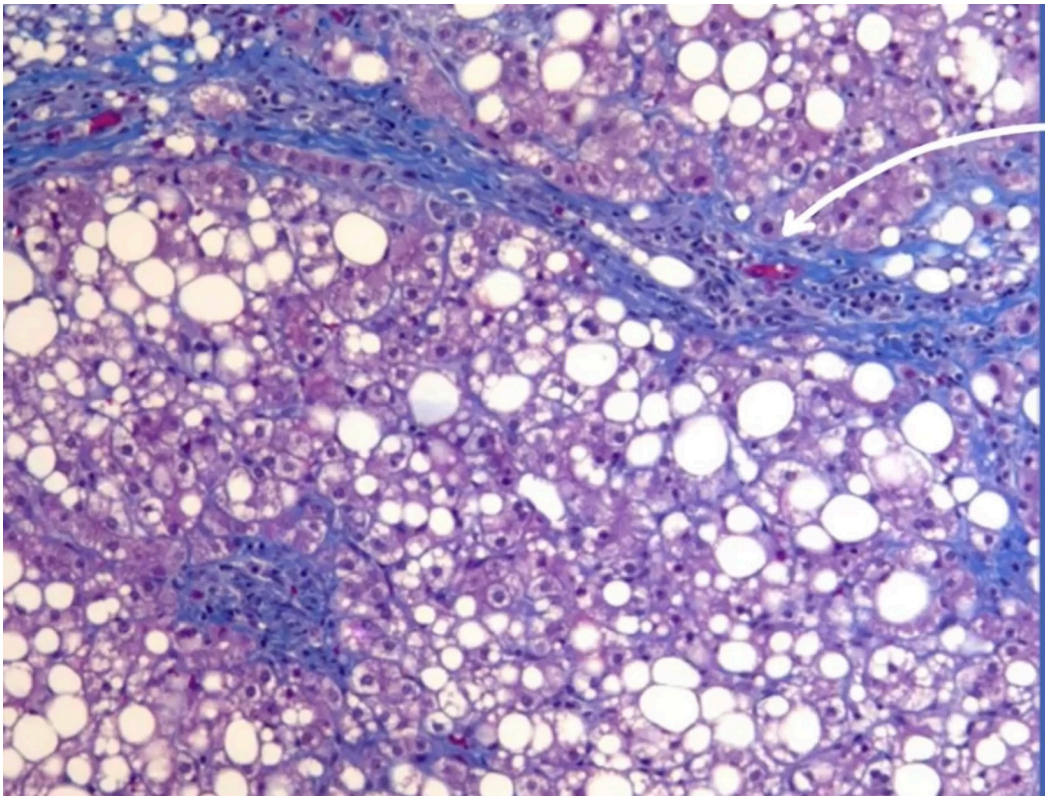


② ↑↑ Acetaldelyde forms adducts which attract immune sys.



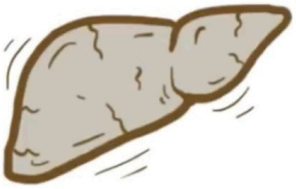
(Mallory bodies best see in hepatitis, & rarely in cirrhosis)





ALCOHOL

TREATMENT



Corticosteroids

- Suppress immune system

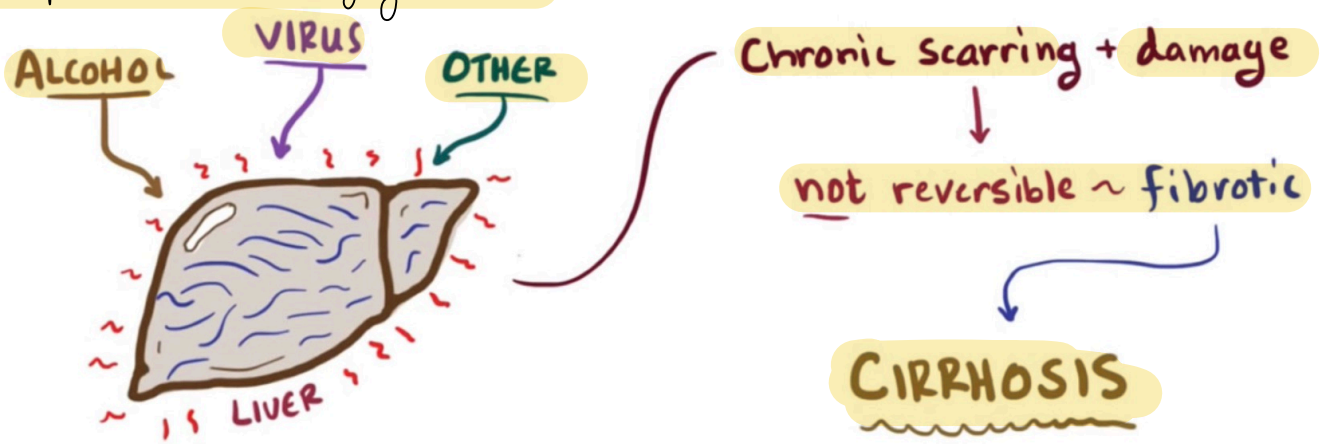
└ **CHRONIC DAMAGE**

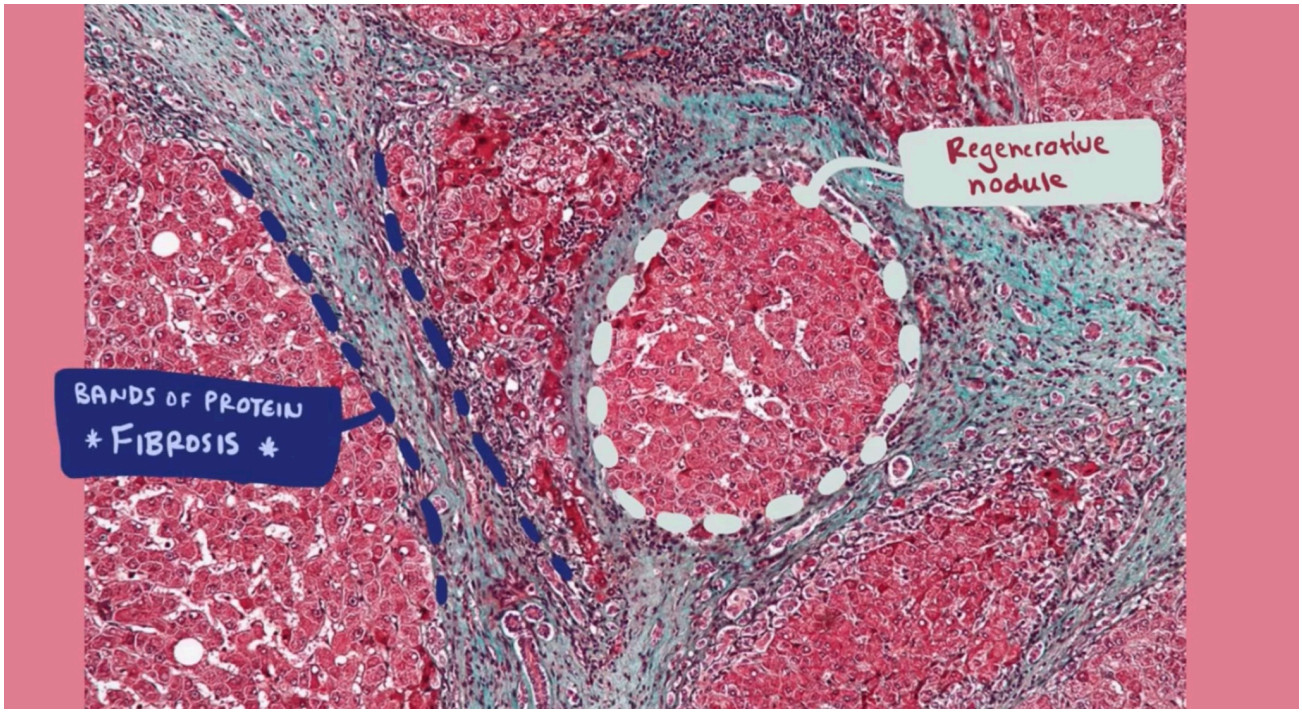
- CIRRHOSIS
- LIVER FAILURE

* Cirrhosis – Lec 3

FIBROTIC ~ thickened with protein

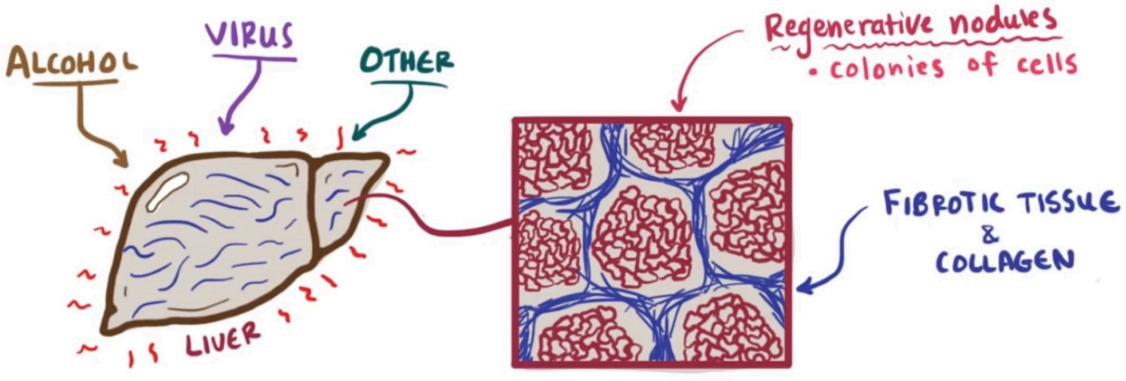
* when liver is continuously exposed to damaging forces:





CIRRHOSIS

* "End-stage" damage *



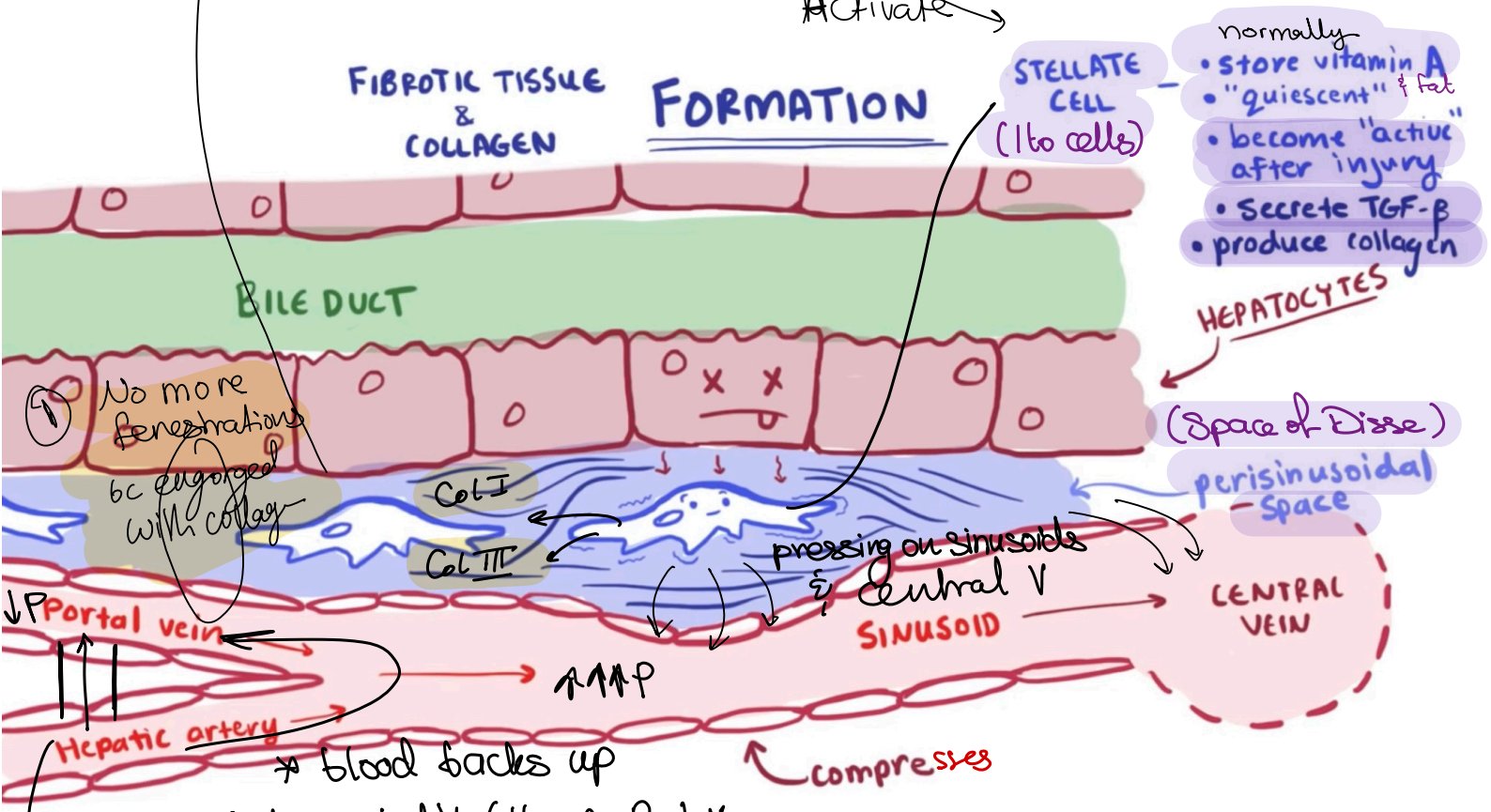
Normal liver: Collagen I, III (Reticular), V, XI
in: 1) Capsule 2) Portal area
3) Central vein
4) Peri-sinusoidal (v. delicate Col IV)

→ Injury: Col I & III in space of Disse

② loss of hepatocyte microvilli = ↓exchange

① ROS
② TNF, IL-1, lymphotoxins
③ GF

Activate →



* blood backs up into portal V (Hep A - Port V anastomosis) = ↑↑ Portal P

Direct anastomosis within fibrous septa

↑ sinusoidal BP

= ↑ Portal pressure

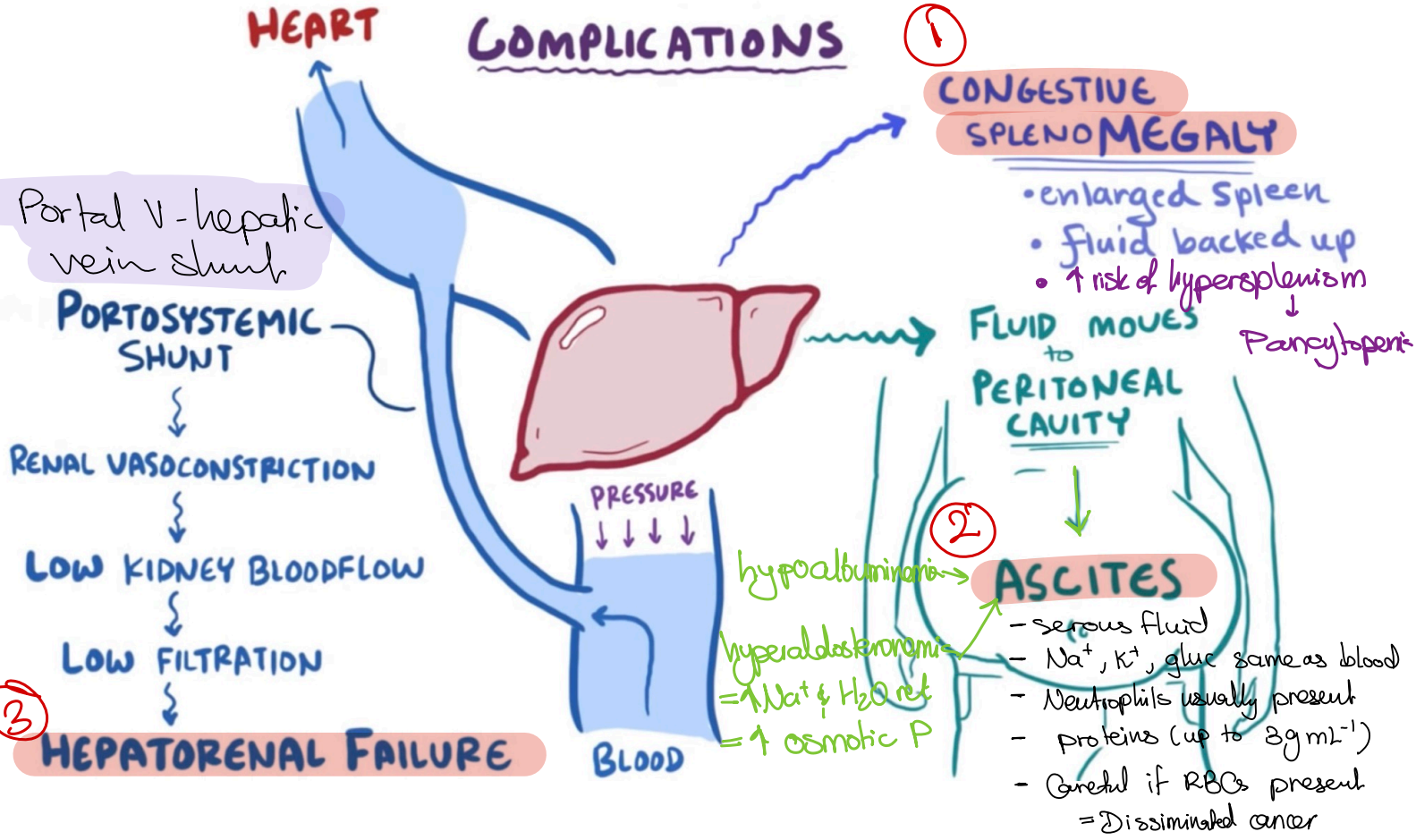
Fluids start squeezing out
↓
lymph drains then
(800-1000mL/day → 20L-day)
↓
Ascitis

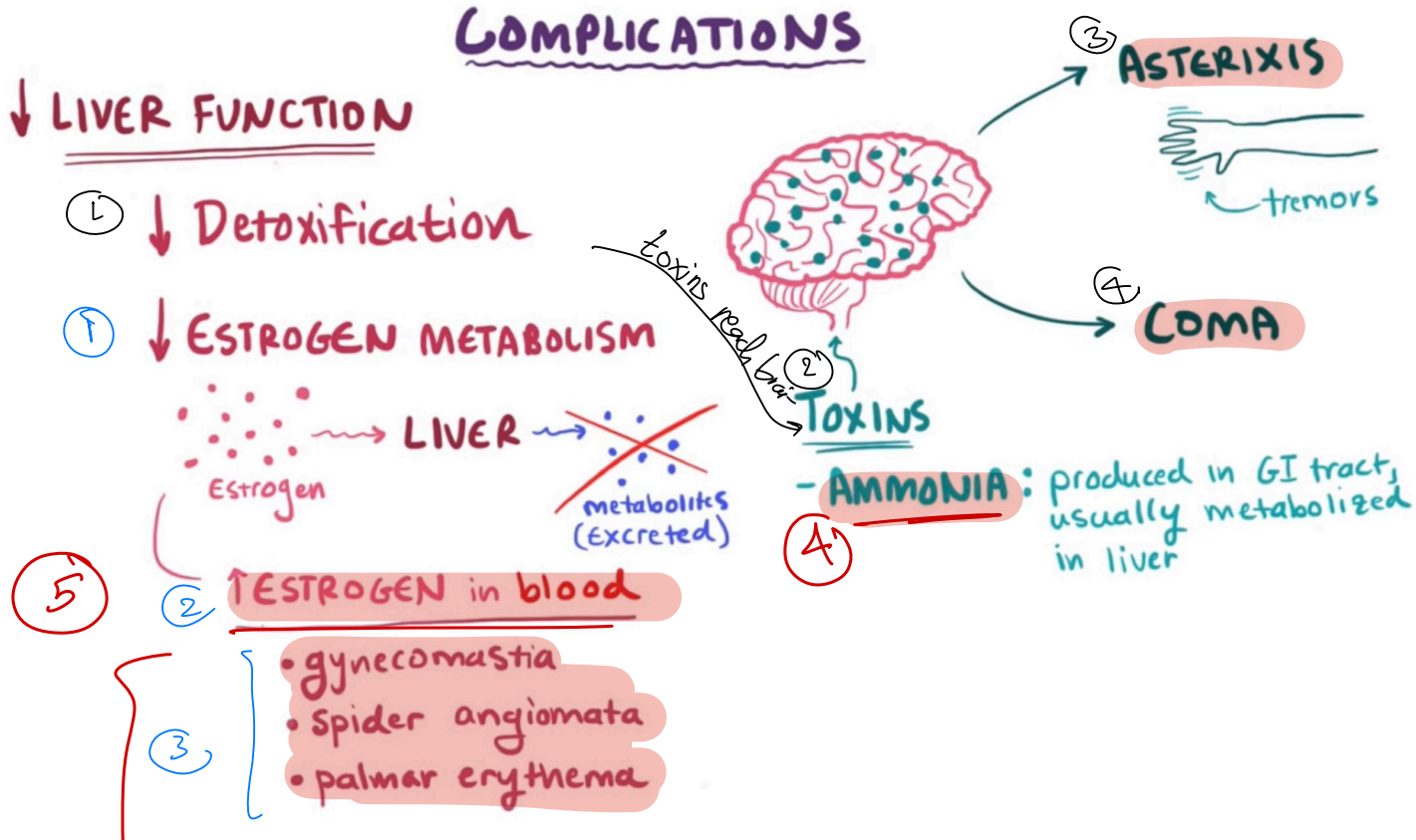
Blood backs up (Splenomegaly)

Stellate cells

↳ NORMAL STATE ~ wound healing

↳ constant injury ~ constant fibrosis





COMPLICATIONS

↓ BILIRUBIN conjugation
- ↑ UNCONJUGATED BILIRUBIN
- JAUNDICE

(6)

↓ Albumin production
- Hypoalbuminemia

(7)

↓ Clotting factor production
- Coagulation issues

(8)

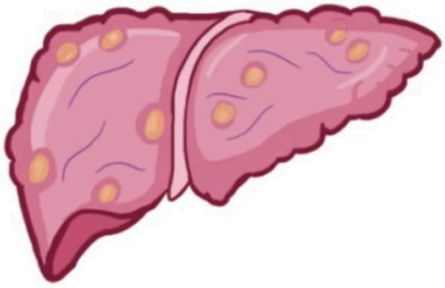
SYMPTOMS

*EARLY ~ SOME FIBROSIS
- ASYMPTOMATIC
- NON-SPECIFIC
  - e.g. weight loss, weakness, fatigue

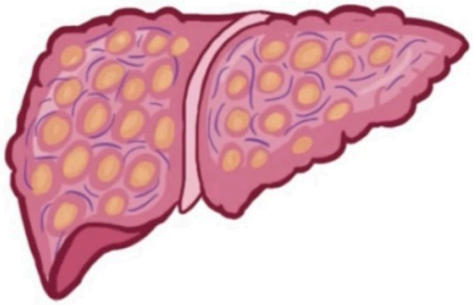
*LATER ~ EXTENSIVE FIBROSIS
- JAUNDICE & PRURITUS (ITCHY SKIN)
- ASCITES
- HEPATIC ENCEPHALOPATHY
  - CONFUSION
- EASY BRUISING

(All symptoms discussed)

COMPENSATED
STILL DOES ITS JOB

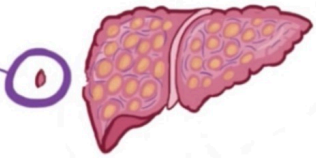


DECOMPENSATED
* CAN'T FUNCTION *



DIAGNOSIS

* LIVER BIOPSY



* LAB FINDINGS
  - ELEVATED BILIRUBIN
  - ELEVATED ENZYMES
    - ~AST > ALT
      - * ASPARTATE AMINOTRANSFERASE (AST)
      - * ALANINE AMINOTRANSFERASE (ALT)
      - * ALKALINE PHOSPHATASE (ALP)
      - * GAMMA GLUTAMYL TRANSPEPTIDASE (GGT)
  - THROMBOCYTOPENIA
    - LOW PLATELETS

Cirrhosis in a nut shell

CAUSES

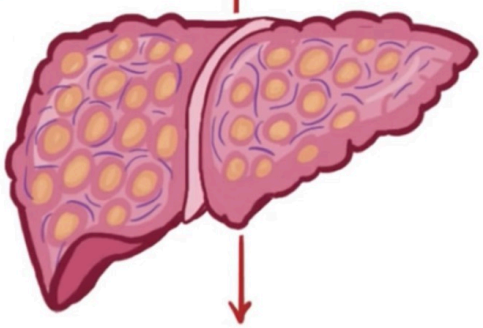
* EXCESSIVE ALCOHOL CONSUMPTION
* PROLONGED VIRAL ATTACK
  - e.g. HEPATITIS B
    HEPATITIS C

SYMPTOMS

* JAUNDICE
* ASCITES
* EASY BRUISING
* HEPATIC ENCEPHALOPATHY

CIRRHOSIS

INFLAMMATION & DAMAGE



FIBROSIS

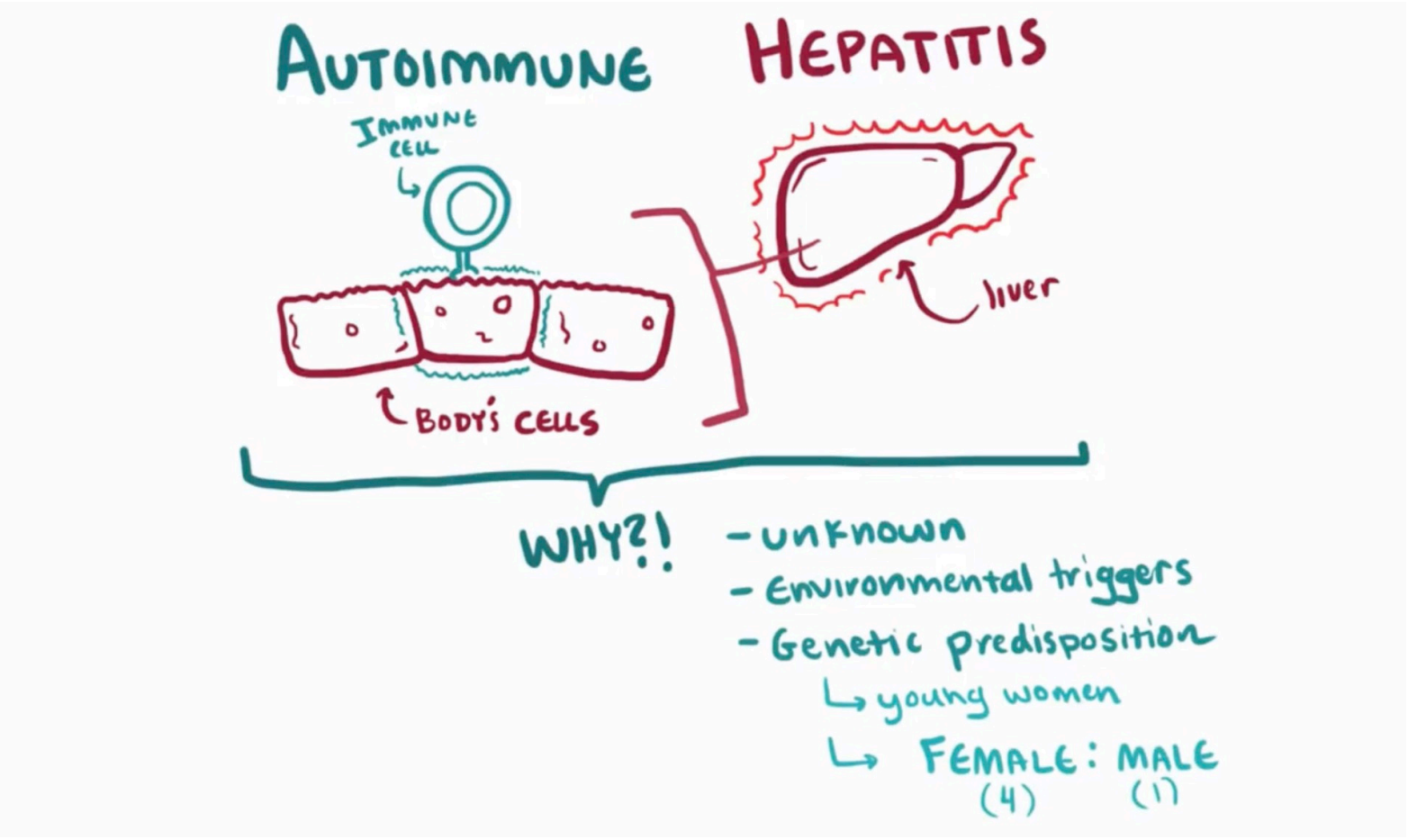
DIAGNOSIS

* BIOPSY
* LAB TESTS

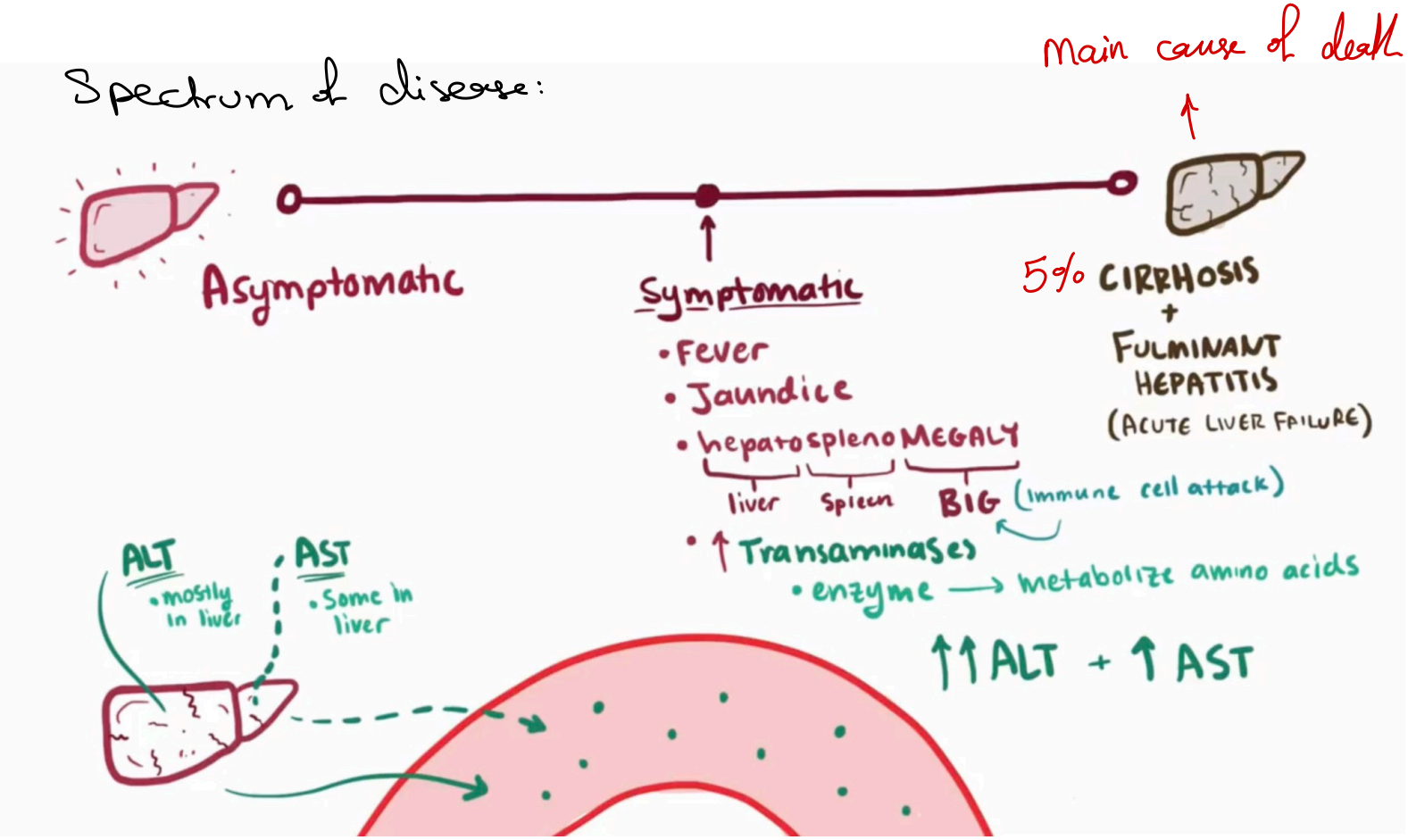
TREATMENT

* UNDERLYING CAUSE
* LIVER TRANSPLANT

* Autoimmune Hepatitis



Spectrum of disease:



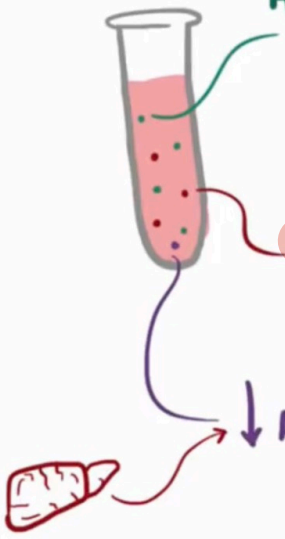
TYPE I

~80% cases

↑ PROTHROMBIN TIME
time for blood to clot

* Histologically similar to chronic viral hepatitis

ANTINUCLEAR ANTIBODIES (ANA)



Antibodies to own nuclei

SELF? NONSELF?

ASMAs
Antibodies to own smooth muscle
↳ anti-actin
↳ troponin
↳ tropomyosin

↓ ALBUMIN
usually produced in liver

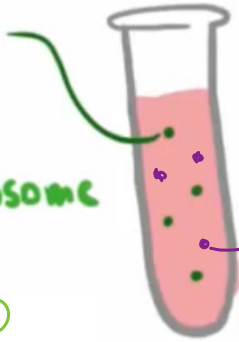
Serum Ig > 2.5 gdL⁻¹

↑ ALKM, ↑ SLA/LP, ↑ ASMA in 80 %
(Not all)

- young girls
- with other autoimmune disease
  - ↳ RA
  - ↳ thyroiditis
  - ↳ Sjogren syndrome
  - ↳ UC

ANTIBODIES TO...

ALKM-1 Liver or kidney microsome



Anti – SLA/LP
anti soluble liver/pancreas antige

↳ Anti – cyt P450

↳ Anti – UDP glucoronyl transferase

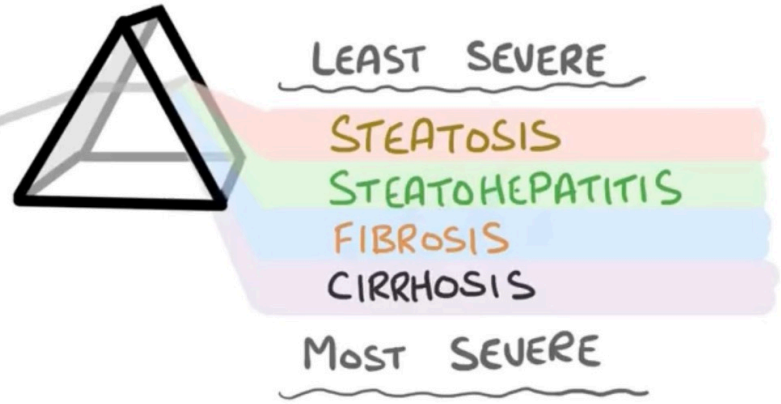
* Non Alcoholic fatty liver disease

→ Not related to alcohol
→ Not related to viruses

NON-ALCOHOLIC FATTY LIVER DISEASE

RESULTS from FAT DEPOSITION in the LIVER
↓
AFFECTS INDIVIDUALS with METABOLIC SYNDROME

SPECTRUM of DISEASES



3 of the 5

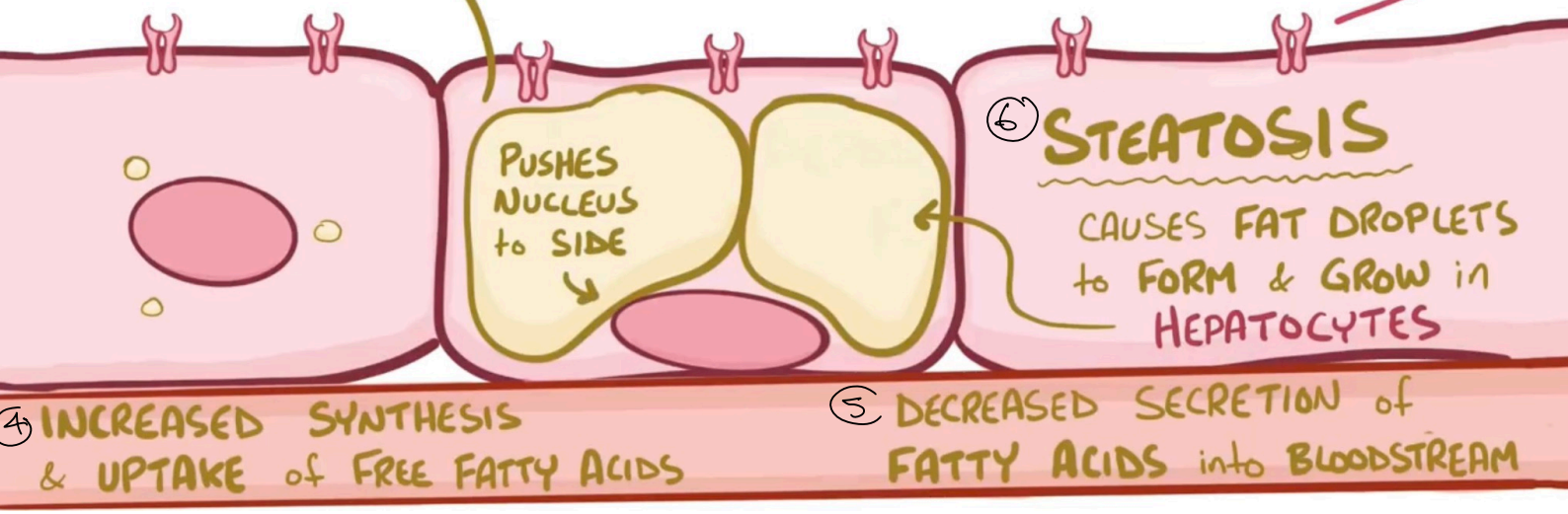
* OBESITY
* HYPERTENSION
* DIABETES
* HYPERTRIGLYCERIDEMIA
* HYPERLIPIDEMIA

① Insulin R → fat deposits → Steatosis

① INSULIN RESISTANCE plays a ROLE

② INSULIN RECEPTORS become less responsive to INSULIN

③ Liver fat pathways still respond to insulin = well fed
↑ FAT STORAGE
↓ FATTY ACID OXIDATION



⑥ STEATOSIS
CAUSES FAT DROPLETS to FORM & GROW in HEPATOCYTES

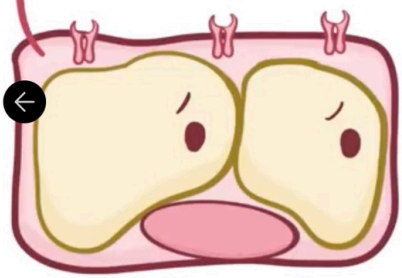
④ INCREASED SYNTHESIS & UPTAKE of FREE FATTY ACIDS

⑤ DECREASED SECRETION of FATTY ACIDS into BLOODSTREAM

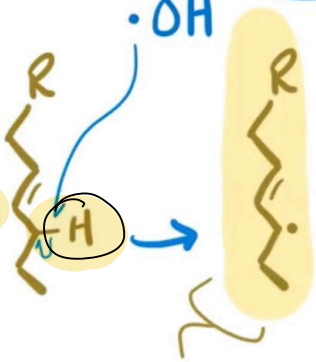
② Fat vulnerable to damage → Steatohepatitis

FAT in HEPATOCYTES is VULNERABLE to DEGRADATION

bc UNSATURATED FATTY ACIDS
- with at least one double bond



have HYDROGENS that are particularly vulnerable to INITIATORS



HYDROXYL RADICAL (ROS)
- have an unpaired electron

·OH + HOH

UNSTABLE
* REACTS with NON-RADICALS
  - molecular OXYGEN
  - other FATTY ACIDS

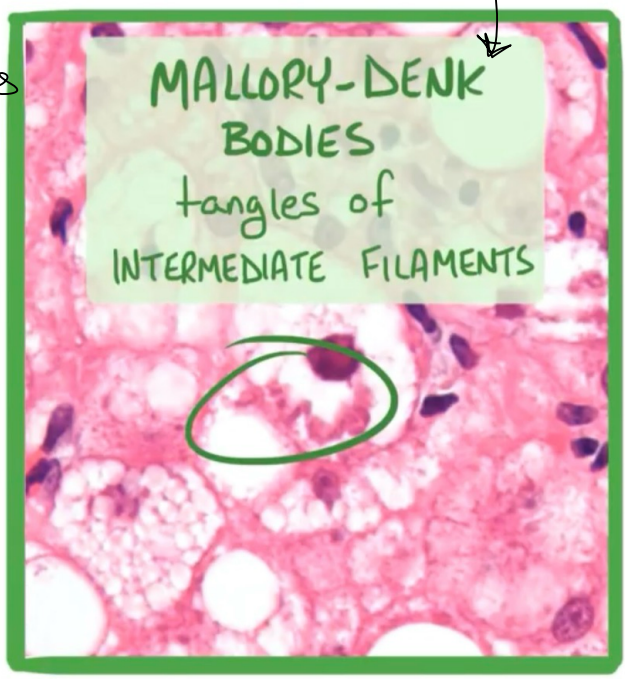
chain rxn that will damage lots of f.a., membranes & proteins

FAT in HEPATOCYTES is VULNERABLE to DEGRADATION

STEATOSIS & INFLAMMATION → STEATOHEPATITIS

TNF
IL6
chemokines

without ALCOHOL this is
NON-ALCOHOLIC STEATOHEPATITIS
NASH



DAMAGES LIPID MEMBRANES

MITOCHONDRIAL DYSFUNCTION

CELL DEATH

↳ GENERATES INFLAMMATION

③ Prolonged steatohepatis → fibrosis → Cirrhosis

STEATOSIS & INFLAMMATION

↓↓

STEATOHEPATITIS

without ALCOHOL this is

NON-ALCOHOLIC STEATOHEPATITIS

NASH

* DAMAGE attracts NEUTROPHILS to LIVER

CHRONIC STEATOHEPATITIS can cause STELLATE CELLS to lay down FIBROTIC TISSUE

FIBROSIS

↓

CIRRHOSIS

SYMPTOMS

* even at **ADVANCED STAGES** there may be **NONE**
* when there **ARE SYMPTOMS** they are often **VAGUE**
  - fatigue
  - malaise

* once there is **SIGNIFICANT DAMAGE**
  - hepatomegaly (enlargement of the **LIVER**)
  - pain in RUQ
  - jaundice
  - accumulation of **FLUID** in the **PERITONEAL CAVITY** - called **ASCITES**

SYMPTOMS

BECAUSE HEPATOCYTES are being **DESTROYED** there can be an **INCREASE** in **LIVER ENZYMES**
- aspartate transaminase **(AST)**
- alanine transaminase **(ALT)**

NON-ALCOHOLIC FATTY LIVER DISEASE

Steatosis
↓
STEATOHEPATITIS
↓
CIRRHOSIS

ALCOHOLIC FATTY LIVER DISEASE

Steatosis
↓
STEATOHEPATITIS
↓
CIRRHOSIS

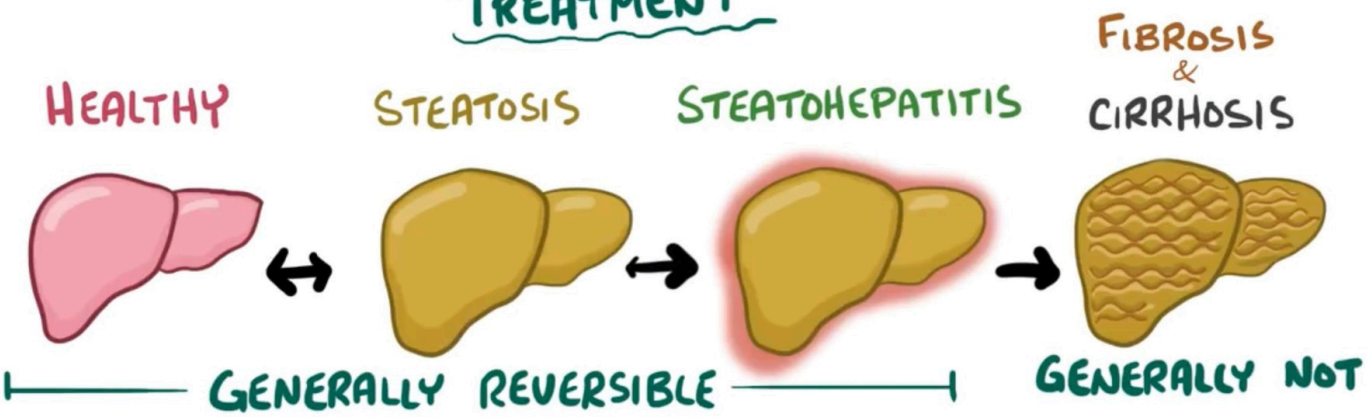
INCREASES ALT & sometimes AST

ALT >> AST

INCREASES AST & AST : ALT > 2

AST >> ALT

TREATMENT



GOAL: REVERSE FACTORS that CONTRIBUTE to INSULIN RESISTANCE

- HEALTHY DIET
- ACTIVE LIFESTYLE
- MEDICATIONS that control BLOOD GLUCOSE

*NAFLT in a nutshell!

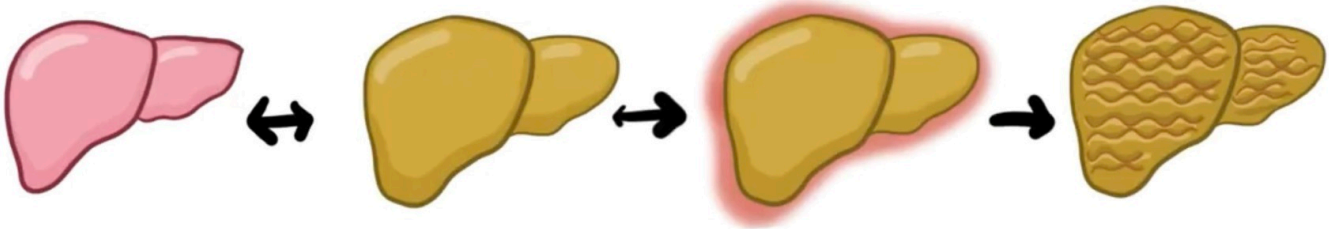
NON-ALCOHOLIC FATTY LIVER DISEASE

fat is deposited in LIVER

inflammation

chronic

HEALTHY → STEATOSIS → STEATOHEPATITIS → FIBROSIS & CIRRHOSIS

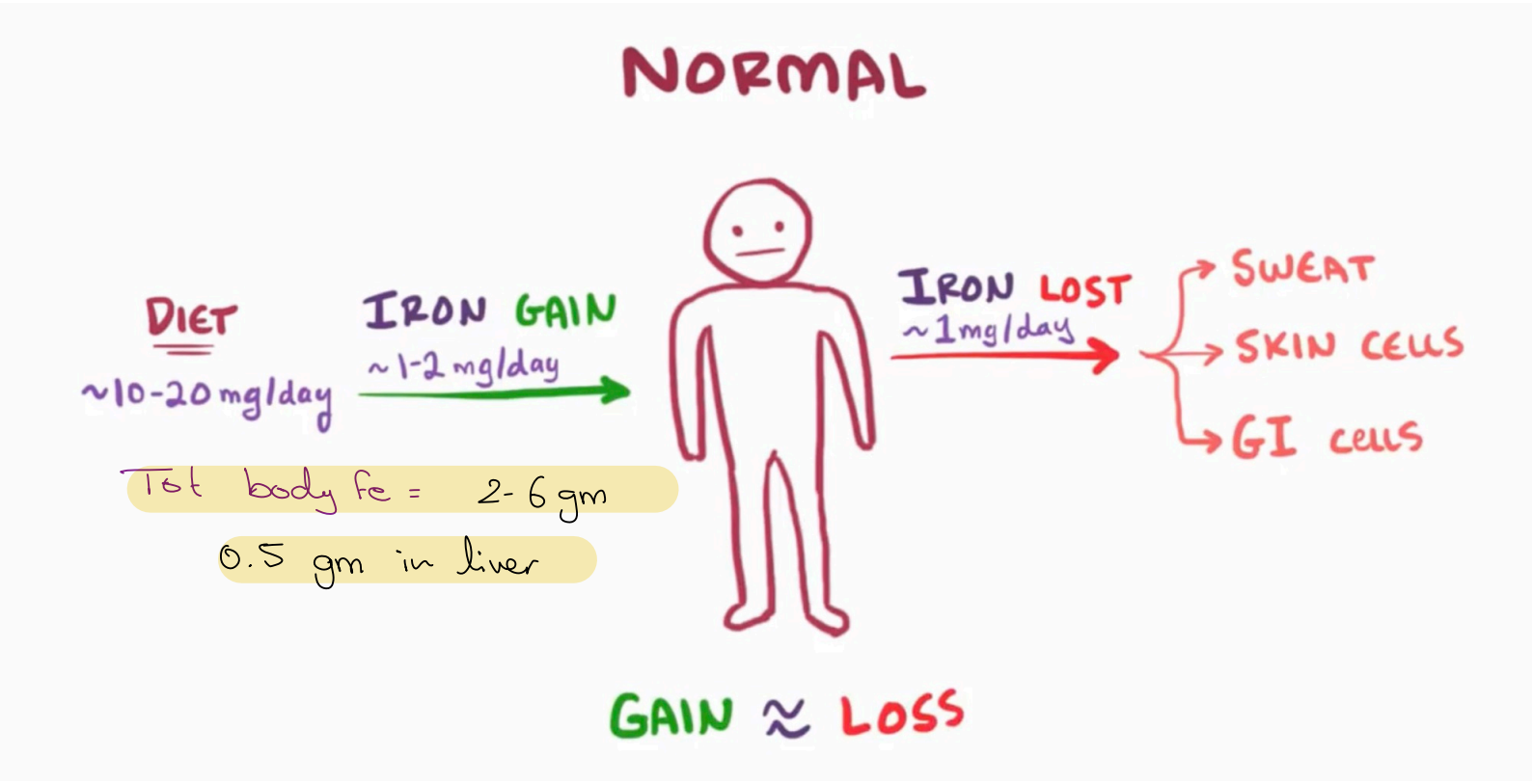


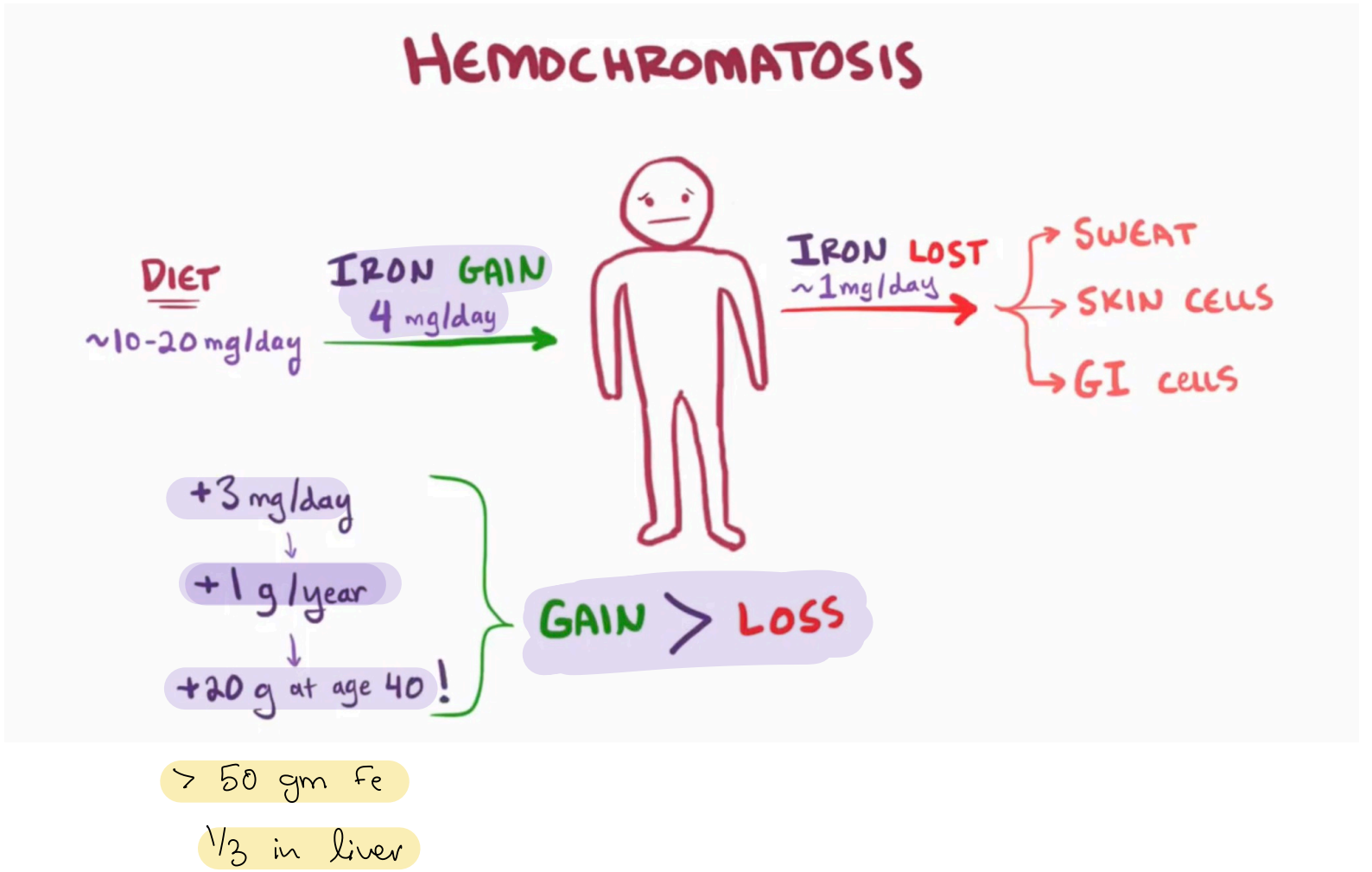
is LIKELY CAUSED by INSULIN RESISTANCE

can be REVERSED with DIET, EXERCISE & MEDICATION

dx : Liver biopsy

+ Hemochromatosis



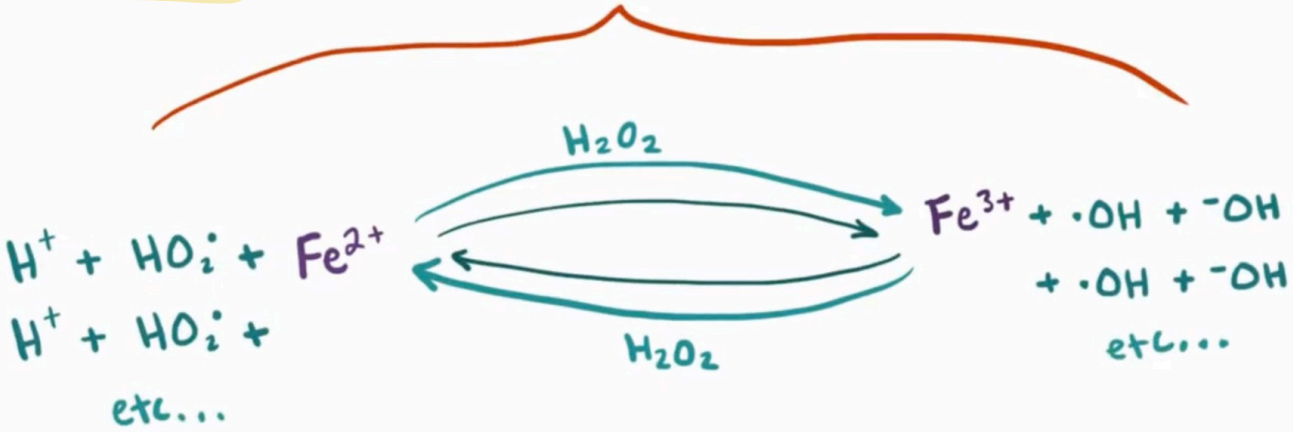


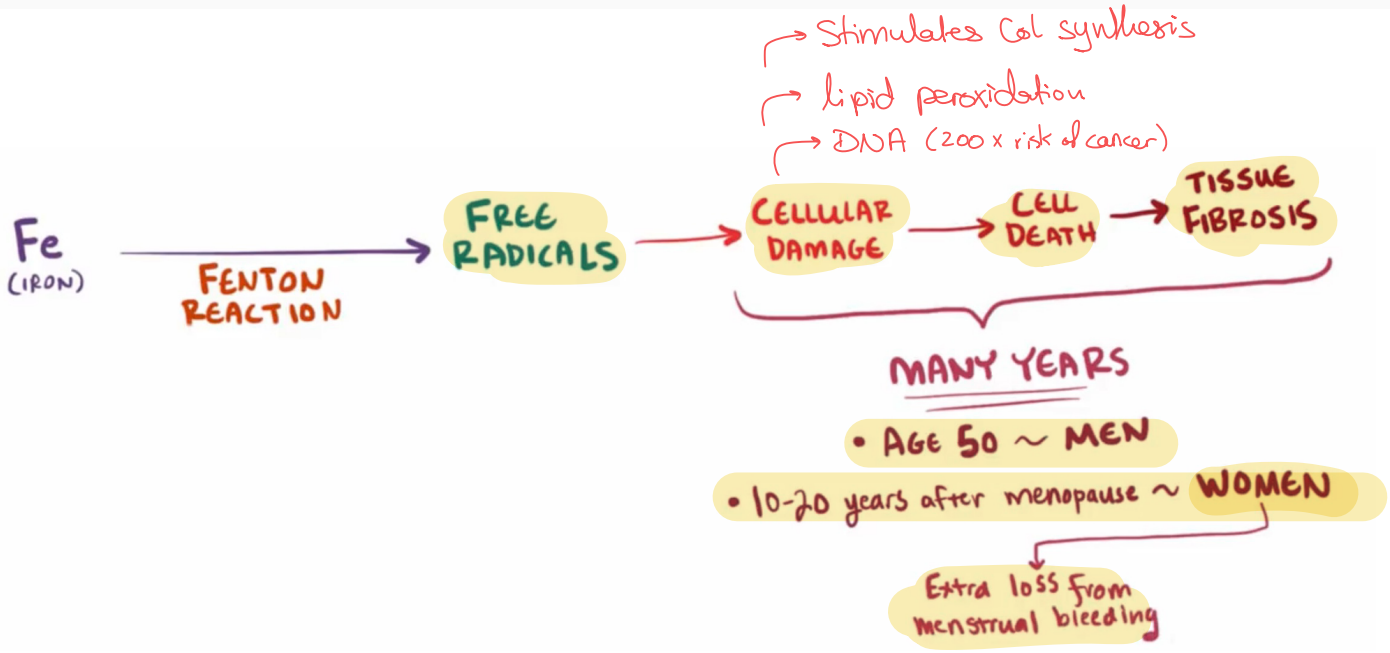
HEMOCHROMATOSIS

EXTRA IRON → DEPOSITS IN → ORGANS + TISSUE → DAMAGED

Fe is great at producing free radicles!

Fe (IRON) → FENTON REACTION → FREE RADICALS





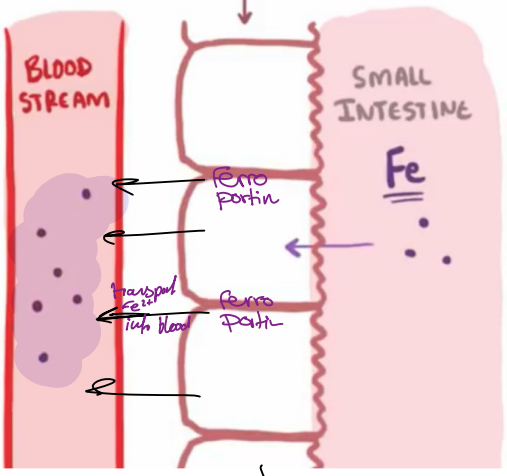
M : F = 5-7 : 1

* No inflammation / neutrophils

damage is due to ROS

what causes ↑ Fe absorption ??

HFE mutation → ENTEROCYTES



enterocytes normally regulate Fe passage into blood (only released when needed)

∴ mutations will disrupt this reg

↓

↑↑↑ Fe going into blood

✱ PRIMARY (HEREDITARY)

- gene mutation ~ HFE (High Fe) — autosomal recessive
  - Location: chromosome 6
  - regulates iron absorption
  - C282Y (Cys, Tyr) or H63D (Histid, Asp) mutation
    - more common (80%)
    - 10%
  - 10% have other mutations

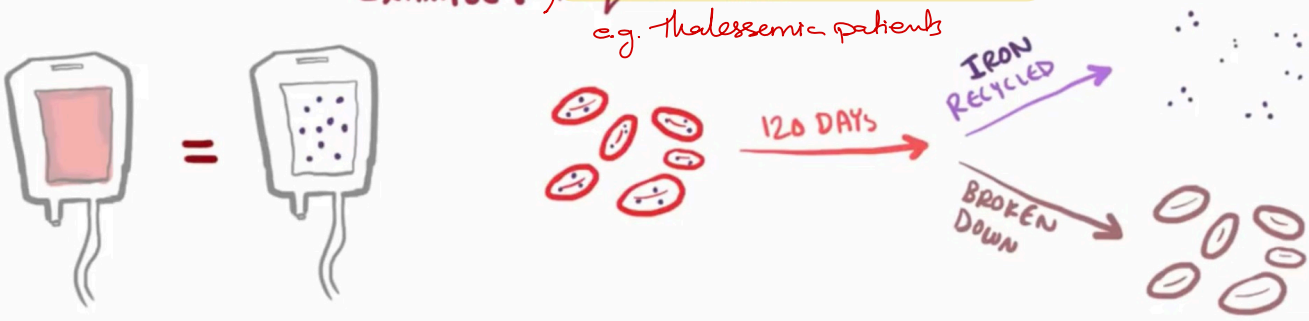
→ CAN'T REGULATE → OVERLOAD BLOOD

→ Produces Hepcidin → ⊖ Ferroportin = ↓ Fe absorption

✱ SECONDARY (NOT GENETIC) i.e. Hemosiderosis

EXAMPLE: 1) Frequent blood transfusions ~ ↑IRON

e.g. thalassemic patients



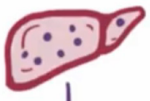
2) Chronic liver disease

liver can't produce Hepcidin = Nothing to inhibit Ferroportin = ↑ Fe transported into blood

3) Bantu siderosis (↑ Fe intake from diet)

COMPLICATIONS

LIVER



↓

Fe Buildup
+
Free radical damage

↓

micronodular CIRRHOSIS + ↑cancer (200×)

Pigmentation

PANCREAS

- Type I Diabetes mellitus (beta islet cells)
- Malabsorption (exocrine pancreas)

SKIN

↑BRONZE PIGMENT

HEART

myocardium

↓

CARDIOMYOPATHY

↳ Arrhythmias

GONADS

- Amenorrhea — women
- Testicular atrophy - men

JOINTS

- Degenerative Joint disease due to fibrosis
- (Polyarthritis - pseudogout)
- Synovitis

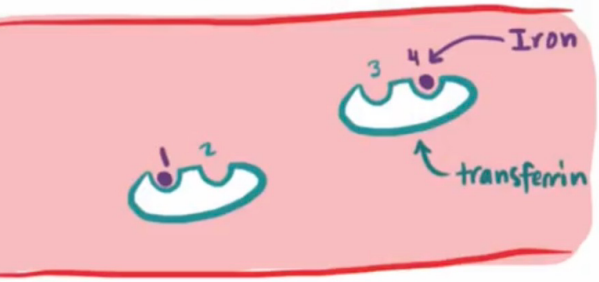
Diagnosis

BLOOD TESTS

* ↑IRON *

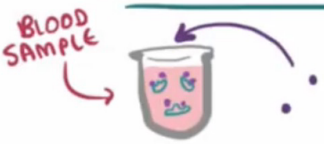
↑ TRANSFERRIN % saturation

- binding sites occupied
- Transferrin = transports Fe



50% Saturation = 2/4 sites occupied

↓ TOTAL IRON BINDING CAPACITY



- measure iron capacity of sample

bc ↑ transferrin sites already occupied

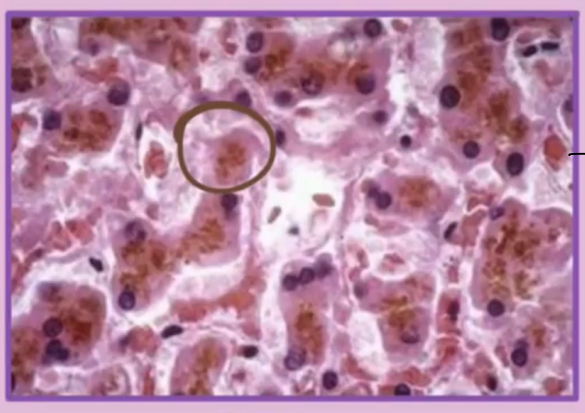
↑FERRITIN PRODUCTION

- Stores iron in cells
- Signals DECREASE TRANSFERRIN PRODUCTION

BROWN SPOTS

LIPOFUSCIN ?

- Normal "wear & tear"
- from lysosomal digestion

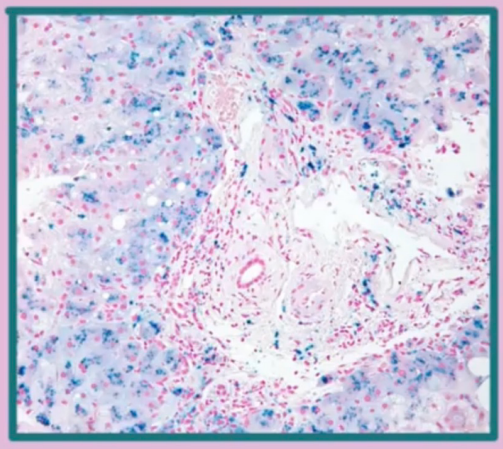


LIPOFUSCIN

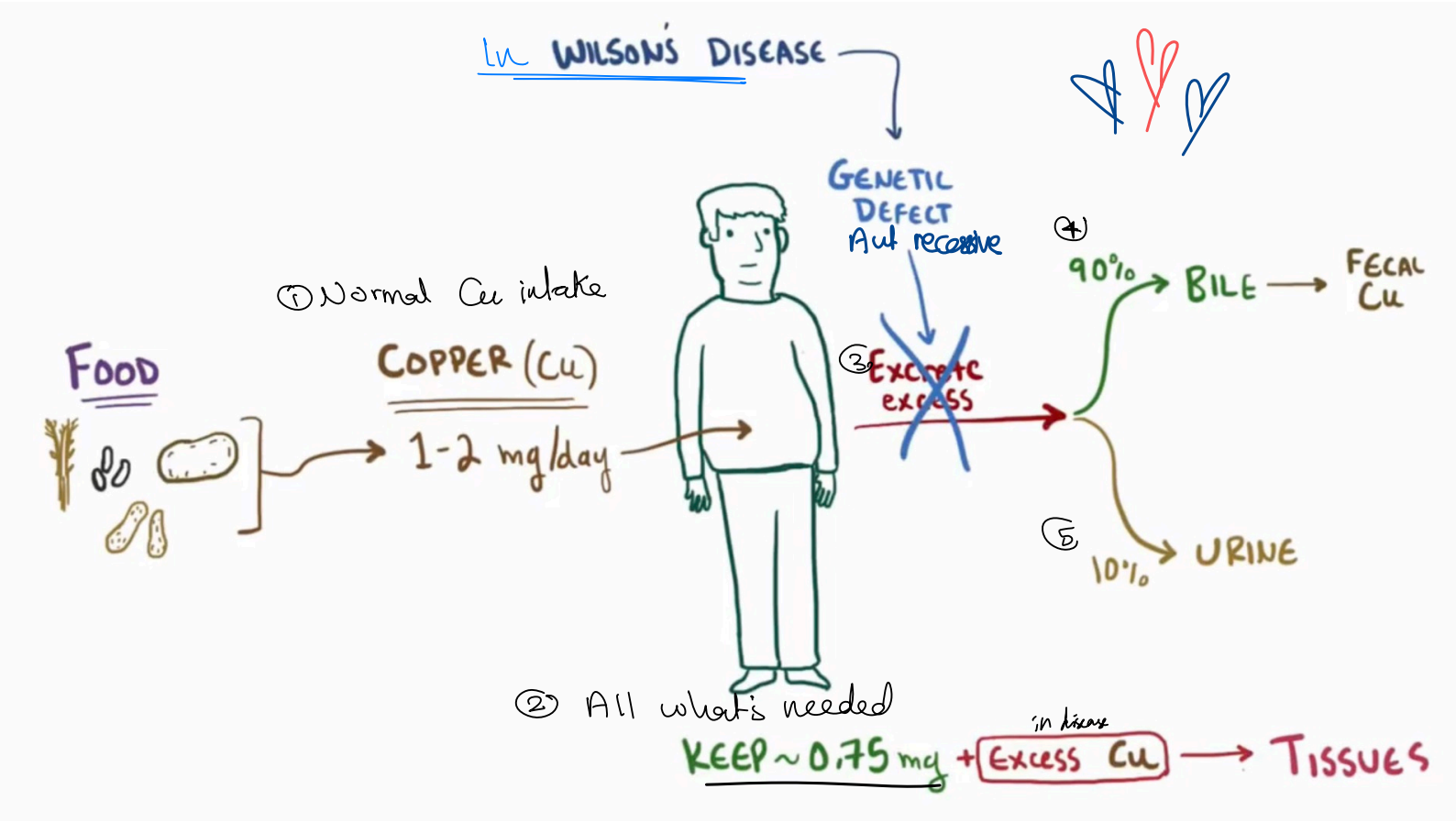
→ to diff lipofuscin from Fe

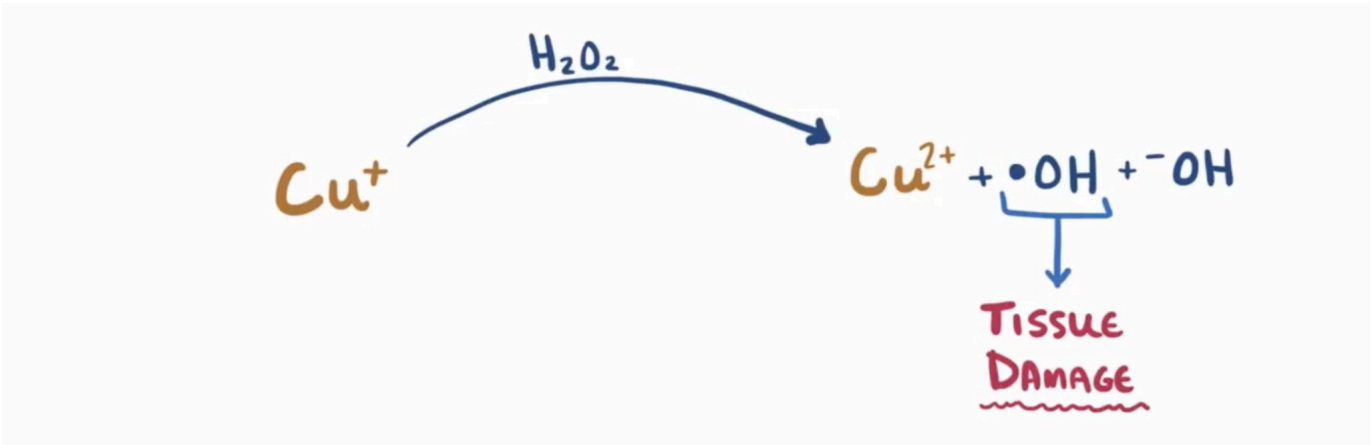
PRUSSIAN BLUE STAIN

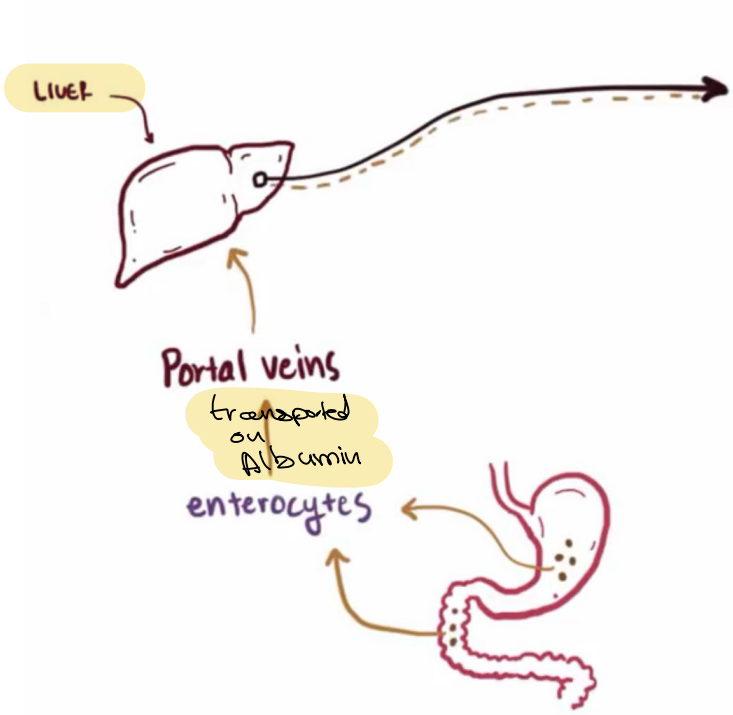
IRON shows as BLUE

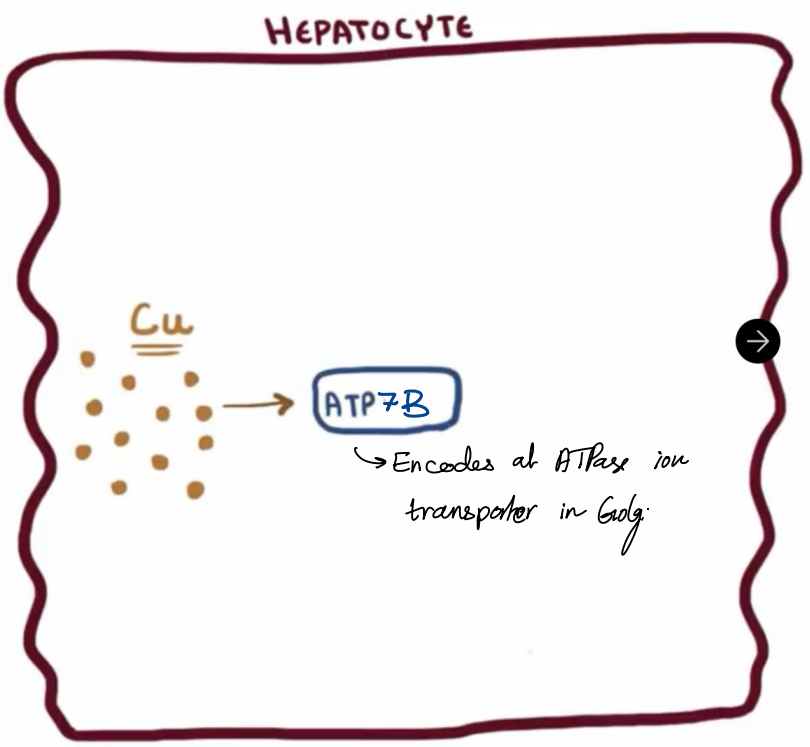


* Wilson's disease



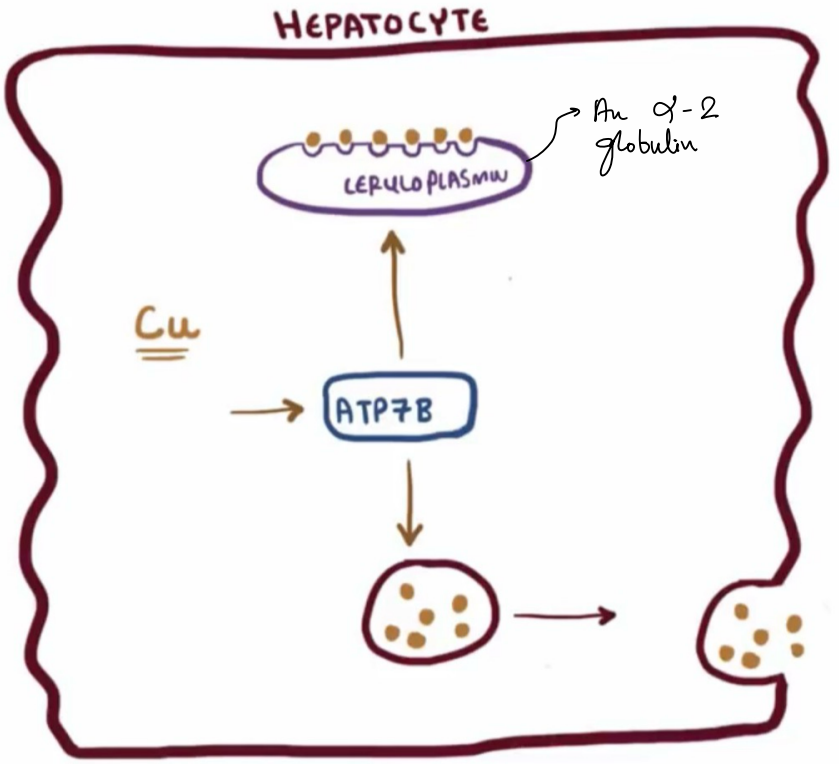




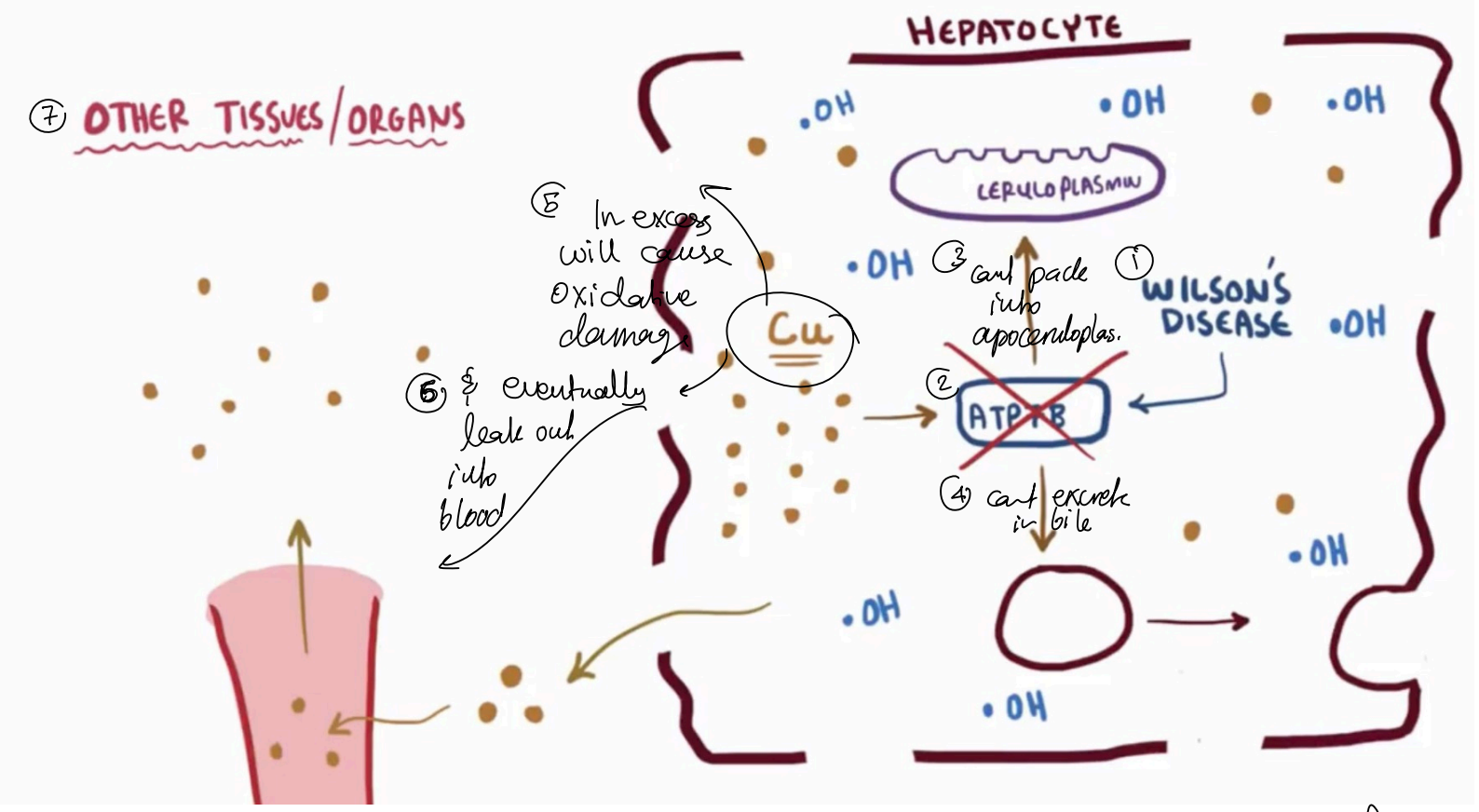


ATP7B on Chrom 13

1. BIND Cu to APOCERULOPLASMIN
   ↳ Cu-carrying protein
2. Package into vesicles for exocytosis to BILE



WILSON'S DISEASE



* Cu also binds SH groups of hepatocyte proteins & displaces other metals in hepatic metalloenzymes

WILSON'S DISEASE

The 2nd 1 common site of Cu accumulation

OTHER TISSUES/ORGANS

BRAIN

BASAL GANGLIA
- movement disorder (parkinson-like syndrome)
  - ↳ Putamen atrophy & cavitation
- Franck psychosis
- Behavioral changes

CEREBRAL CORTEX
- Dementia

DESCEMET'S MEMBRANE

EYE

ENDOTHELIAL LAYER

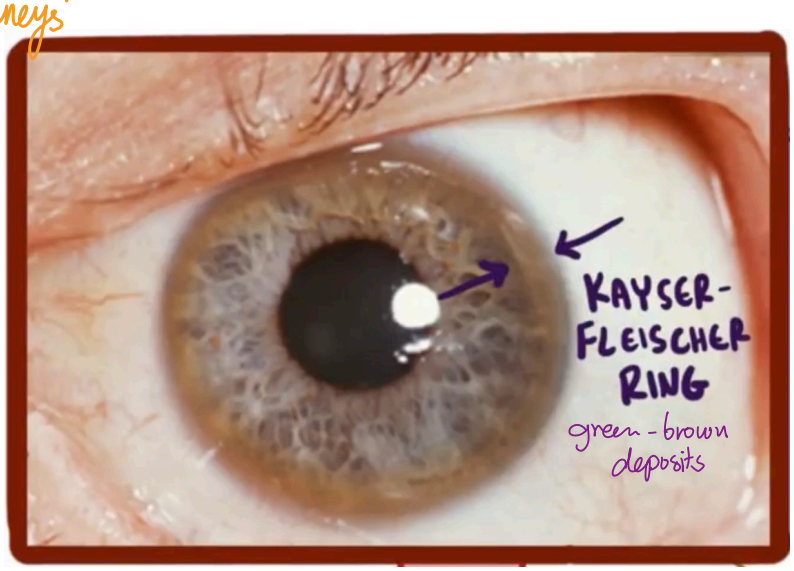
STROMA

Joints

Bone

PT glands

Kidneys



Helpful in diagnoses

— Hepatolenticular degen —

WILSON'S DISEASE

LIVER DAMAGE

- symptoms ~ late childhood (>6 y.o.)
- Acute on chronic hepatitis

BLOOD

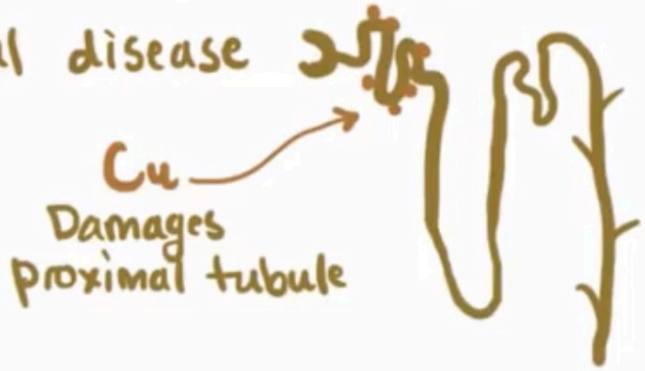
1. ↓ ceruloplasmin
2. ↑ Cu

URINE

1. ↑ Cu

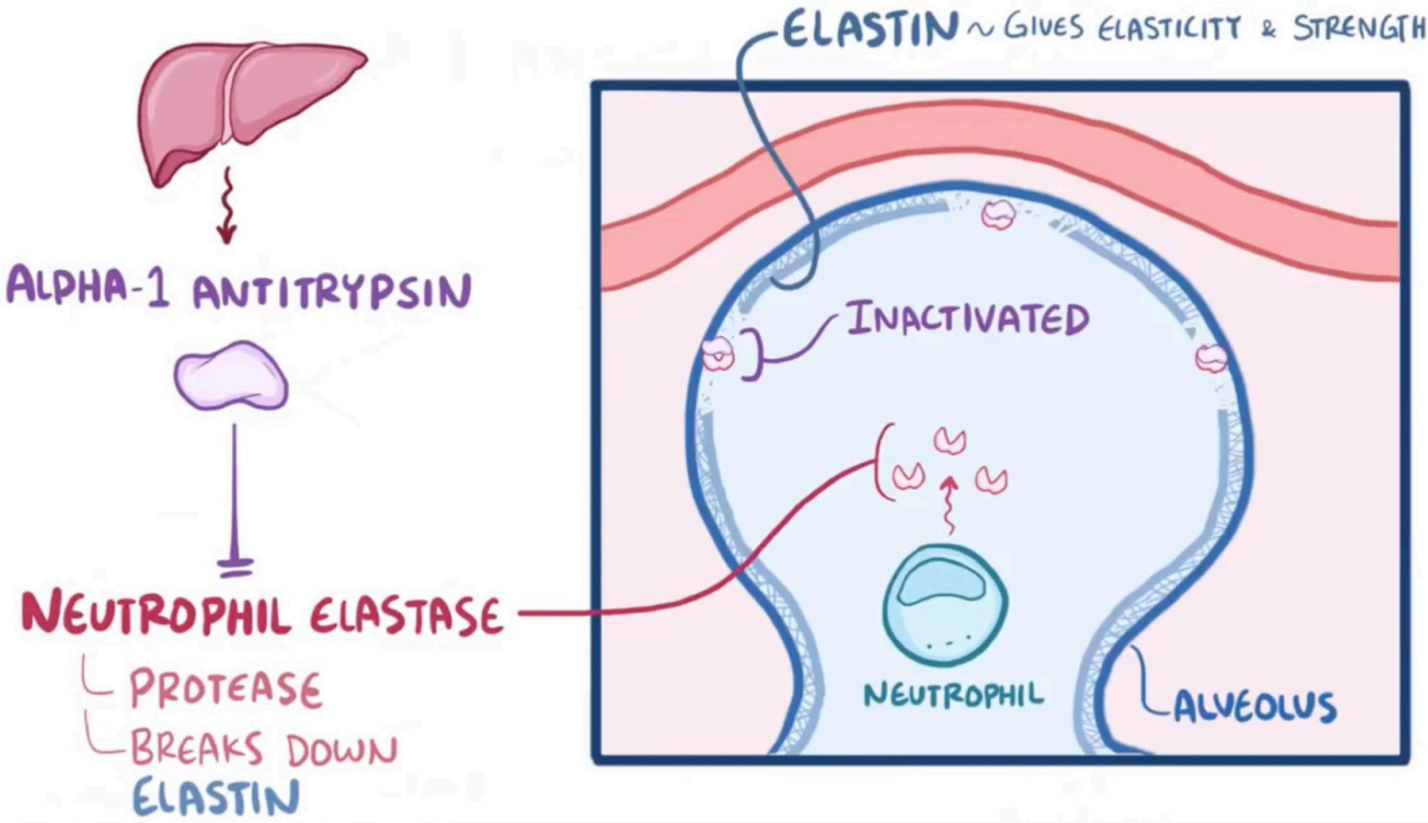
OTHER COMPLICATIONS

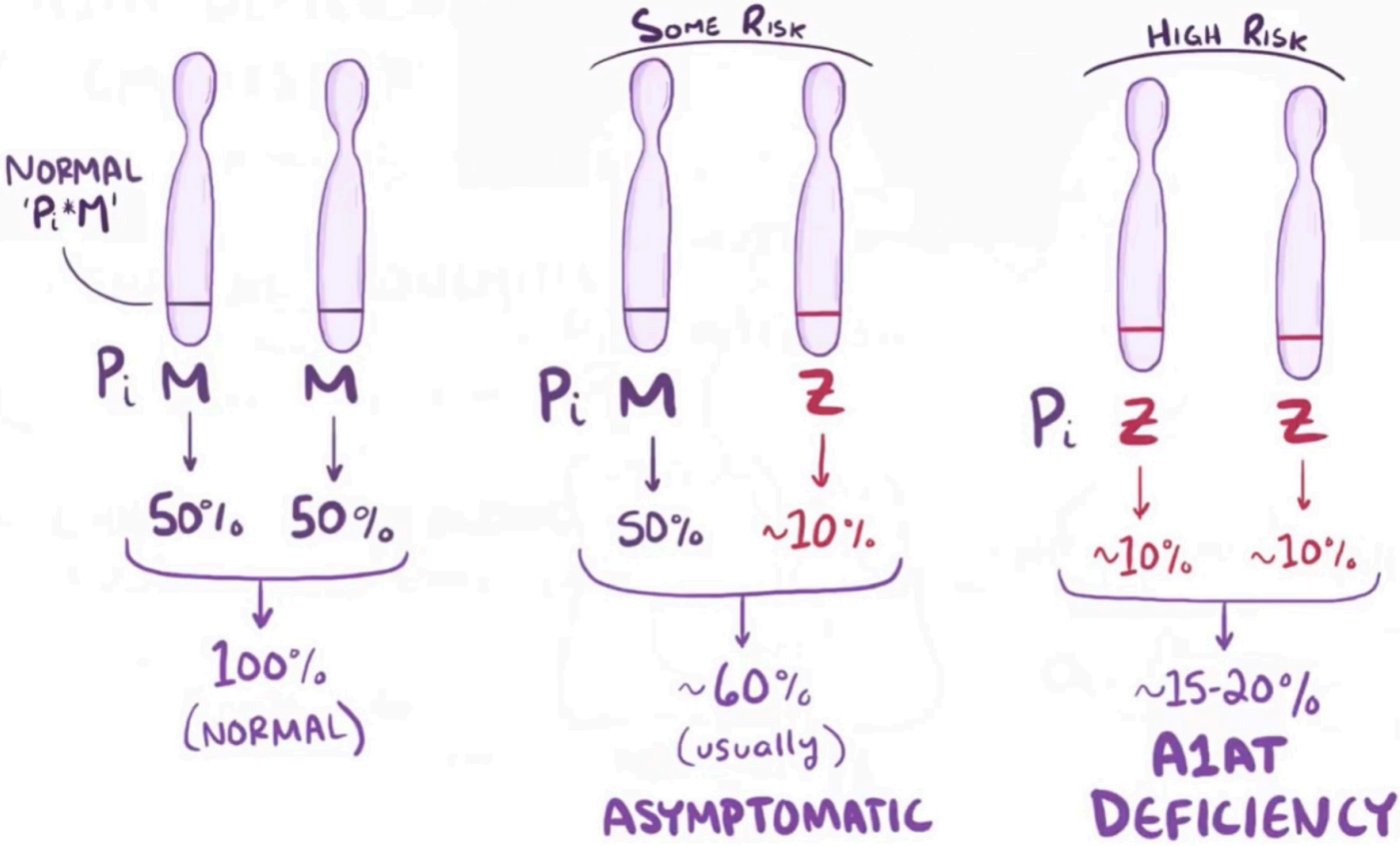
- Enlarged liver & spleen (HepatosplenoMEGALY)
- Renal disease



- Hemolytic anemia

* α-1 Antitrypsin deficiency





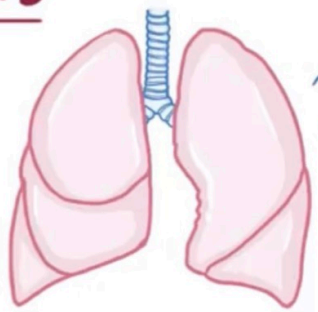
only 10% develop liver symptoms

it depends on ER protein deg. pathways

(damage due to autophagocytosis of mt)

CAN AVOID LIVER & LUNG DISEASE IF ENVIRONMENTAL EXPOSURES ARE MINIMAL

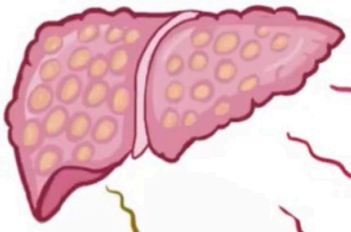
SYMPTOMS



- SHORTNESS of BREATH
- WHEEZING
- MUCUS PRODUCTION
- CHRONIC COUGH

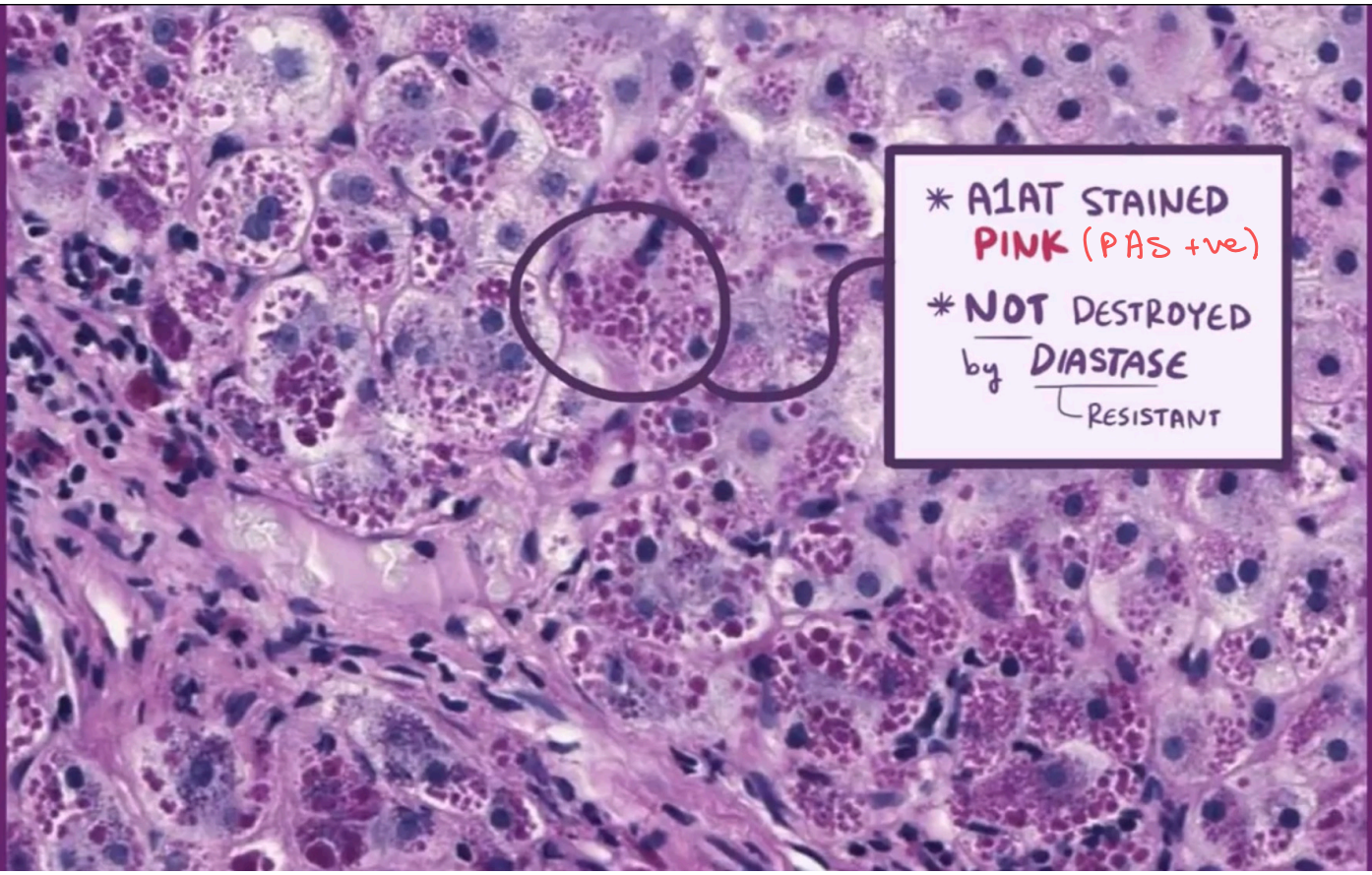
A MINORITY of INFANTS with PiZZ CAN DEVELOP LIVER FAILURE

CIRRHOSIS



- INABILITY to make COAGULATION FACTORS
- BUILDUP of TOXINS
  - HEPATIC ENCEPHALOPATHY
- PORTAL HYPERTENSION
  - ESOPHAGEAL VARICES
- HEPATOCELLUR CARCINOMA

JAUNDICE (EVEN IN NEWBORNS)



* Reye's Syndrome

REYE('S) SYNDROME → * extremely rare * children age 4-12

Encephalopathy + **LIVER DAMAGE**

BRAIN DYSFUNCTION

① mt damaged

Energy producers → MITOCHONDRIA

LIVER CELL (HEPATOCYTE)

LIVER

* ~~OXIDATIVE PHOSPHORYLATION~~ + ~~BETA OXIDATION~~ *

② Can't produce ATP

③ hepatocytes die

④ hepatitis & liver damage

= fat accumulates in liver → Microvesicular Steatosis

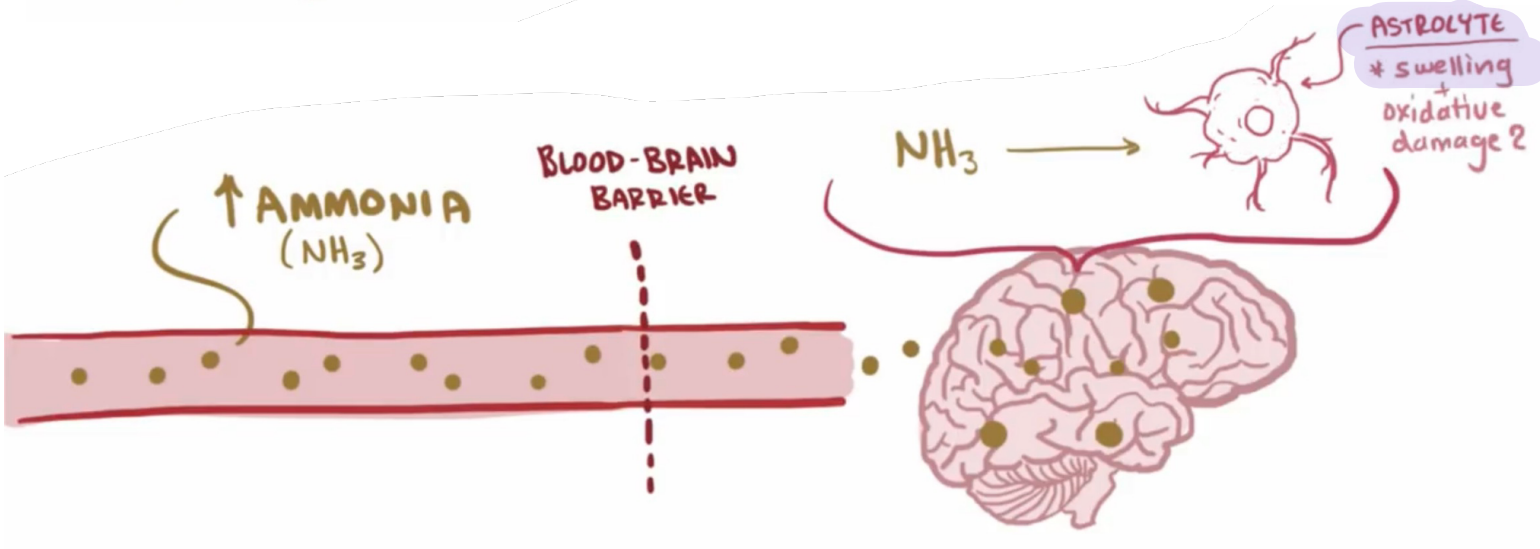
HOW?

SALICYLATES + **VIRUS**

* uncouple oxidative phosphorylation

1. Lethargy
2. Vomiting
3. 25% coma

← Brain edema



* 1° Sclerosing cholangitis

PRIMARY — not caused by something else

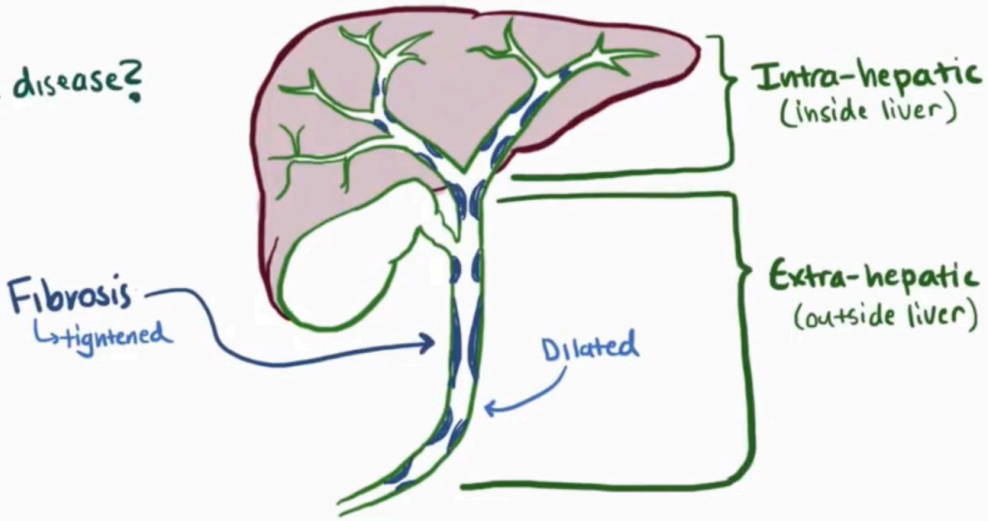
SCLEROSING — Hardening of tissue

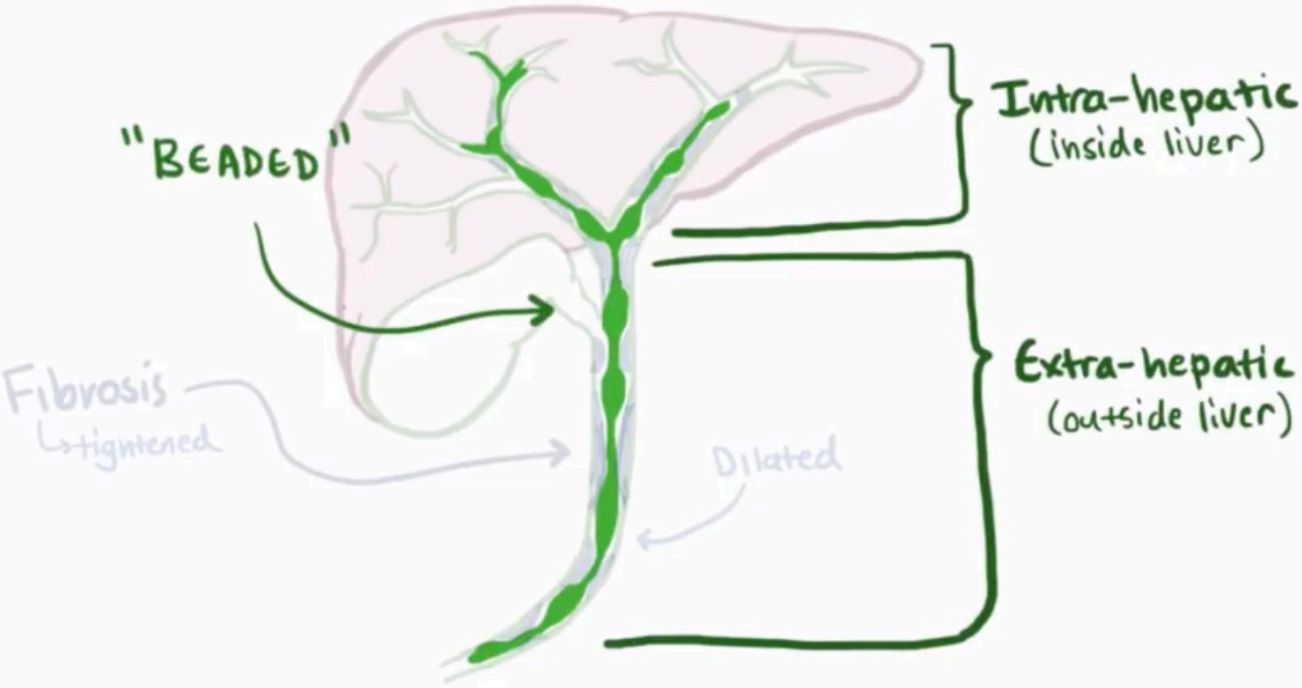
CHOLANGITIS — Bile ducts

(PSC) — Inflammation

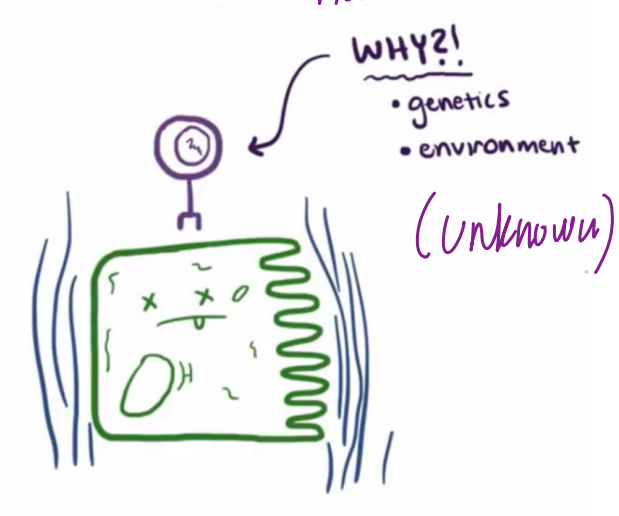
PSC ~ autoimmune disease?

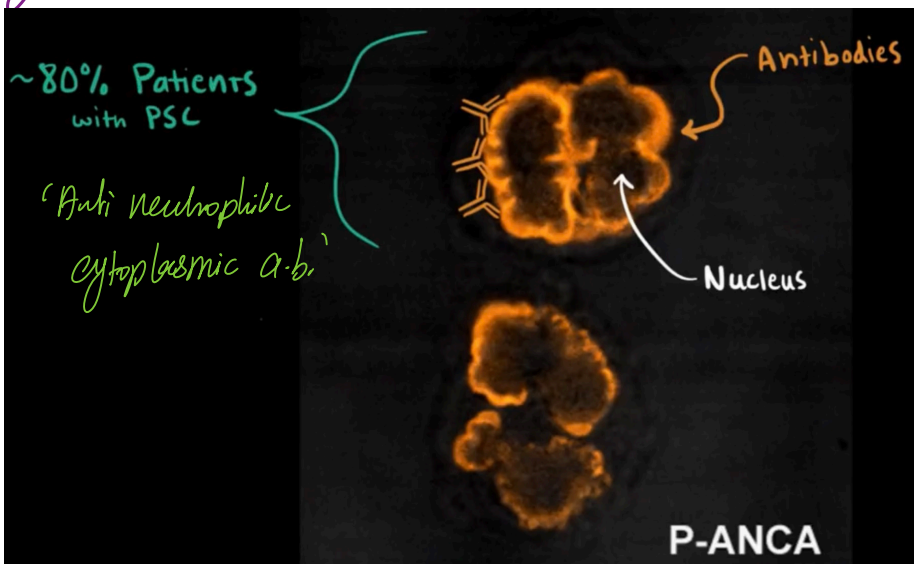
- **Ulcerative colitis** — Autoimmune disease
- **Crohn disease** — Immune system related





Autoimmune but why ?!



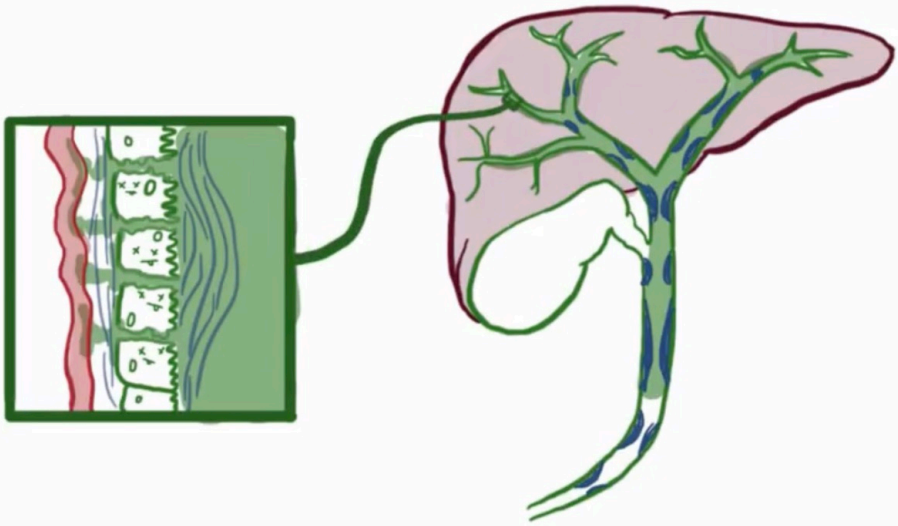


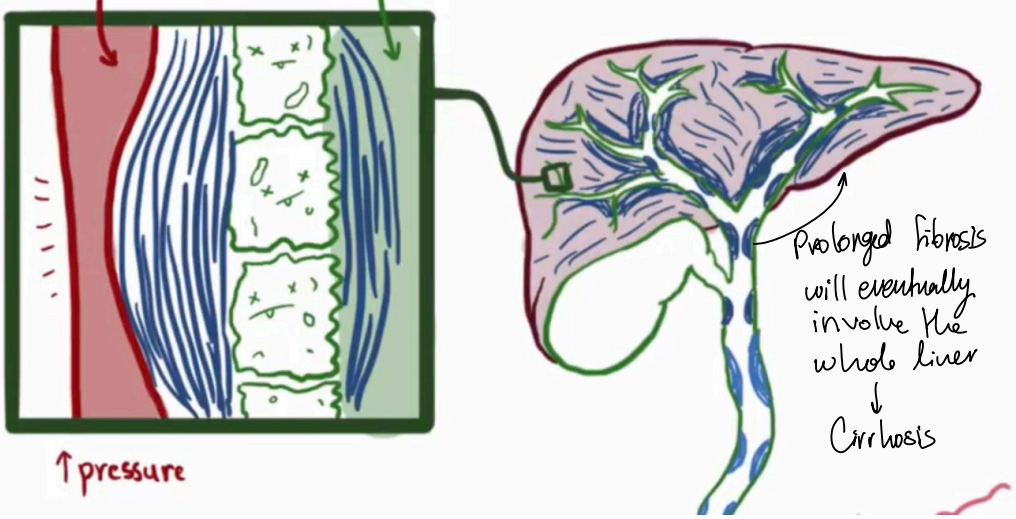
BILE in the BLOOD

Pruritus (itchiness)
Bile salts

↑ conjugated bilirubin

↑ ALP + GGT
↳ enzymes





LIVER COMPLICATIONS

* Portal hypertension
↓
Fluid in Spleen + liver
(hepatosplenomegaly)

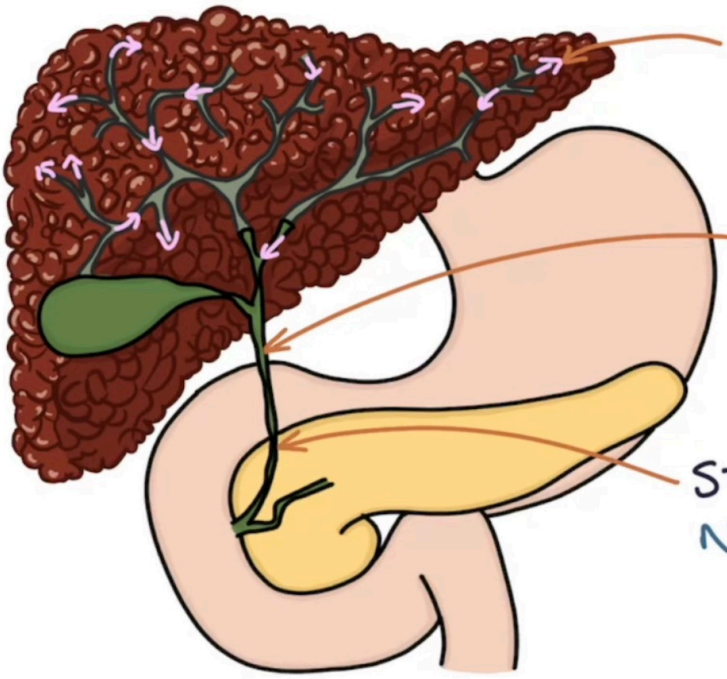
* CIRRHOSIS
↳ Stops functioning from damage

BILE DUCT COMPLICATIONS

* ↑ cholangiocarcinoma

* 1° sclerosing cholangitis

PRIMARY SCLEROSING CHOLANGITIS



BACKPRESSURE OF BILE → LIVER

HEPATITIS → FIBROSIS → CIRRHOSIS

BILE DUCTS

TAKE BILE LIVER → INTESTINE

OBSTRUCTION

STRICTURE
NARROWING

FIBROSIS
HARDENING

CAUSE UNCLEAR

PROBABLY COMBINATION
- GENETIC
- AUTOIMMUNE
- MICROBIOME
- ENVIRONMENTAL

WELL ESTABLISHED LINK → ULCERATIVE COLITIS

COMMON IN EXAMS!

RISK FACTORS
- MALE
- AGED 30-40
- ULCERATIVE COLITIS
- FAMILY HISTORY

PRESENTATION

JAUNDICE

CHRONIC RIGHT UPPER QUADRANT PAIN

PRURITIS (ITCHING)

FATIGUE

HEPATOMEGALY

CIRRHOSIS SIGNS

LIVER FUNCTION TESTS: "CHOLESTATIC PICTURE" → CHOLESTASIS

AUTOANTIBODIES: NOT SPECIFIC OR SENSITIVE TO PSC

NOT TYPICALLY HELPFUL

INDICATE AUTOIMMUNE ELEMENT

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA) 94%

ANTINUCLEAR ANTIBODIES (ANA) 77%.

ASSOCIATIONS AND COMPLICATIONS

ACUTE BACTERIAL CHOLANGITIS (INFECTION IN BILE DUCTS)

CHOLANGIOCARCINOMA (CANCER IN BILE DUCTS) 10-20%

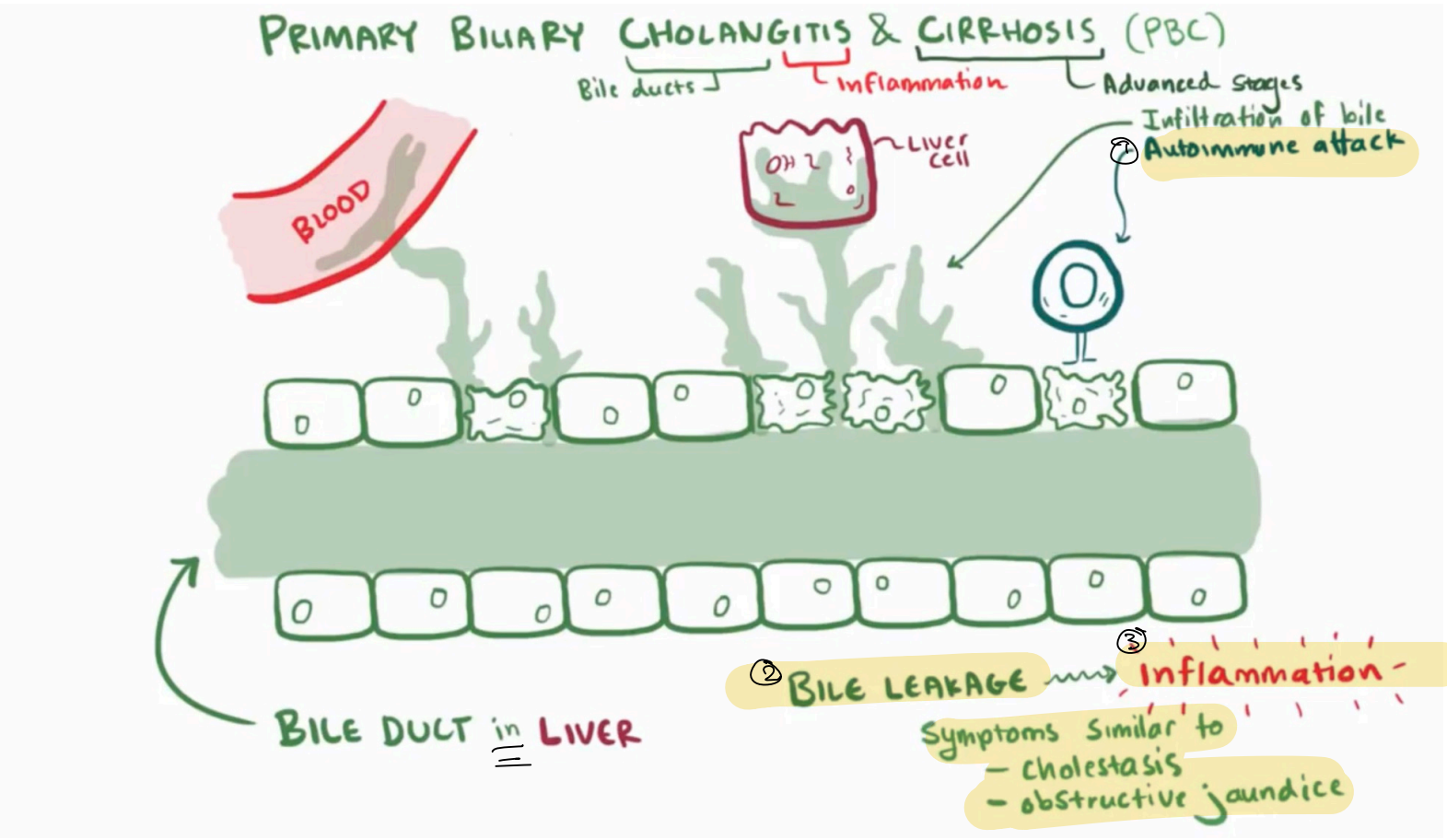
COLORECTAL CANCER

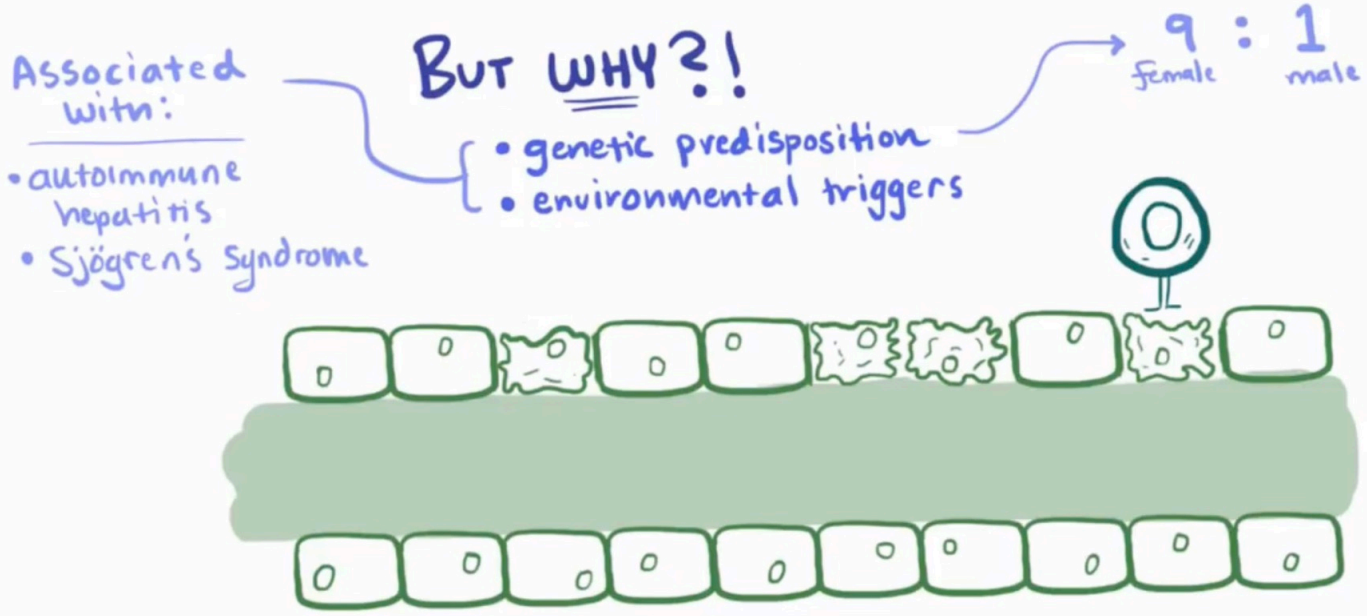
CIRRHOSIS AND LIVER FAILURE

BILIARY STRICTURES → CHOLESTASIS → DAMAGE LIVER

DEFICIENT FAT SOLUBLE VITAMINS (NO BILE → NO DIGESTION)

* Biliary cholangitis & cirrhosis

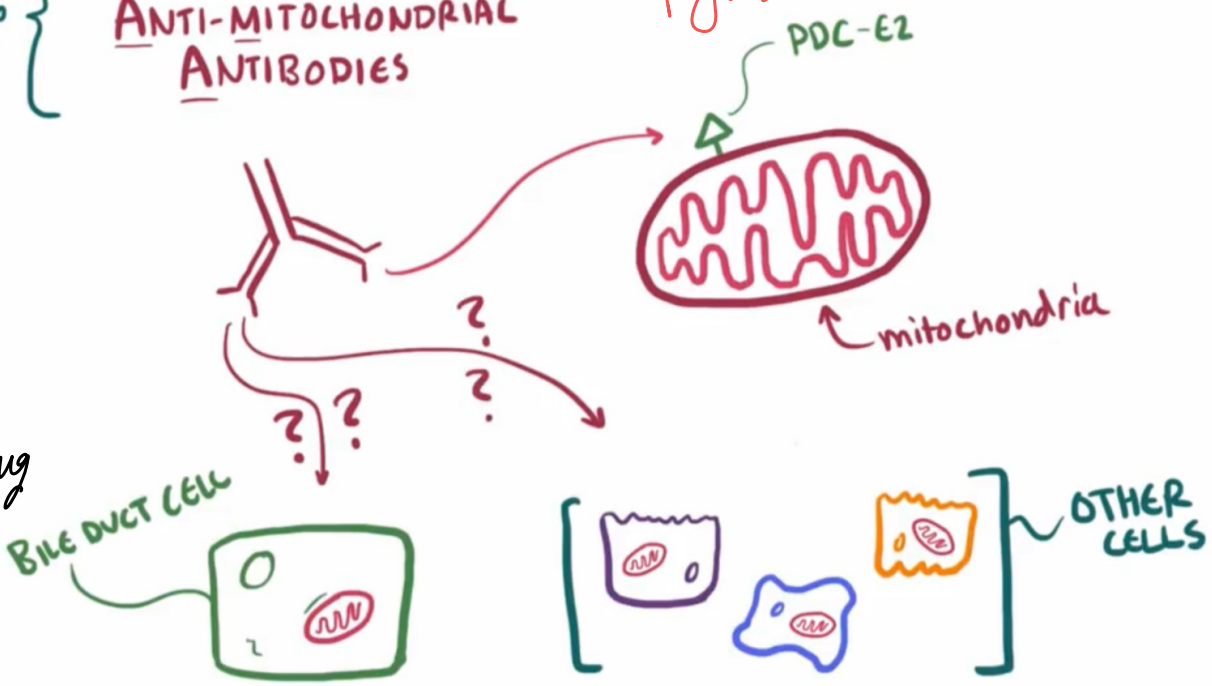




95% patients

AMAs
ANTI-MITOCHONDRIAL ANTIBODIES

& Anti mitochondrial pyruvate DH



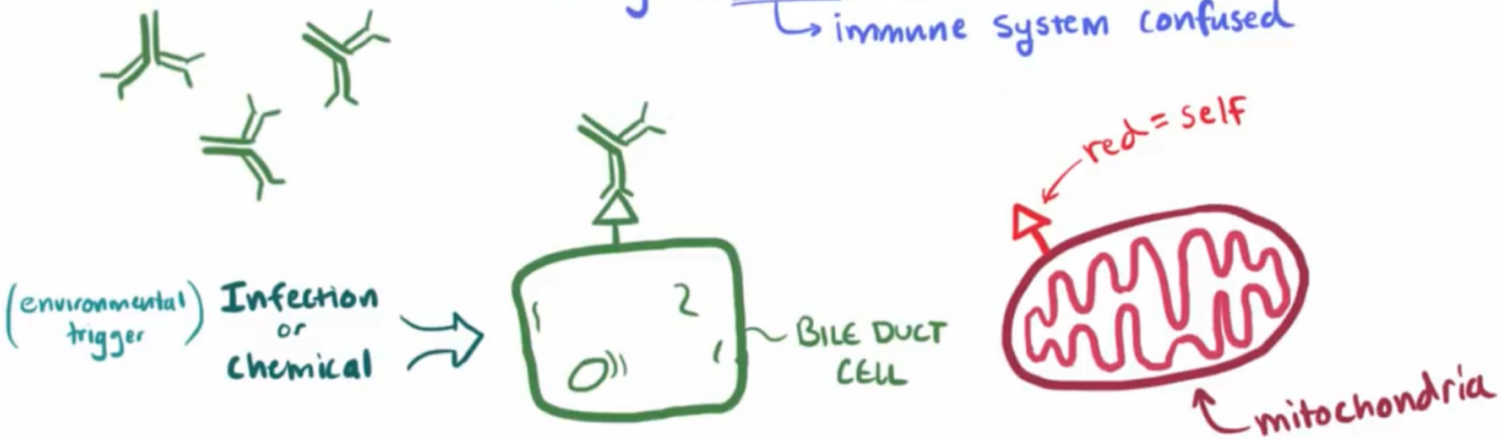
AMA

Only attacking bile duct cells mt

AMAs

MOLECULAR MIMICRY

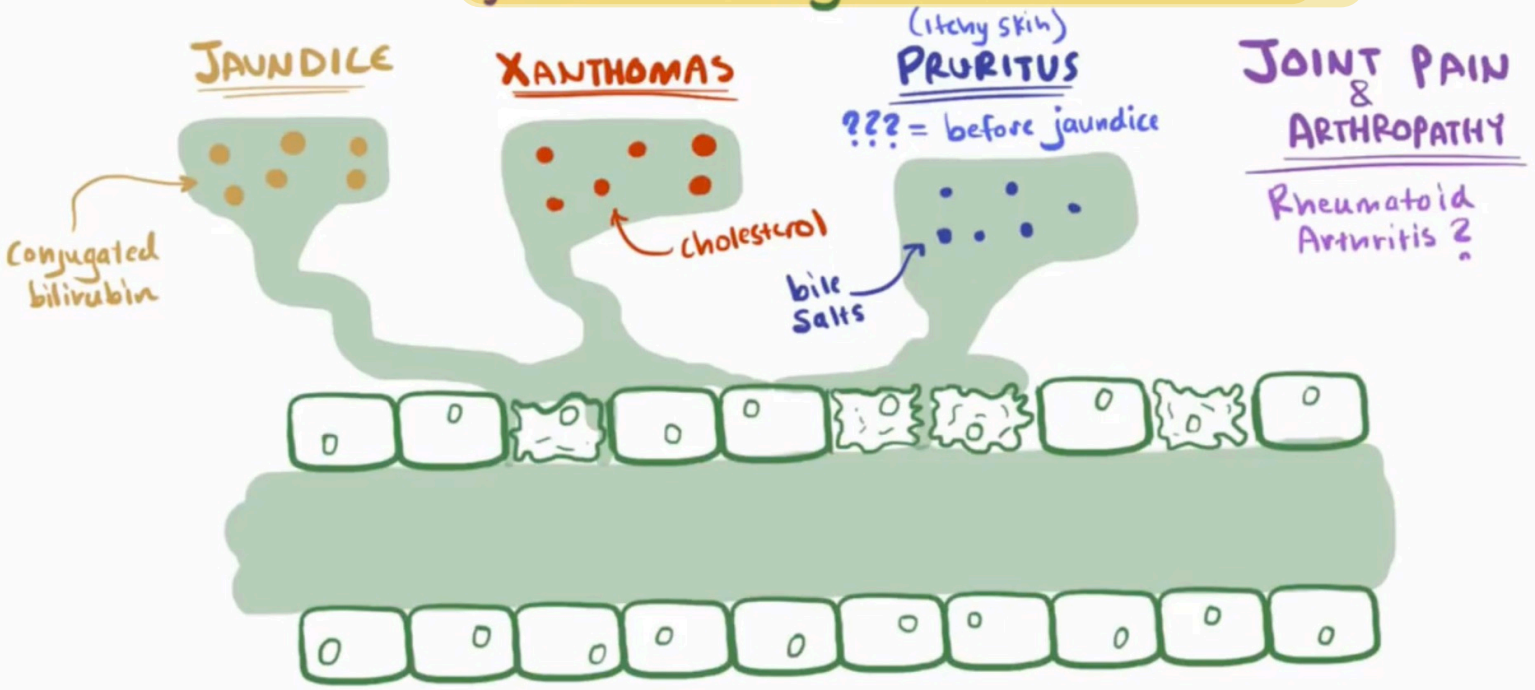
* antigen similar to another protein *
↳ immune system confused



mimics
(Same shape)

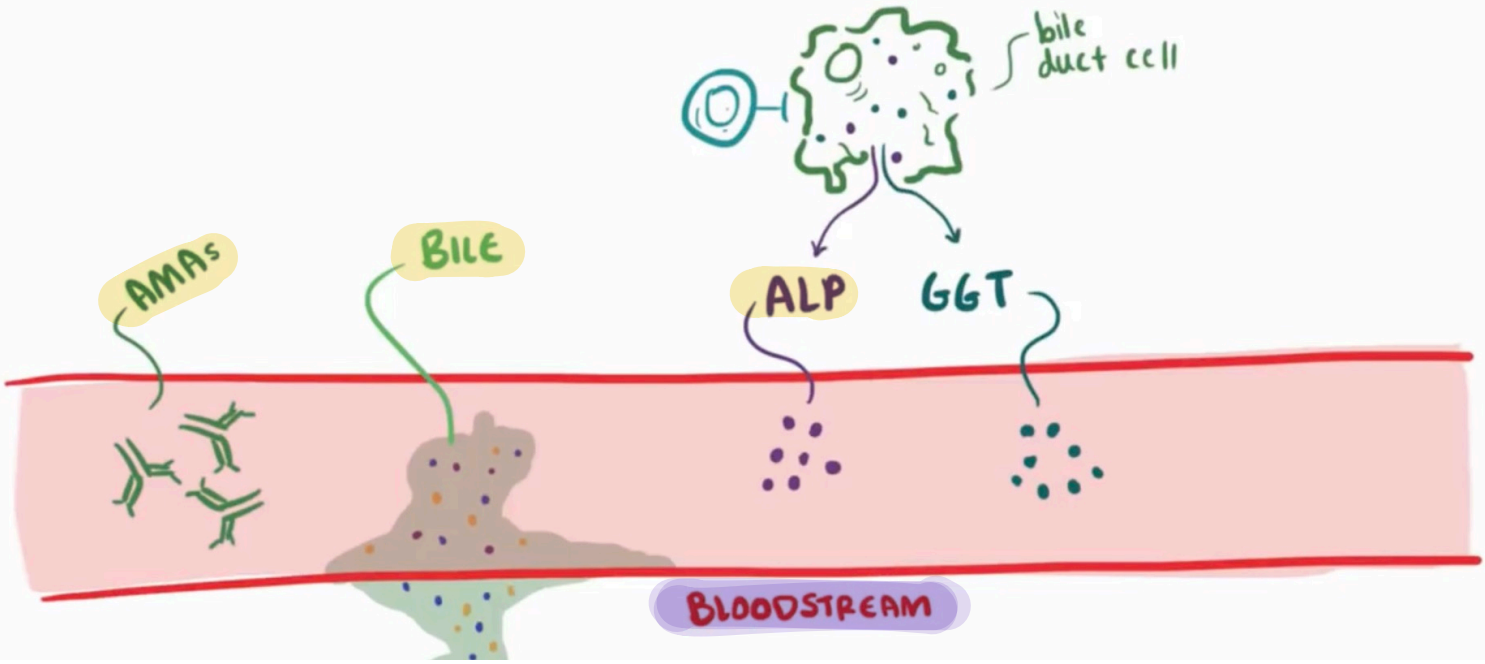
COMPLICATIONS

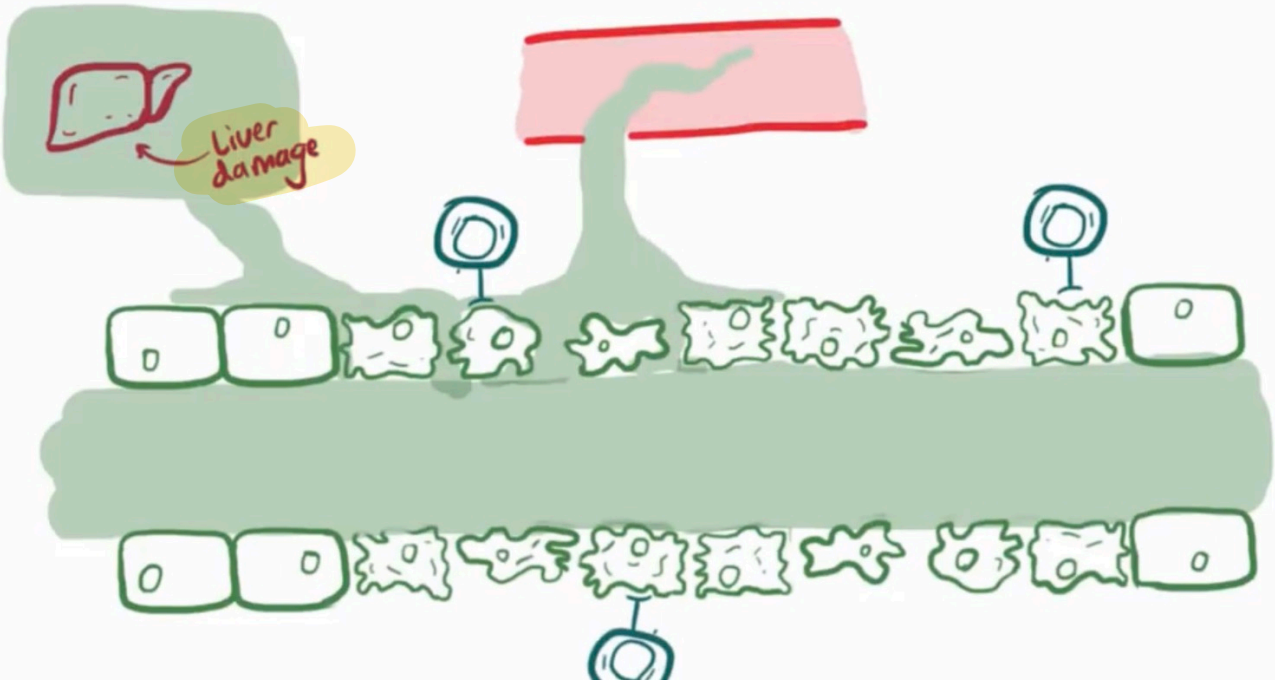
from bile leakage & Liver inflammation



COMPLICATIONS

from bile leakage & Liver inflammation





SECONDARY BILIARY CHOLANGITIS/CIRRHOSIS

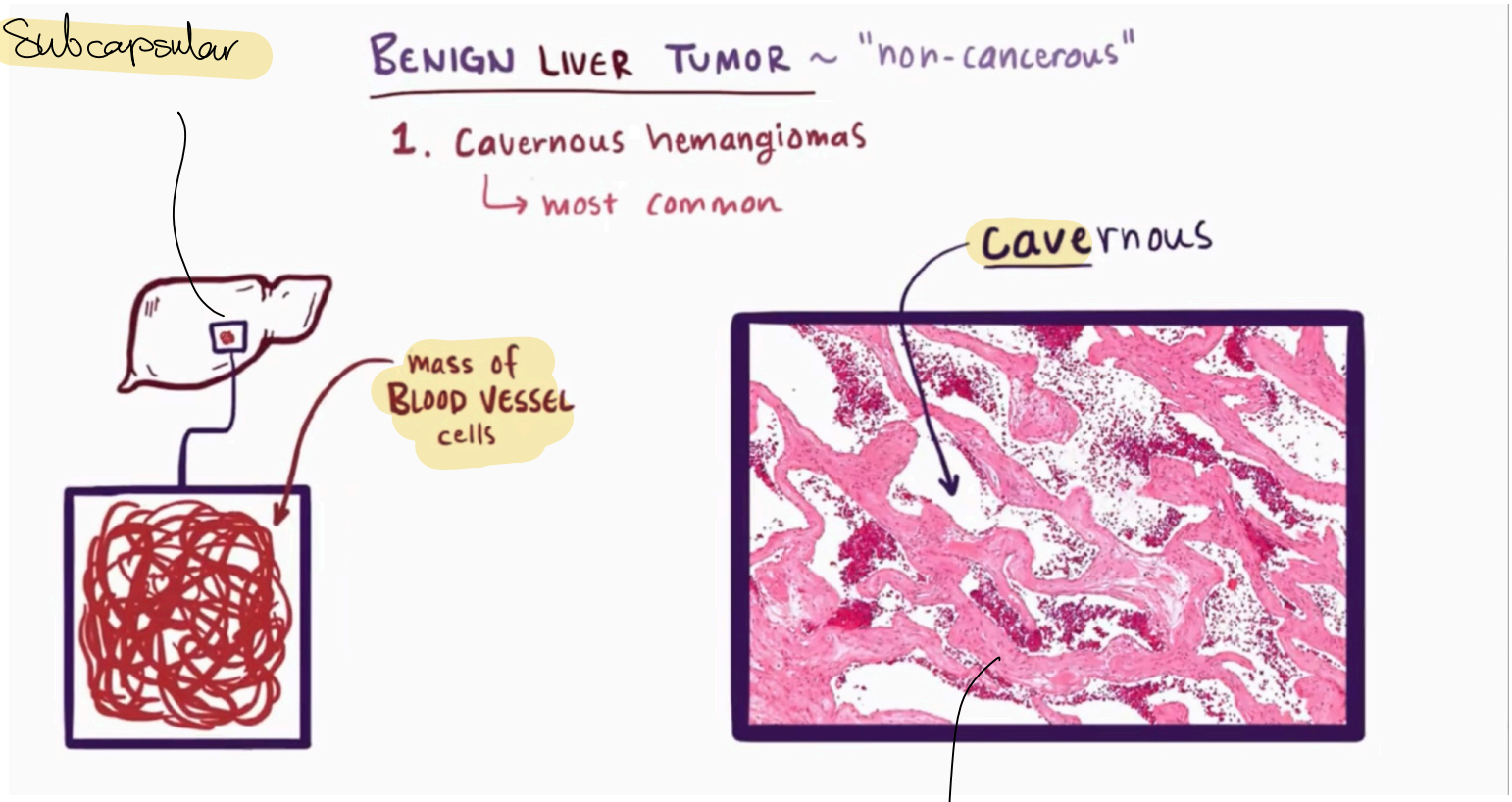
Similar complications

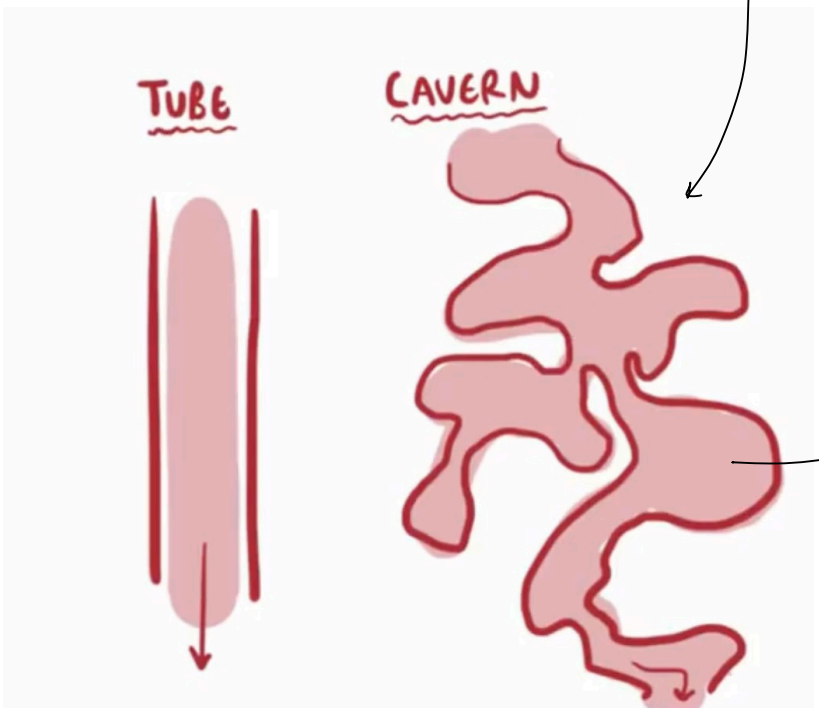
* NO AMAs *

Due to obstructing things like,

→ BENIGN LIVER TUMORS

1) Cavernous hemangioma

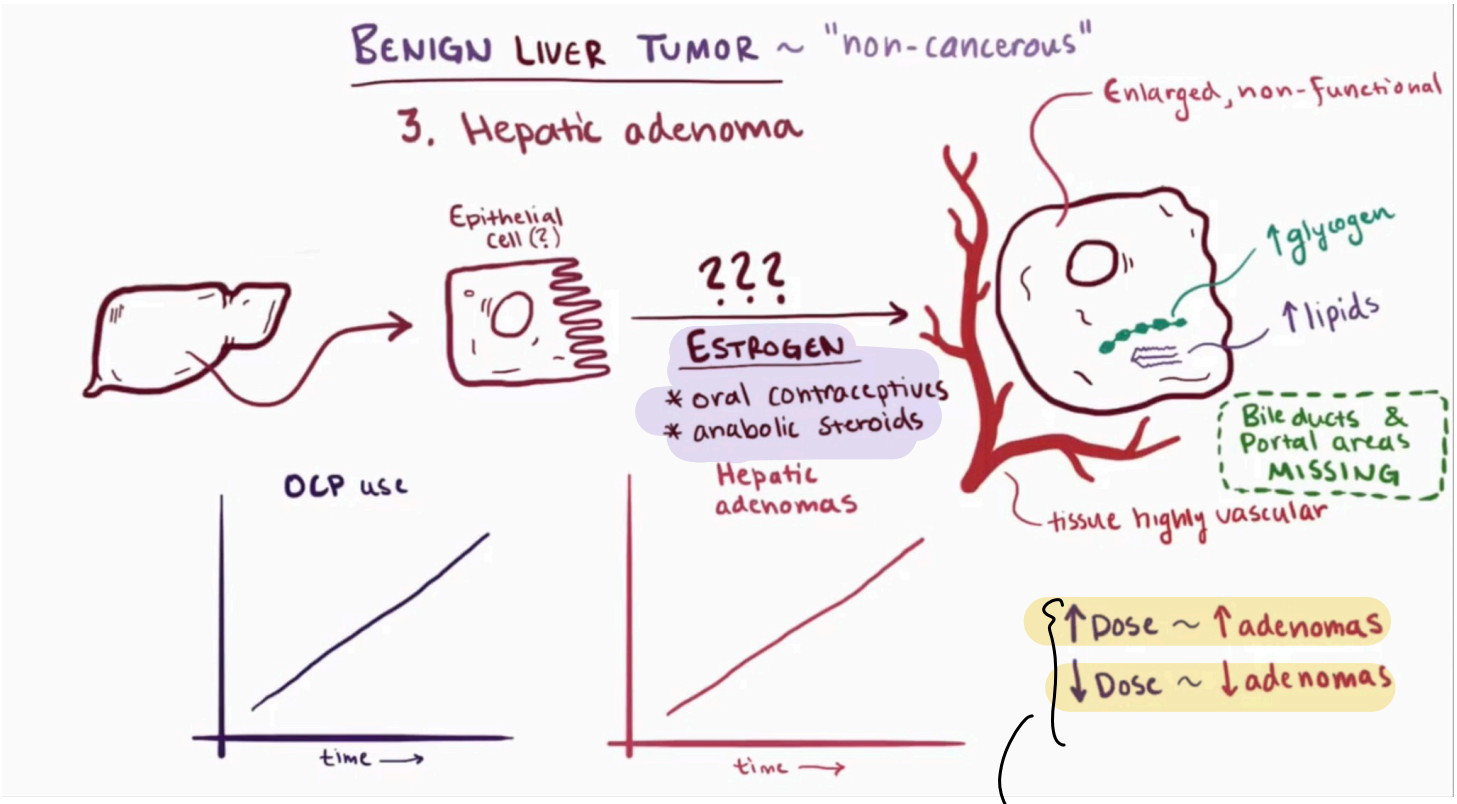




No complications

No risk of malignancy

2) Hepatic adenoma



Suggest relation between estrogen & adenomas

In young F
due to OC
could rupture during preg.
↳ Severe intraperitoneal hemorrhage
Rarely HCC present

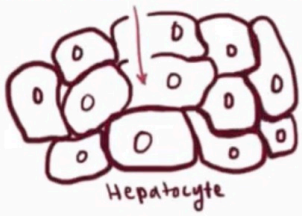
3) Focal Nodual hyperplasia

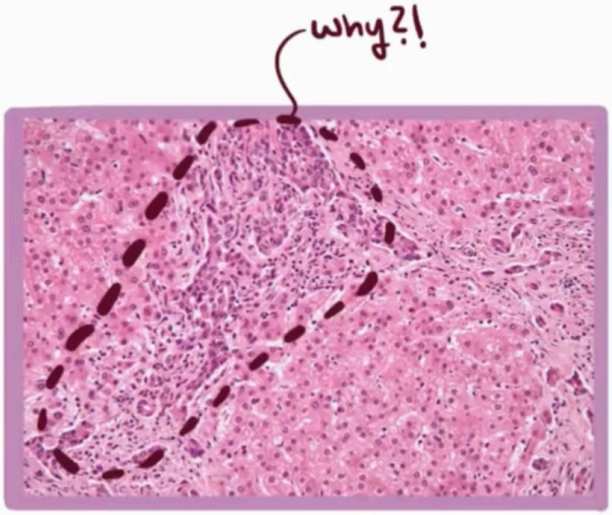
"Regenerative"

BENIGN LIVER TUMOR ~ "non-cancerous"

2. Focal nodular hyperplasia (FNH)

Localized Aggregates of Rapidly reproducing **LIVER CELLS** from VASCULAR INJURY?





BENIGN LIVER TUMOR ~ "non-cancerous"

2. Focal nodular hyperplasia (FNH)

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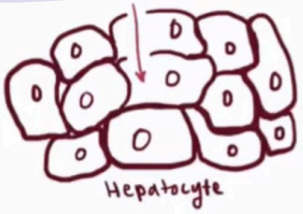
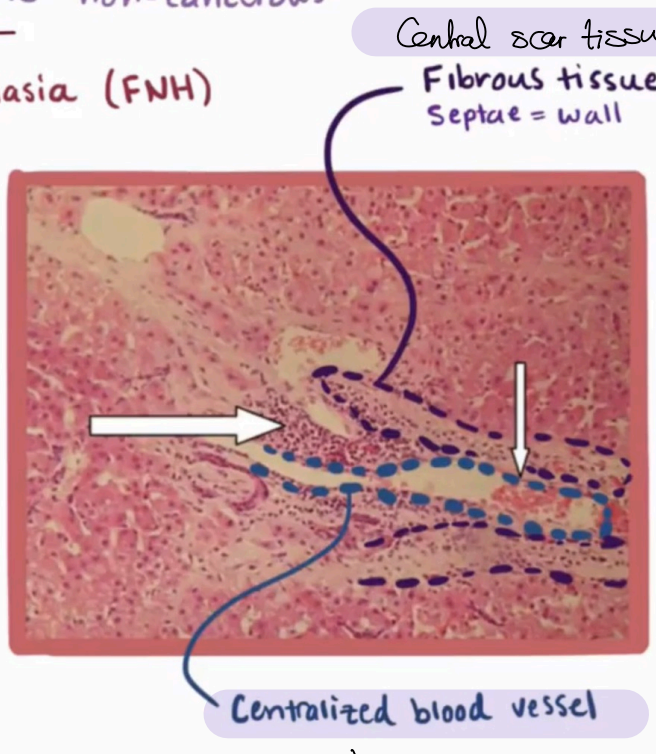
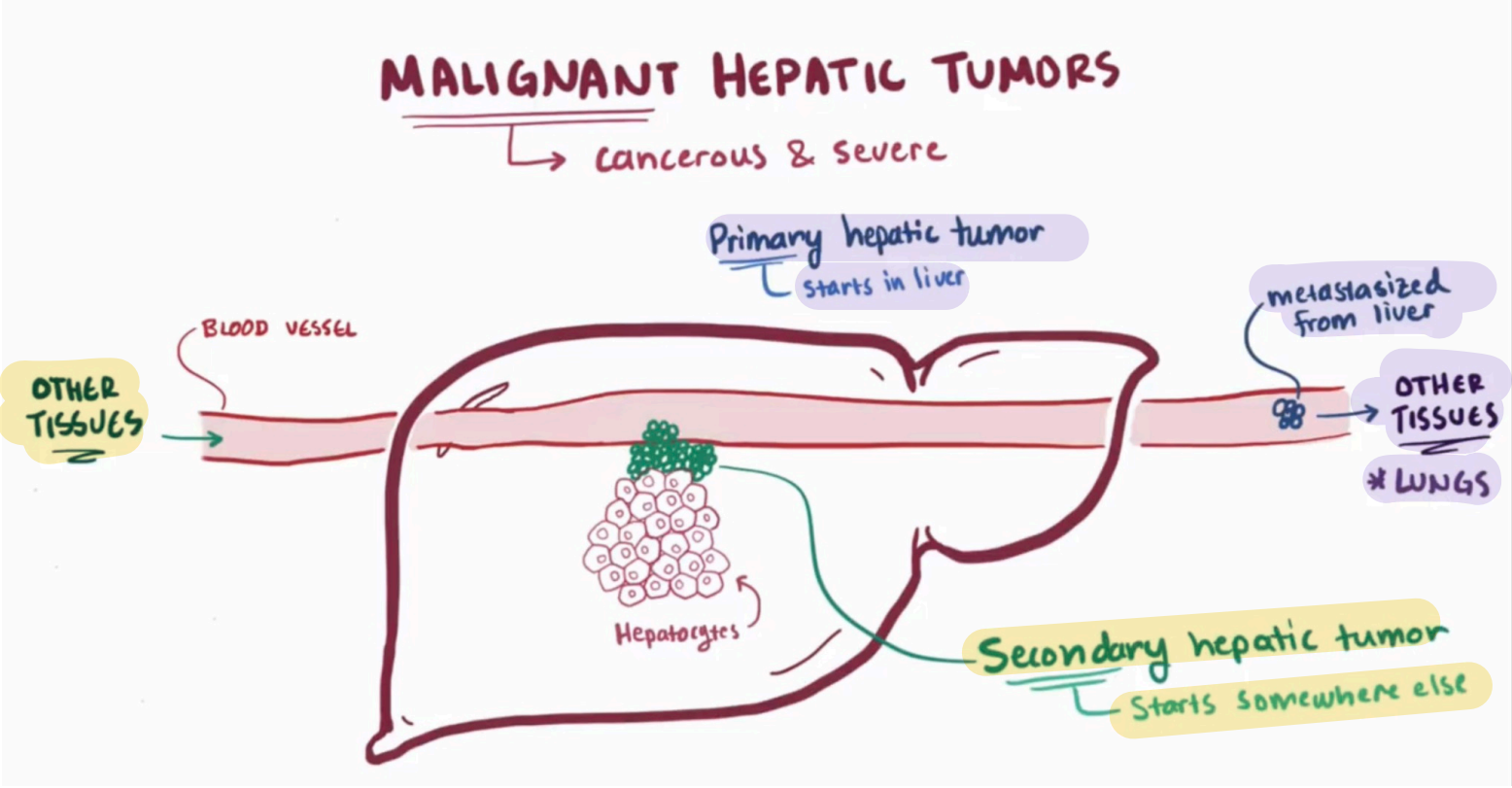


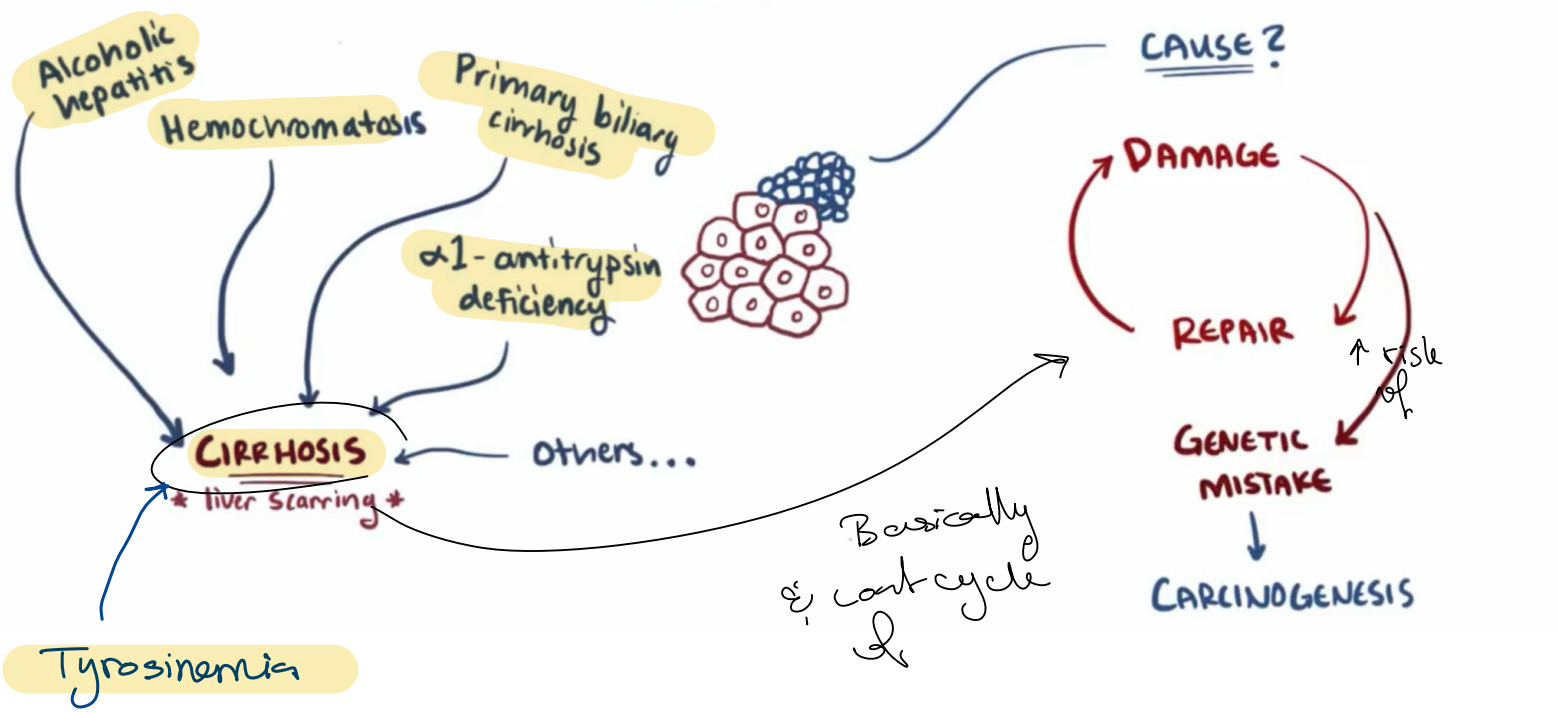


- In non-cirrhotic liver
- No risk of malignancy
- 20% have cavernous hemangioma
- Rep. age f

Always see in histology so seems that it's a vascular injury initiating it
- with radiating smaller B.V.

* Malignant liver tumors (1° : HCC , & 2°)





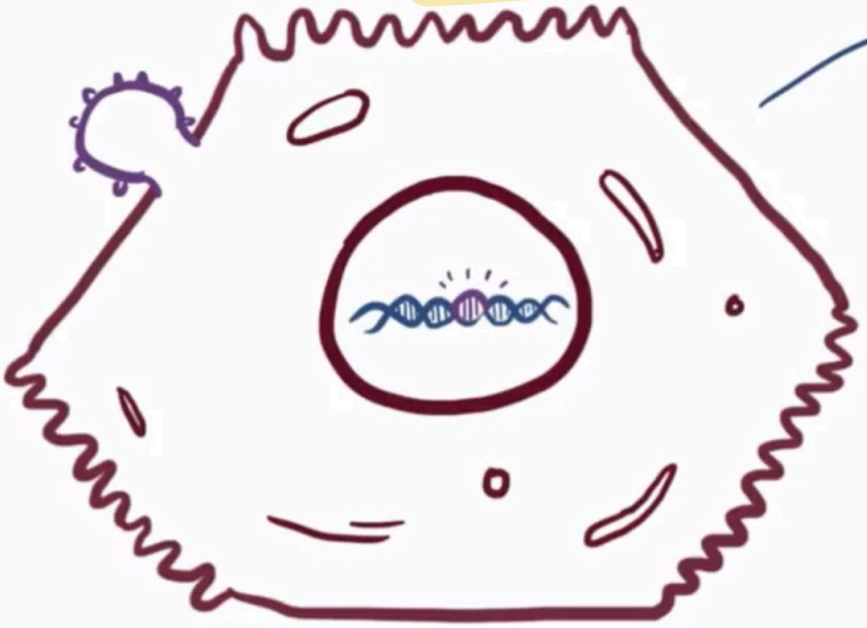
The ↑ common cause:

HEPATITIS B & C VIRUSES

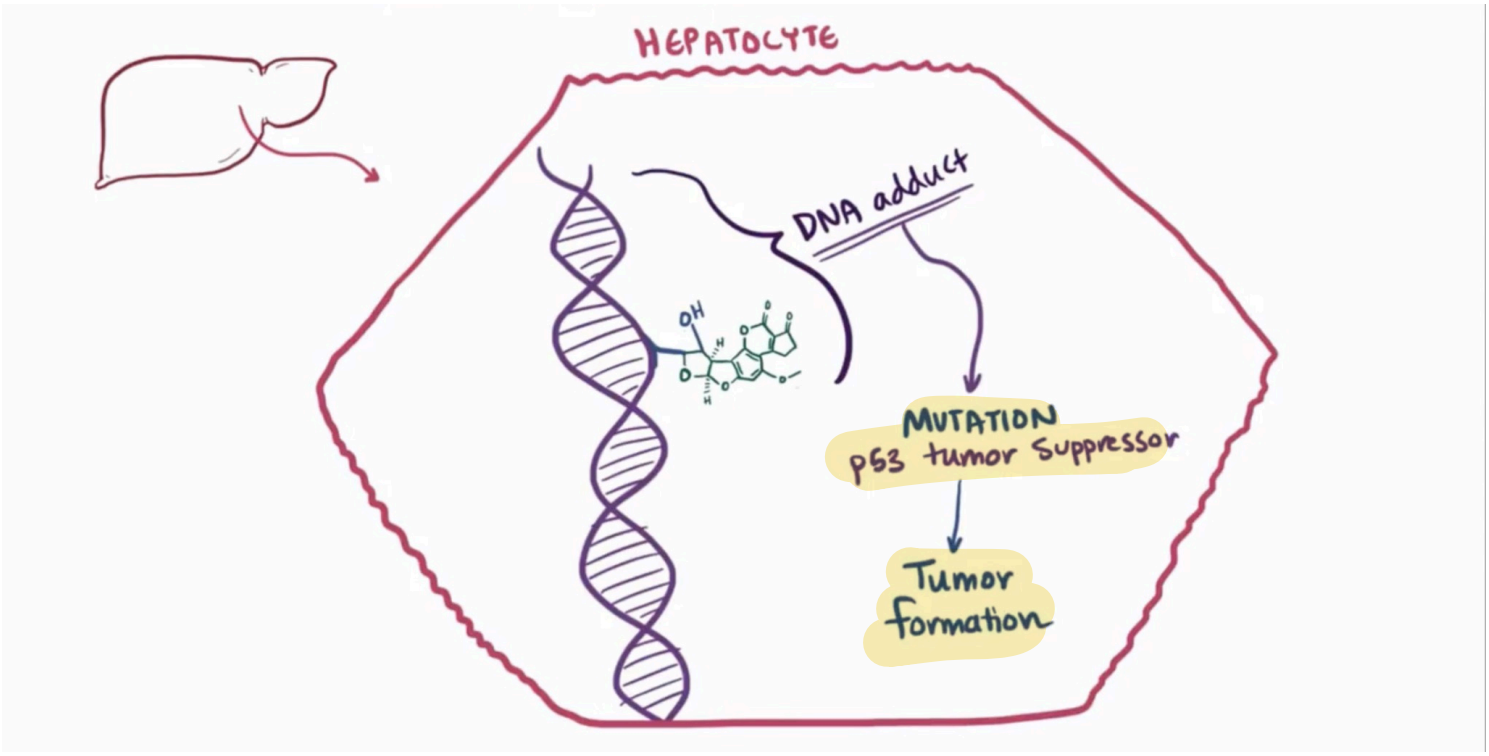
Chronic ~ long-lasting

Infection + immune attack → DAMAGE + REPAIR ⇒ CARCINOGENESIS

HEPATITIS B ~ integrates into hepatocyte DNA

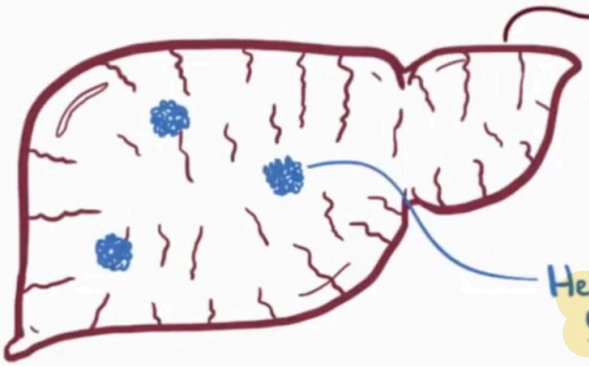


Also Aflatoxins produced by Aspergillus



PRIMARY CANCER
- * focal
- * multi-focal
- * spread diffusely

Secondary cancer
- * usually multi-focal



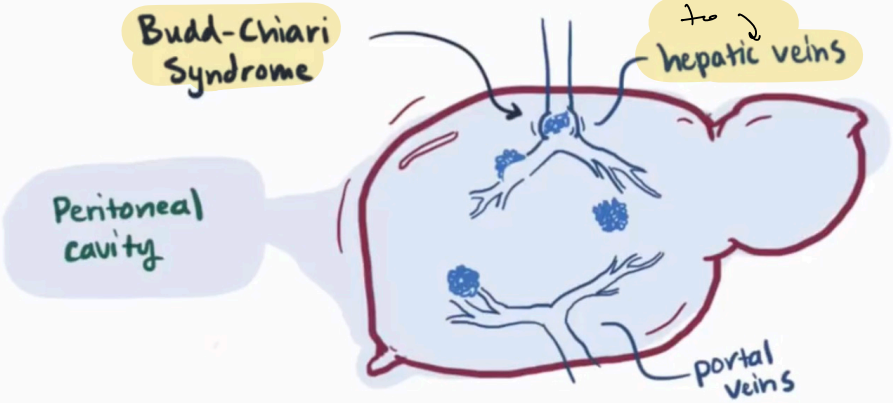
Cirrhosis
Symptoms mask carcinoma

Hepatocellular carcinoma
often no symptoms

This is called:

Budd-Chiari Syndrome

① Tumor can spread to hepatic veins

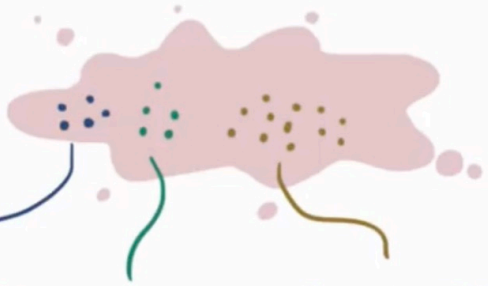


② VEINS BLOCKED
↓
↑ PRESSURE
↓
abdominal swelling
ASCITES
+
HEPATOMEGALY

Symptoms

* abdominal pain
* fever
* NONE (1/3 patients)

BLOOD



↑ Alpha fetoprotein (AFP)

* found in fetal plasma
* reduced in adulthood
* produced by tumor cells

↑ ALP + GGT

* enzymes in liver
* released with liver cell damage

↑ Other proteins

- erythropoietin
- insulin-like growth factor
- parathyroid hormone-related protein

Micronodular cirrhosis:

1) ALD (Macrovesicular steatosis)
2) Hemochromatosis

Mallory Hyaline bodies:

1) ALD
2) α 1 Antitrypsin deficiency

To visualize Cu^{2+} in liver biopsy:

Rhodanine stain
Orcein stain

	Hemochromatosis	Wilson's	α1 ATD
Chrom.	6	13	14
Mutation (all AR)	HFE: C282Y or H63D	ATP7B	Pi ZZ > Pi MZ
Age	M: > 50, F: 10-20 y. post menopause	> 6. y.o. (young)	Adolscence & neonates
Special	DM (80%), bronze skin (80%), synovitis, pseudogout/polyarthritis No inflammation (ROS)	Kayser-Fleischer rings, hemolytic anemia, kidney damage, Franck psychosis & behavioral changes	PAS +ve diastase R Mallory bodies HCC in 2-3% Neonatal jaundice

Autoimmune hepatitis — ASMA, ALKM, ASL / LP

1° Sclerosing cholangitis — ANCA, AMA