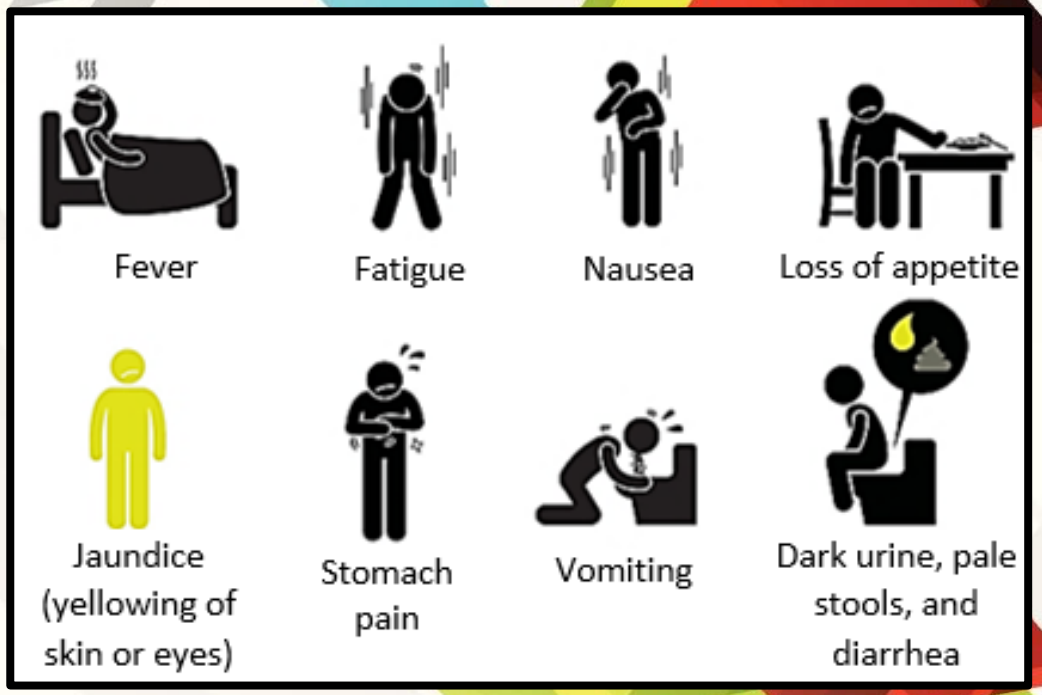
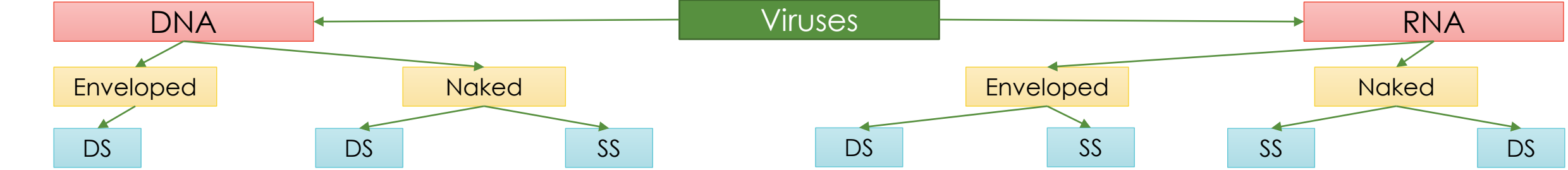
→ Viral hepatitis is a systemic disease primarily involving the inflammation of the liver, characterized by fever, gastrointestinal symptoms such as nausea and vomiting, hepatomegaly (sometimes) and jaundice.



Overview of hepatitis viral infections

Done by: Abdelhadi Okasha



Herpesviridae (Ic)

-Herpes simplex virus 1&2

-Varicella-zoster

-Epstein-Barr virus

-Cytomegalovirus

-HHV 6 (A & B)

-HHV 7

-KSHV

Adenoviridae (Ic)

Adenovirus

Parvoviridae (Ic)

Parvovirus B19

Bocaviruses

Hepadnaviridae (Ic)

-HBV

Unclassified (Ic)

-HDV

Falviviridae (Ic)

-HCV

Picornaviridae (Ic)

-HAV

Hepeviridae (Ic)

-HEV

Guidelines:
SS: single stranded
DS: Double stranded
Ic: Icosahedral capsid
He: Helical capsid
Co: Complex capsid

Viral cause	Disease
hepatitis A virus (HAV)	viral hepatitis type A disease (infectious hepatitis)
hepatitis B virus (HBV)	viral hepatitis B disease (serum hepatitis)
hepatitis C virus (HCV)	hepatitis C disease (common cause of posttransfusion hepatitis)
hepatitis D (HDV)	Note: HDV is a defective virus that cause Co-infection or super-infection associated with HBV only
hepatitis E virus (HEV)	enterically transmitted hepatitis

- Additional well characterized viruses that can cause sporadic hepatitis, such as yellow fever virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, rubella virus, and the enteroviruses

TABLE 35-1 Characteristics of Hepatitis Viruses

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Family	Picornaviridae	Hepadnaviridae	Flaviviridae	Unclassified	Hepeviridae
Genus	*Hepatovirus*	*Orthohepadnavirus*	*Hepacivirus*	*Deltavirus*	*Hepevirus*
Virion	27 nm, icosahedral	42 nm, spherical	60 nm, spherical	35 nm, spherical	30–32 nm, icosahedral
Envelope	No	Yes (HBsAg)	Yes	Yes (HBsAg)	No
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Genome size (kb)	7.5	3.2	9.4	1.7	7.2
Stability	Heat and acid stable	Acid sensitive	Ether sensitive, acid sensitive	Acid sensitive	Heat stable
Transmission	Fecal–oral	Parenteral	Parenteral	Parenteral	Fecal–oral
Prevalence	High	High	Moderate	Low, regional	Regional
Fulminant disease	Rare	Rare	Rare	Frequent	In pregnancy
Chronic disease	Never	Often	Often	Often	Never
Oncogenic	No	Yes	Yes	Unknown	No

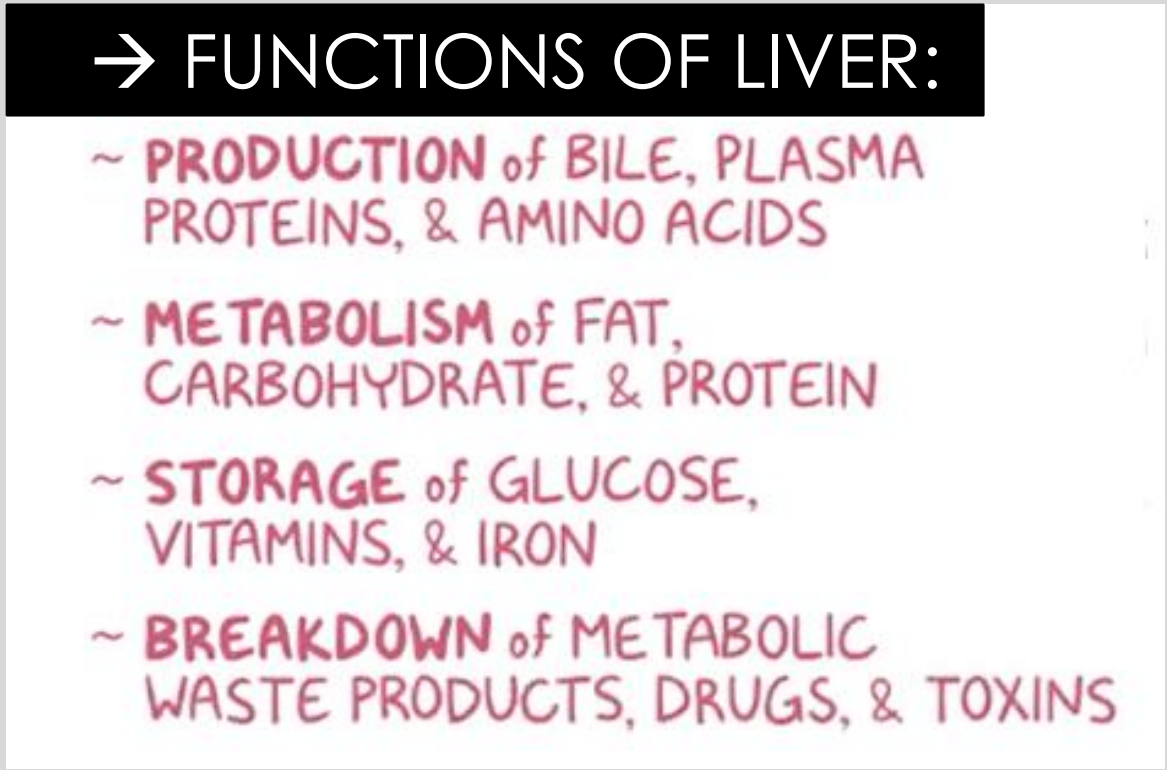
ds, double stranded; HBsAg, hepatitis B surface antigen; ss, single stranded.

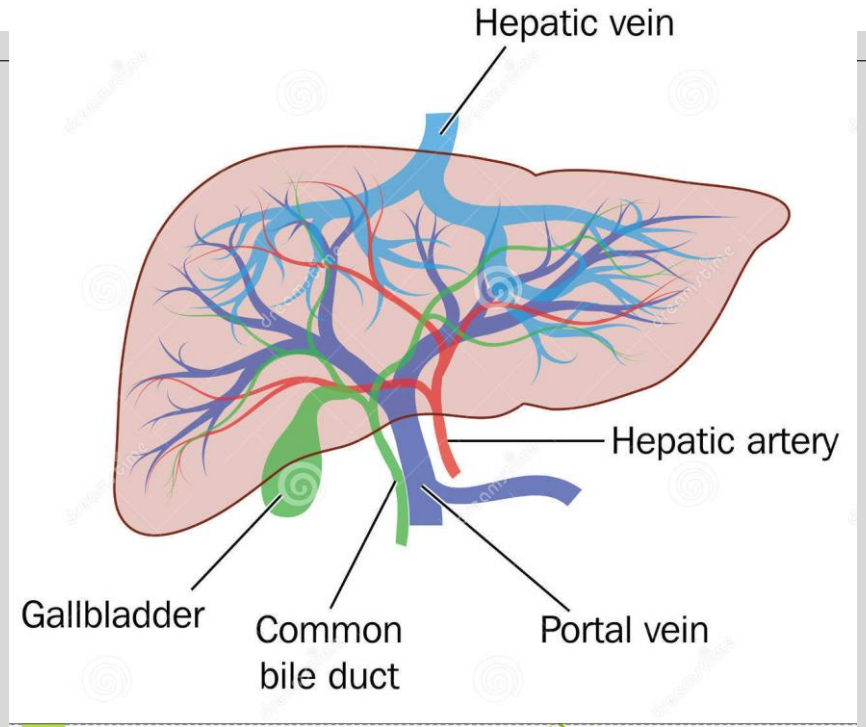
Topics discussed in this lecture

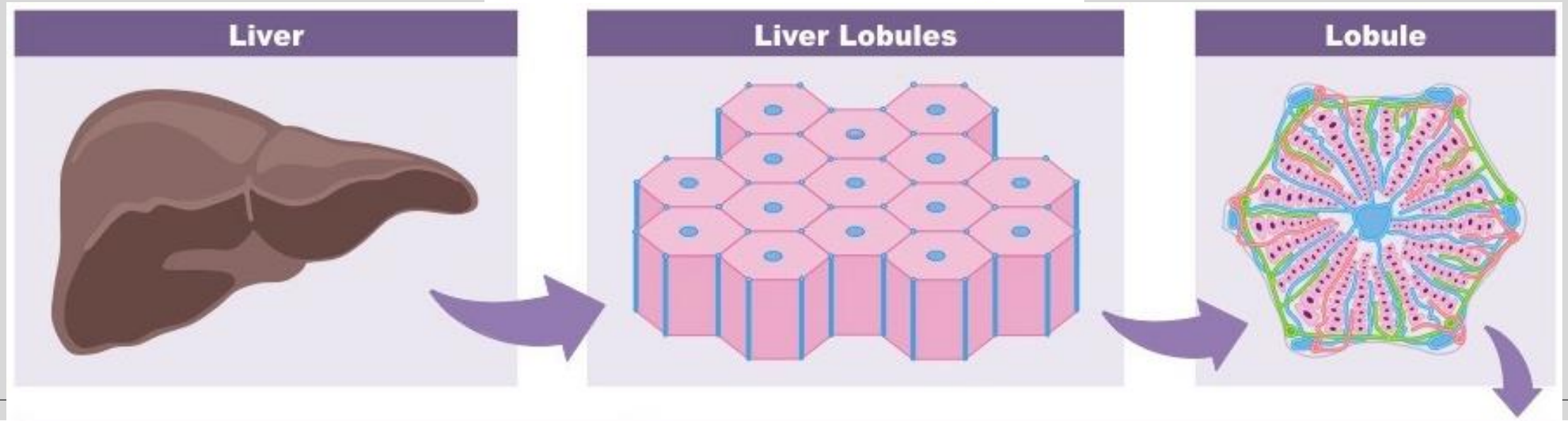
- 0- Liver histology, anatomy & physiology (Not included in exam but important for understanding)
- 1- Pathogenesis & clinical manifestations (Just take a general idea & all info's here will be repeated in the next concept)
- 2- Quick view for the 5 viral hepatitis agents (sooooo important)

0- Liver histology, anatomy & physiology

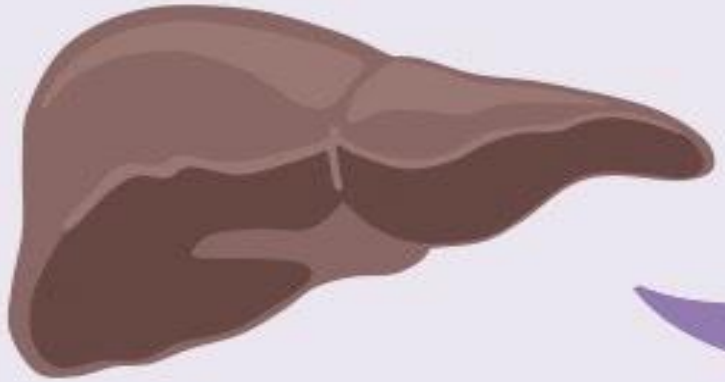
- Remember: Any organ in the body contain two types of tissues:
  1) Parenchymal tissues (Achieve the main function of the organ)
  2) Stromal tissues (Supportive tissues)



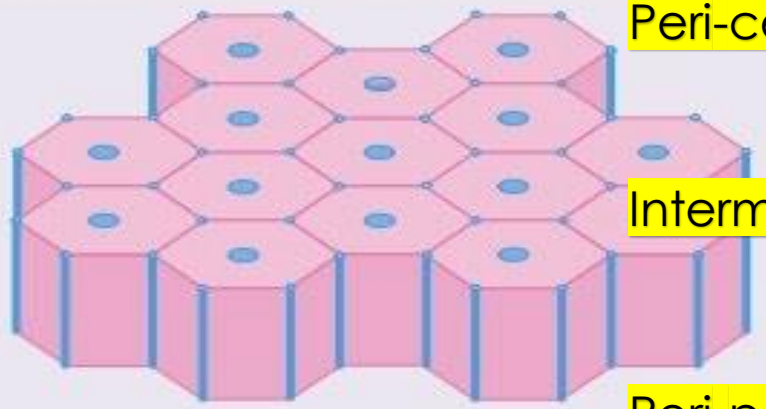




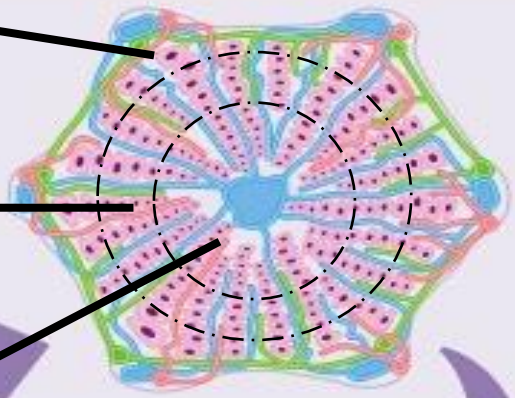
Liver



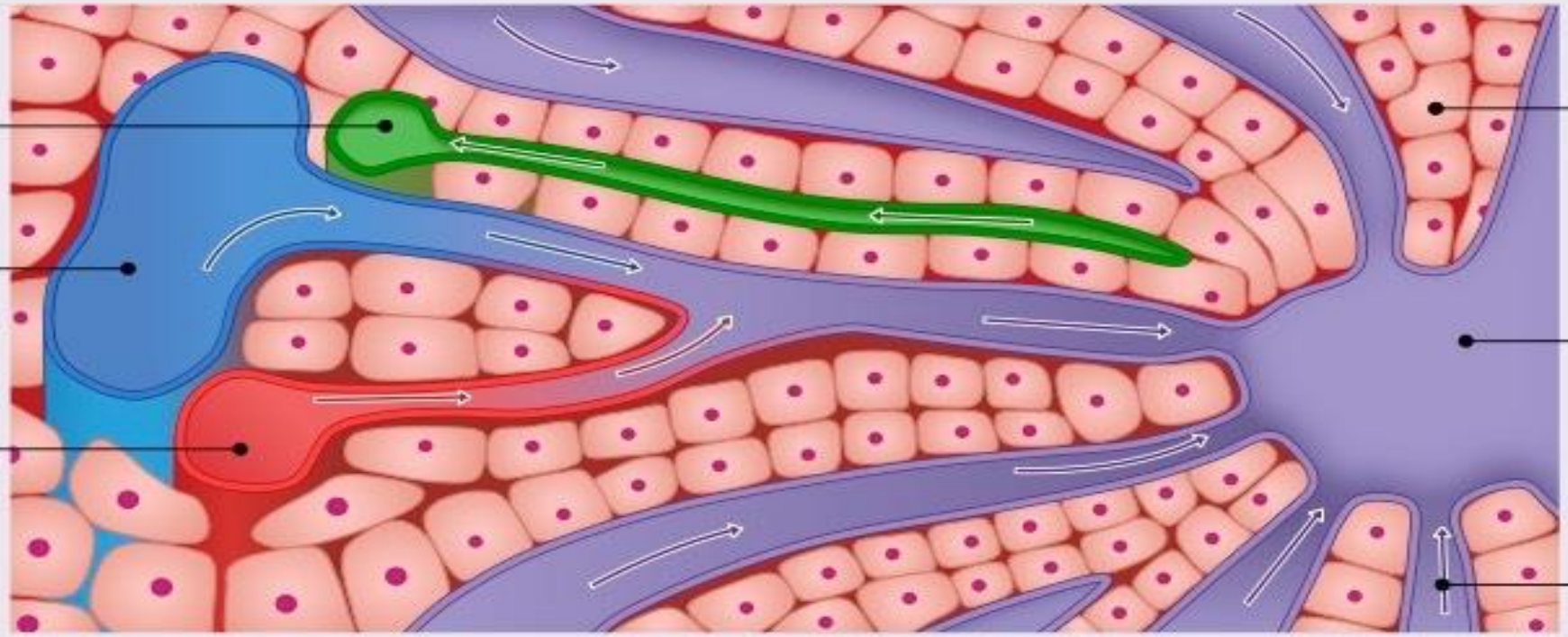
Liver Lobules

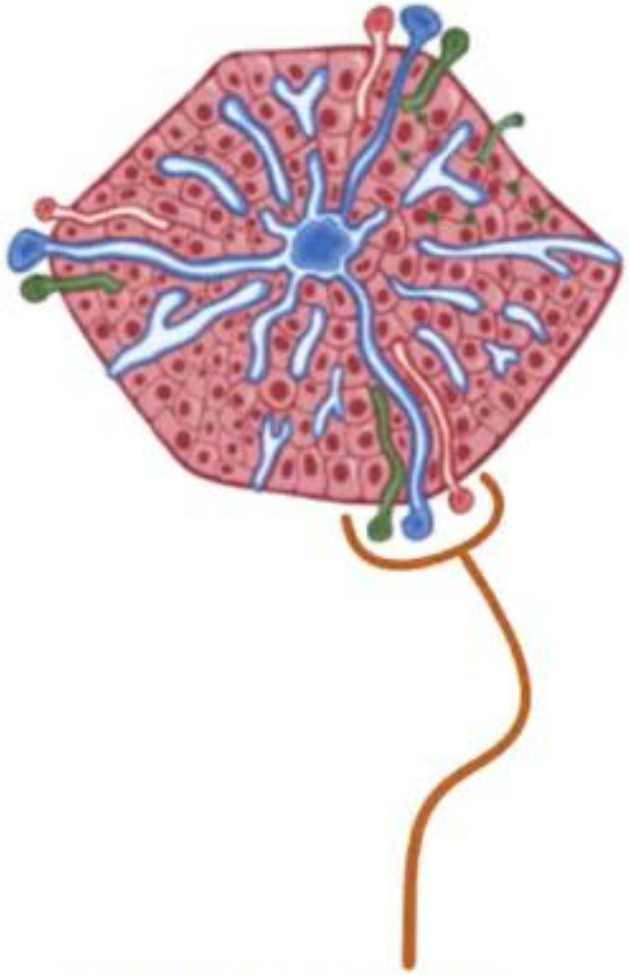


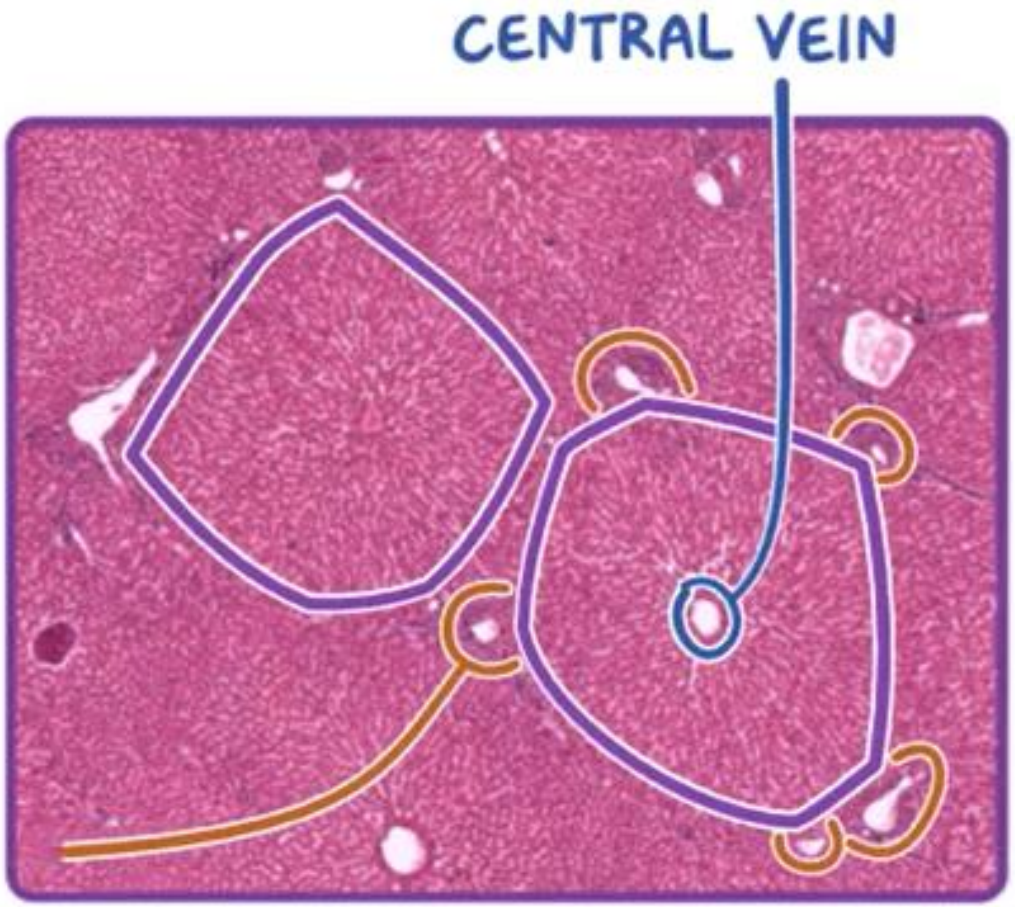
Lobule



Cross-Section of a Liver Lobule

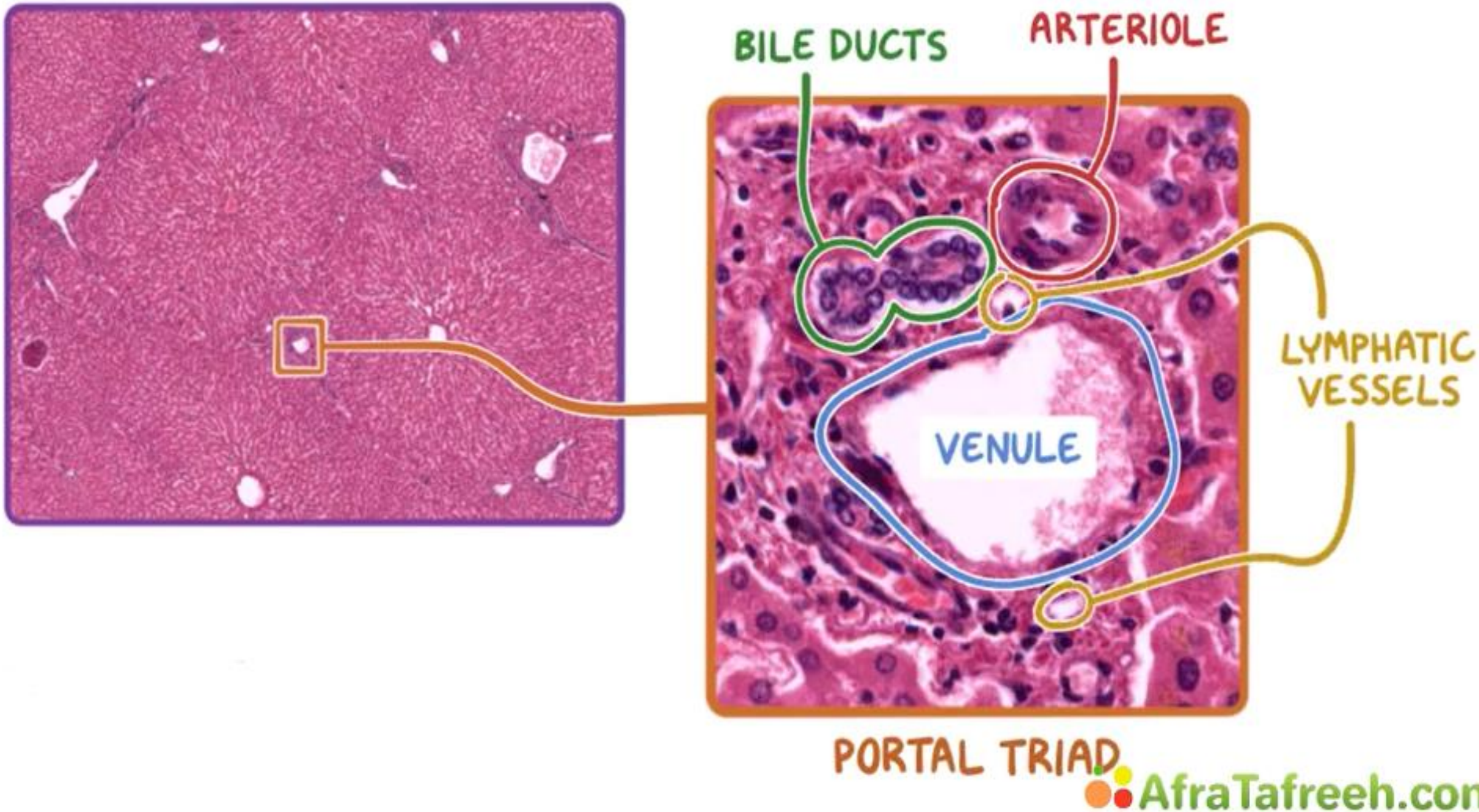






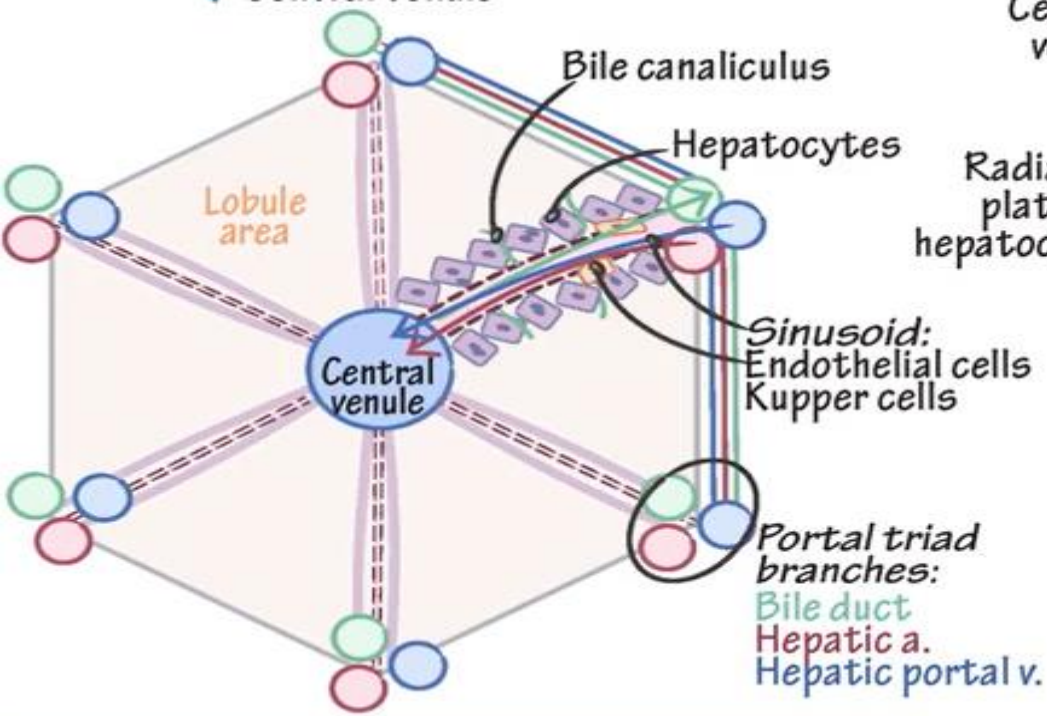
PORTAL TRIAD

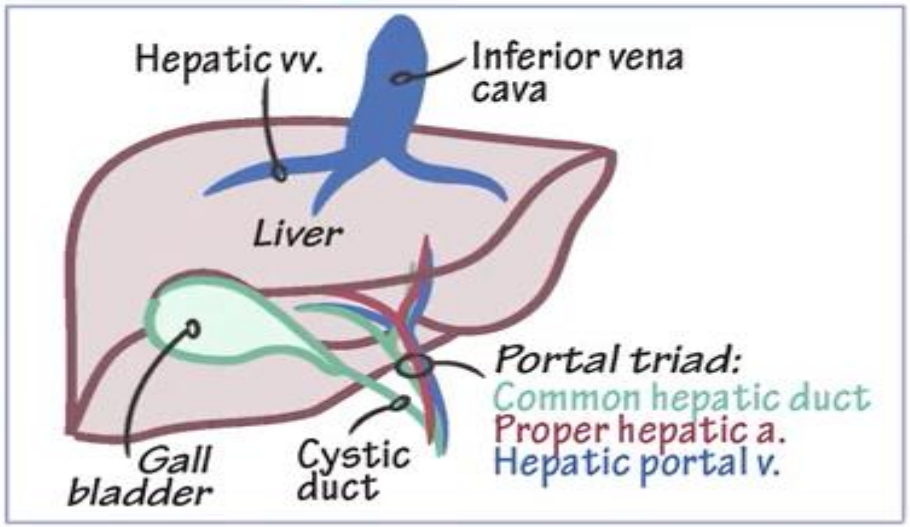
~ BILE DUCTULE
~ PORTAL VENULE
~ ARTERIOLE
~ LOCATED at CORNERS of LOBULES

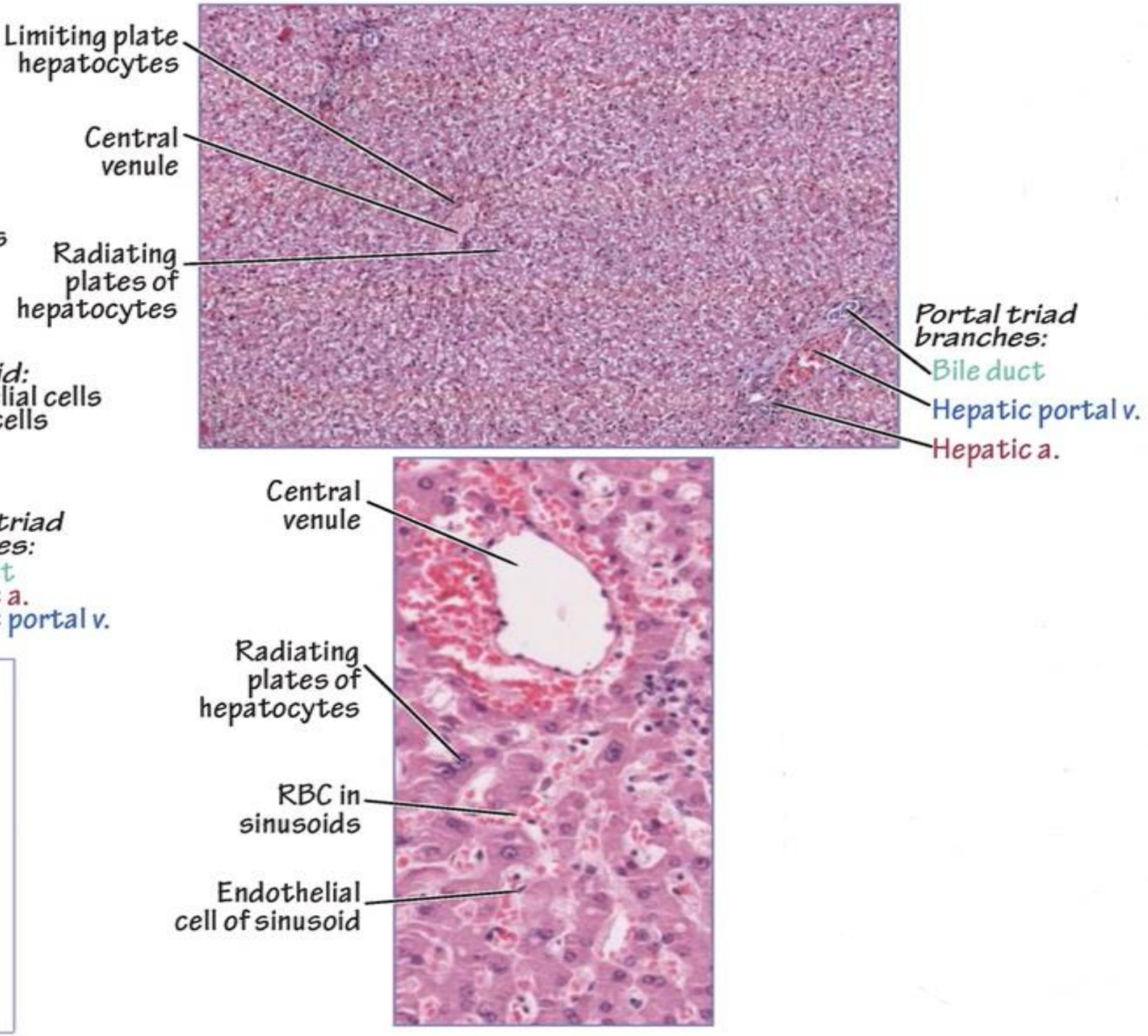


LIVER HISTOLOGY

Classic Lobule Model







0- Liver histology, anatomy & physiology

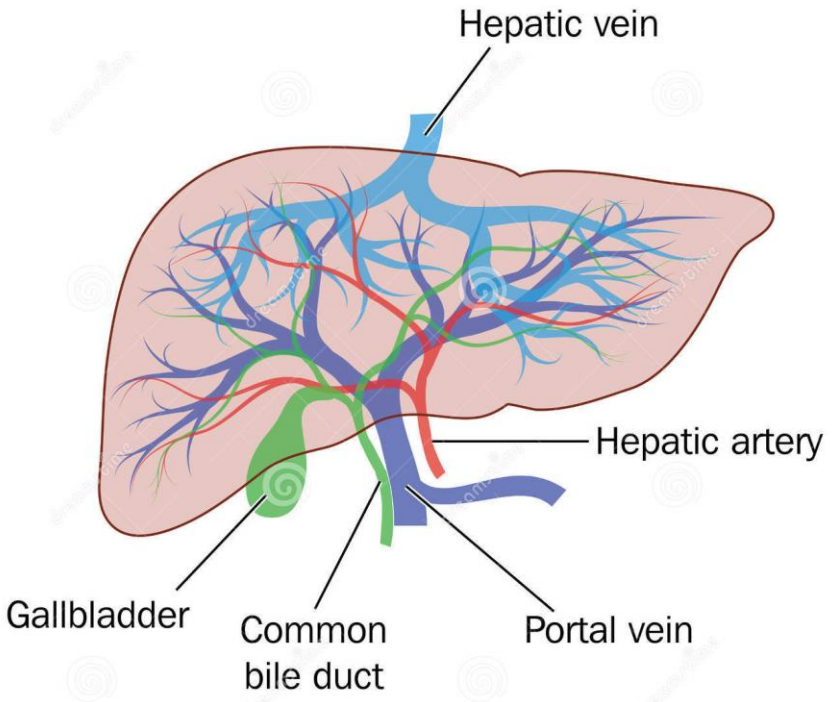
→ FUNCTIONS OF LIVER:

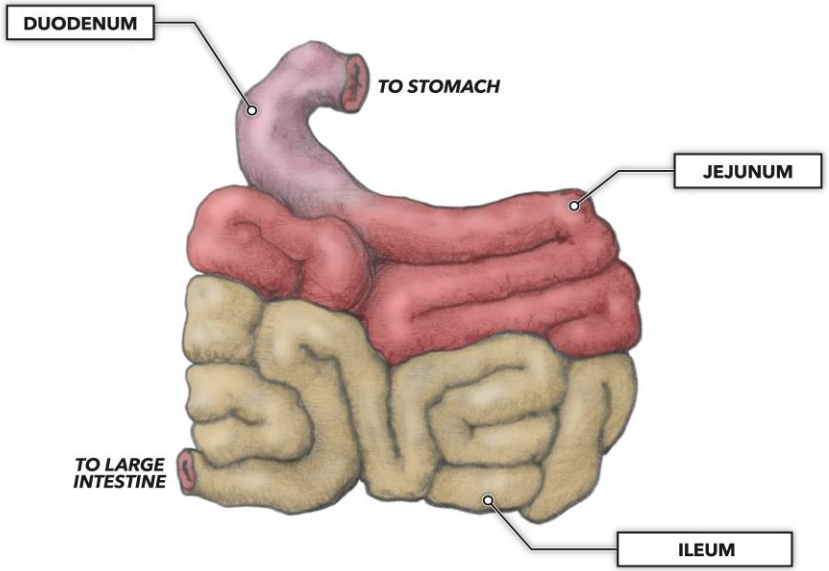
~ **PRODUCTION** of BILE, PLASMA PROTEINS, & AMINO ACIDS

~ **METABOLISM** of FAT, CARBOHYDRATE, & PROTEIN

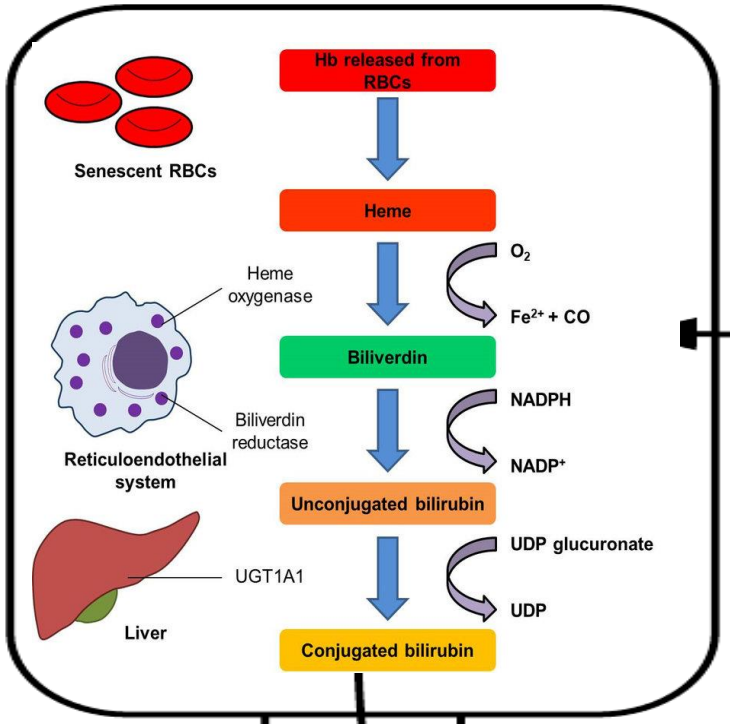
~ **STORAGE** of GLUCOSE, VITAMINS, & IRON

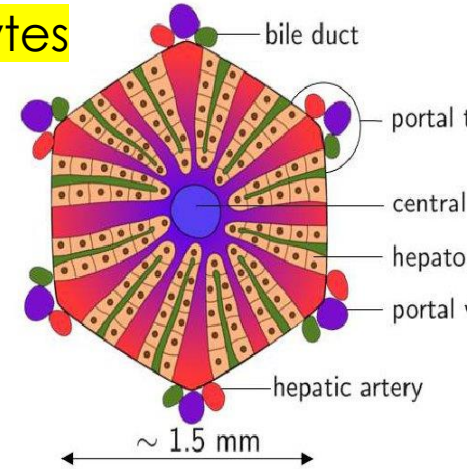
~ **BREAKDOWN** of METABOLIC WASTE PRODUCTS, DRUGS, & TOXINS





ALT/ AST: Enzymes stored in hepatocytes





Enterohepatic Circulation (via Portal System)

Bile Duct

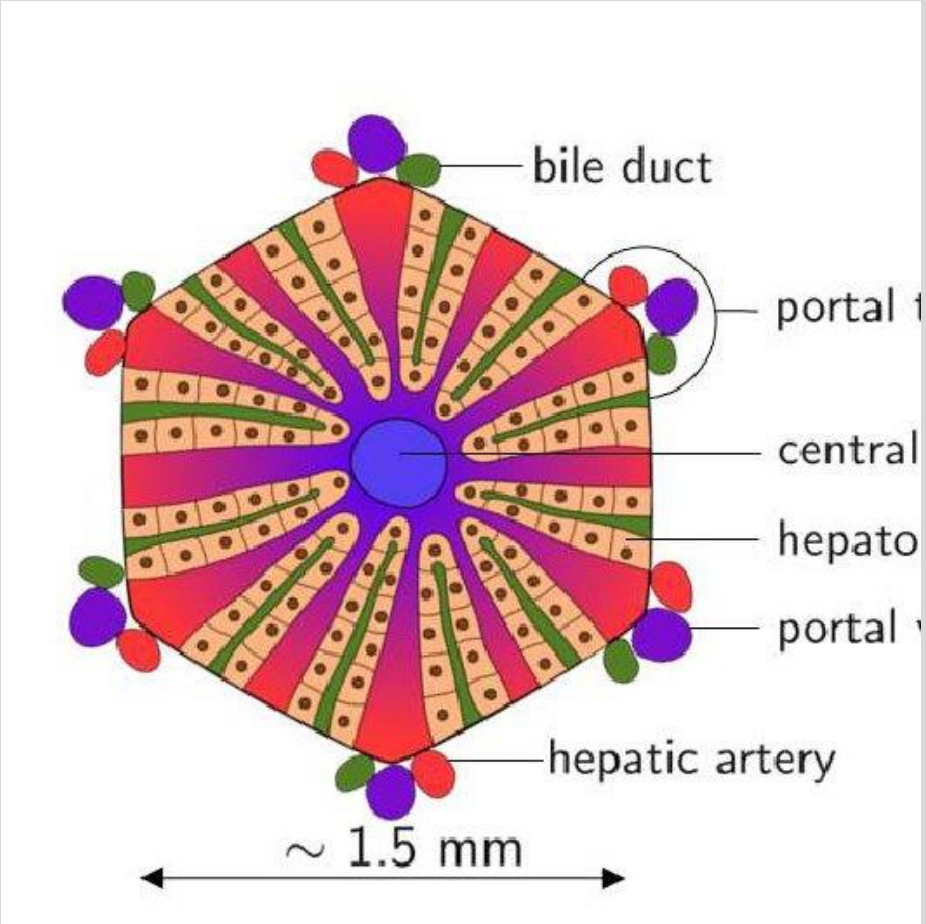
Glucuronic acid removed by bacteria

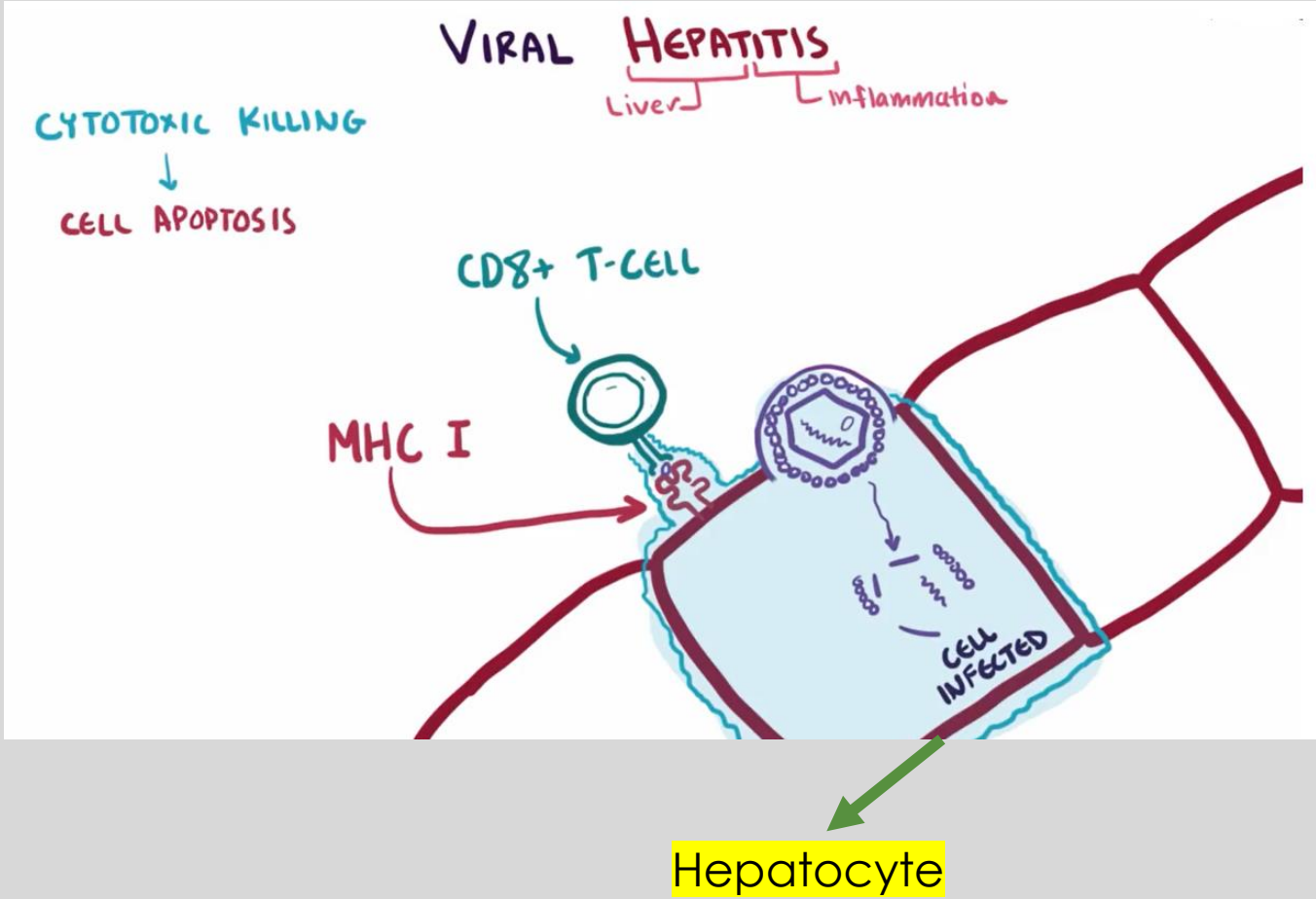
Stercobilin

Urobilinogen (Stercobilinogen)

Intestine

1- Pathogenesis & clinical manifestations





1- Pathogenesis & clinical manifestations

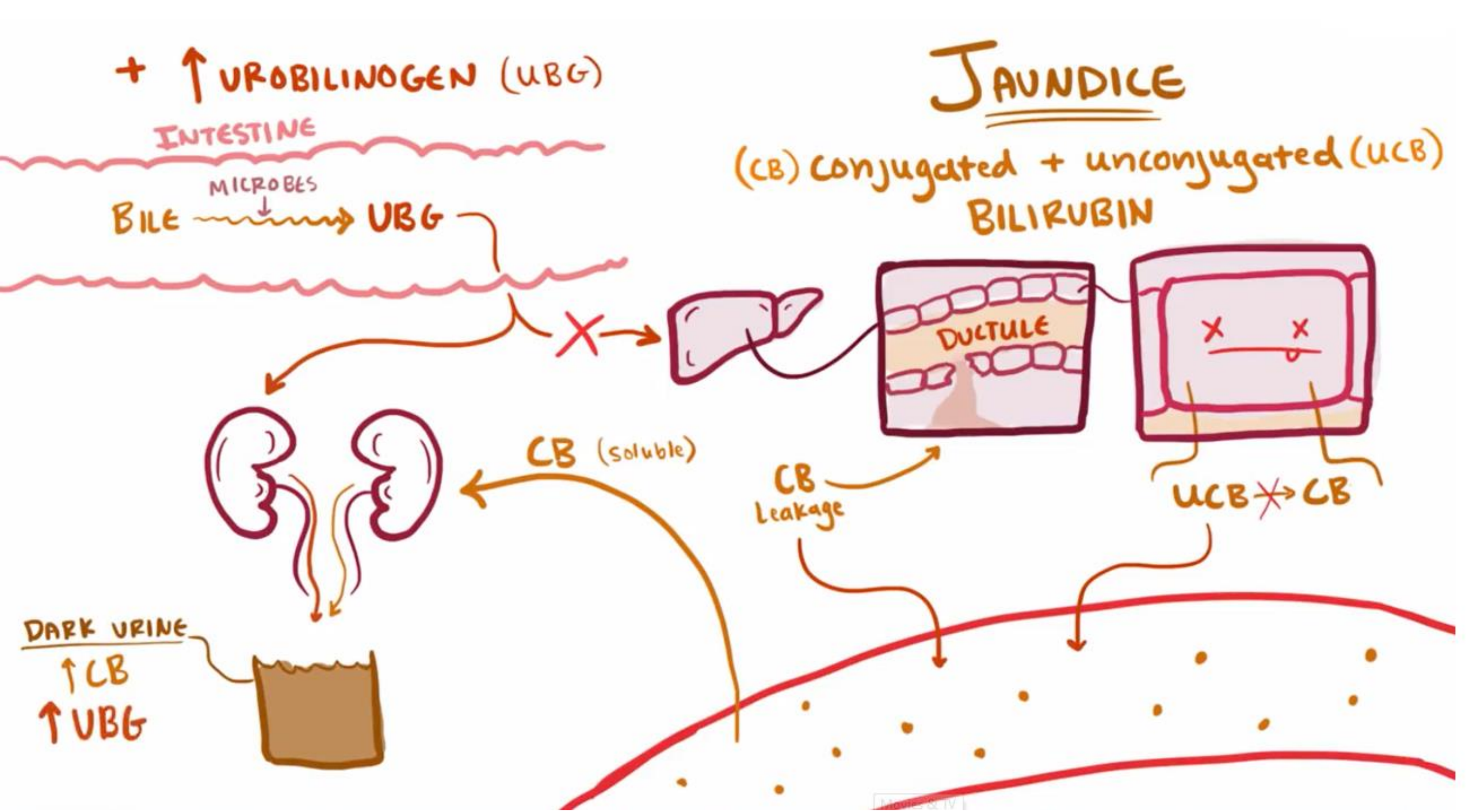
- Hepatitis is a general term meaning inflammation of the liver, it can take several pathway including:
  1. Asymptomatic infection
  2. Acute hepatitis
  3. Chronic hepatitis
  4. Fulminant hepatitis
  5. Cirrhosis
  6. Hepatocellular carcinoma (cancer)
  7. Extrahepatic manifestations
  8. Hepatic encephalopathy: a nervous system disorder brought on by severe liver disease

1- Pathogenesis & clinical manifestations

- 2) Acute hepatitis:
  - Microscopically, there is spotty parenchymal cell degeneration, with necrosis of hepatocytes, a diffuse lobular inflammatory reaction, and disruption of liver cell cords.
  - These parenchymal changes are accompanied by reticuloendothelial (Kupffer) cell hyperplasia, periportal infiltration by mononuclear cells, and cell degeneration.
  - Localized areas of necrosis are frequently observed.
  - Later in the course of the disease, there is an accumulation of macrophages near degenerating hepatocytes.
  - Preservation of the reticulum framework allows hepatocyte regeneration so that the highly ordered architecture of the liver lobule can be ultimately regained.
  - The damaged hepatic tissue is usually restored in 8–12 weeks.

1- Pathogenesis & clinical manifestations

- Symptoms:
  1) Initial symptoms: gastrointestinal symptoms such as nausea, vomiting, anorexia, and mild fever
  2) Distinct symptoms: Jaundice sometimes occur after prodromal period (if it occur we call this phase icteric, if not: we call it anicteric phase)
- alanine-aminotransferase & aspartate-aminotransferase enzymes elevate in the blood
- Dark urine and pale stool will present (why?)
  → bilirubin metabolism to get rid of it happen in GI tract (2/3) & renal secretion (1/3).
  In hepatitis there is a problem in excretion by GI tract so we will have bale stools and all excretion will be by renal secretion resulting dark color urine.
- Urobilinogen and bilirubin increase in urine
- Uncomplicated viral hepatitis rarely continues for more than 10 weeks without improvement. Relapses occur in 5–20% of cases and are manifested by abnormalities in liver function with or without the recurrence of clinical symptoms.


+ ↑ UROBILINOGEN (UBG)
JAUNDICE
(CB) conjugated + unconjugated (UCB)
BILIRUBIN
INTESTINE
MICROBES
BILE
UBG
DUCTULE
CB (soluble)
CB
Leakage
UCB ✕→ CB
DARK URINE
↑CB
↑UBG

1- Pathogenesis & clinical manifestations

- 3) Chronic hepatitis: Chronic carriers of HBsAg may or may not have demonstrable evidence of liver disease. Persistent (unresolved) viral hepatitis, a mild benign disease that may follow acute hepatitis B in 8–10% of adult patients, is characterized by sporadically abnormal aminotransferase values and hepatomegaly. Histologically, the lobular architecture is preserved, with portal inflammation, swollen and pale hepatocytes (cobblestone arrangement), and slight to absent fibrosis. This lesion is frequently observed in asymptomatic carriers, usually does not progress toward cirrhosis, and has a favorable prognosis.
- Chronic active hepatitis features a spectrum of histologic changes from inflammation and necrosis to collapse of the normal reticulum framework with bridging between the portal triads or terminal hepatic veins. HBV is detected in 10–50% of these patients.

1- Pathogenesis & clinical manifestations

- 4) Fulminant hepatitis: Occasionally during acute viral hepatitis, more extensive damage may occur that prevents orderly liver cell regeneration. Such fulminant or massive hepatocellular necrosis is seen in 1–2% of jaundiced patients with hepatitis B. It is 10 times more common in those coinfected with HDV than in the absence of HDV
- 5) Cirrhosis: scarring (fibrosis) of the liver caused by long-term liver damage.
- 6) Hepatocellular carcinoma: Both HBV and HCV have significant roles in the development of hepatocellular carcinoma that may appear many (15–60) years after establishment of chronic infection.

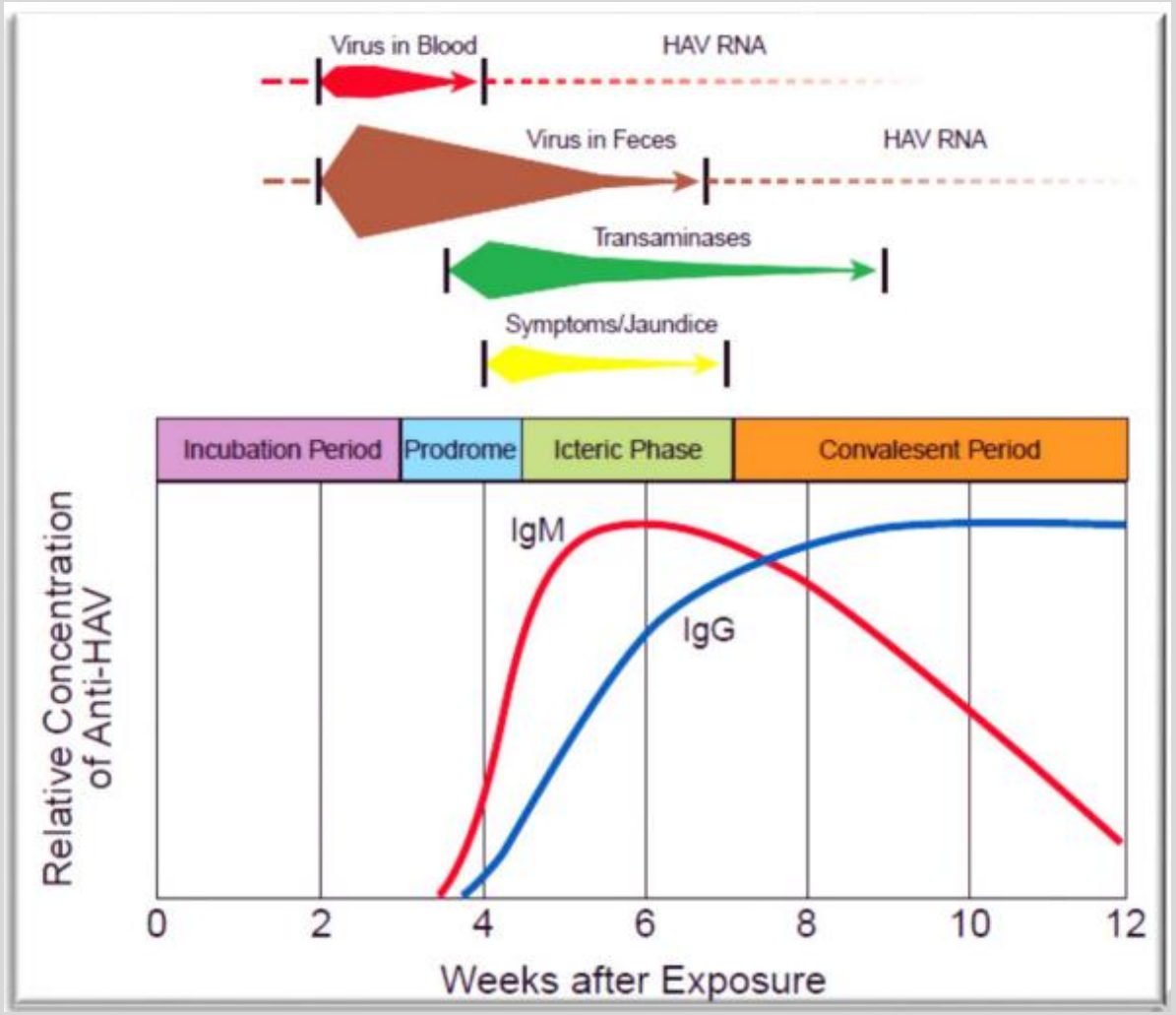
1- Pathogenesis & clinical manifestations

- 7) Extrahepatic manifestations of viral hepatitis (primarily HBV) include a transient serum sickness-like prodrome consisting of fever, skin rash, and polyarthritis; necrotizing vasculitis (polyarteritis nodosa); and glomerulonephritis. Circulating immune complexes have been suggested as the cause of these syndromes. Diseases associated with chronic HCV infections include mixed cryoglobulinemia and glomerulonephritis. Extrahepatic manifestations are unusual with HAV infections.
- 8) Hepatic encephalopathy: When the liver doesn't work properly, toxins build up in the blood. These toxins can travel to the brain and affect brain function

2- Quick view for the 5 viral hepatitis agents

- 1st) Hepatitis A:
  → Genome: Single stranded RNA virus, length about 7.5 kb
  → Envelope: Not enveloped
  → HAV is stable at low pH, heating.
  → Only one serotype is known. Genomic sequence analysis divided HAV isolates into seven genotypes.
  → Transmission occur through fecal-oral route most commonly by person-to person contact. Common source outbreaks can occur. (that's why there is a high prevalence of sero-positive people in contaminated areas "developing countries")
  → HAV has been found to survive for days to months in experimentally contaminated fresh water, seawater, waste water, soils, marine sediment and live oysters.
  → Principal age distribution: Children, young adults.
  → Seasonal incidence: Throughout the year but tends to peak in autumn.

2- Quick view for the 5 viral hepatitis agents



- Pathogenesis & clinical manifestations:

  1) Hepatitis A is transmitted through feco-oral route and start replicating in the liver
  2) Incubation period: 10–50 days (average, 25–30).
  3) Most infections are asymptomatic, however, some infections cause symptoms
  4) Prodromal symptoms start: gastrointestinal symptoms such as nausea, vomiting, anorexia, and mild fever
  5) Jaundice may occur after about 4 weeks of infection and may last for about two weeks
  (Note: If jaundice occur, the phase is called icteric, if it doesn't, the phase is called anicteric)
  6) Symptoms ranging from mild and transient to severe and prolonged can accompany anicteric or icteric hepatitis. Most patients recover completely after 8-12 week of infection ; however, complications may occur(and sometimes cause death), such as:
  a- Fulminant hepatitis: extensive necrosis of the liver occurs during acute viral hepatitis A, leading to severe impairment of hepatic synthetic processes, excretory functions, and detoxifying mechanisms.
  B- hepatic encephalopathy: Occurs sometimes after fulminant hepatitis because of accumulation of toxins (occurring of encephalopathy during the first 6 to 8 weeks of illness or within 1 to 4 weeks after jaundice indicate fulminant hepatitis)
  hepatic encephalopathy is characterized by the sudden onset of high fever, marked abdominal pain, vomiting, and jaundice followed by the development of encephalopathy associated with deep coma and seizures.

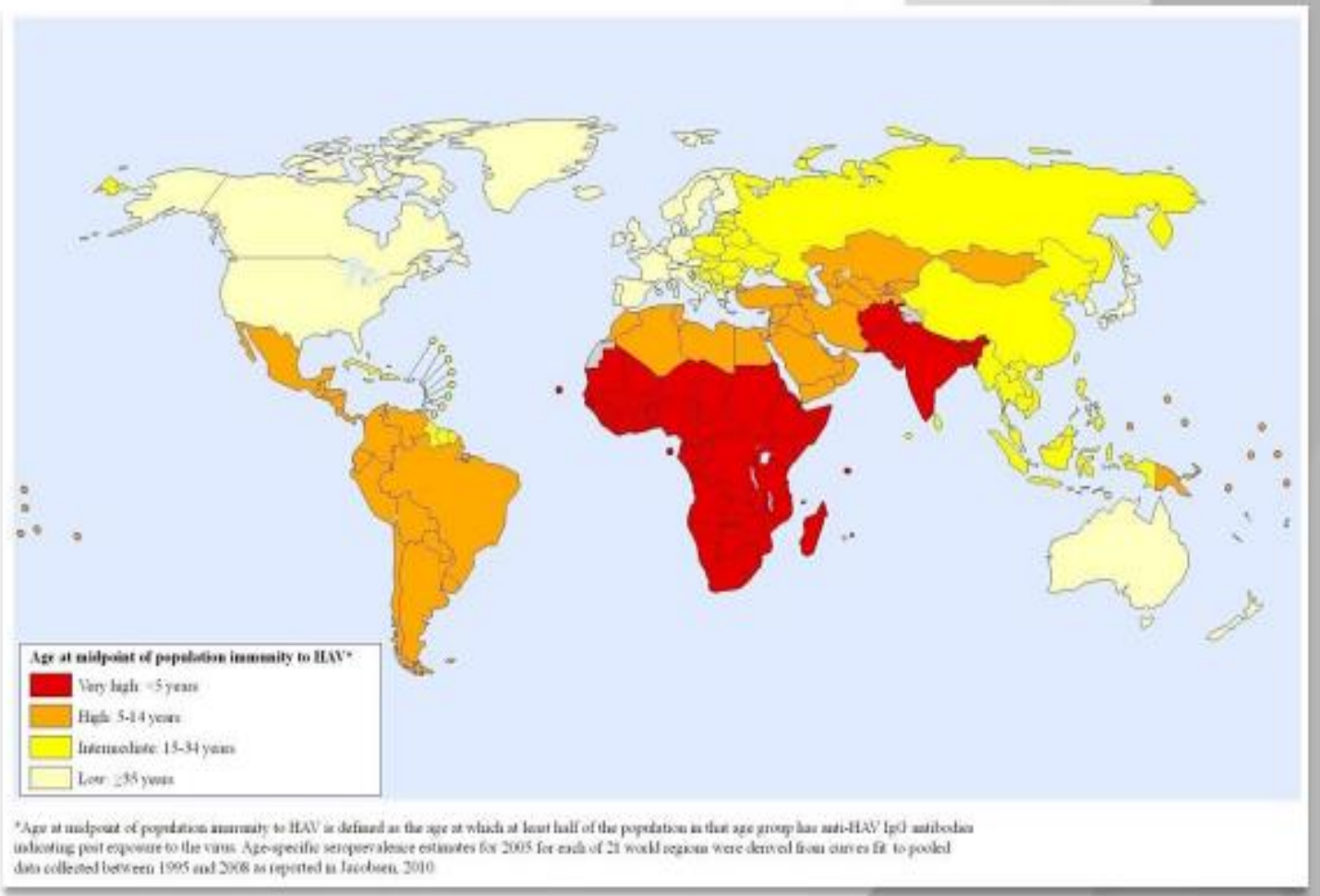
2- Quick view for the 5 viral hepatitis agents

- Laboratory diagnosis and treatment of hepatitis A:
- → Duration of aminotransferase elevation: 1–3 weeks
  → Occurrence of virus in blood: 2 weeks before to ≤1 week after jaundice.
  → Occurrence of virus in stool: 2 weeks before to 2 weeks after jaundice.
- → IgM = current infection while IgG = past infection or immunization
  → hepatitis A infection will Lead to Life long immunity
  → No antiviral drug to hepatitis A, we provide supportive therapy (sometime we give antibodies for the patient to prevent jaundice)

Epidemiology of Hepatitis A

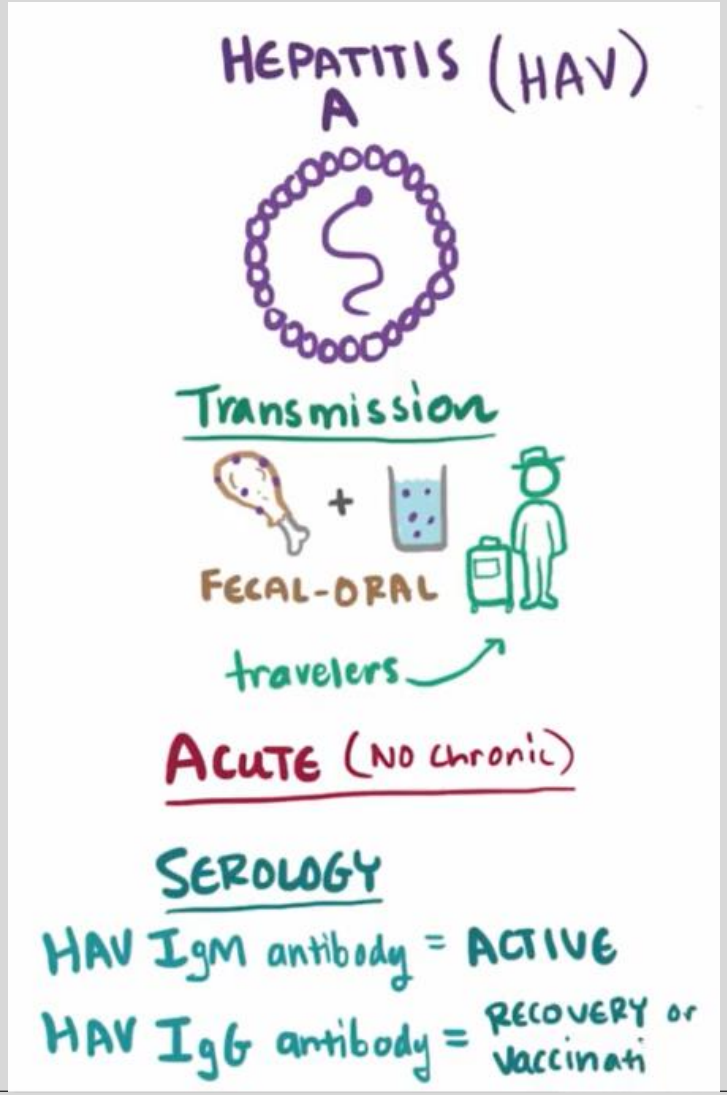
- Hepatitis A is one of the most common causes of infectious jaundice in the world today and is frequently associated with recurrent epidemics.

- HAV communicability is apparently highest during the clinically silent incubation period when virus replication reaches a peak.



*Age at midpoint of population immunity to HAV is defined as the age at which at least half of the population in that age group has anti-HAV IgG antibodies indicating past exposure to the virus. Age-specific seroprevalence estimates for 2005 for each of 21 world regions were derived from curves fit to pooled data collected between 1995 and 2008 as reported in Jacobsen, 2010

2- Quick view for the 5 viral hepatitis agents



2- Quick view for the 5 viral hepatitis agents

- 2nd) Hepatitis E: an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis.
- All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25% and the existence of five genotypes.
- Entry of the virus into the host is by the oral route with incubation period ranging from 2 weeks to 2 months.
- Mortality of hepatitis E has varied in different reports but has been as high as 1%, compared to 0.2% for hepatitis A. More important, however, is the severity of hepatitis E in pregnant women, which may reach 20%.

HEPATITIS A (HAV)

Transmission

FECAL-ORAL

travelers

ACUTE (NO chronic)

SEROLOGY

HAV IgM antibody = ACTIVE

HAV IgG antibody = RECOVERY or vaccination

HEV

Transmission

FECAL-ORAL

ACUTE (NO chronic)

SEROLOGY

HEV IgM antibody = ACTIVE

HEV IgG antibody = Recovery

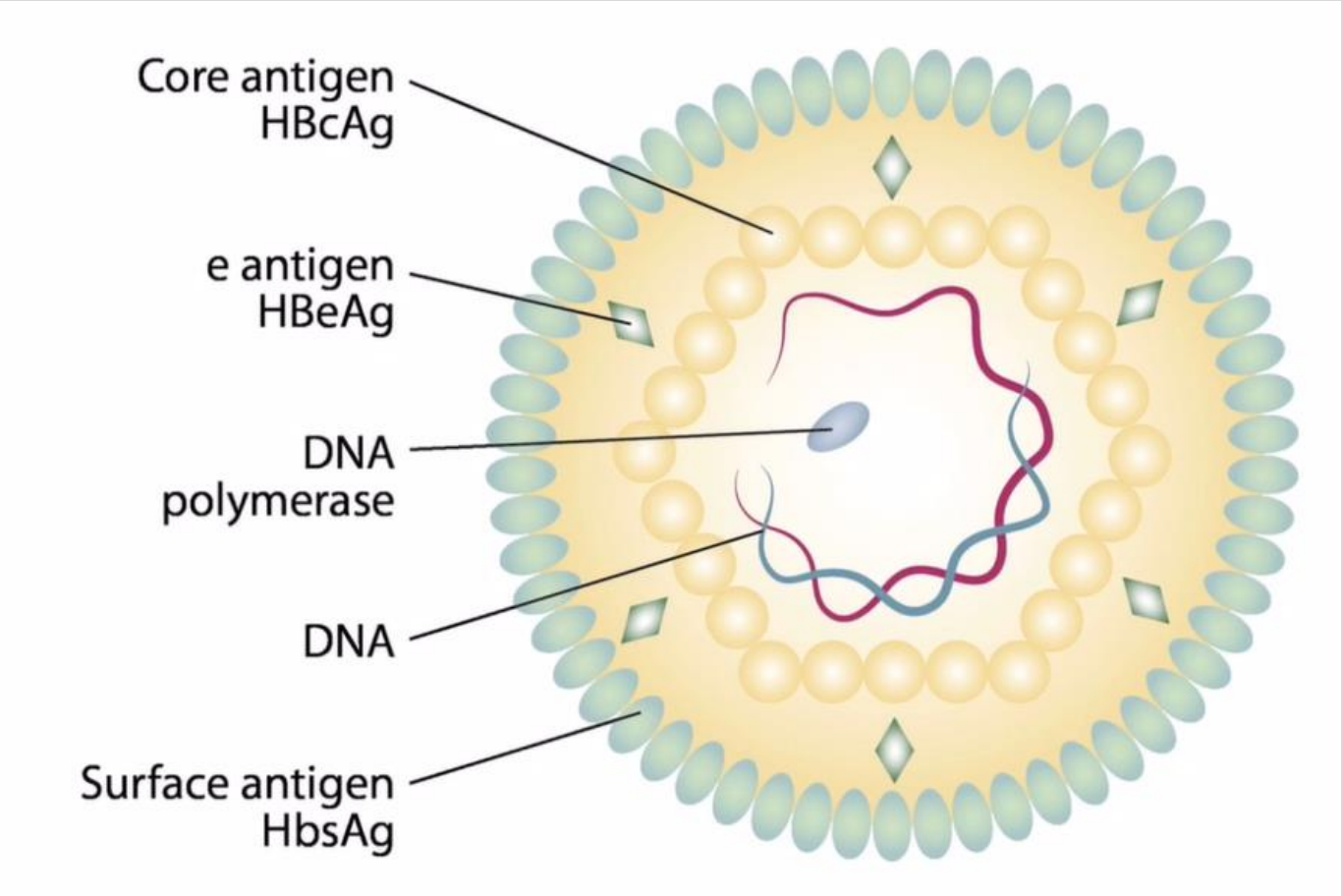
PREGNANT + HEV

NO vaccination!

FULMINANT HEPATITIS

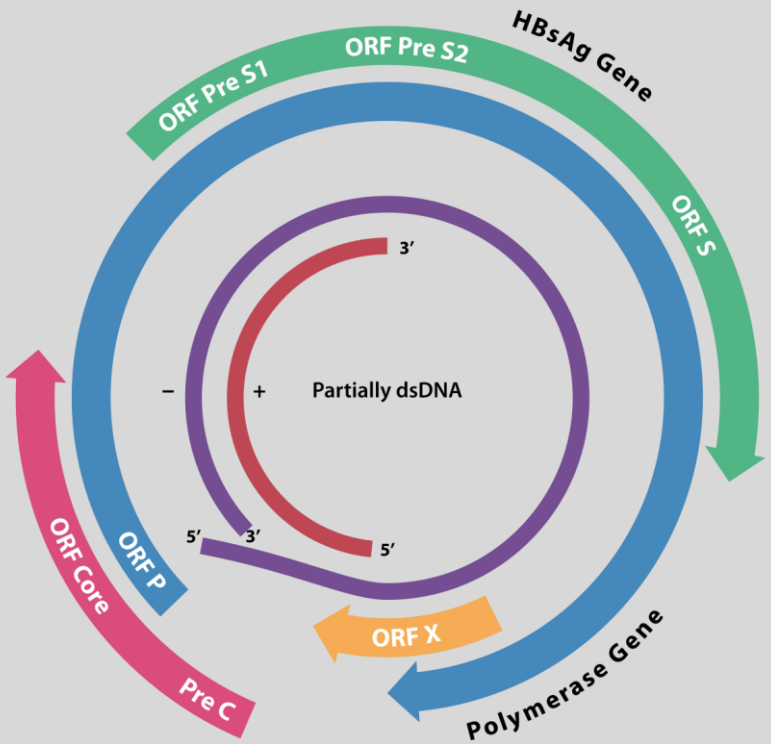
2- Quick view for the 5 viral hepatitis agents

- 3rd) Hepatitis B:
  → HBV is currently classified into at least eight genotypes designated with capital letters (A-H), and recently genotypes I and J are added (so there's 10 genotypes)
- This virus has only 4 important (7 in total) proteins:
  A. HBsAg (hepatitis B surface antigen) (3 subtypes)
  b. C-proteins (core proteins "on the capsid")
  c. X-protein (regulator for transcription)
  D. Polymerase protein (for the replication process)



2- Quick view for the 5 viral hepatitis agents

- 3rd) Hepatitis B:
  → Genome: The virus is a partially circular & partially double-stranded DNA virus of about 3.3 kb.
  Genome is made of: a partial + sense strand and a complete –ve sense strand.
  Genome is Peculiar: overlapping reading frames, causing a sort of genetic economy.
  → Each gene rise for a specific structure:
  1) C gene (ORF core): rise for core antigen, it form the capsid and exists as a dimer
  2) Pre C + C gene :E antigen (soluble form of core protein (HBeAg) with its presence in serum marking higher transmissibility)
  3) P Gene (P ORF): DNA polymerase
  4) X gene: trans-activator of transcription
  5) S gene (ORF S): small surface antigen protein
  6) Pre- S2 + S gene: Medium surface antigen protein
  7) Pre- S1 + Pre- S2 + S gene: Large surface antigen protein



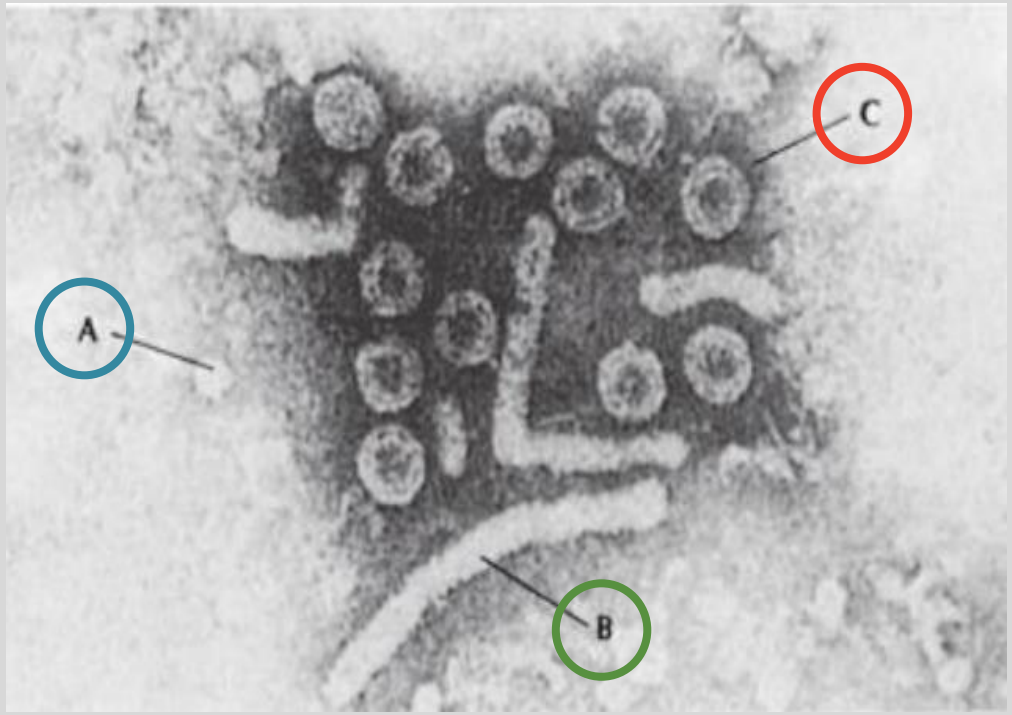
2- Quick view for the 5 viral hepatitis agents

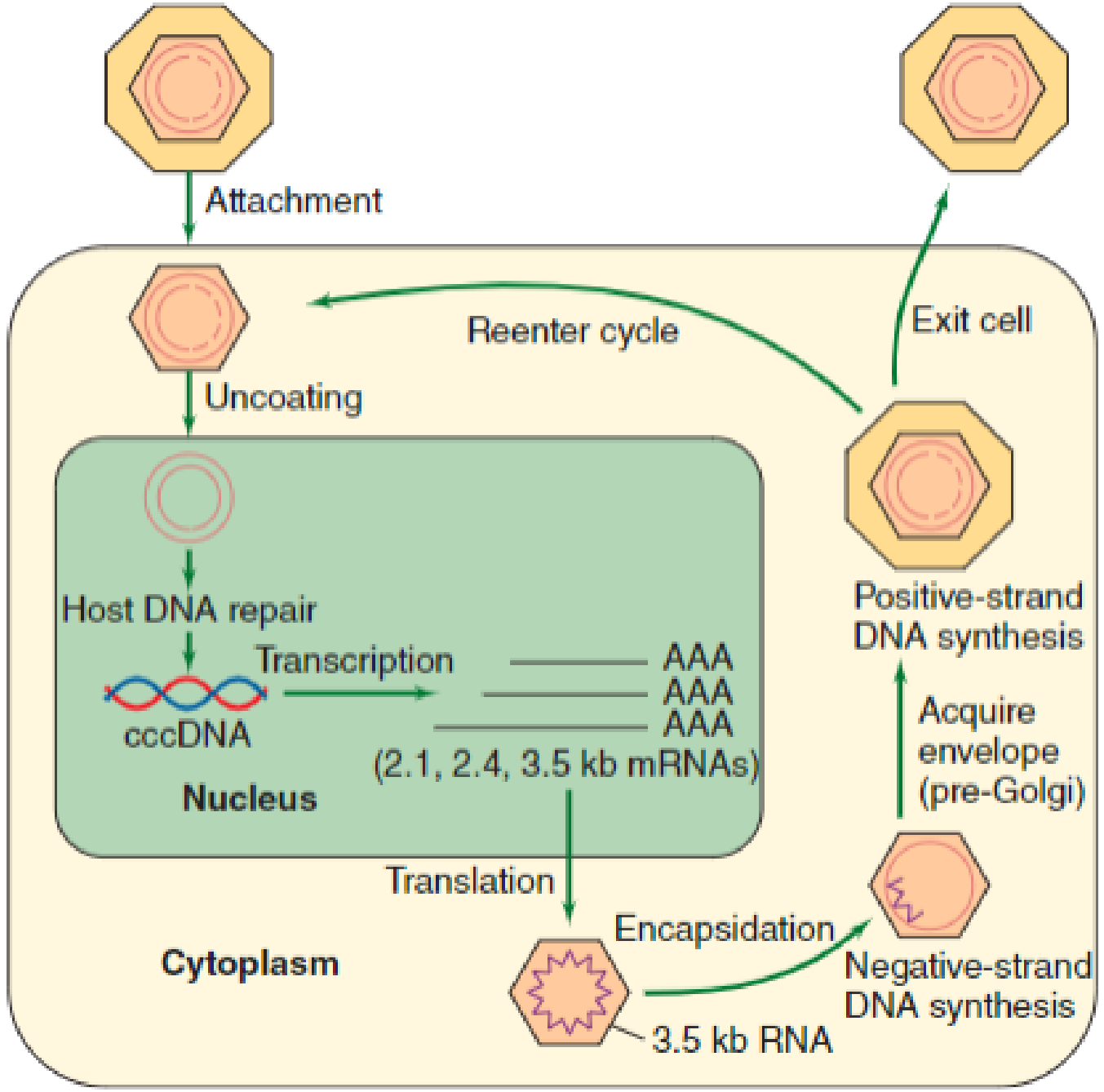
- Its important to understand that replication of HBV produce three different EM morphologically structures:

C) The 42-nm virion particles (real viruses that cause infection) (they have large surface antigen)

A) the 22-nm spherical particles : non-infectious particles, are produced in excess compared to the virions which might be a viral decoy mechanism to trick the immune system.

B) the 22-nm tubular particles that are up to 200 nm in length.




Attachment
Reenter cycle
Exit cell
Uncoating
Host DNA repair
Transcription
AAA
AAA
AAA
cccDNA
(2.1, 2.4, 3.5 kb mRNAs)
Nucleus
Positive-strand
DNA synthesis
Acquire
envelope
(pre-Golgi)
Translation
Encapsidation
Cytoplasm
Negative-strand
DNA synthesis
3.5 kb RNA

- Steps of replication of Hepatitis B:

1) The pre-S1 domain of the L protein binds to the hepatic receptor of HBV namely sodium taurocholate co-transporting polypeptide (NTCP).

2) the virion enter the nucleus, it uncoats and starts replication there

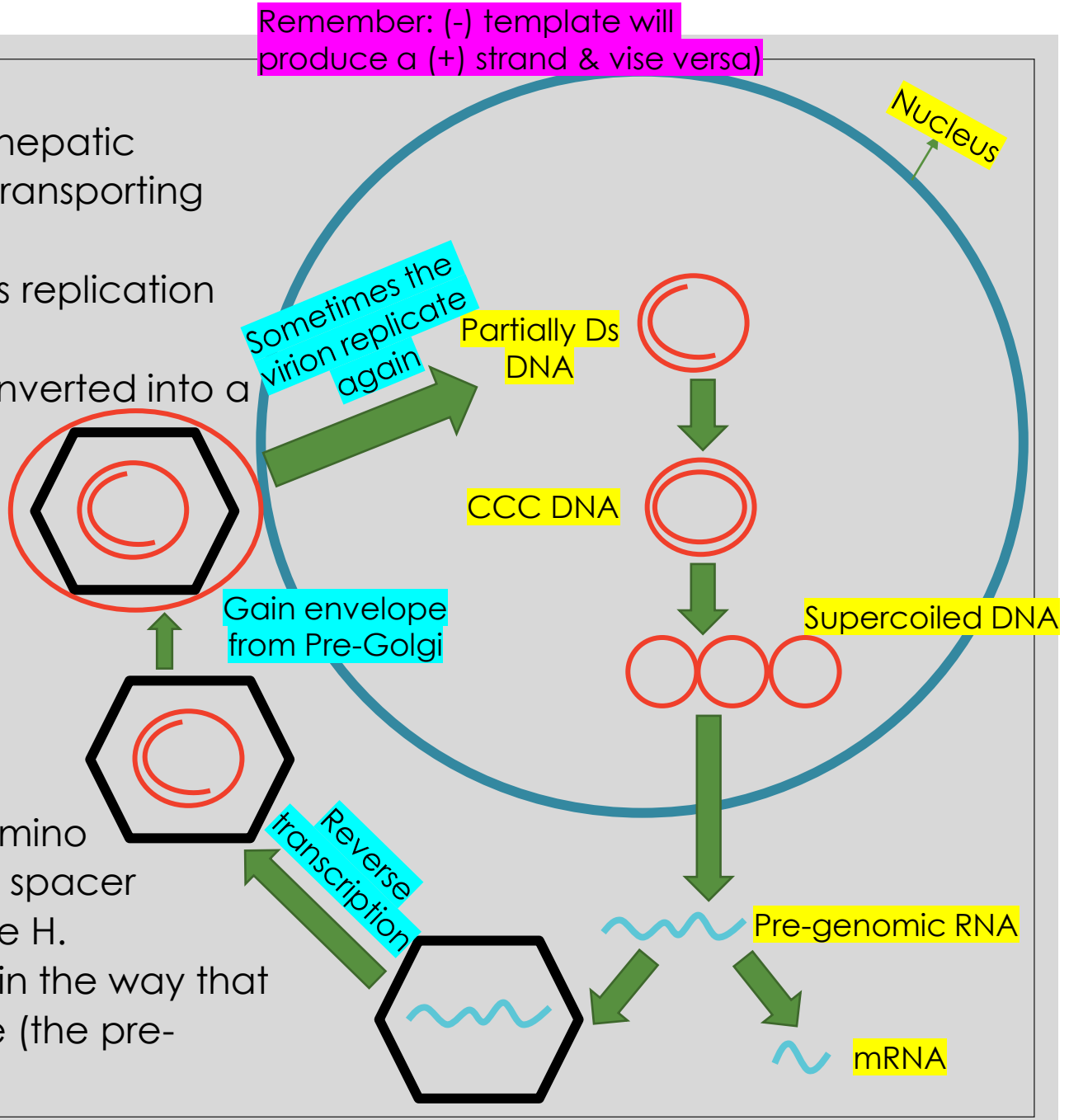
3) the partially double stranded relaxed DNA is converted into a covalently closed circular DNA, called a triple C DNA template that will take a supercoiled form.

4) the (-) strand DNA will undergo transcription to release a pre-genomic RNA & mRNA

5) The pre-genomic will undergo reverse transcription to make partially DS DNA that will be coated to form a virion particle

→ Note: The polymerase of HBV has the following activities in four domains: terminal protein at the amino end that has a role in initiation of DNA synthesis, a spacer domain that is not critical in function, RT and RNase H.

→ So as a quick recap! : HBV replication is unique in the way that its replication occurs through an RNA intermediate (the pre-genomic RNA) from the minus DNA strand.



2- Quick view for the 5 viral hepatitis agents

- Pathogenesis & clinical manifestations of Hepatitis B:
  1) Virus is transmitted through:
  a- Injection drug use (needle sharing) is common between drug abuser (most common mode of transmission)
  b- Vertical transmission (Most common mode in high endemicity areas)
  c- sexual transmission
  d- needle stick injuries
  e- Blood transfusion (rare nowadays because of blood screening)

2- Quick view for the 5 viral hepatitis agents

- Clinical manifestations can be:

  1) Acute infection:

  → After virus is transmitted, it has an incubation period for about 50–180 days (average, 60–90) the first markers of the disease is viral DNA in the liver and plasma together with circulating HBsAg. High levels of viremia is followed by rise in the level of markers of hepatocyte damage (mainly ALT that rise after 2 months of infection and remain until the 5th month) and the appearance of clinical features

  → Prodromal phase :the 1st phase occurs, defined by fever (usually low-grade), malaise, fatigue, nausea and vomiting, anorexia, (sometimes right upper quadrant pain but can be associated with hepatomegaly), it might take 2 weeks

  → After the prodromal phase, the icteric phase occurs: Accompanied by jaundice, dark urine (usually precedes the presence of jaundice) & lasts about 1 month

  → HBsAg becomes undetectable 1–2 months after the appearance of jaundice.

  → The infection is eliminated completely after 6 months, if it's not eliminated, then the infection will convert into a chronic infection

  → Note: Fulminant hepatitis & hepatic encephalopathy may follow the acute infection in 1-2% of patients (this percentage is higher than that of hepatitis A)

2- Quick view for the 5 viral hepatitis agents

2) Chronic hepatitis: Occurs if the infection last for more than 6 months
→ The persistence of HBsAg beyond 6 months marks HBV chronicity, majority will have hepatitis B surface antigen positivity for the rest of their lives (unless there's some sort of a treatment)
→ Majority, unless on treatment, will have a presence of nucleic acid in their blood, indicated by positive results in PCR.
→ For some of those who acquired chronic infection, there will be spontaneous resolution, especially in the elderly after the age of 40 years.
3) hepatocellular carcinoma: Hepatitis b virus is an oncovirus that can lead to cancer after some chronic infections
→ Multiple factors are proposed to link between the infection and the development of hepatocellular carcinoma.
→ Cause is still under investigation, but the strong association is linked to the integration of HBV DNA to hepatocytes, which are proposed to activate protooncogenes, or suppress certain growth regulation genes inside hepatocytes.

TABLE 35-6 Transmission of Hepatitis B Virus and Spectrum of Outcomes of Infection

Feature	Transmission[a]		
	Vertical (Asia)	Contact (Africa)	Parenteral, Sexual
Age at infection	Newborns, infants	Young children	Teenagers, adults
Recovery from acute infection (%)	5	20	90–95
Progression to chronic infection (%)	95	80	5–10
Chronic carriers[b] (% of total population)	10–20	10–20	0.5

[a]Vertical and contact-associated transmission occurs in endemic regions; parenteral and sexual transmissions are the main modes of transmission in nonendemic regions.

[b]At high risk of developing hepatocellular carcinoma.

→ In adults, the majority clear the infection and a minority develops chronic infection during which, hepatocyte damage occurs as a result of T cell mediated immune attack on hepatocytes expressing HBV antigens on the context of their HLA molecules.

2- Quick view for the 5 viral hepatitis agents

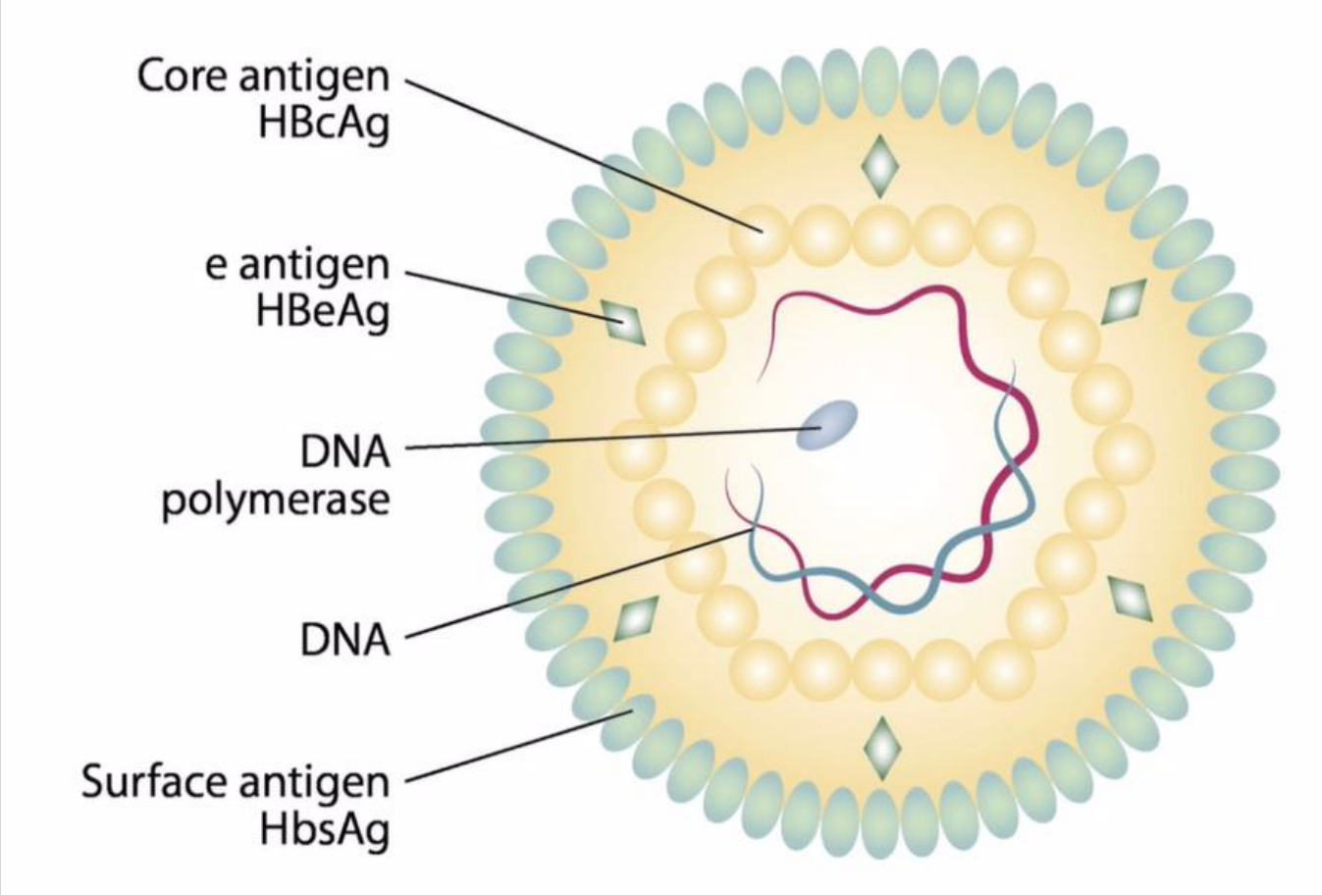
4) Cirrhosis: scarring (fibrosis) of the liver caused by long-term liver damage.
5) Extrahepatic manifestations of viral hepatitis (primarily HBV) include a transient serum sickness-like prodrome consisting of fever, skin rash, and polyarthritis; necrotizing vasculitis (polyarteritis nodosa); and glomerulonephritis. Circulating immune complexes have been suggested as the cause of these syndromes.

Clinical Outcomes of Hepatitis B

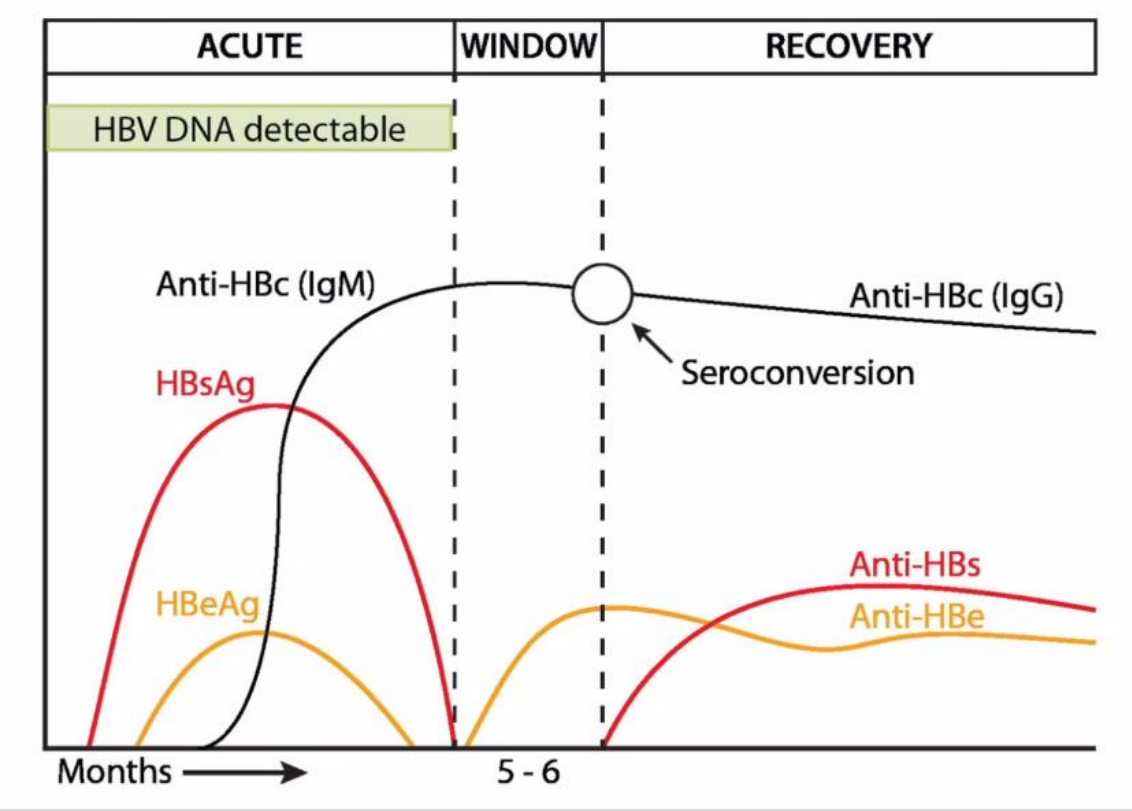
- Acute infection that resolves within 6 months (most common)
  - -May have arthralgias, rash, fever, jaundice
  - -May be asymptomatic (anicteric)
- Fulminant liver failure and hepatic necrosis
- Chronic infection (stable)
- Chronic infection → cirrhosis
- Chronic infection → cirrhosis → hepatocellular carcinoma
- Chronic infection → hepatocellular carcinoma

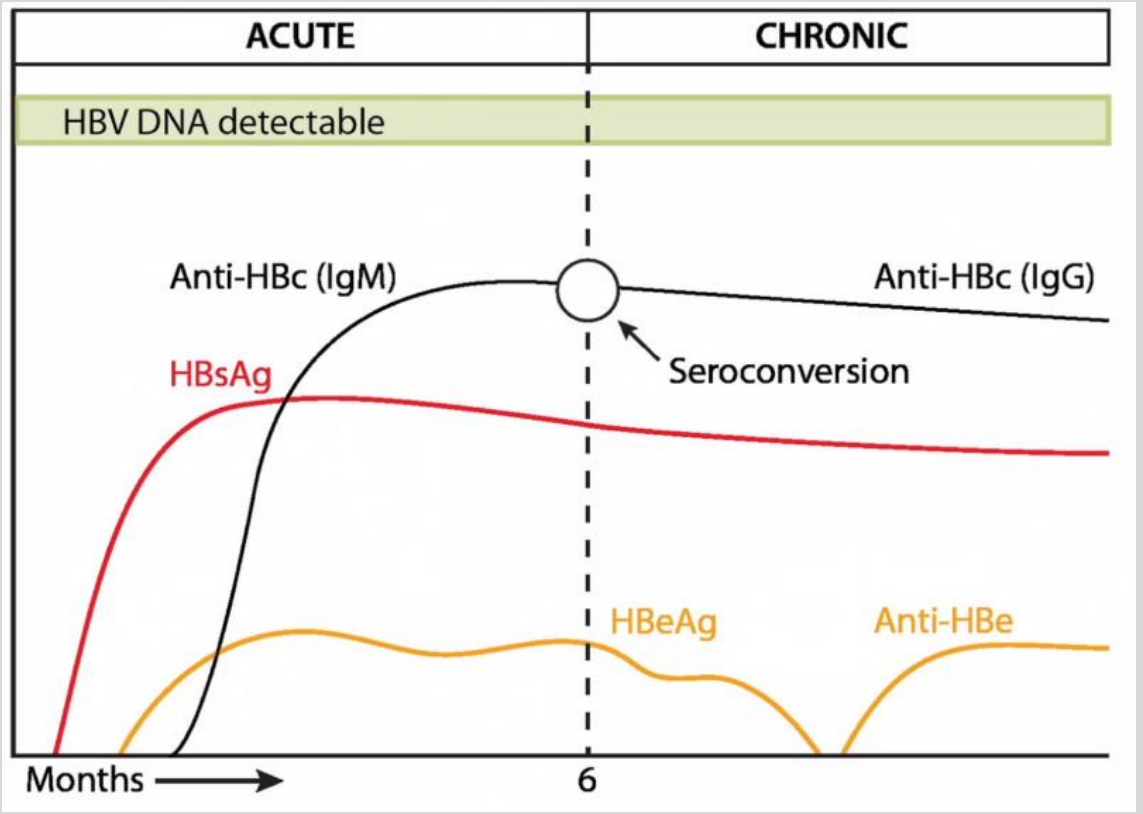
2- Quick view for the 5 viral hepatitis agents

- Hepatitis b diagnosis:
  1) PCR (High cost)
  2) Clinical symptoms are un-helpful
  3) Serology (best and ***MOST IMPORTANT WAY***)
  4) NAT is also available for screening blood/blood products



Abbreviation	Meaning	Example
Ag	antigen	HBsAg = Hepatitis b surface antigen
Ab	Anti-body	HBsAb = Hepatitis b surface antibody
Anti- …	Antibody	Anti-Hbe = Antibody for hepatitis b “e” antigen

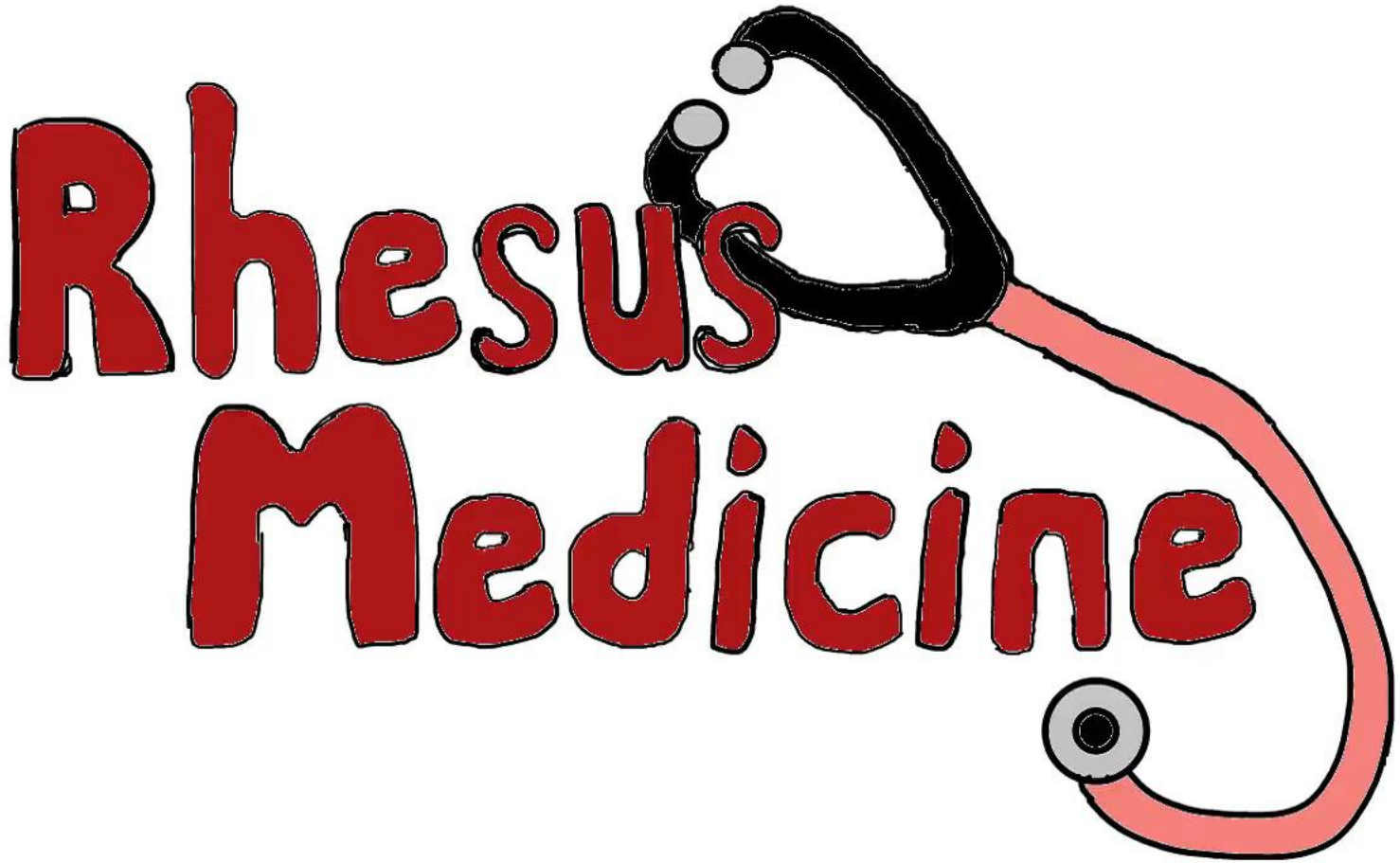




	HBsAg	Anti-HBs	Anti-HBc
Susceptible	-	-	-
Vaccinated	-	+	-
Past infection	-	+	+
Acute infection	+	-	IgM (+)
Chronic infection	+	-	IgG (+)
May be: 1. Window period 2. "low-level" HBV carrier 3. false-positive	-	-	+

2- Quick view for the 5 viral hepatitis agents

- After HBV infection, circulating HBsAg rises in the blood
- HBcAb appears within the first two weeks after the appearance of HBsAg and preceding HBsAb.
- HBsAg becomes undetectable after 5 months if the acute infection is cleared
- The window between decline of HBsAg and rise HBsAb is associated with HBcAb as the only serologic evidence of infection.
- Clearance is associated with the appearance of HBsAb.
- The persistence of HBsAg beyond 6 months marks HBV chronicity, also late elimination of HBeAg marks HBV chronicity


Rhesus
Medicine

Diagnosis, Treatment and Prevention of Hepatitis B

- Multiple options are available for treatment of chronic hepatitis B including **IFNs** and several **nucleotide and nucleoside analogs** with the goal of reducing the viral load to an undetectable level and to reach HBsAg clearance.

- For prevention of HBV infection, an effective vaccine (**recombinant HBsAg**) has been available from mid-1980s, with many countries worldwide implementing universal vaccination of infants.

2- Quick view for the 5 viral hepatitis agents

- Just little information about hepatitis C & D:
  4th) Hepatitis D: it's known to be defective and require a helper function from HBV for its transmission. HDV is coated with HBsAg, which is needed for release from the host hepatocyte and for entry in the next round of infection.
  → The genome consists of a single-stranded, circular RNA of around 1700 nucleotides, the delta antigen being encoded by antigenomic RNA.
  → Two types of infection are described:
  Co-infection: Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute coinfection with both the viruses at the same time.
  Super-infection: When an HBV carrier is exposed to infected blood from coinfected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.
  → Delta hepatitis can be prevented by vaccinating HBV susceptible persons with hepatitis B vaccine

2- Quick view for the 5 viral hepatitis agents

- 5th) Hepatitis C:
  → Chronic infection more in hepatitis C than B
  → The age here most important factor to determine if the viral infection(C) can lead to chronic infection or not as HBV
  → Most common of mood transmission in hepatitis C & D is injection drug use
  → Mode of transmission is same for HBV