Hepatitis virus, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma

The epidemiology and pathogenesis of viral hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) are summarized and reviewed. Persistent infection of hepatitis B virus (HBV) and hepatitis C virus (HCV) is closely related to the occurrence of liver cirrhosis and HCC. Non-alcoholic steatohepatitis (NASH) or metabolic dysfunction-associated steatohepatitis (MASH) is also important for the pathogenesis of non-viral liver cirrhosis and subsequent HCC. Pathology of the infection of hepatitis virus, chronic hepatitis, liver cirrhosis and HCC will be presented below.

Ref.: Llovet JM, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021; 7: 6. doi: 10.1038/s41572-020-00240-3

Non-alcoholic steatohepatitis (NASH)

1) NASH is seen in obesity patients without alcohol history.

2) NASH microscopically resembled alcoholic hepatitis. Microscopically, NASH shows prominent fatty change with milder inflammation. The lesion is accentuated in the centrilobular zone (zone 3), and fibrosis is seen in the portal zone (zone 1).

3) NASH is now re-called as "metabolic dysfunction-associated steatohepatitis" (MASH). Risk factors include obesity and type 2 diabetes mellitus.

4) NASH may be provoked by taking steroid or Tamoxifen (anti-estrogen medicine).

5) NASH is a chronic progressive disease, resulting in liver fibrosis and steatotic liver cirrhosis.

6) Excessive supply of free fatty acids activates drug-metabolizing enzymes (P450) in the centrilobular zone of the liver to yield activated peroxidative reactions. Kupffer cells secrete inflammatory cytokines such as TNF-alpha.

Non-alcoholic steatohepatitis (NASH)

Obesity and hyperlipidemia provoke oxidative stresses.

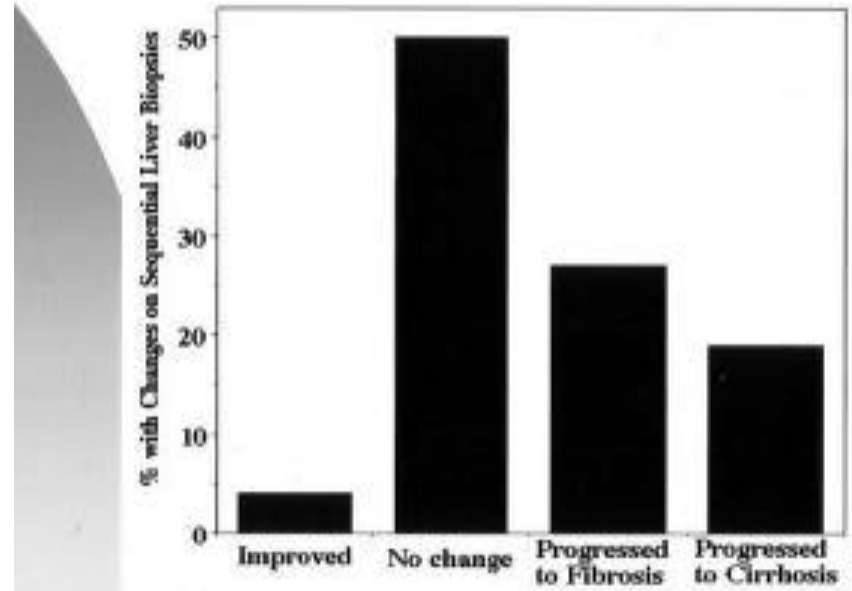
The oxidative stress involves the hepatocytes.

Lipid peroxides accumulate in mitochondria, and the mitochondria are enlarged as giant mitochondria.

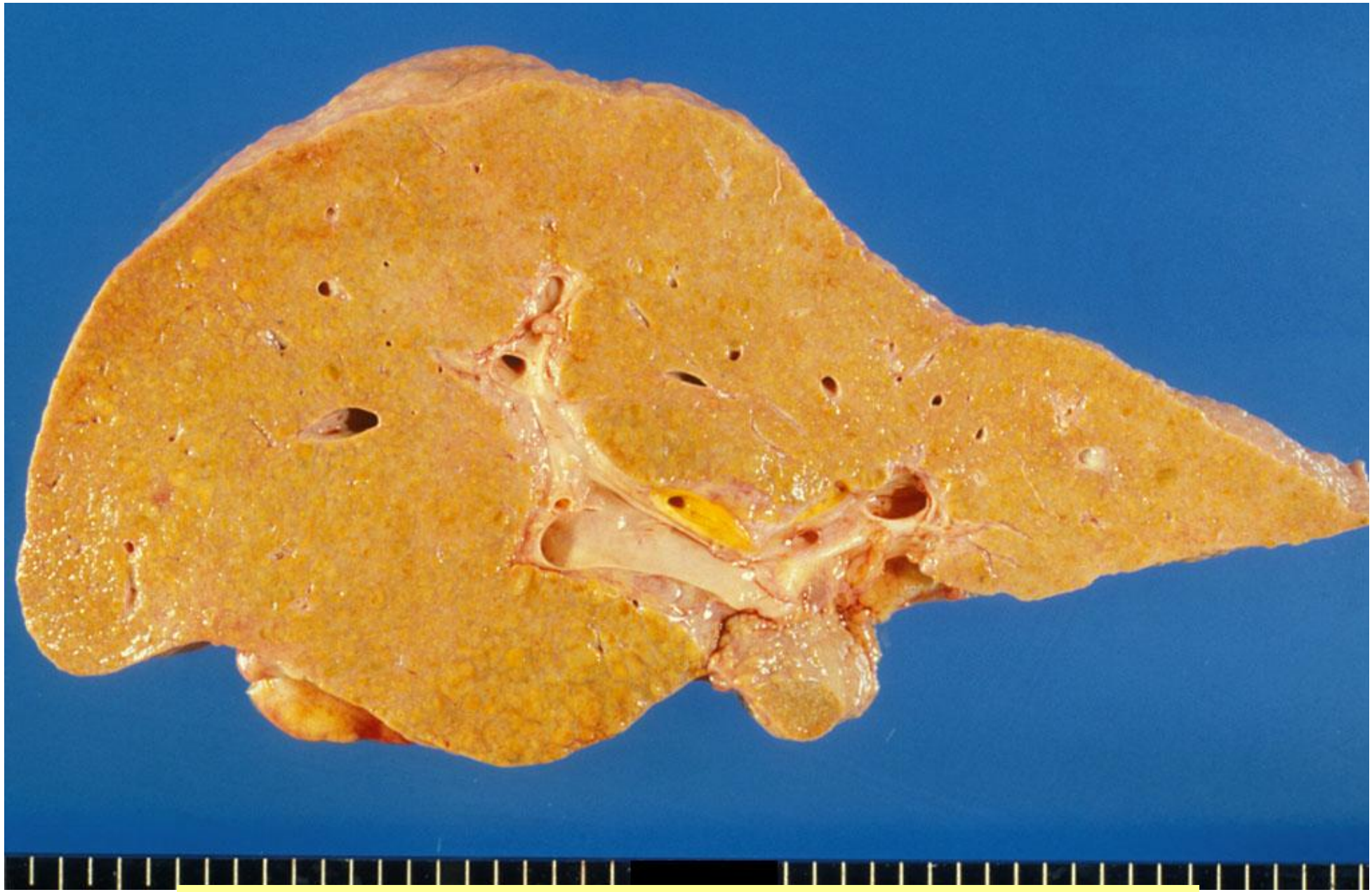
Crystalloid inclusions are deposited in the giant mitochondria.

In the near future, the incidence of hepatitis caused by HBV and HCV will decrease, and NASH should thus be the main cause of liver cirrhosis.

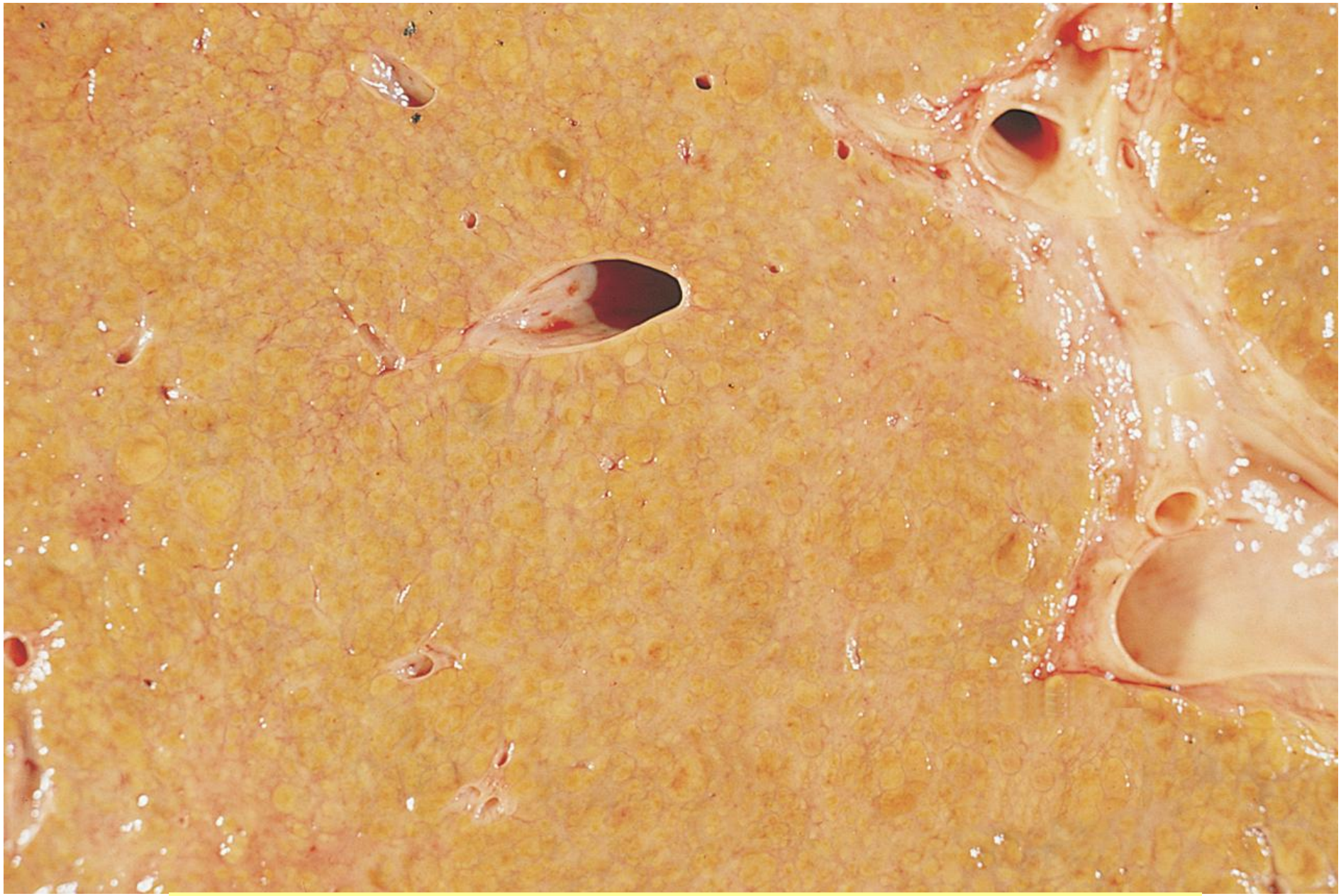
Prognosis of NASH



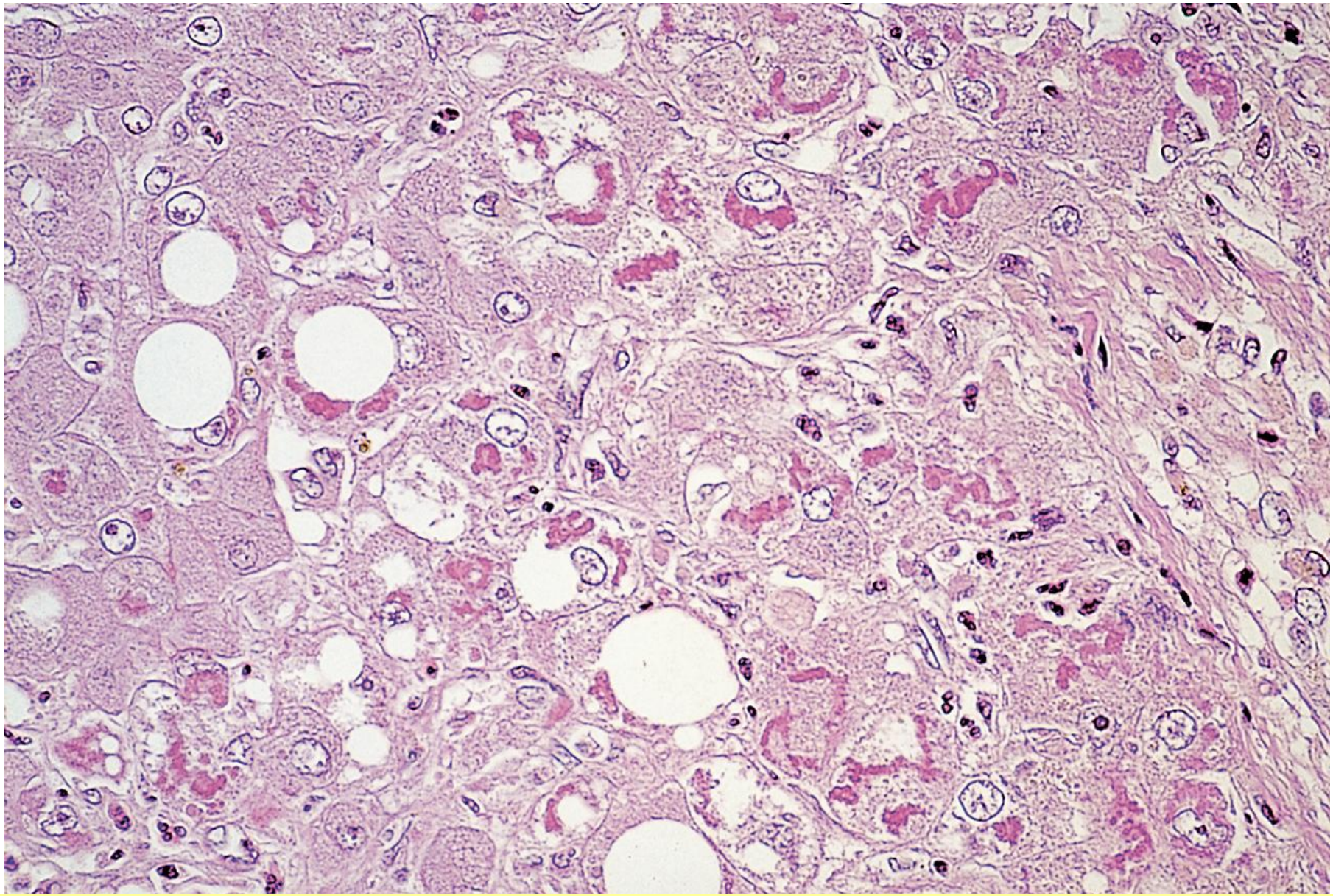
Younossi ZM, et al. Hepatology 35:746-752,2002



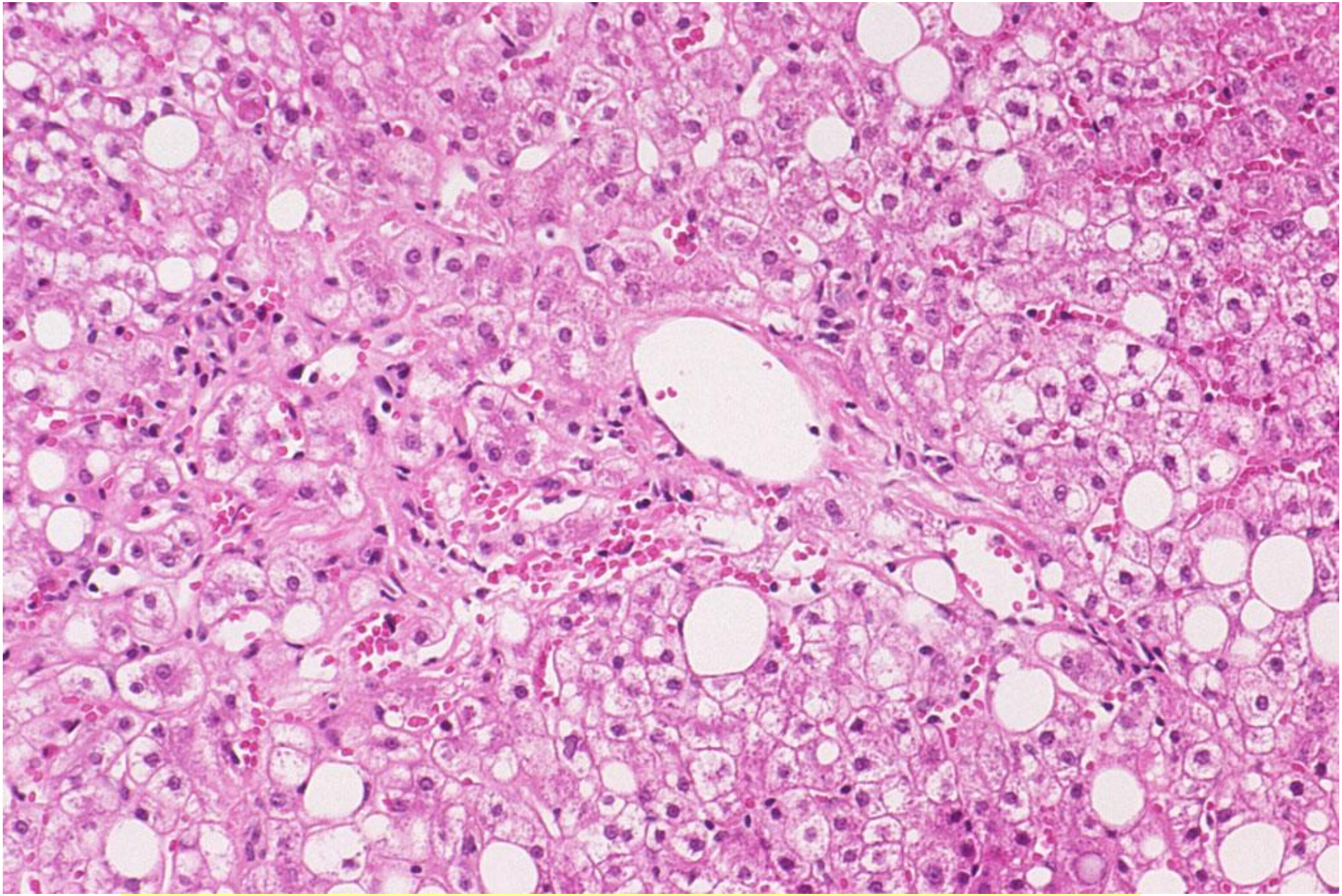
Gross appearance of steatotic liver cirrhosis-1



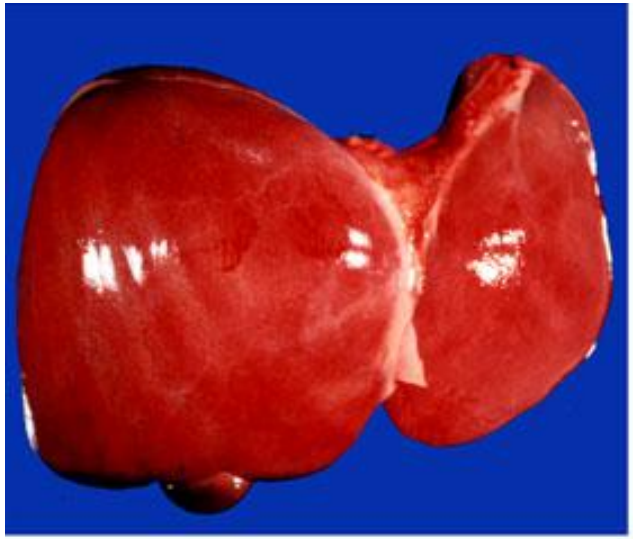
Gross appearance of steatotic liver cirrhosis-2



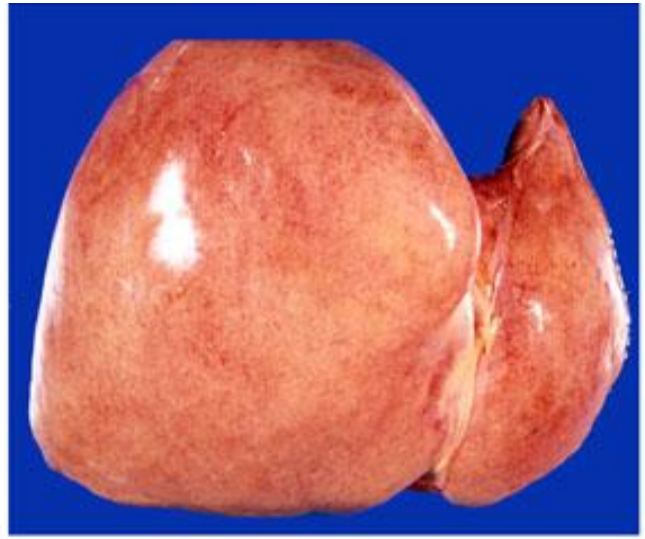
Alcoholic hepatitis with alcoholic hyaline bodies (Mallory bodies) and neutrophilic infiltration, H&E



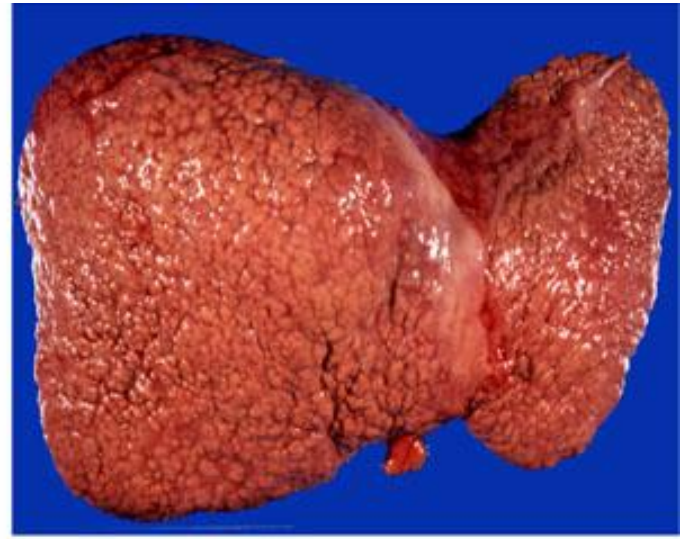
Non-alcoholic steatohepatitis (NASH), H&E



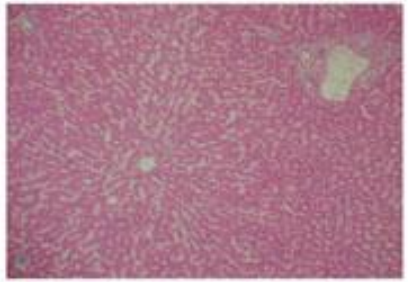
Normal liver

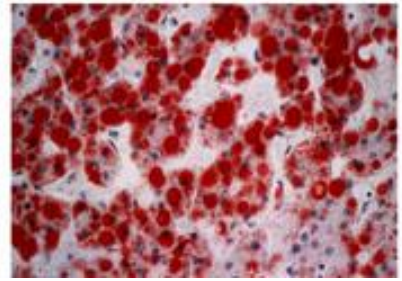


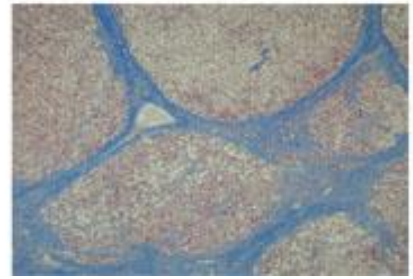
Fatty liver



Steatotic liver cirrhosis







- Alcoholic changes (from fatty liver to liver cirrhosis)
- Obesity-related non-alcoholic steatohepatitis (NASH) progresses to steatotic liver cirrhosis.

Hepatitis virus

1.	Hepatitis A virus	ingestion of raw oyster
2.	Hepatitis B virus	transfusion, sexual intercourse and mother–to–child infection
3.	Hepatitis C virus	transfusion, vaccination, tatooing and drug addiction

HBV and HCV infection can cause chronic hepatitis and HCC.

Acute hepatitis and chronic hepatitis

- Acute hepatitis (most cases subside to cure)

  Hepatitis A virus (not causing chronic hepatitis)

  Hepatitis B virus (horizontal transmission through transfusion and sexual intercourse)

  Hepatitis C virus (rarely causing acute hepatitis)

- Chronic hepatitis (not cured to persist)

  Hepatitis B virus (vertical, mother to child transmission)

  (Hepatitis B virus genomic type A, often persisting as chronic hepatitis)

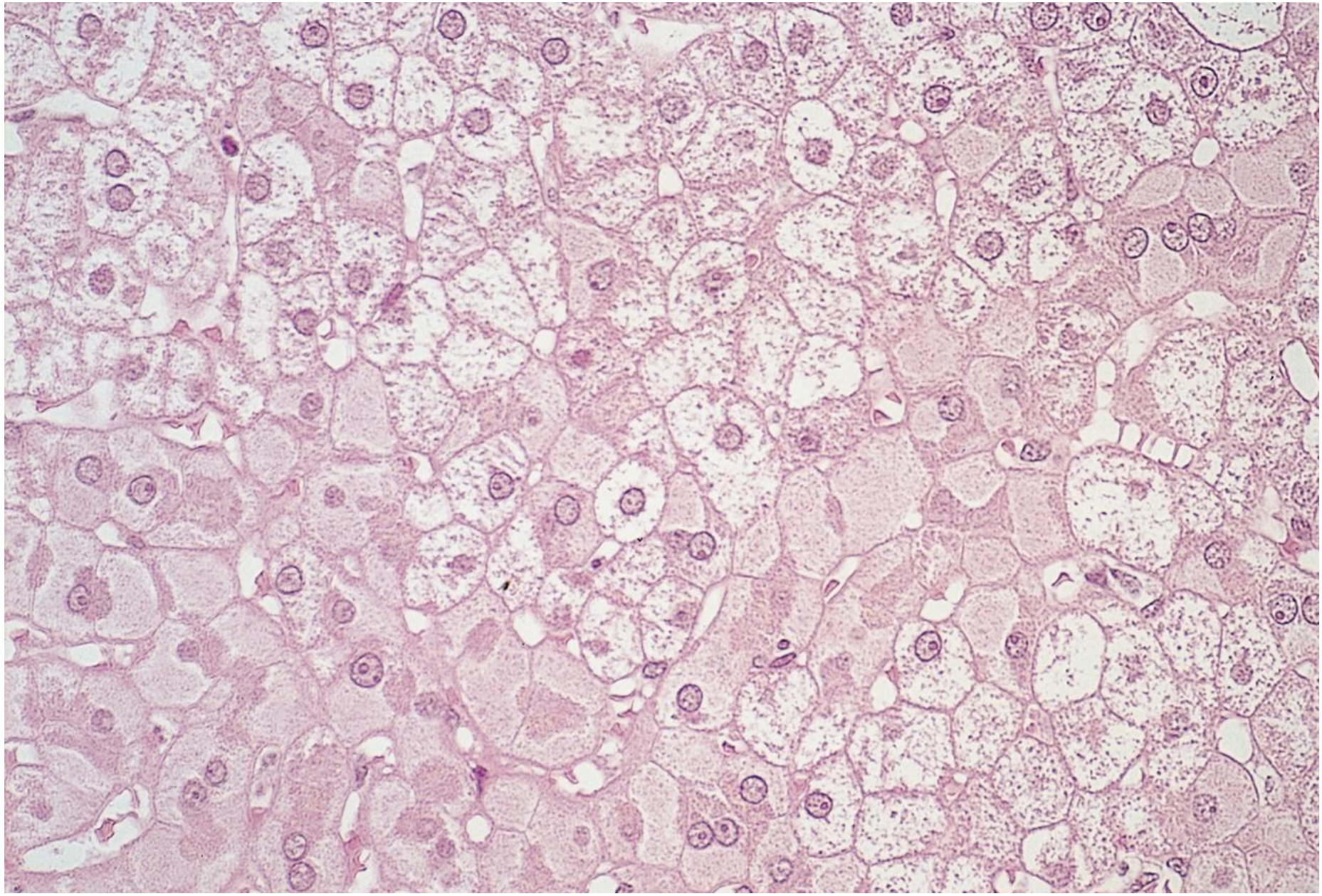
  Hepatitis C virus (commonly persisting as chronic hepatitis)

Healthy carriers of hepatitis virus

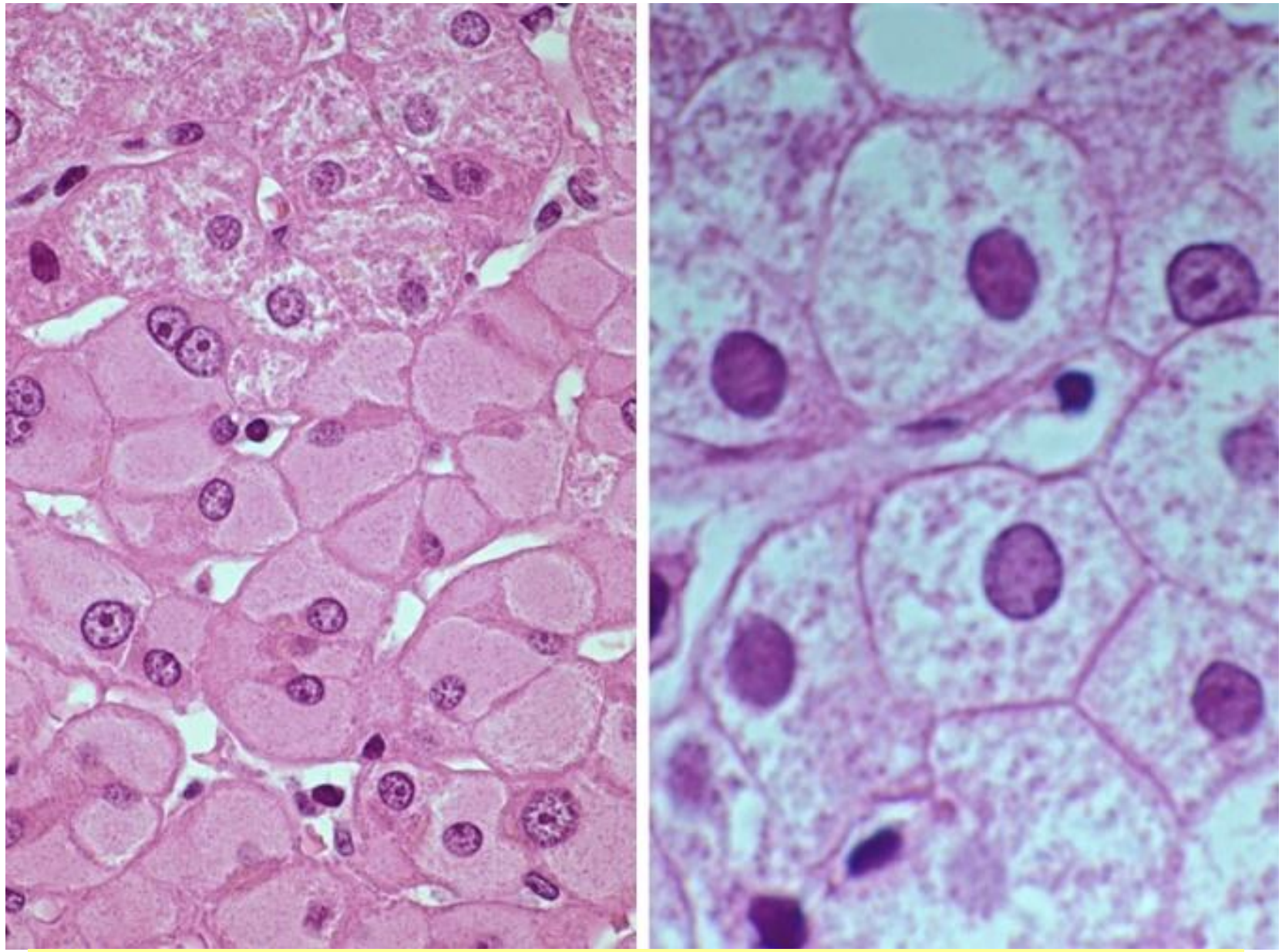
- Normal liver function (as an immune tolerance state)
  - ・Hepatitis A virus never shows the healthy carrier state.
  - ・Hepatitis B virus under vertical transmission often accompanies the healthy carrier state (characterized by “ground-glass hepatocytes”)
  - ・Hepatitis C virus may show the healthy carrier state.
- Healthy carriers may cause vertical viral transmission.

The transmission may occur by transfusion or organ transplantation.

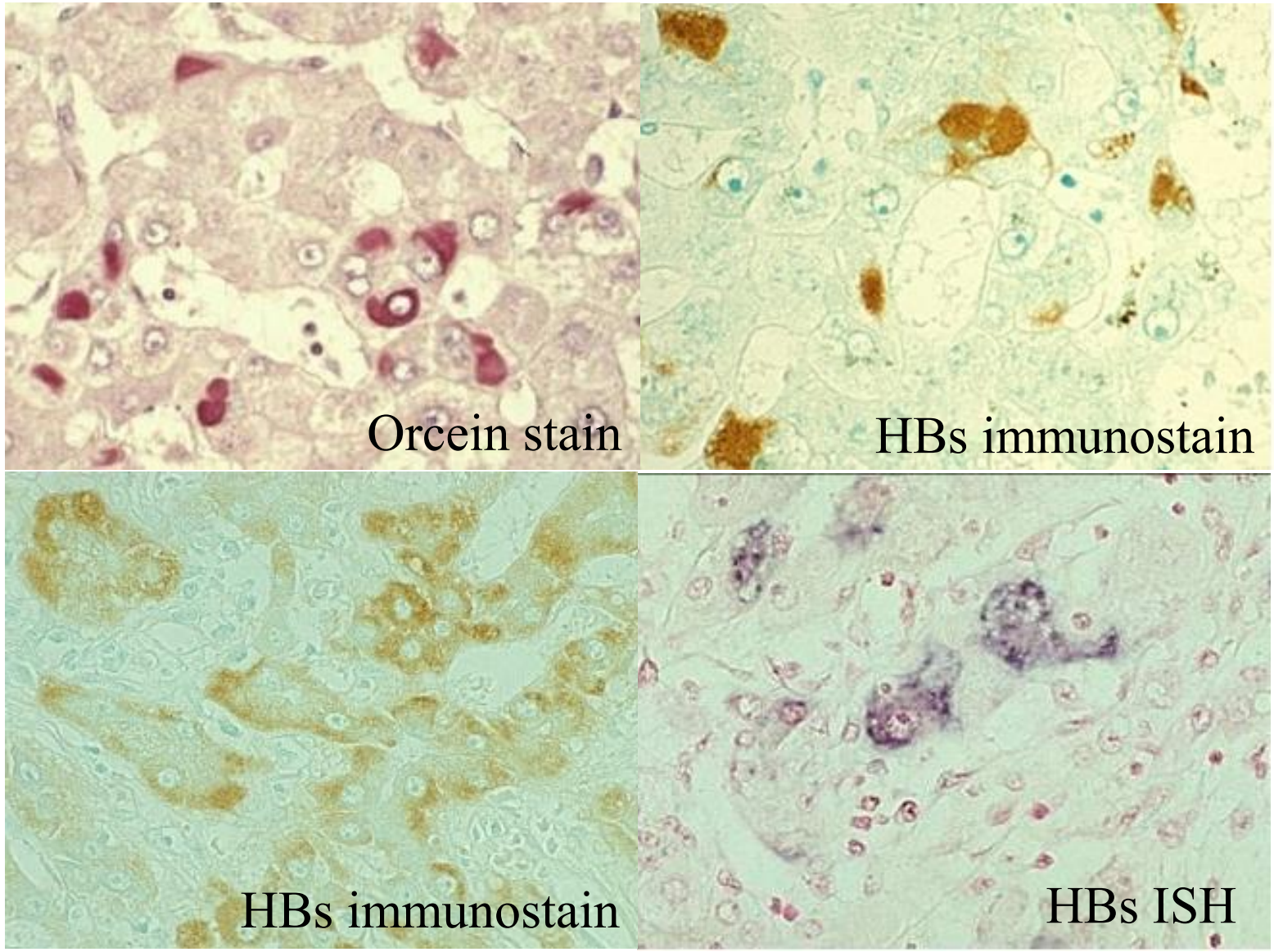
Hepatitis B virus may transmit through sexual intercourse.



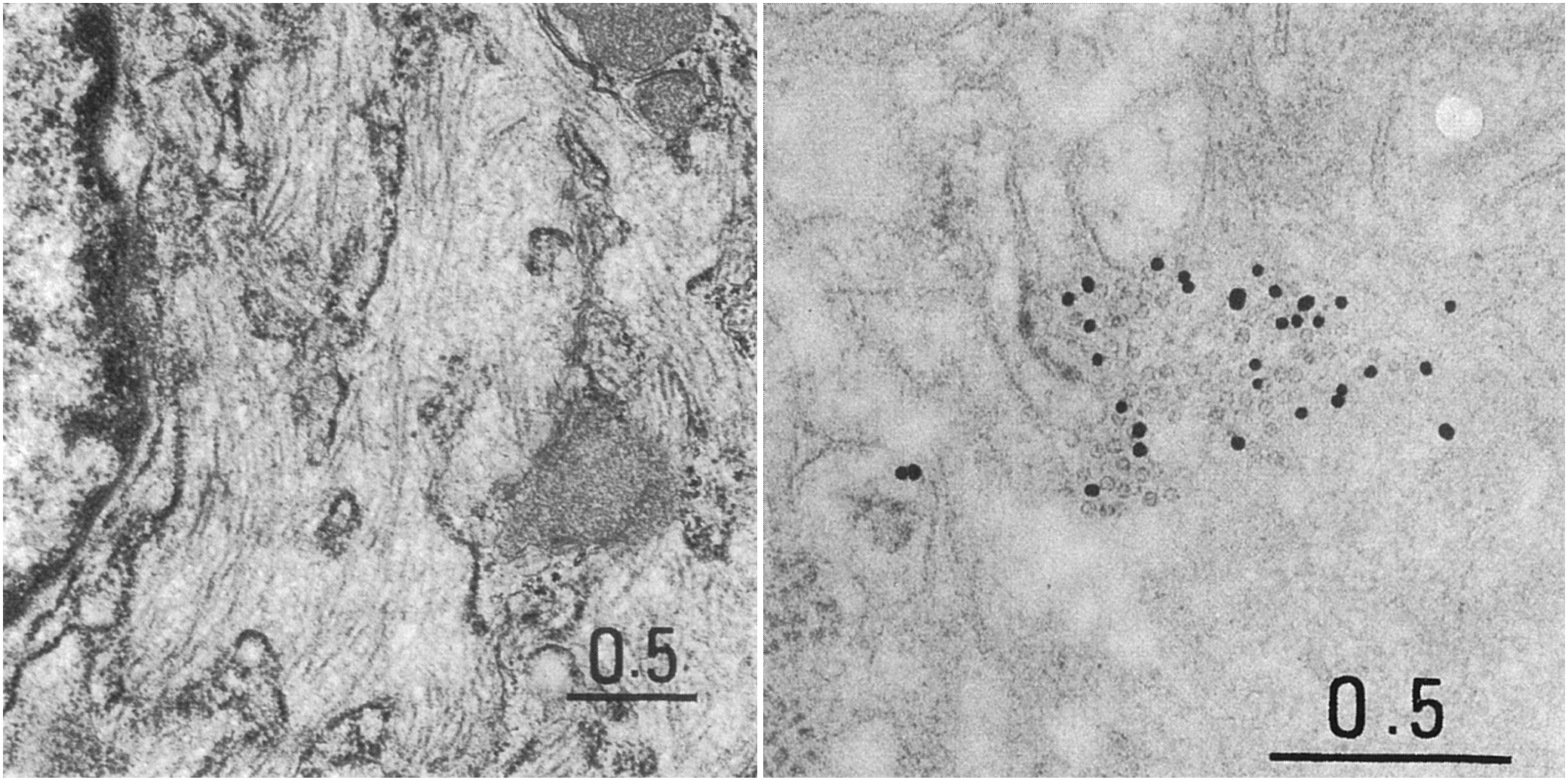
The healthy carrier of HBV with ground-glass hepatocytes (H&E)



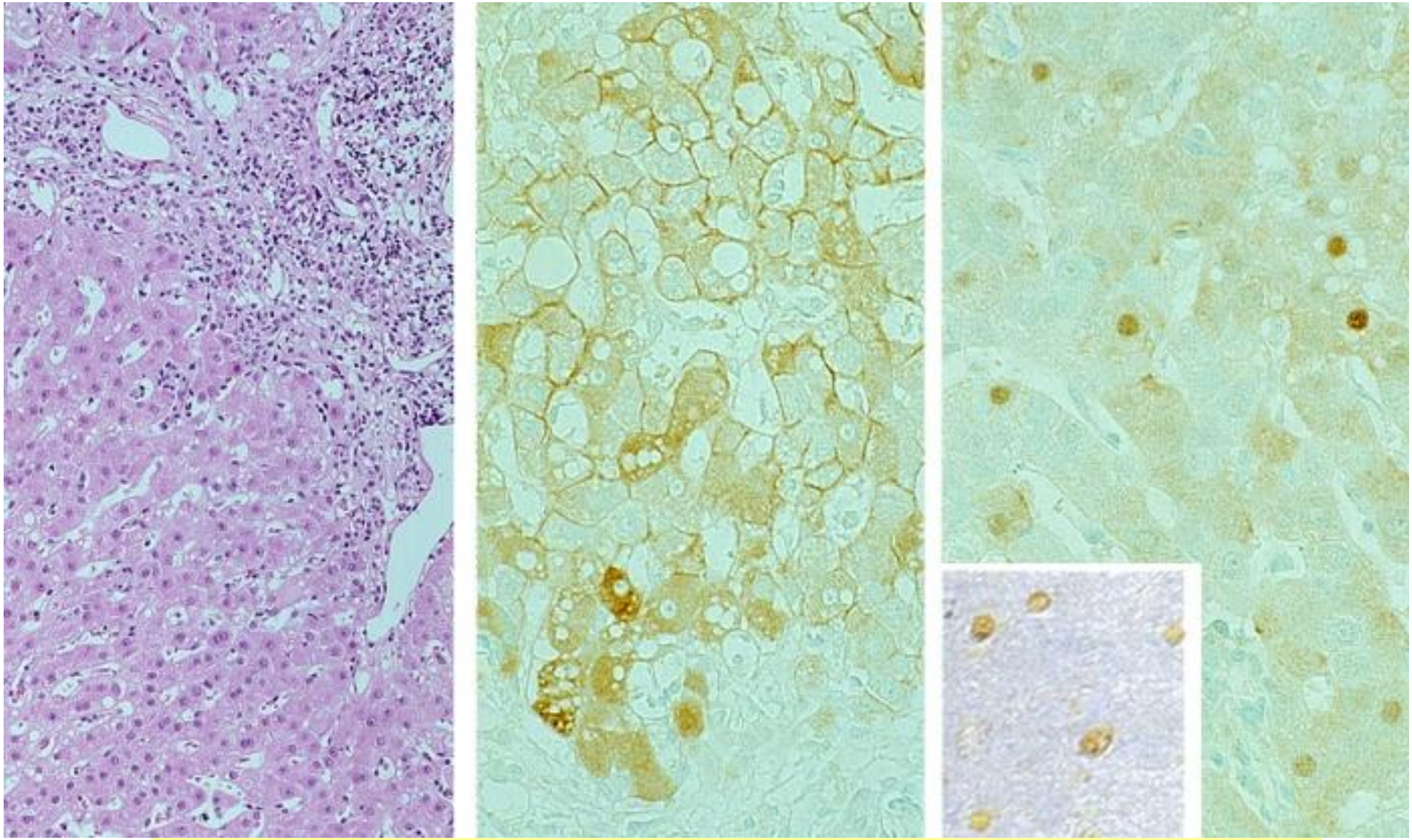
HBV-infected ground-glass hepatocytes (left) and HBc-antigen-positive intranuclear inclusions (the sanded nuclei）(right), H&E



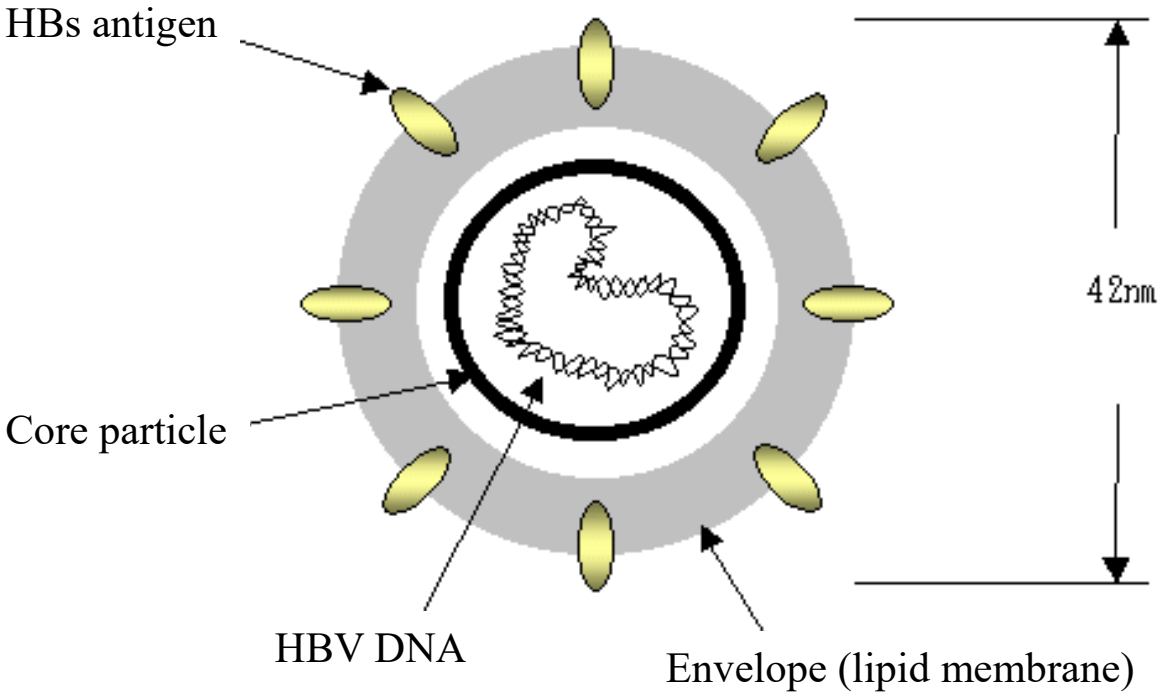
Demonstration of HBs antigen (conventional Orcein stain, immunostaining for HBs antigen and *in situ* hybridization for HBs genome. The upper panels demonstrate the ground-glass hepatocytes.

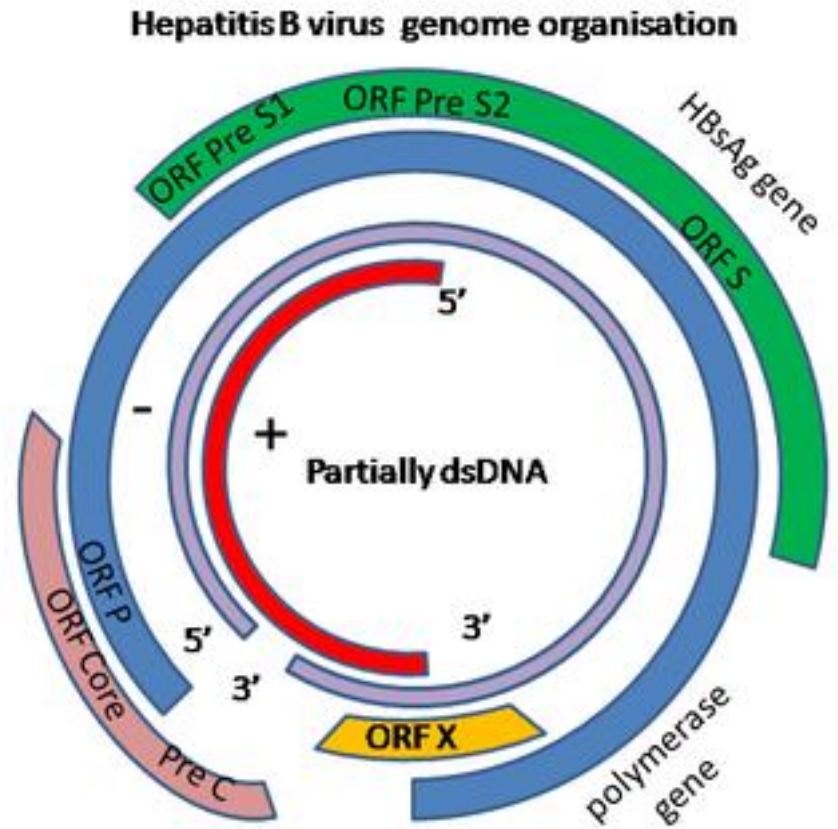


Ultrastructural demonstration of HBs and HBc antigens (left: a ground-glass hepatocyte with accumulation of fibrillar substances, right: HBc antigen-positive small viral particles in the cytoplasm)



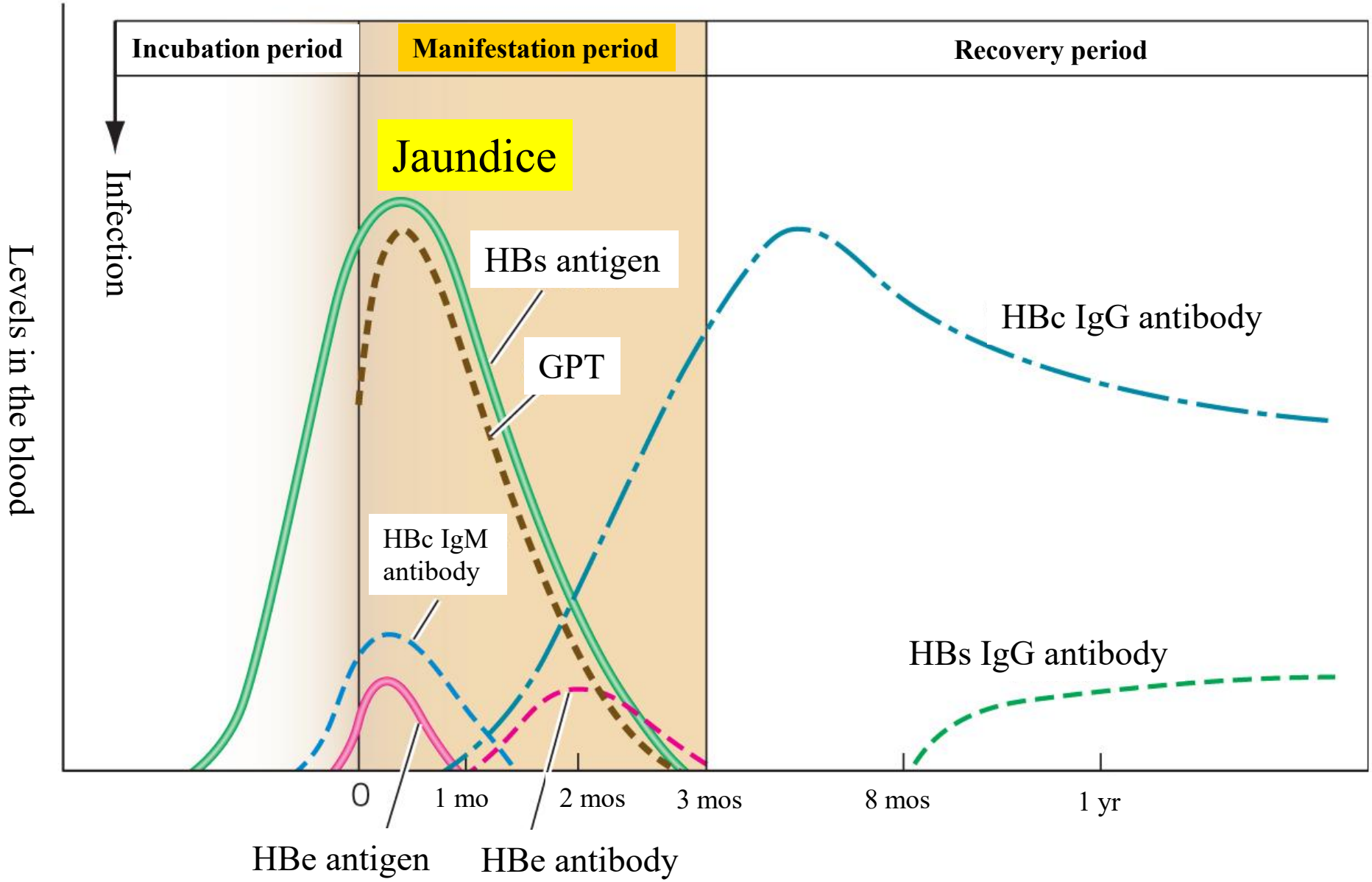
HBV-positive chronic active hepatitis showing a replicative carrier state (left: H&E, center: HBs antigen with a membranous pattern, right; HBc antigen, inset: HBe antigen)



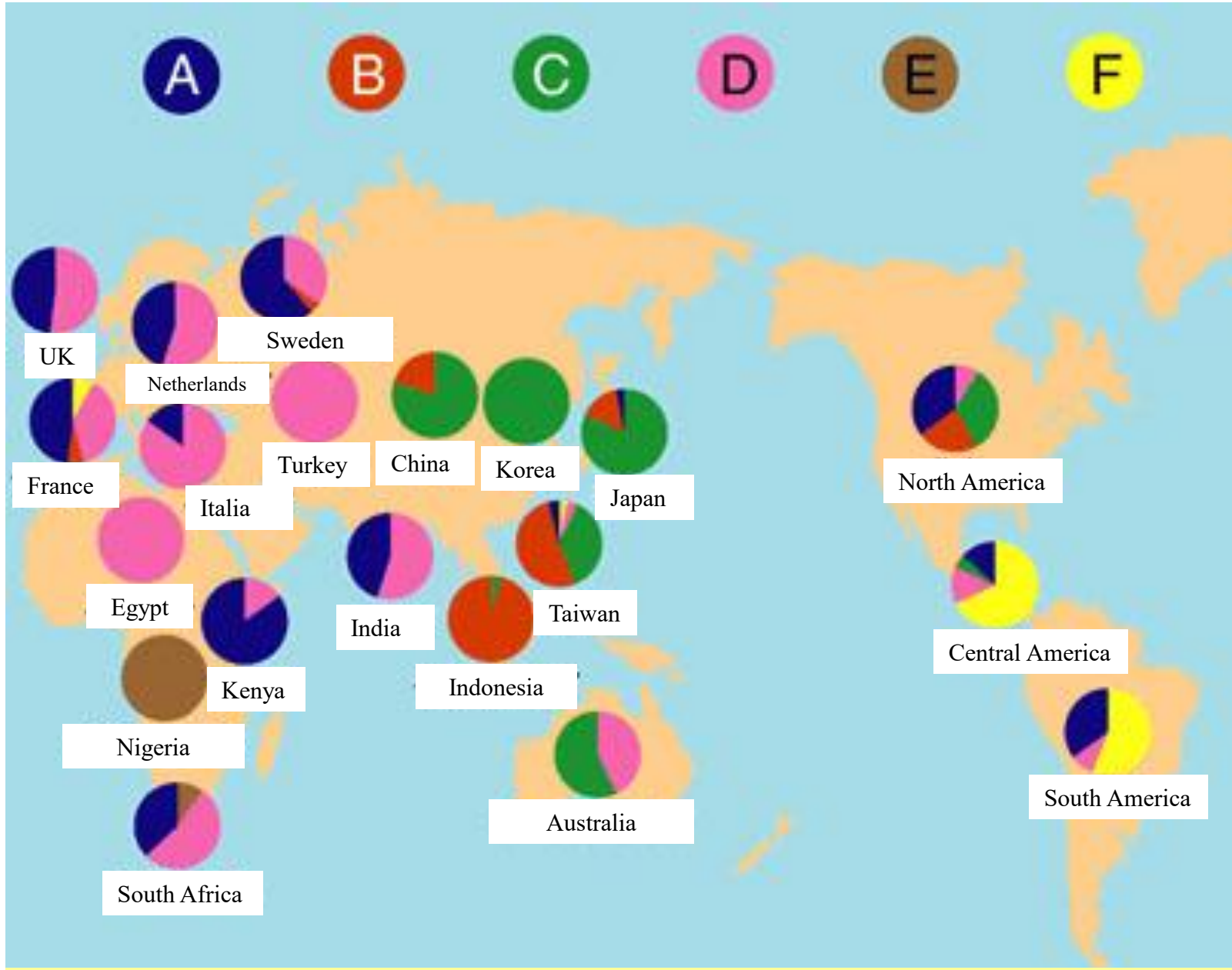


Scheme of HBV particle

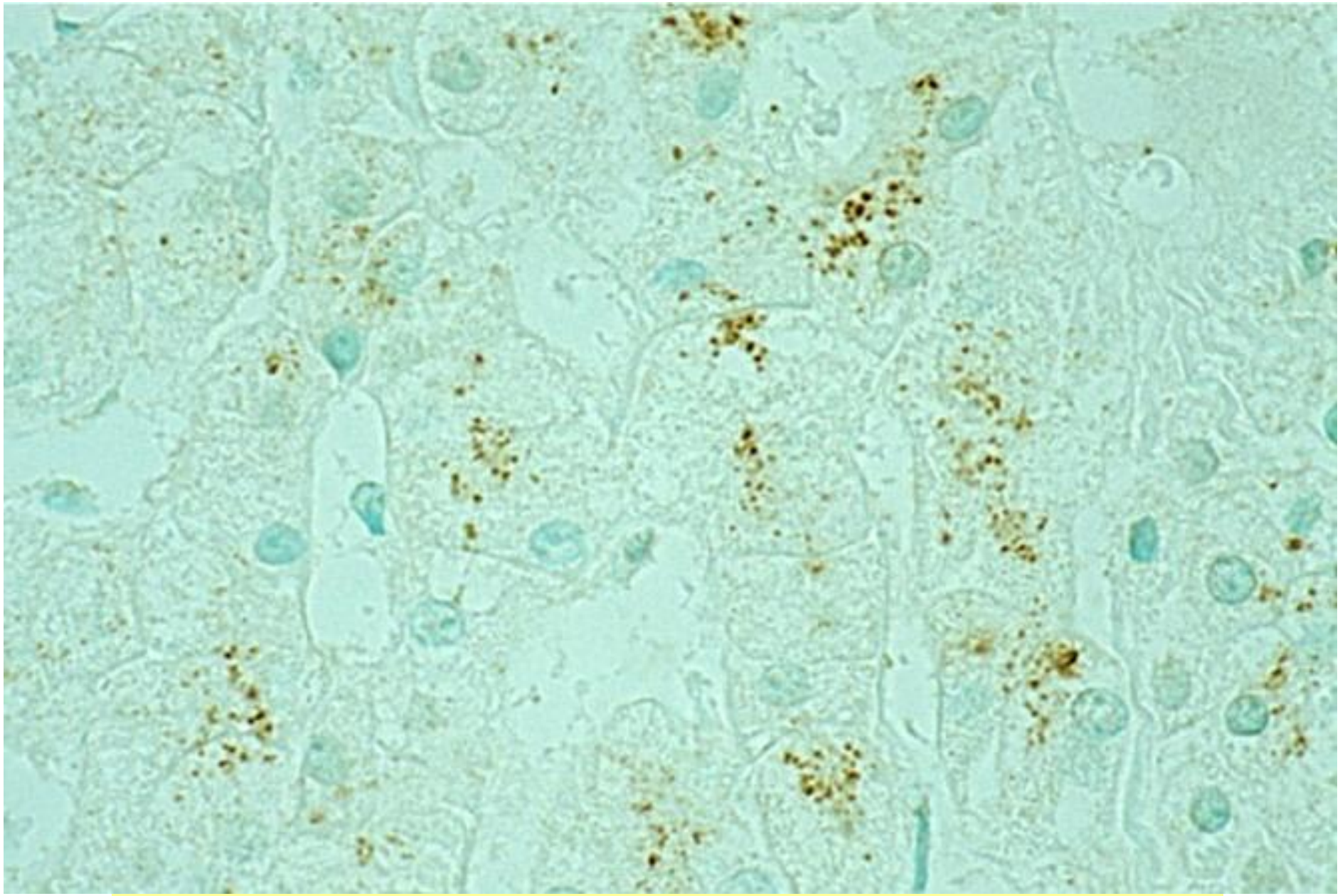
(HBc antigen can not be detected in the serum)



Changes of hepatitis markers in acute hepatitis B virus infection



Genomic types of HBV（type C predominates in Japan）



HCV-induced chronic hepatitis (Immunostain for HCV antigen)

Vaccines for hepatitis virus

- Vaccines induce neutralizing antibodies

  Hepatitis A virus (inducing neutralizing HAV antibodies)

  Hepatitis B virus (inducing neutralizing HBs antibodies)

  Hepatitis C virus (no vaccine available at present)

  Yellow fever virus (vaccination may be requested at immigration)
- HBV antibodies (HBs antibody, HBc antibody and HBe antibody)

  ～Only HBs antibodies belong to neutralizing antibodies.～
- HCV antibodies＝the marker of HCV infection

  (no neutralizing antibodies induced)

Fulminant hepatitis

- A type of acute viral hepatitis with a poor prognosis

Hepatitis A virus (infrequent)

Hepatitis B virus (hepatocellular injury through immune reactions against the virus)

Hepatitis C virus (very rare)

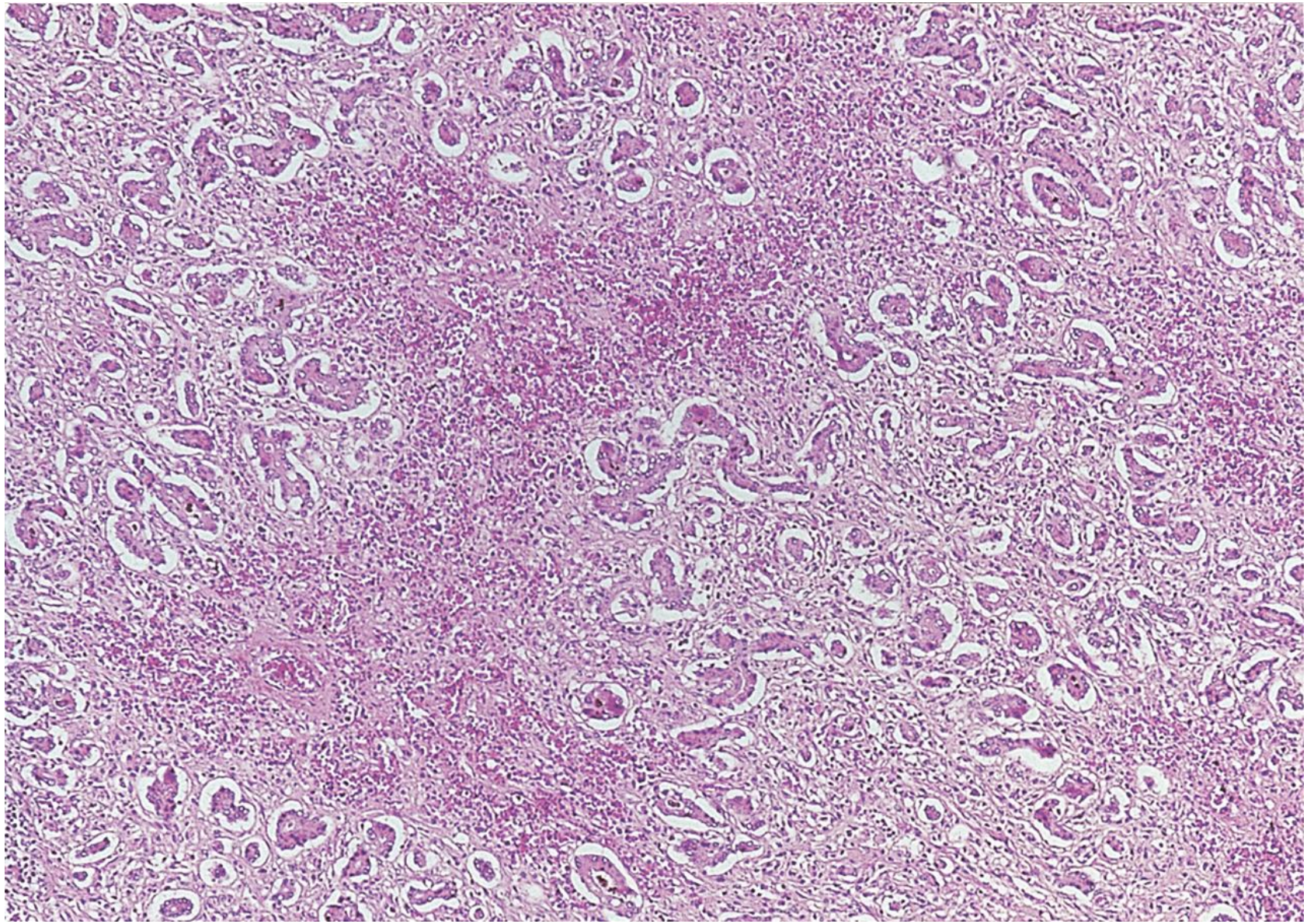
Yellow fever virus (in tropical areas, mediated by mosquitos)

- Non-viral fulminant hepatic injury

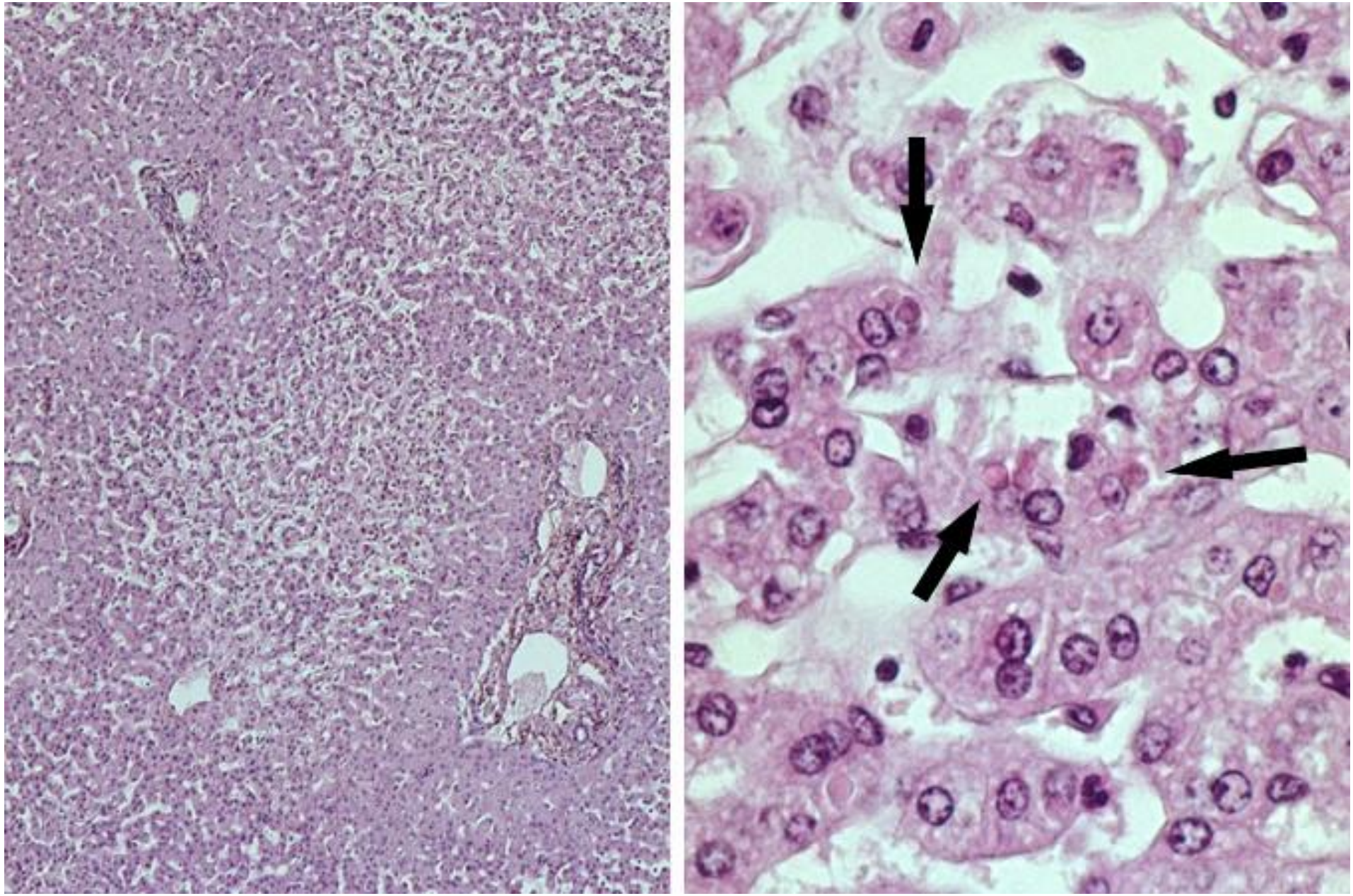
Drug-induced (anesthetics=Halothane, acetoaminophen, etc)

Mushroom intoxication (*Amanita phalloides*, *Amanita virosa*)

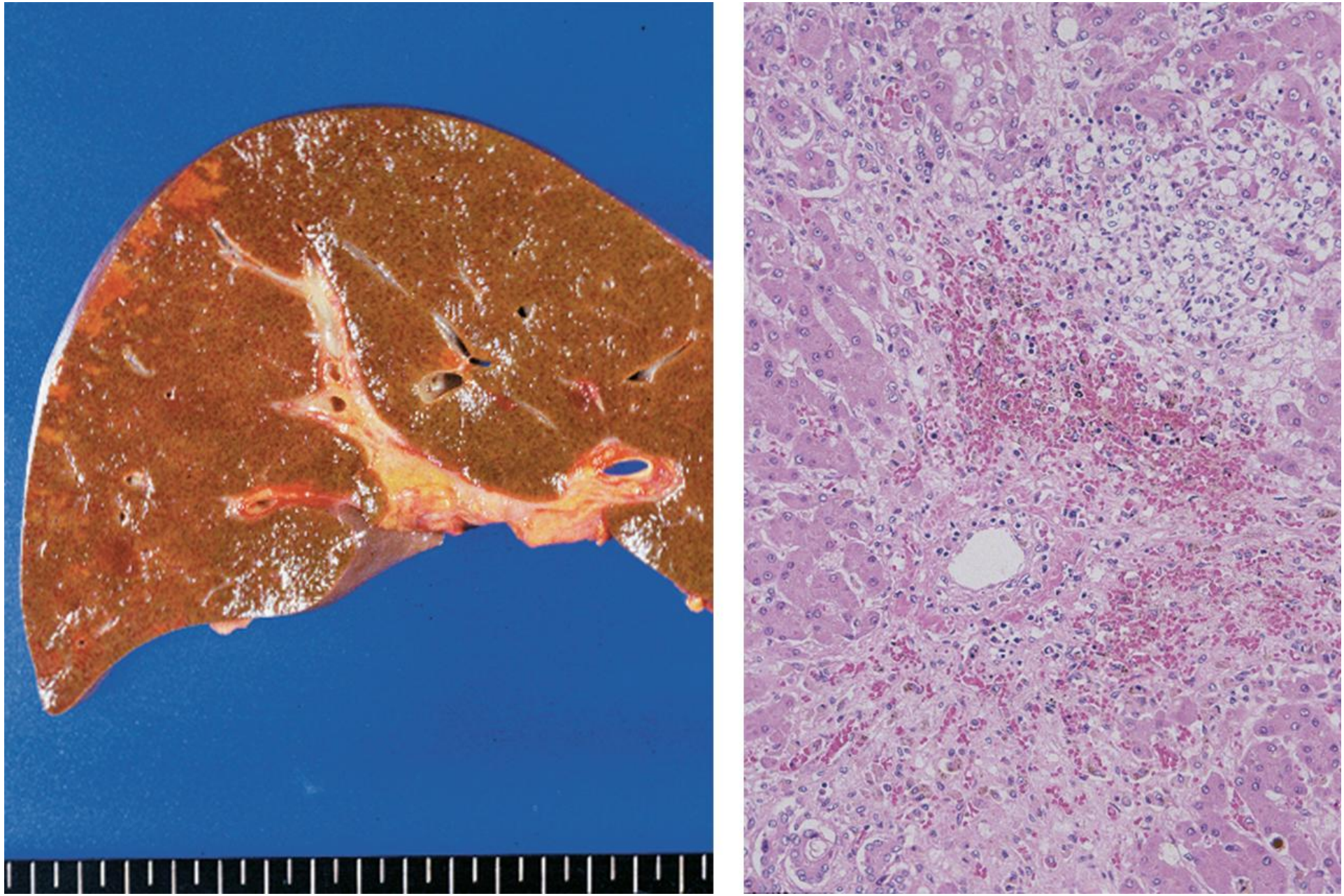
Toxins (carbon tetrachloride, yellow phosphorus, etc)



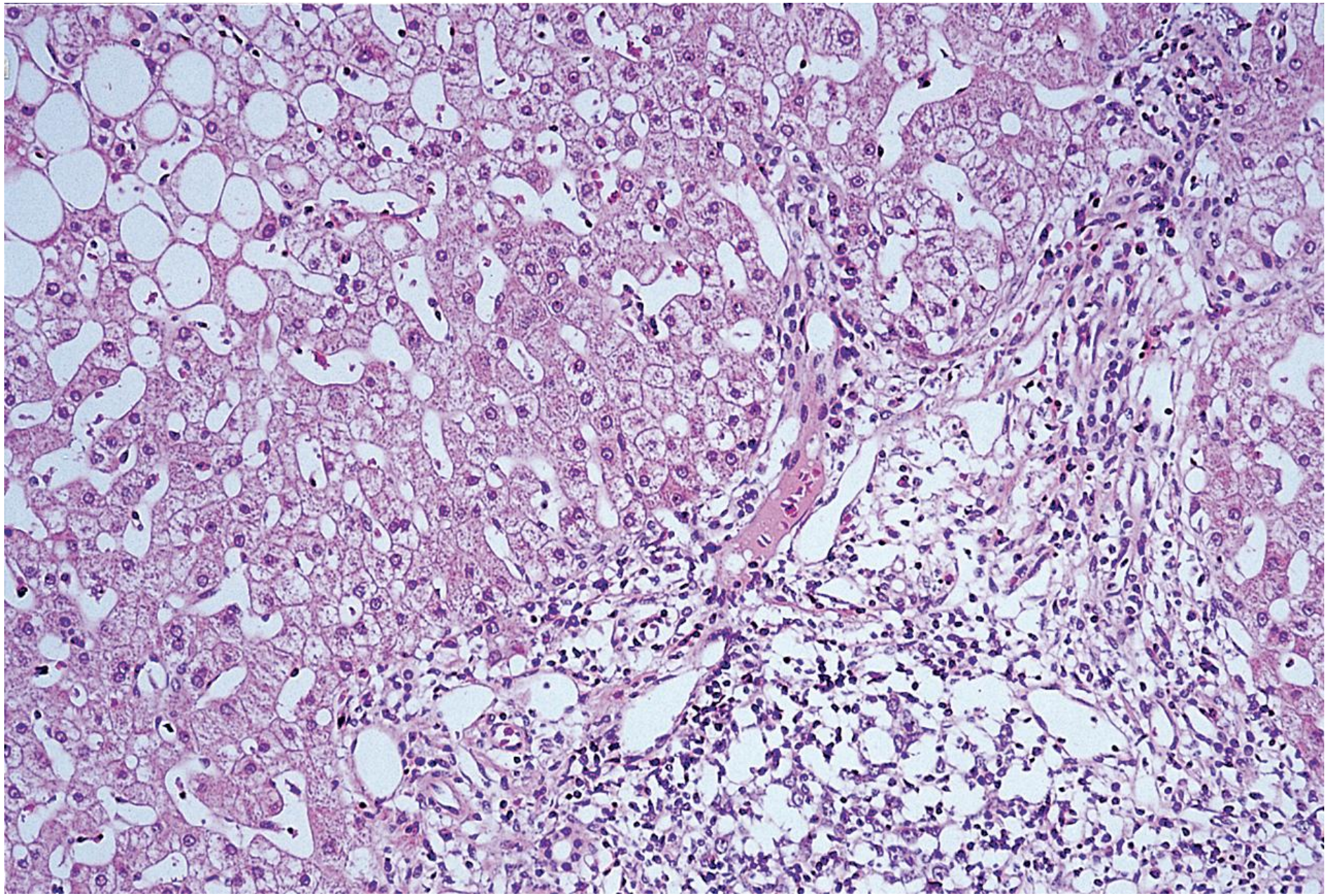
Fulminant hepatitis (non-A, non-B, non-C, non-autoimmune): total loss of hepatocytes with the growth of pseudobile duct cells



Yellow fever (fulminant type, H&E. Arrows: Councilman bodies=eosinophilic inclusion bodies



Halothane hepatitis (fulminant type, left: macro, right: H&E）

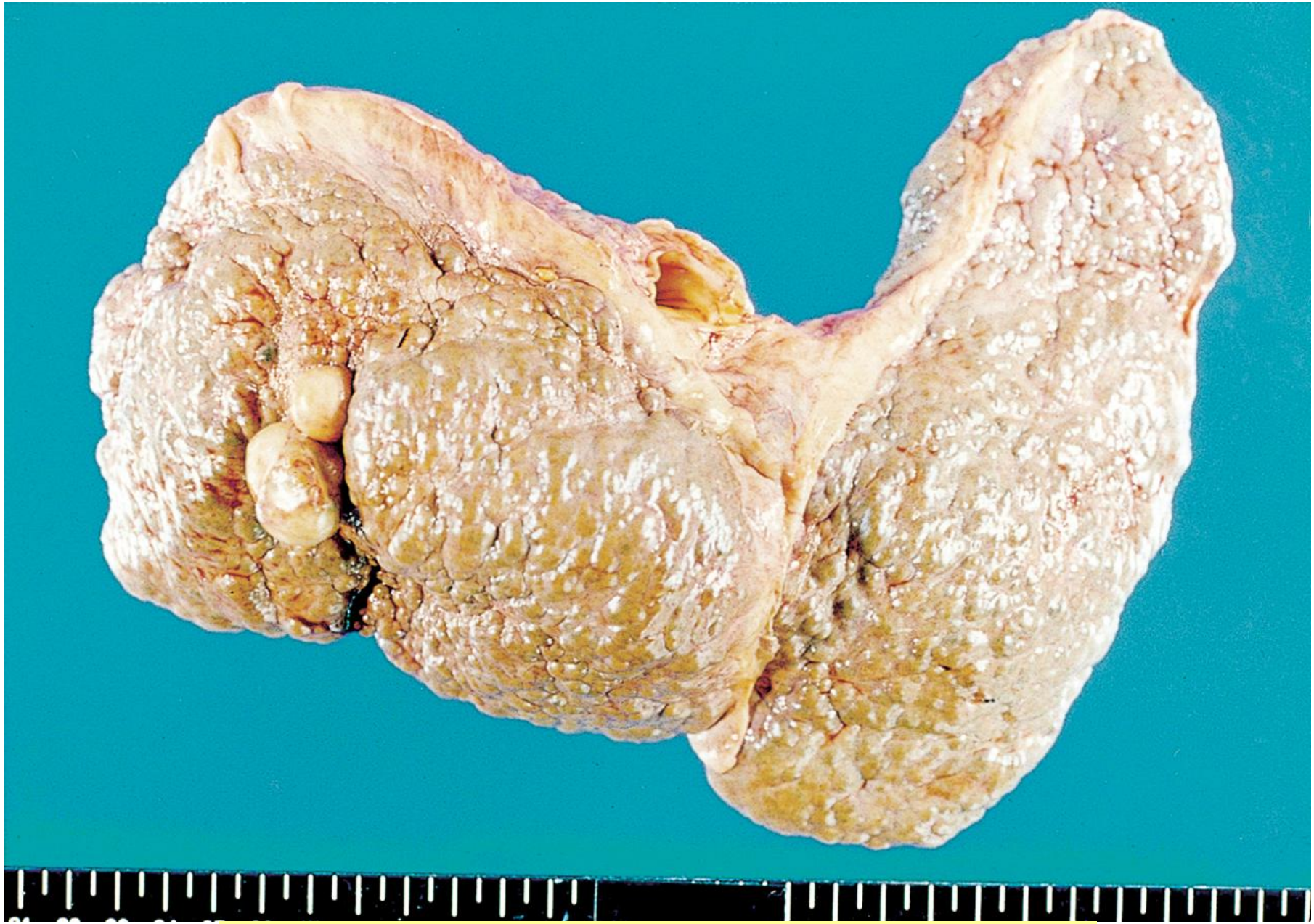


Chronic active hepatitis (HCV infected: fibrosis and piecemeal necrosis)

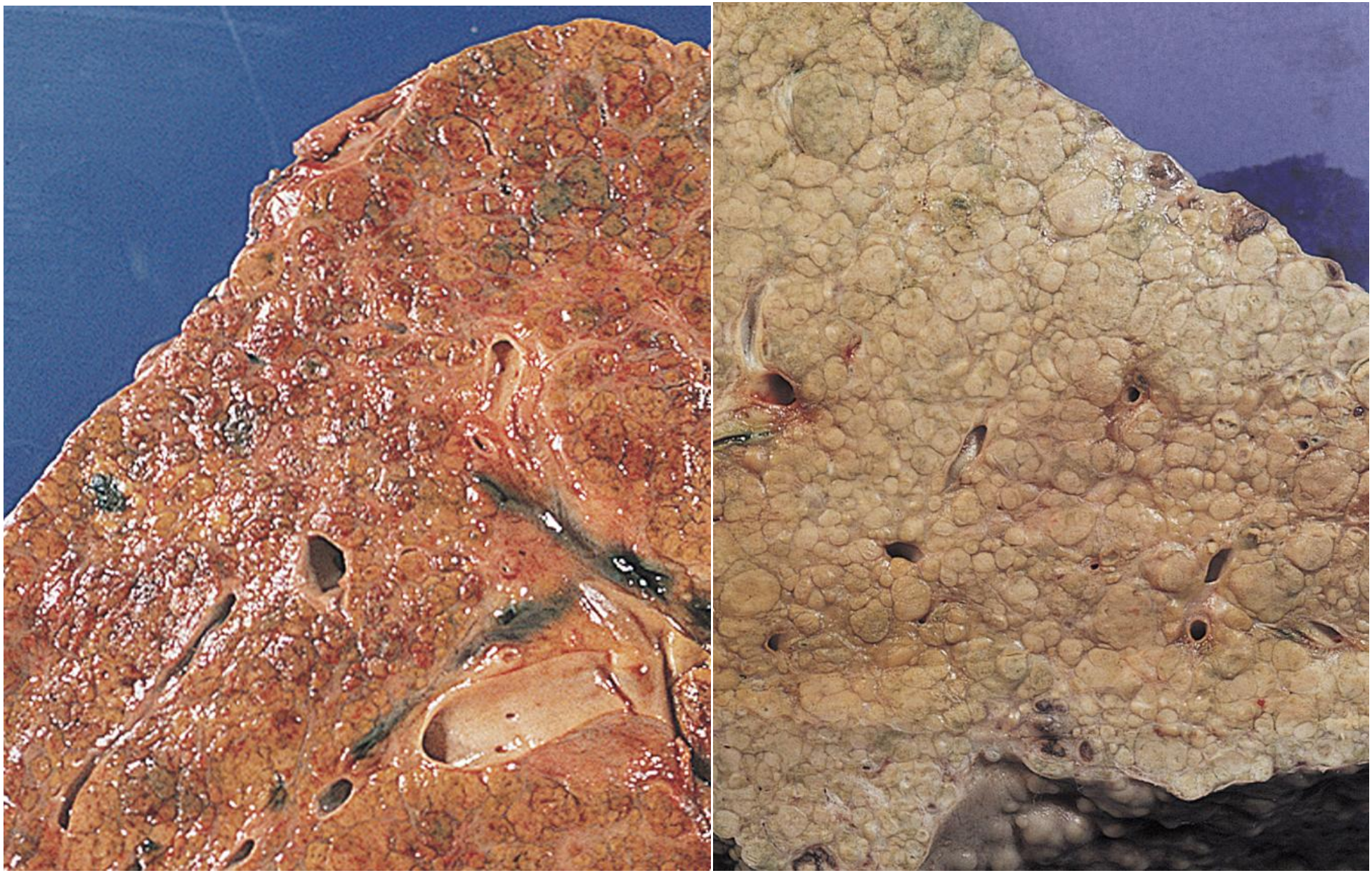
Clinical states of HBV infection classified by viral markers

HBs antigen	HBs antibody	HBe antigen	HBe antibody	HBV-DNA	Clinical state
(-)	(+)	(-)	(-)	(-)	History of infection/healed state
(+)	(-)	(-)	(+)	(-)	HBe antibody-positive healthy carrier
(+)	(-)	(+)	(-)	(+)	HBe antigen-positive asymptomatic carrier
(+)	(-)	(+)	(-)	(+)	Chronic type B hepatitis

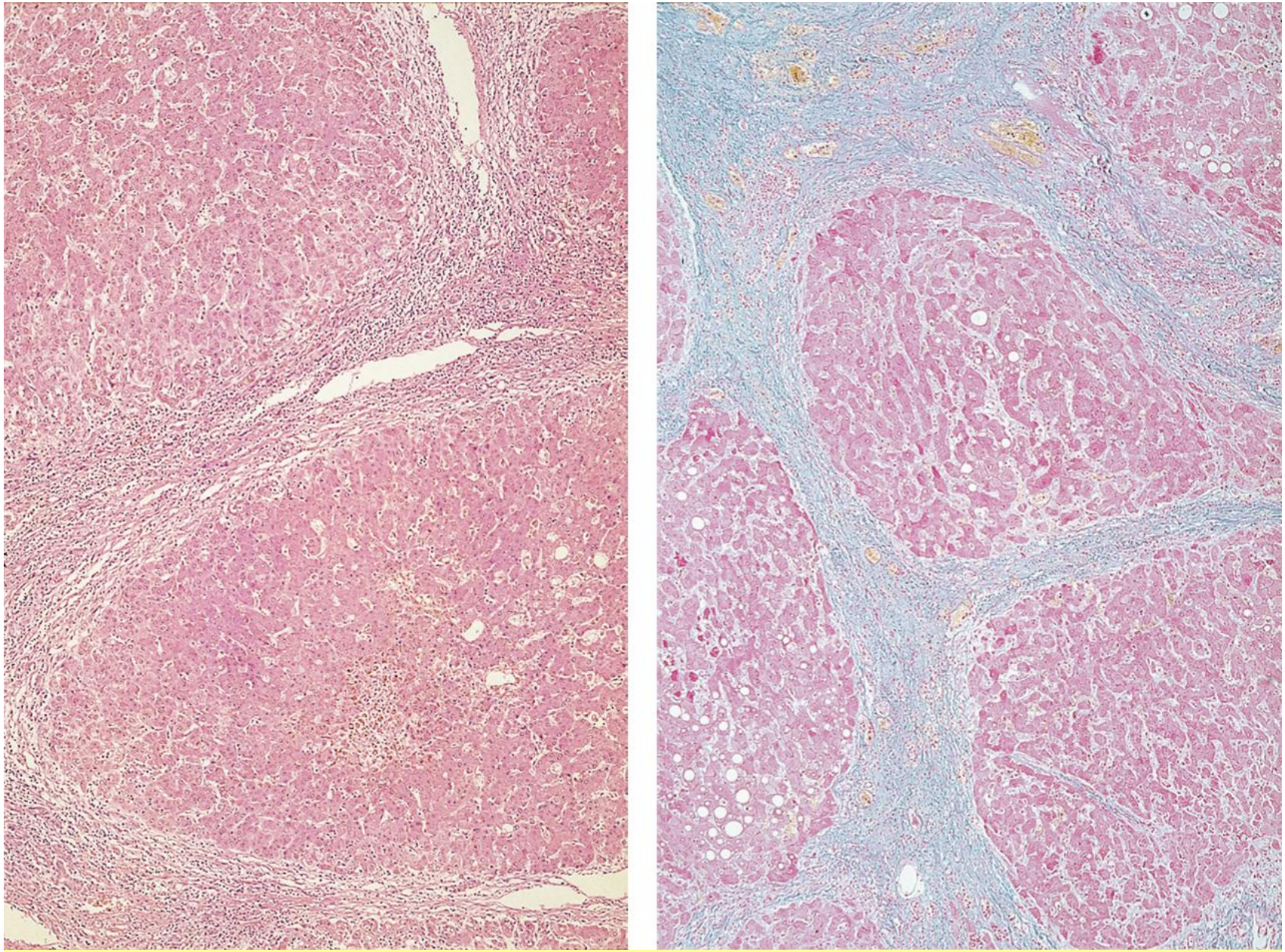
Major seroconversion ＝HBs antigen-positive→HBs antibody-positive
Minor seroconversion ＝HBe antigen-positive→HBe antibody-positive (HBs antigen persisted)



Liver cirrhosis (HCV-infected, focally with HCC)



Cut surfaces of liver cirrhosis (left: fresh liver tissue, right: after formalin fixation)



Microscopic features of liver cirrhosis (left: H&E, right: Azan staining）

Colateral venous pathways associated with portal hypertension secondary to liver cirrhosis

1) **Esophageal veins with esophageal varices**
   ～Rupture of esophageal varices may be lethal～
2) **Hemorrhoidal veins of the anus with hemorrhoids**
   ～Hemorrhoids are often associated with liver cirrhosis～
3) **Periumbilical abdominal veins with caput Medusae**
   ～Caput medusae (engorged superficial epigastric veins) shows apparent similarity to Medusa's head, having venomous snakes in place of hair in Greek mythology～

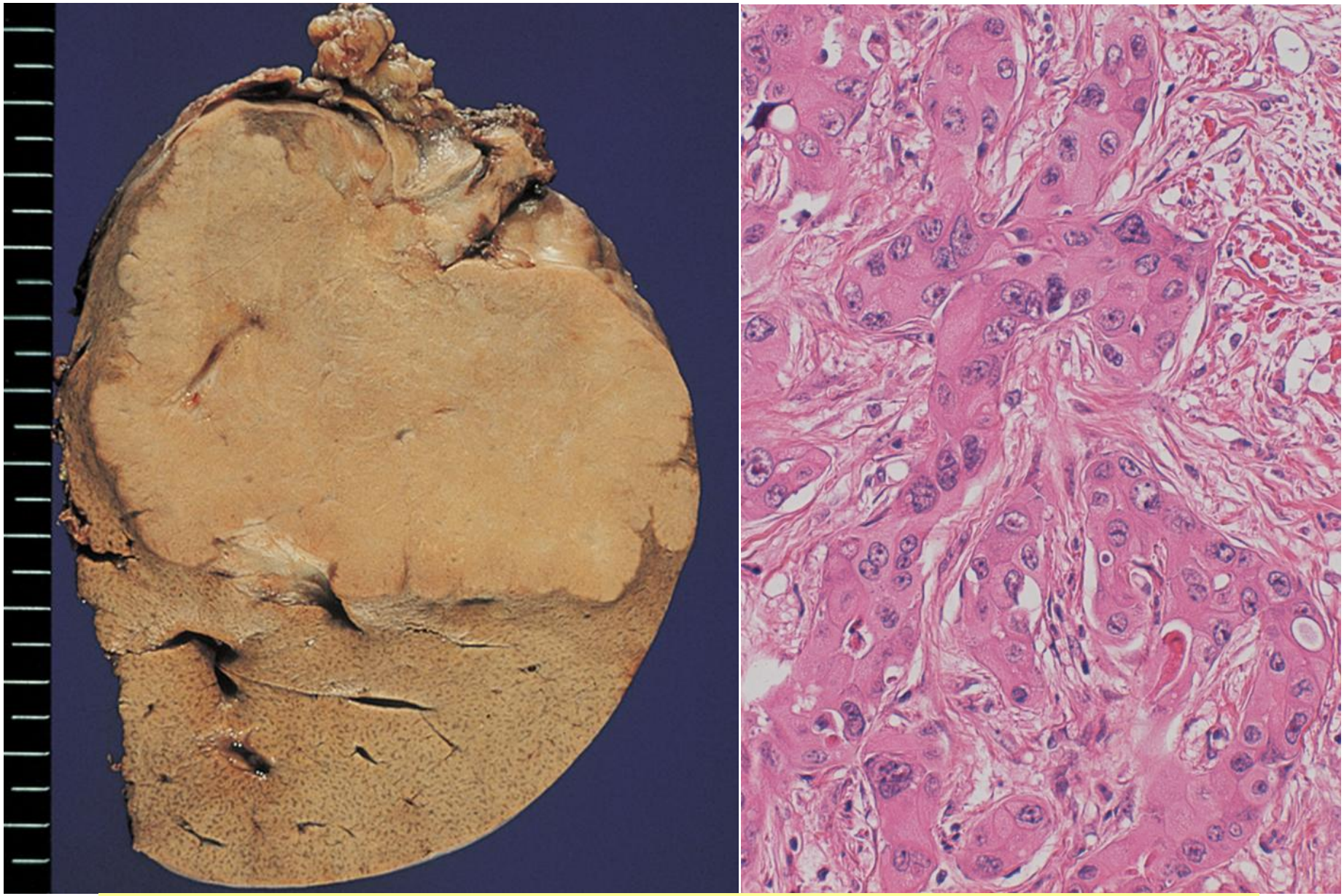
Two types of liver cancer

1. **Hepatocellular carcinoma** (90%): caused by hepatitis virus

2. **Cholangiocellular carcinoma** (10%): etiology unknown

   Opistorchis viverrini infestation in Thailand

   Occupational exposure to dichloromethane



Cholangiocellular carcinoma without cirrhotic background (left: gross features after formalin fixation, right: adenocarcinoma, H&E）

The occurrence of hepatocellular carcinoma

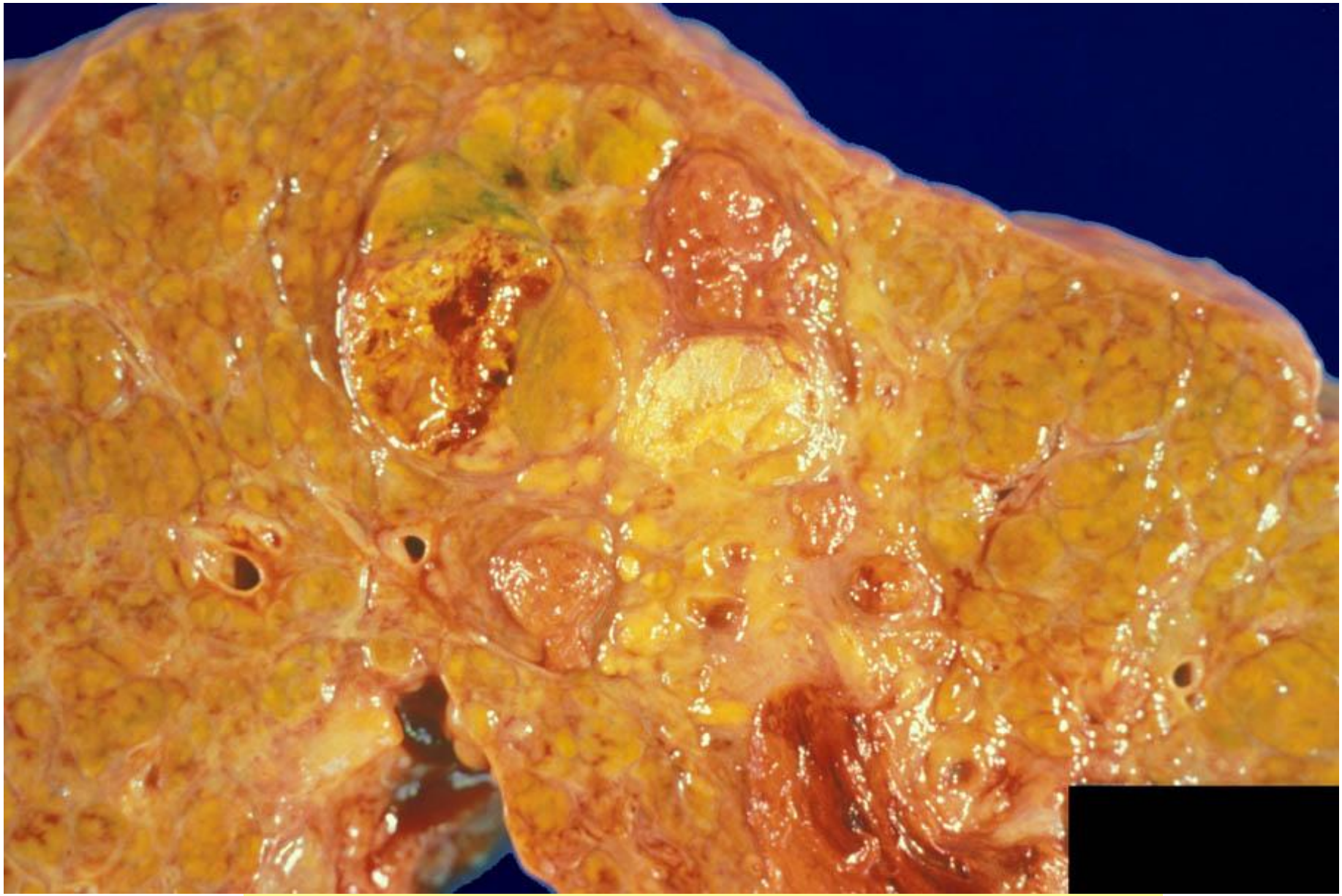
Viral hepatitis → Liver cirrhosis → HCC

HCC in younger generation (<49 years): mainly HBV infection

HCC in older generation (>50 years): mainly HCV infection

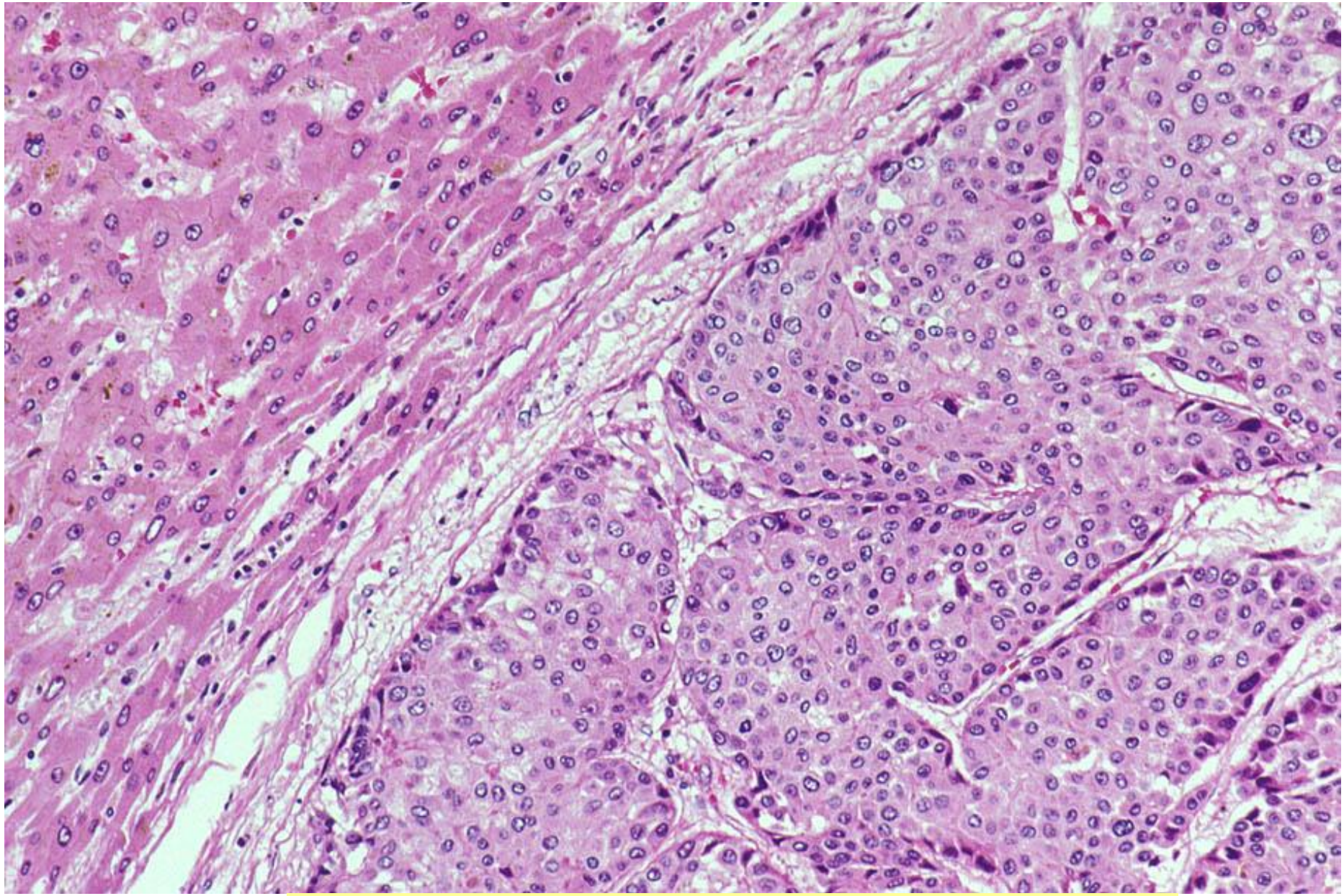
HCC in near future: mainly caused by obesity

～Non-alcoholic steatohepatitis (NASH)～



Liver cirrhosis with hepatocellular carcinoma (HCC)
(green color indicates bile production by cancer cells)

Liver cirrhosis with hepatocellular carcinoma (portal vein invasion+)



Liver cirrhosis with hepatocellular carcinoma.
Cirrhotic liver is compressed by the HCC cells (H&E).

Cause of death of patients with HCC

1. Hepatic failure with hepatic coma due to exacerbation of liver cirrhosis
2. Rupture of esophageal varices due to portal hypertension caused by liver cirrhosis
3. Advanced HCC (with systemic hematogenous metastasis or extensive involvement of the liver tissue or venous invasion into the portal vein or hepatic vein)

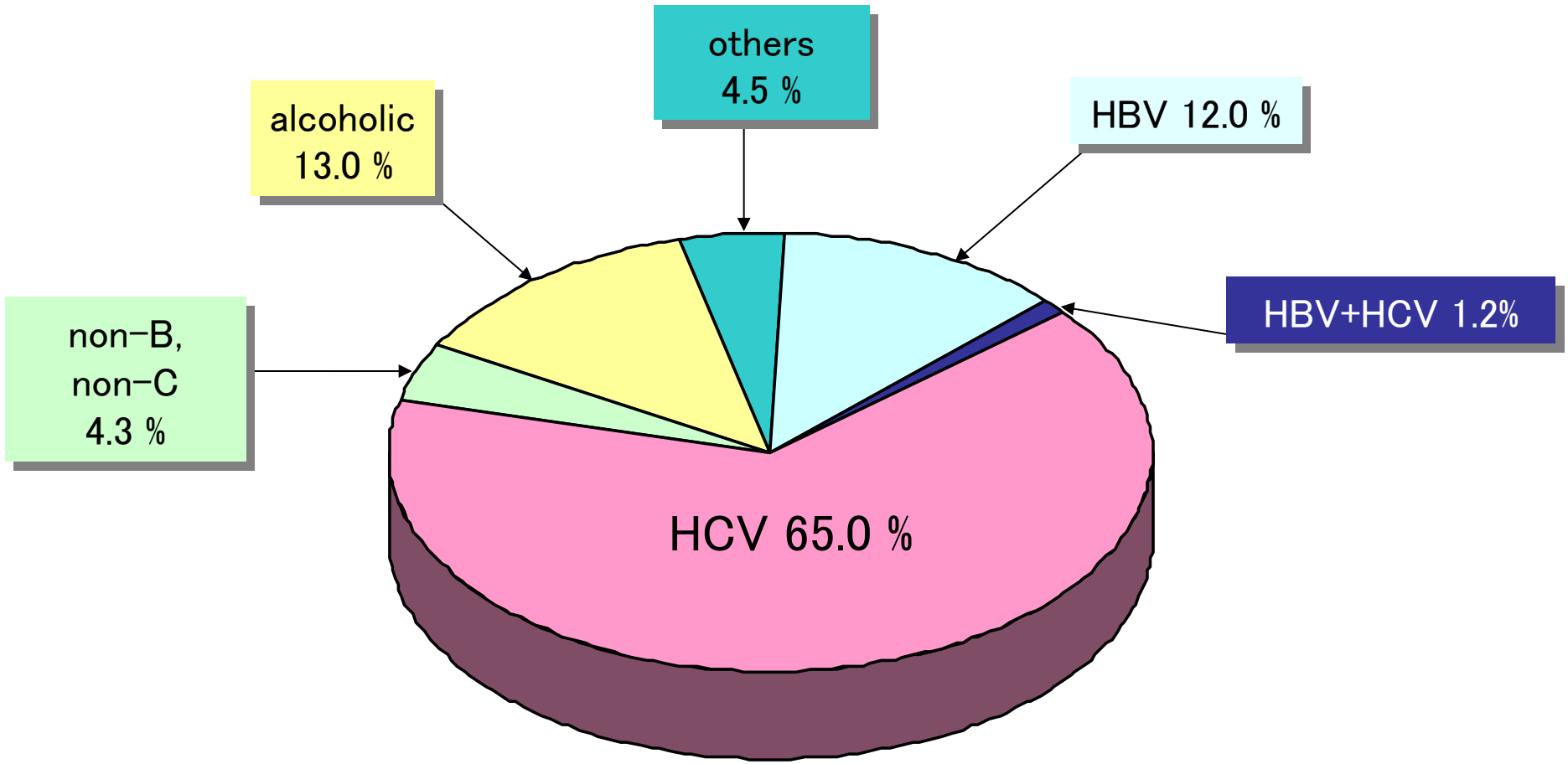
The percentage of #3 (advanced cancer) is increasing.

Cancer stages and the prognosis (5-year survival rate) (Osaka, 2007)

Site	Localized	Locally-invasive	Metastatic	Total
Total cancer	88.7%	54.9%	15.4%	60.7%
Prostate	99.7%	96.0%	49.0%	96.5%
Breast	98.2%	87.2%	35.6%	91.0%
Uterus	94.5%	68.1%	25.5%	77.5%
Stomach	94.6%	51.1%	5.9%	62.6%
Lung	79.0%	26.7%	4.9%	29.5%
Liver	46.2%	15.4%	4.2%	33.6%

The cause of liver cirrhosis

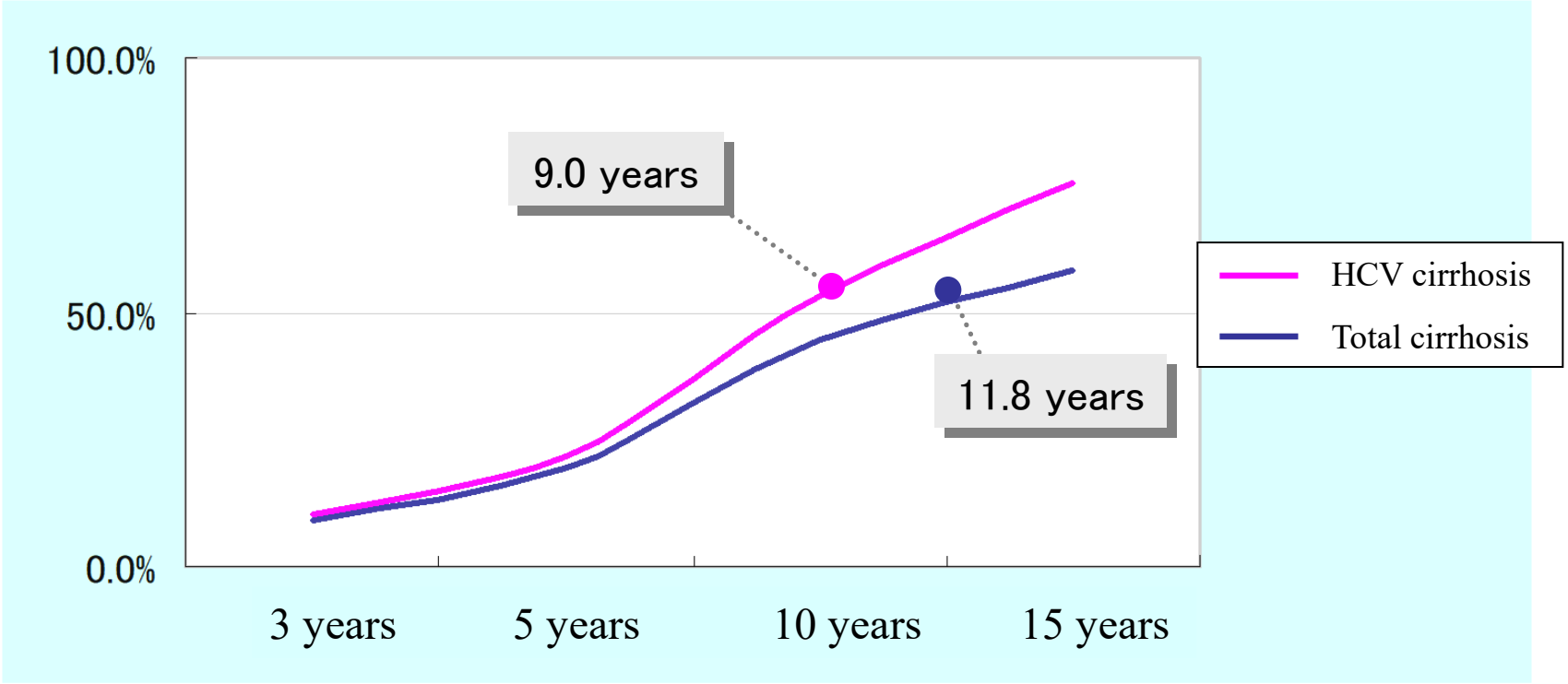
（n = 11,187） The Japan Society of Hepatology, 1991～1996



Carcinogenesis of liver cirrhosis

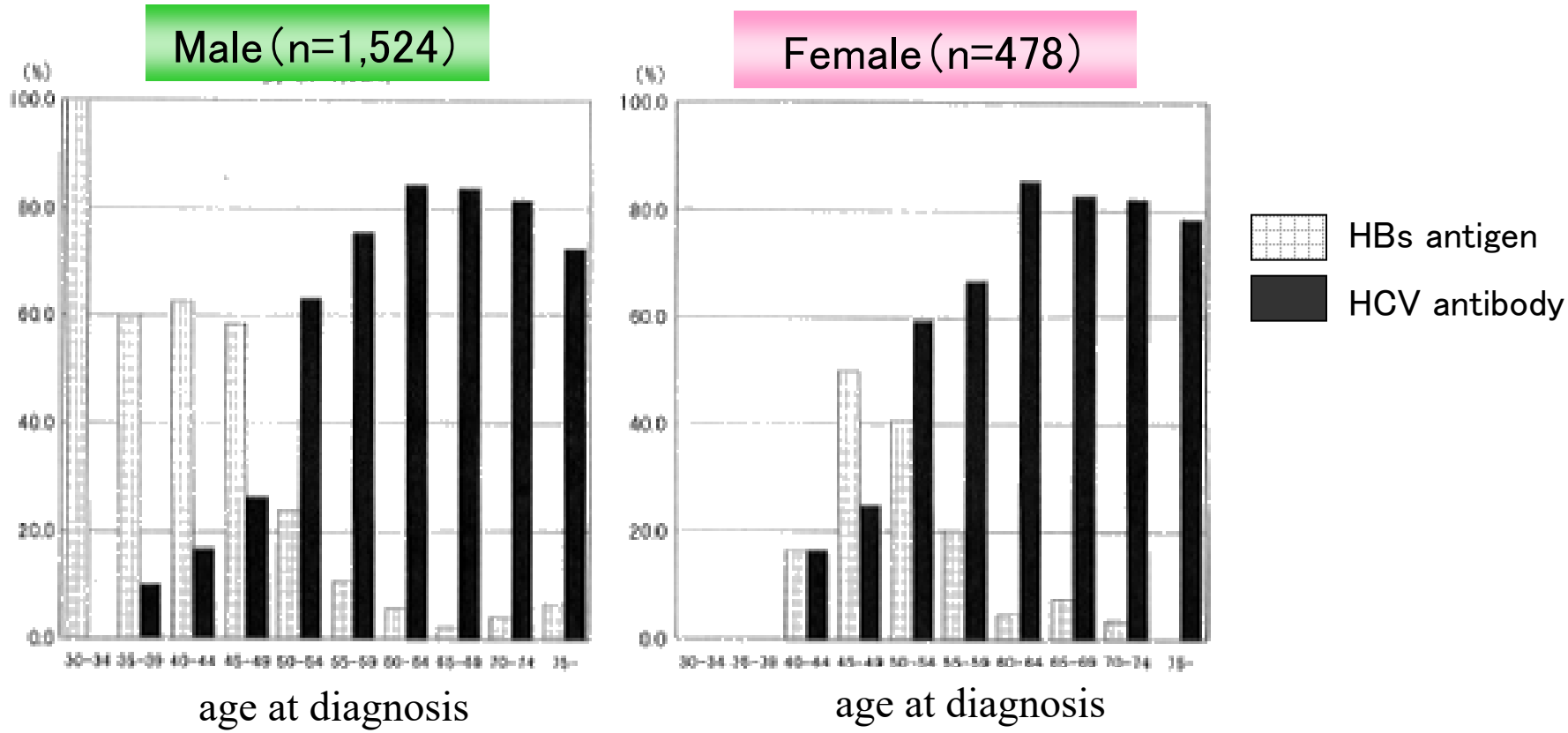
（n = 795） Toranomon Hospital, Tokyo

	Total cirrhosis	HCV cirrhosis
3 years	9.2%	10.4%
5 years	19.4%	21.5%
10 years	44.3%	53.2%
15 years	58.2%	75.2%
50% carcinogenesis	11.8 years	9.0 years



Positivity rates of HBs antigen and HCV antibody in patients with hepatocellular carcinoma

Liver cancer and severe cirrhosis treatment research promotion project, Osaka, 1992–1997



The Japan Society of Hepatology,
Liver Cancer White Paper, Chapter 2

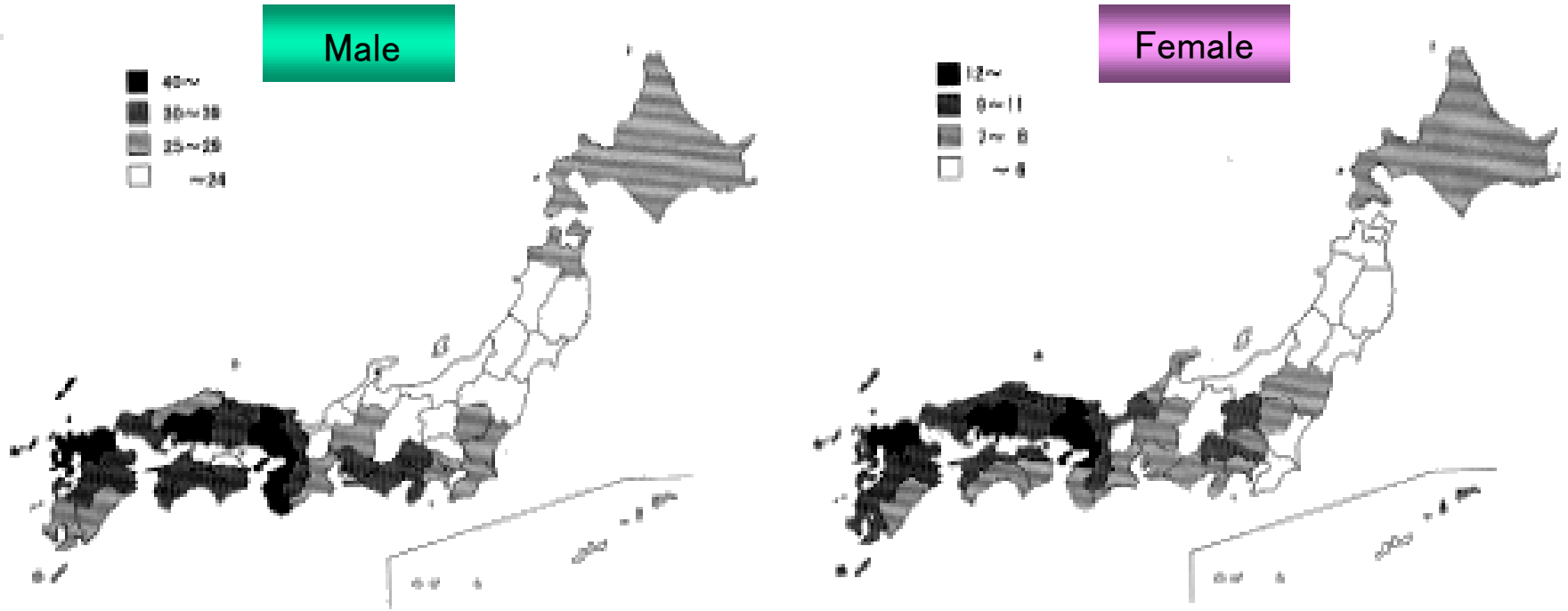
Carrier rates of hepatitis virus are decreasing in Japan

Carrier rate of HBs antigen	1.5% (1.50 million persons)
≤ 30 years	1.0%
≤ 18 years	0.05%
Western countries	0.1%
Asia/African countries	10～20%
Carrier rate of HCV antibody	1.4% (1.44 million persons)
≥ 55 years	3.0%
41–54 years	1.6%
≤ 40 years	0.4%

Transmission of HCV in Japan

1. Vaccinations in childhood caused transmission of HCV in the Japanese people of middle age and the elderly.
2. At present, the risk of HCV transmission by transfusion is nearly zero in Japan.
3. Low risk of HCV transmission: mother–to–child, sexual and peroral transmissions
4. High risk of transmission: drug abuse, tatoo and hemodialysis

Age-adjusted death rates of liver cancer: comparisons at the regional (prefectural) level per 100,000 persons, 1995



HCV carrier rates are high in western areas of Japan.

The Japan Society of Hepatology, Liver Cancer White Paper, Chapter 2

Reuse of vaccination needles caused HCV transmission in certain areas in Japan.

「注射針を使い回し」

「C型肝炎の町」では

地区の4割感染でも、よそは2%

原因特定 名士への遠慮が

時時刻刻

（1面から続く）

「町へ行くと肝臓をやられる」「だれが外国でうつされてきた」「水が悪い」。人口二万足らずの中国地方の町に、二十年以上前に持ち上がった肝炎騒動では、こんなうわさが飛び交った。

今でも、肝臓がんなどで亡くなるお年寄りが毎年十数人はいる。人口からみたら、驚くほどの多さだ。

町は、一九九八年度から三年間、六十歳以下の希望者にC型肝炎ウイルス（HCV）検査を実施した。

町の担当者が、しぶしぶ出してくれた検査結果を見て、不思議なことに気がついた。

HCVに感染している人の割合が、海沿いのA地区だけ四〇%と高いのだ。海沿いでも隣のB地区は一五%。少し山沿いにいくと三%と、さらに下がる。

A地区の六十歳以上のお年寄りだと八割以上が感染しているとも言われる。逆に二十歳以下の若い世代にはほとんどいない。

HCVは主に血液を通して感染する。性交渉や経口による感染はほとんどないとも言われる。

実は、二十年前、大学医学部が疫学調査に入った。その三年間の成果をまとめた論文を見せてもらった。漁師の多量飲酒など生活習慣を「促進要因」と指摘しているが、感染源については一言も触れていない。

研究チームのメンバーを何人も訪ねた。そのうちの一人が打ち明けた。

当時、C型肝炎のメカニズムはわかっていなかった。でも調査結果は、感染源は輸血でも母子感染でもないことを示していた。

「その診療所が、限りなく黒に近かった」

しかし、診療所の「回し打ち」の現場を押さえることは出来なかった。「医師会の総活部分に、こんな文言がある。「一般の医療の際の注射器具による感染防止のため、使い捨ての注射器、注射針の普及が望まれる」

当時、県内の医師に、報告書の趣旨が徹底されていた。

鈍い国の対応 感染拡大

日本のC型肝炎感染者は二百万人と推定される。日本肝臓学会の肝がん白書（九九年度）によると、肝がんの八割がHCVと関連する肝炎の集団発生のピーは、医療現場での不十分な滅菌や消毒であることを認めている。

注射器の使い回しなどによる肝炎の集団発生のピーク潜伏期間を経て、肝がんの発症は今後も増えることが予想される。

七二年、ウコンの町と同じ県内の別の町で肝炎が多

C型肝炎

集落のお年寄り ほとんど感染

あれは二十年以上も前のことだろうか。この町に赴任してきた鮮在さんや、教師が次々と肝臓をやられて入院したのは。

以来、肝炎の町と言われる。

たたらと細い渠道を上っていくと、農家の軒先や畑の片隅に、必ずといっていいほどウコンが植わっている。

「なぜ、ウコンを？」

結婚の料理をしている女性（六八）に尋ねてみた。

「肝臓に効くっていうでねえ」

ショウガのような根っこを細く切り、日干しした後、ミキサーで粉にする。飲ませてもらうと、口の中に苦みが広がった。

人口二千人に満たないこの集落を歩いてみると、ほとんどのお年寄りが、肝臓に「ムシ」がいると答える。C型肝炎ウイルスのことだ。

「なぜ、ここだけ？」

おじいさんやおは、首を横にふけ。県も町も、感を試みたことは、一思い当たる節はみんな口を閉ざし

3面に続く

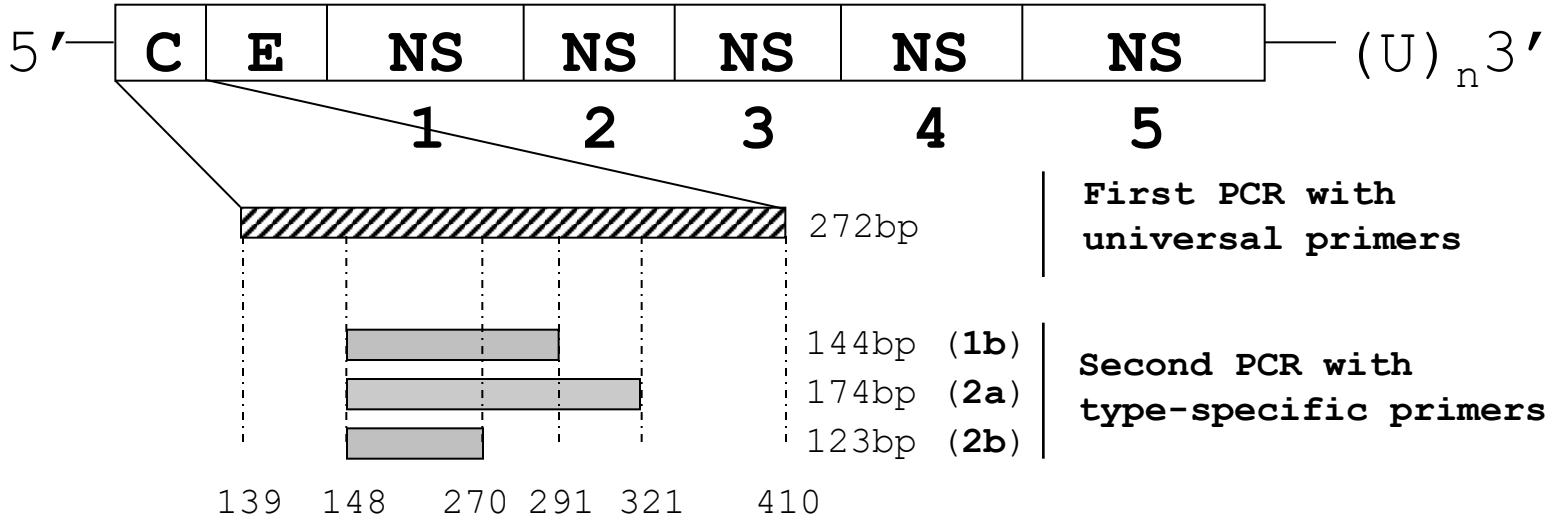
（11面に

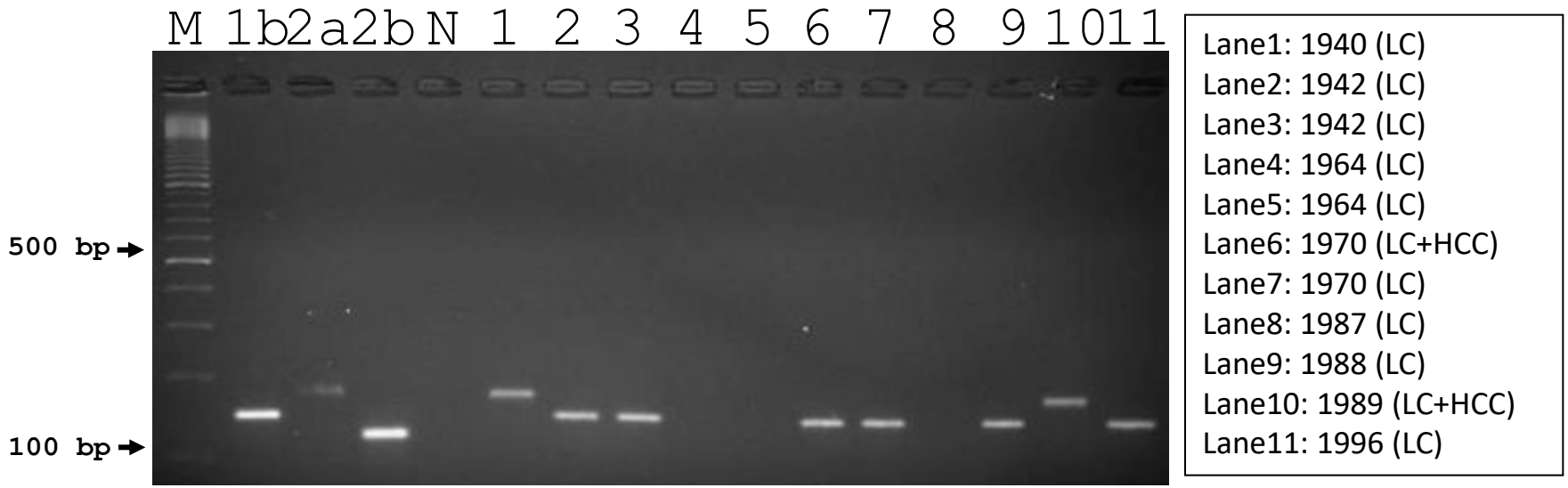
Asahi Shinbun (newspaper): Dec 18, 2000

40% of inhabitants are HCV carriers in a small town in western Japan!

Risks of viral transmission by needle stick accidents in hospitals

HBV hepatitis	(in HBe antigen+ cases)	30%
HCV hepatitis		3%
HIV		0.3%

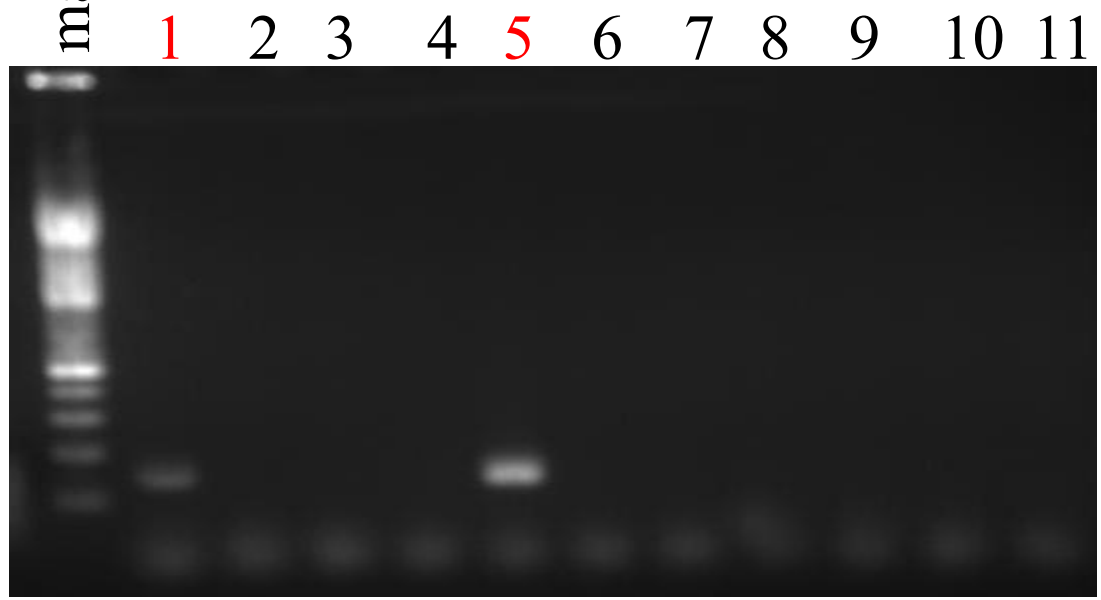




Typing HCV by PCR with type-specific primers

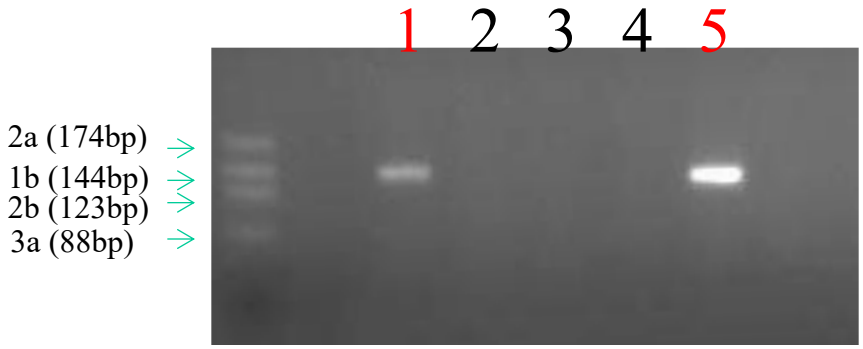
Formalin-fixed liver cirrhosis samples autopsied in Kyushu University, Fukuoka, in 1907～1930

Type 1b HCV (144 bp) was detected in case 1 (in 1909) and case 5 (in 1914).



1: 1909年
2: 1912年
3: 1916年
4: 1915年
5: 1914年
6: 1912年
7: 1907年
8: 1930年
9: 1914年
10: 1914年
11: 1914年

HCV had invaded Japan as early as in 1909!



Ref.: Tsutsumi Y, et al. Detection of hepatitis virus B and C in archival autopsy specimens of liver cirrhosis. J Sci Tech Res 2019. doi: 10.26717/BJSTR.2019.22.003757