Viral Hepatitis (I)

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Definition

Hepatitis means inflammation of the liver characterized by a variable combination of :

- mononuclear inflammation (lymphocytes and plasma cells)
- hepatocellular necrosis/apoptosis
- hepatocellular regeneration

Viral Hepatitis

Unless otherwise specified, the term "viral hepatitis" is reserved for infection of the liver caused by a group of viruses having a particular affinity for the liver

Systemic viral infections that can involve the liver include:

1.infectious mononucleosis (Epstein-Barr virus), which may cause a mild hepatitis during the acute phase;

2.cytomegalovirus, particularly in the newborn or immunosuppressed patient;

3.yellow fever, which has been a major and serious cause of hepatitis in tropical countries.

Hepatotropic viruses cause overlapping patterns of disease

Viral Hepatitis

The Hepatitis Viruses

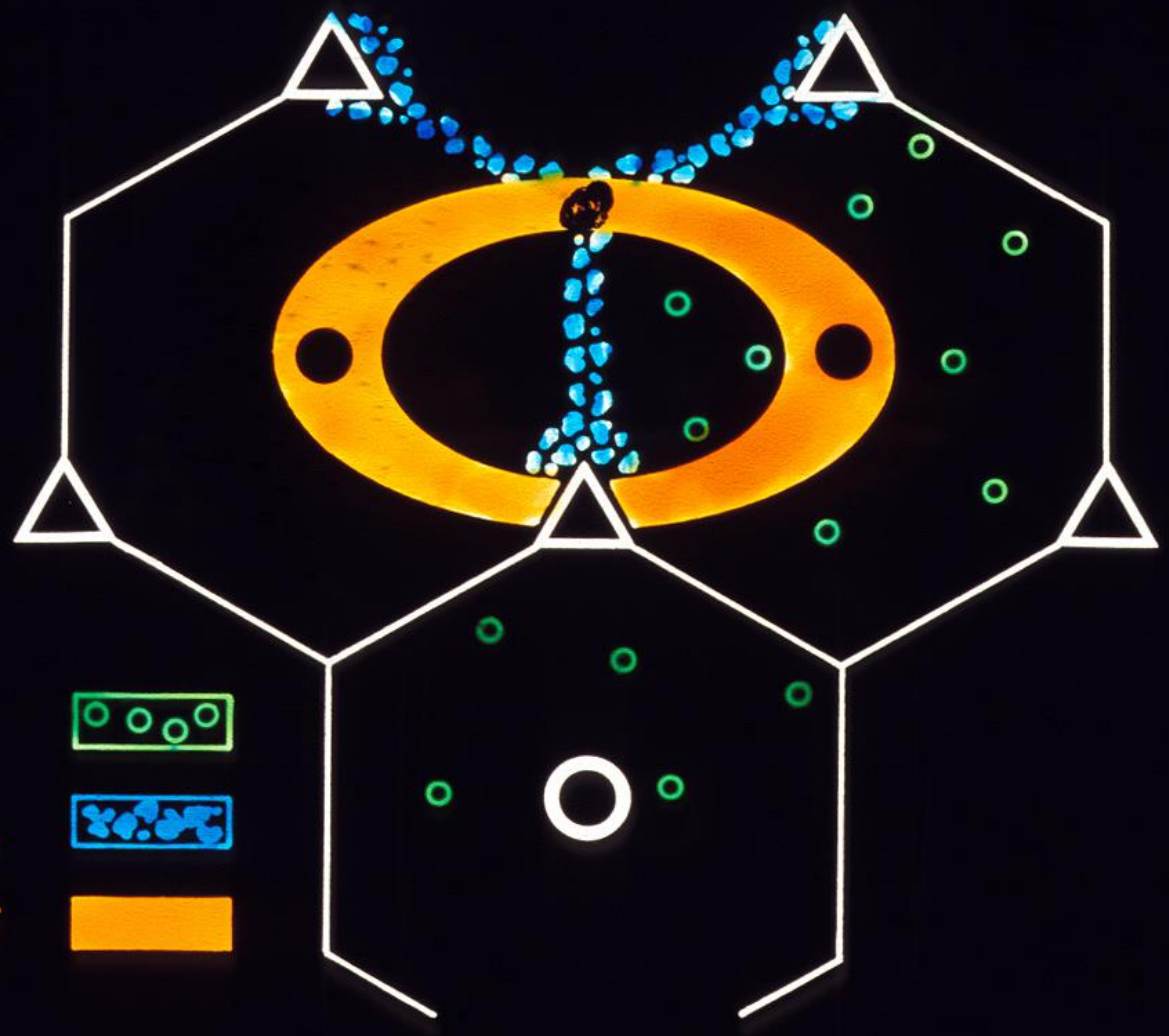
	Hepatitis A Virus	Hepatitis B Virus	Hepatitis C Virus	Hepatitis D Virus	Hepatitis E
Agent	Icosahedral capsid, ssRNA	Enveloped dsDNA	Enveloped ssRNA	Enveloped ssRNA	Unenveloped ssRNA
Transmission	Fecal-oral	Parenteral; close contact	Parenteral; close contact close contact	Parenteral;	Waterborne
Incubation Period	2-6 wk	4-26 wk	2-26 wk	4-7 wk	2-8 wk
Carrier state	None	0.1-1.0% of blood donors in U.S. and Western worldi 1-2% of blood donors	0.2-1.0% of blood donors. in U.S and Western world	1-10% in drug addicts and hemophiliacs	Unknown
Chronic hepatitis	None	5-10% of acute infections	>50%	<5% coinfection, 80% upon superinfection	None / Very rare
Hepatocellular carcinoma	No	Yes	Yes	No increase above HBV	Unknown

Viral Hepatitis

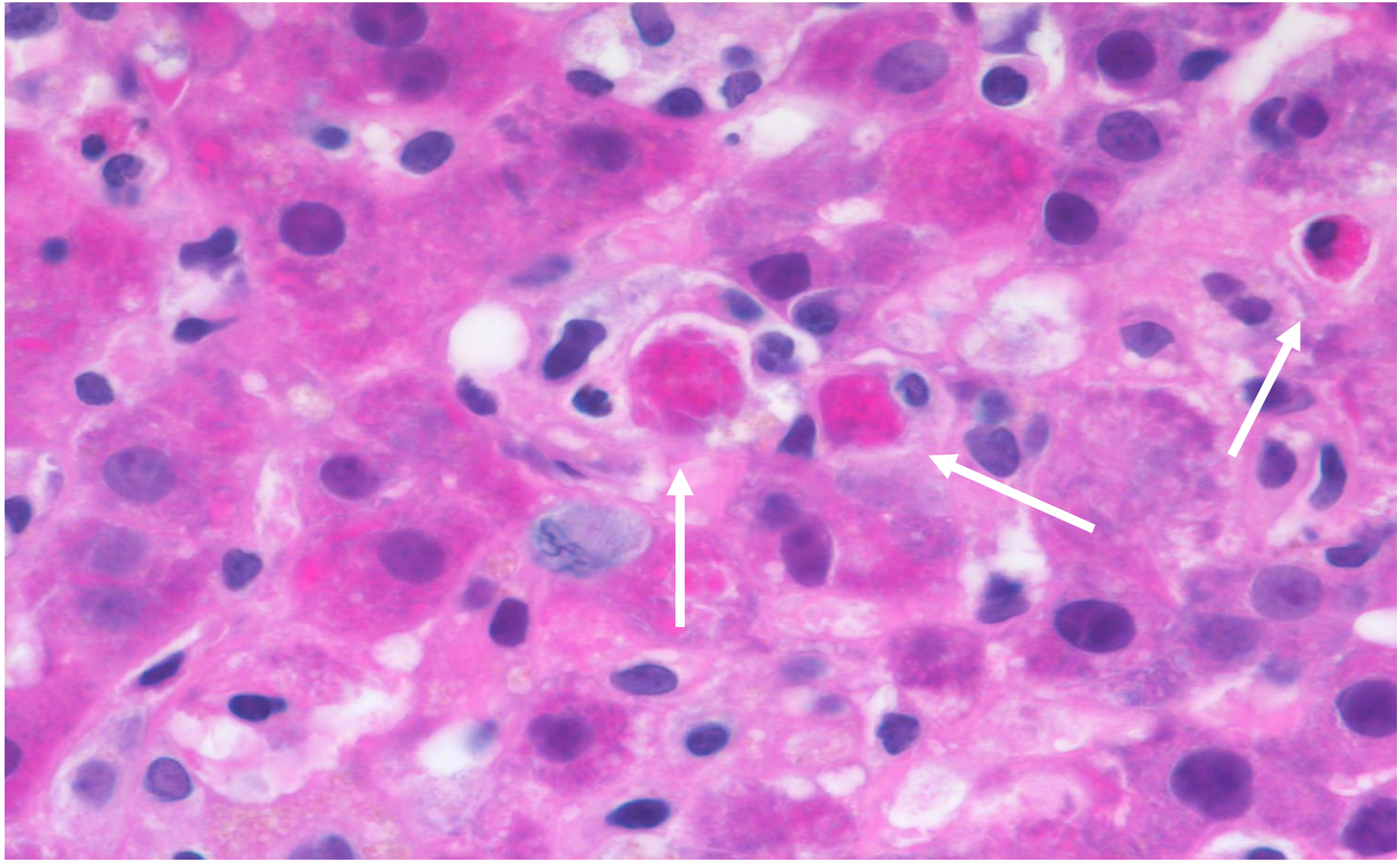
Types of necrosis

- Spotty (focal) necrosis / apoptosis
- Confluent and bridging necrosis
- Interface hepatitis („piecemeal necrosis“)

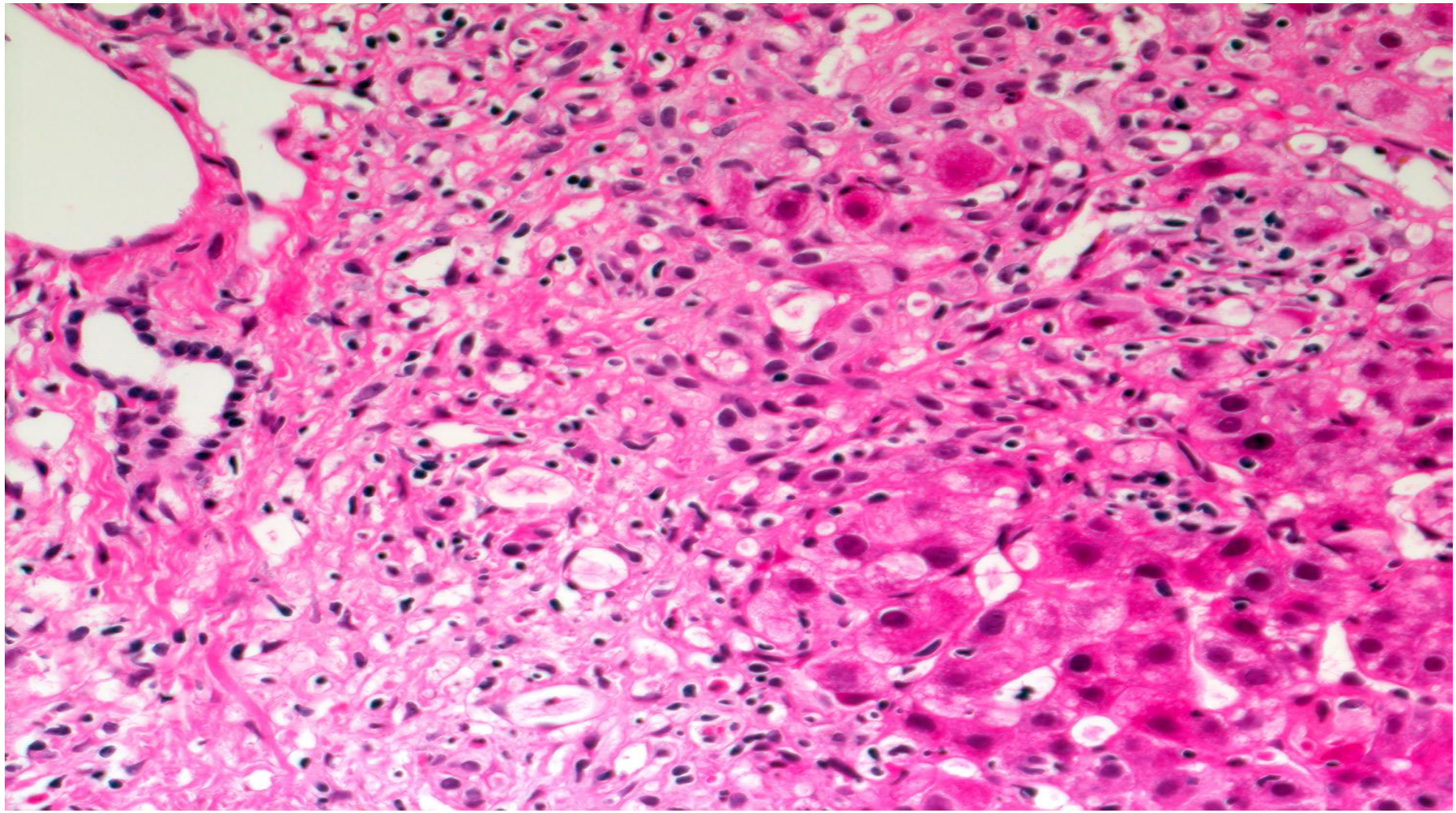
THE THREE TYPES OF NECROSIS IN CHRONIC HEPATITIS



Apoptotic bodies („Councilman bodies“)



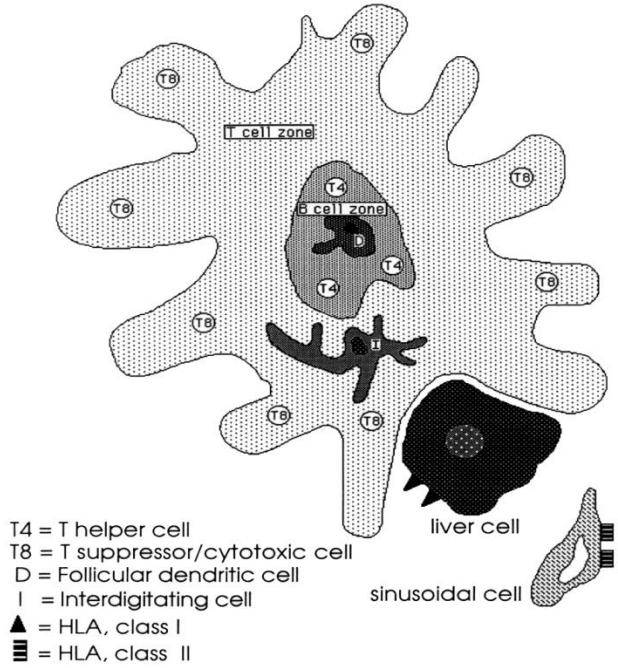
Interphase Hepatitis („Piecemeal“ necrosis)

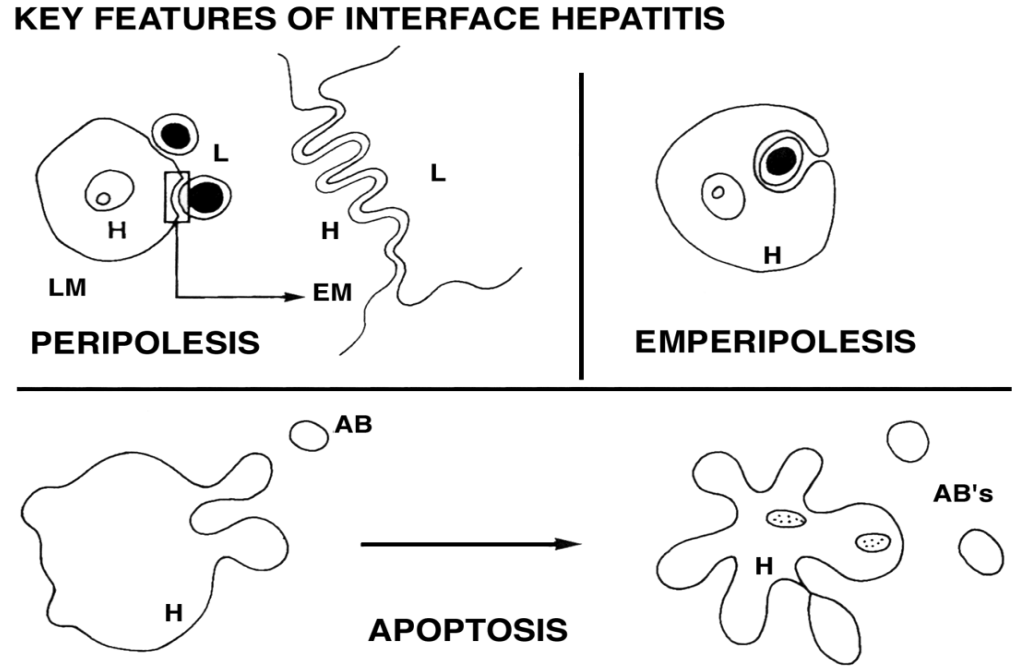


(Chronic) Viral Hepatitis

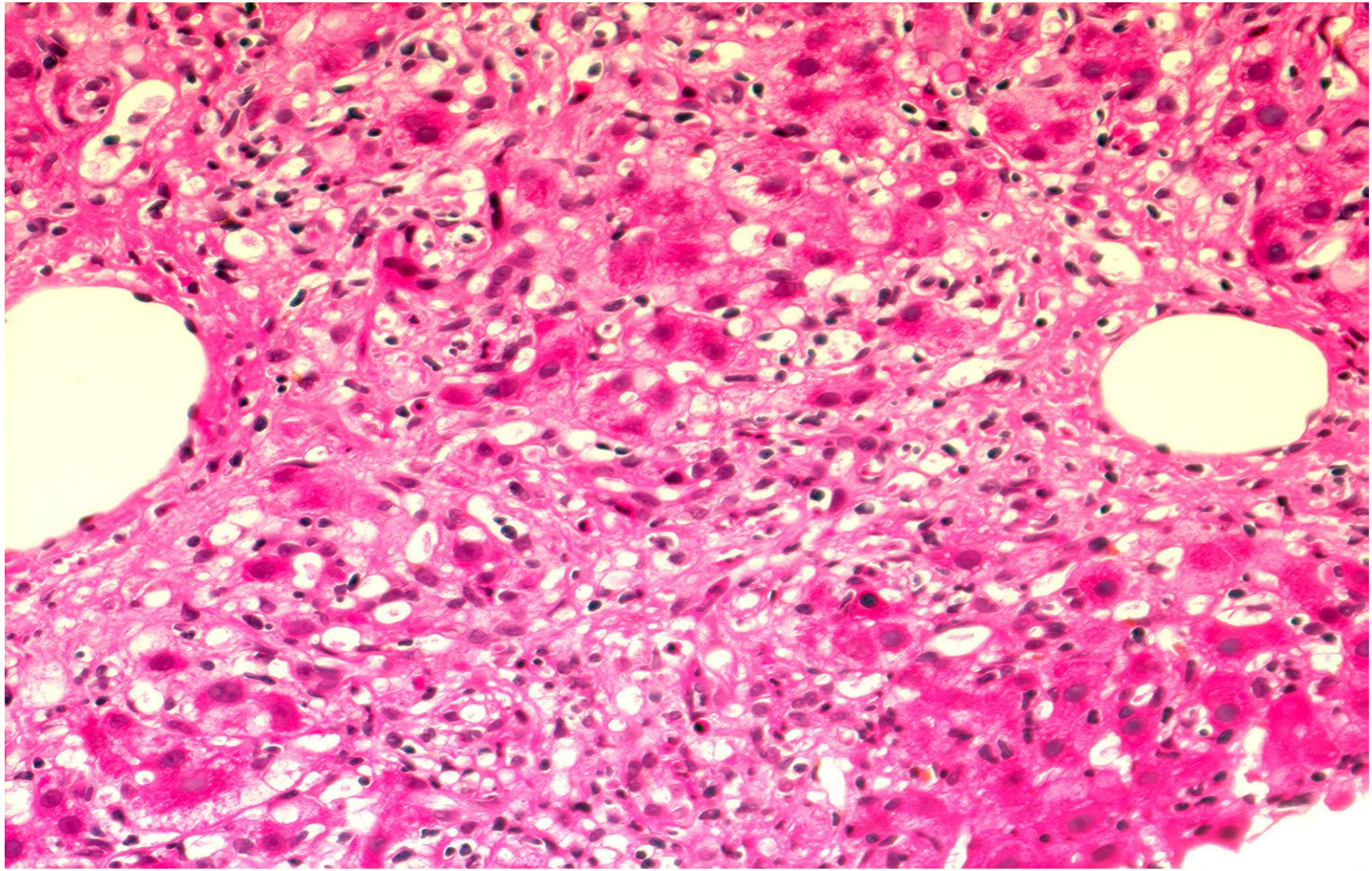
Interface hepatitis (Piecemeal necrosis)

Liver cell apoptosis and inflammation of the region where the hepatic parenchyma comes into contact with the mesenchymal stroma of the portal tract (interface region)





Confluent necrosis



Viral Hepatitis

Confluent necrosis

Necrosis of large areas of contiguous liver cells

Bridging hepatic necrosis

Central-Central

Central-Portal

Bridging Hepatic Necrosis

Central-to-portal bridging necrosis disrupt the microcirculatory integrity of the acinus scaffold upon which fibrous septa form with subsequent porto-systemic shunting.

Prognostic significance: ?

- 170 acute hepatitis: 37% incidence of cirrhosis and 19% incidence of mortality (Boyer & Klatskin, 1970)
- Others have not considered BHN as a good predictor of chronicity (Spitz RD,1978; Nisman RM,1979)
- BHN is seen in the most severe, coma -producing, and often fatal forms of hepatitis!

Bridging Hepatic Necrosis

Clinical Conditions associated with BHN

- Acute and Chronic viral hepatitis
- Autoimmune hepatitis
- Drug-induced and toxic hepatitis
- Massive or submassive hepatic necrosis of unknown cause
- Acute hepatic allograft failure
- .....

Acute Viral Hepatitis - Pathology

Clinical evaluation has largely replaced the need for liver biopsy in the diagnosis of most patients with acute viral hepatitis

*< 1% of liver biopsies in many reference centers

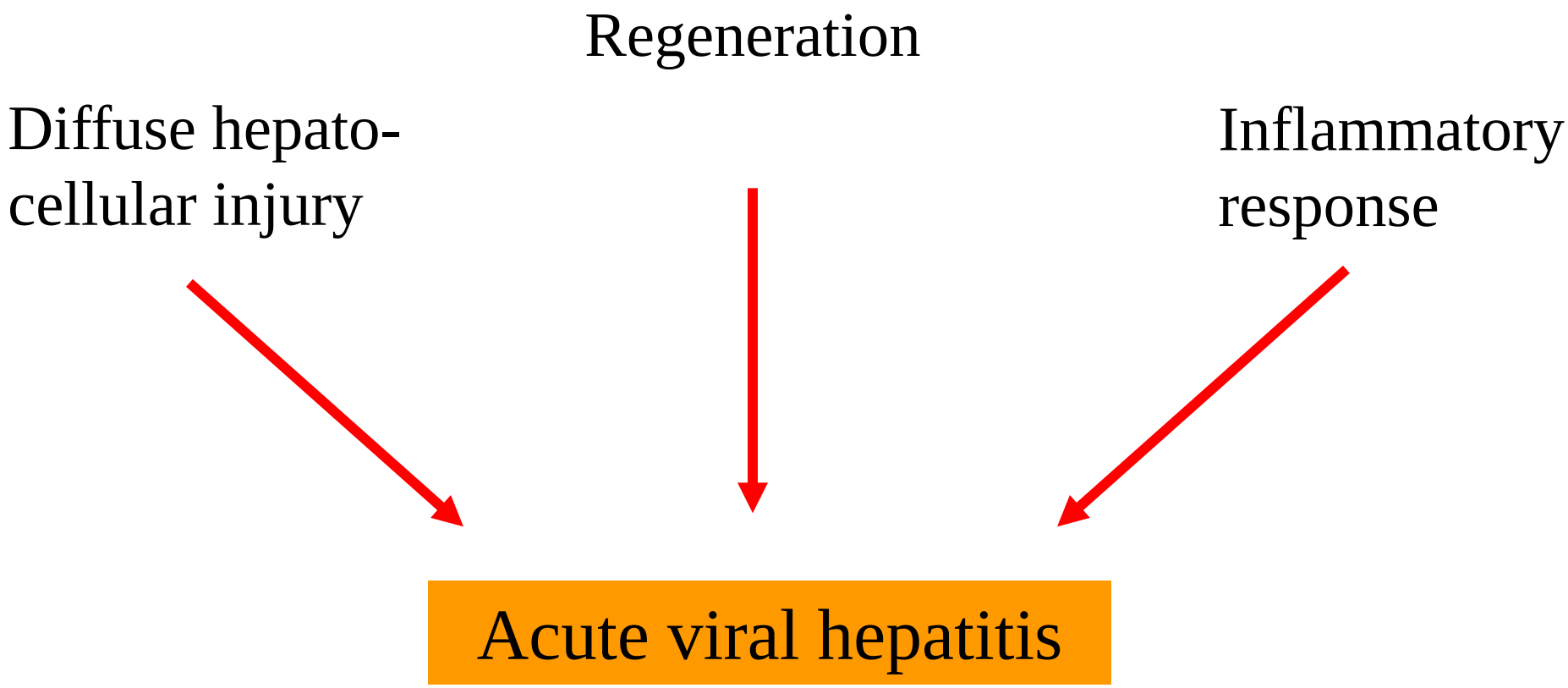
Clinical setting 1:

Clinical setting or progress of the hepatitis is unusual:ddx with alcoholic hepatitis, drug-induced and ischemic hepatitis

Clinical setting 2:

Immunosuppressed population: ddx with opportunistic viral, fungal infections

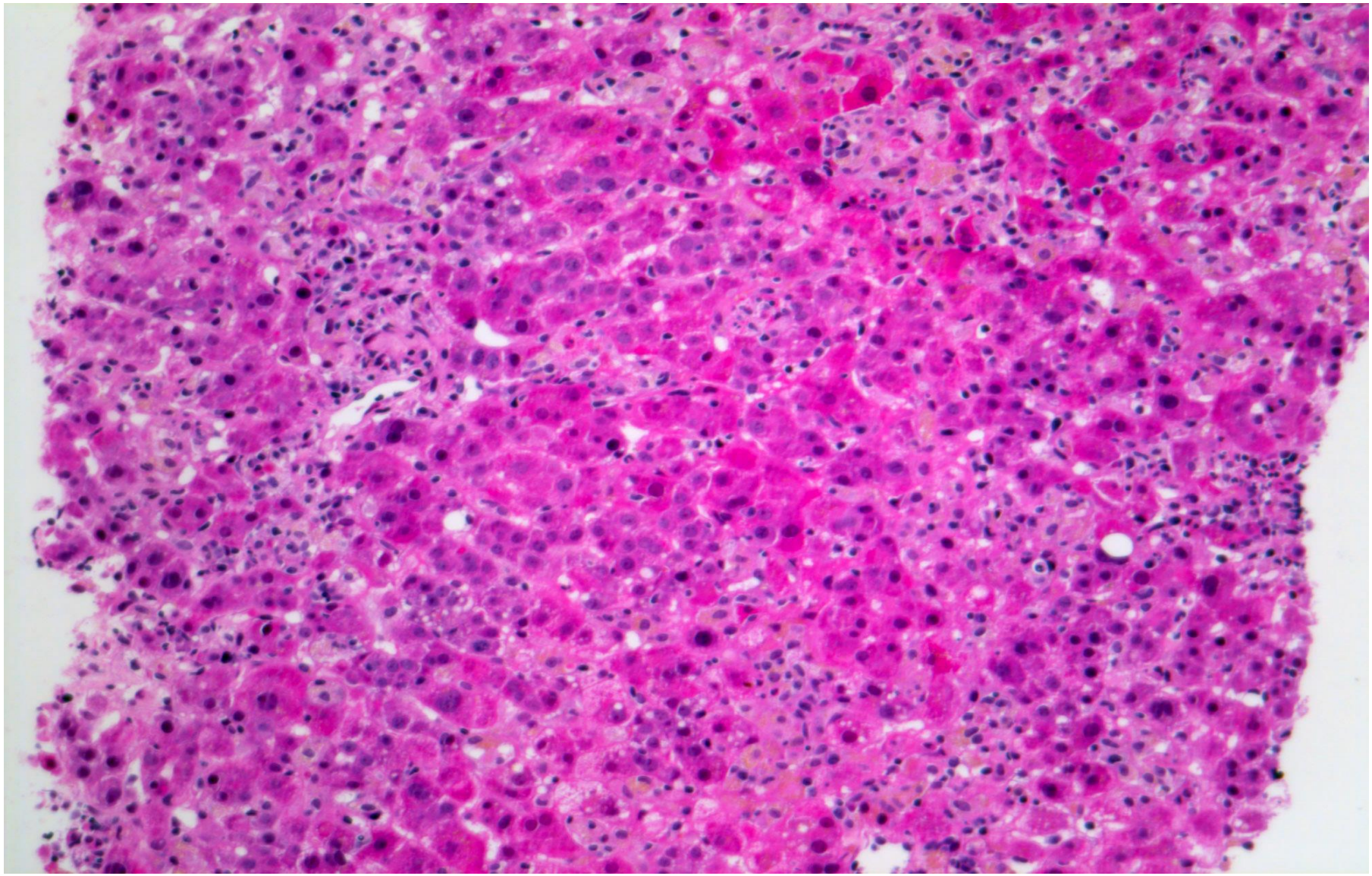
Acute Viral Hepatitis
Histologic Findings



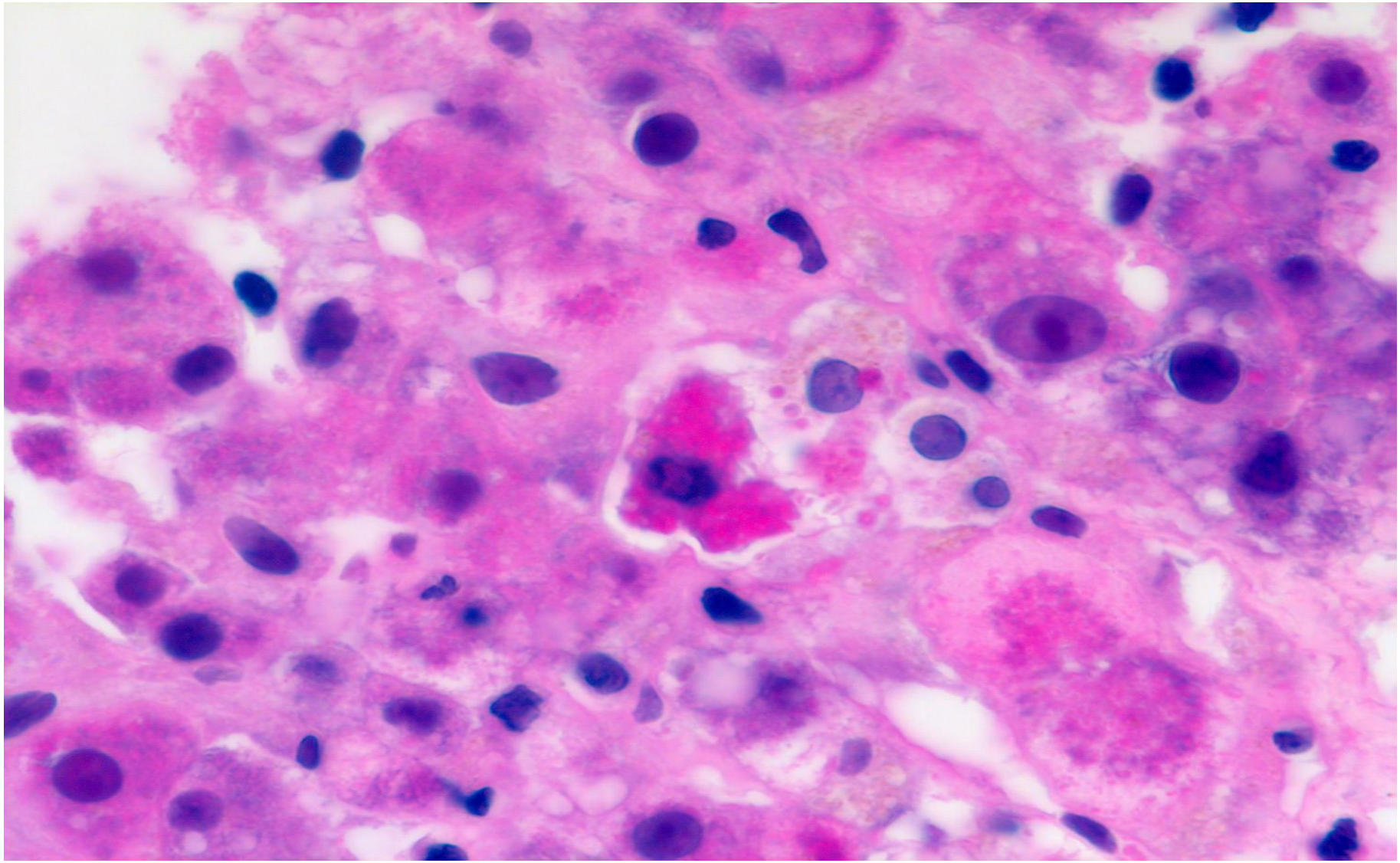
Acute Viral Hepatitis
Histologic Findings

- Lobular disarray
- Necrosis
- Lobular inflammation (lymphocytes, plasma cells and macrophages)
- Ballooning degeneration
- Portal tract changes: inflammation and bile duct lesions
- Endotheliitis (up to 69%of cases)
- Cholestasis

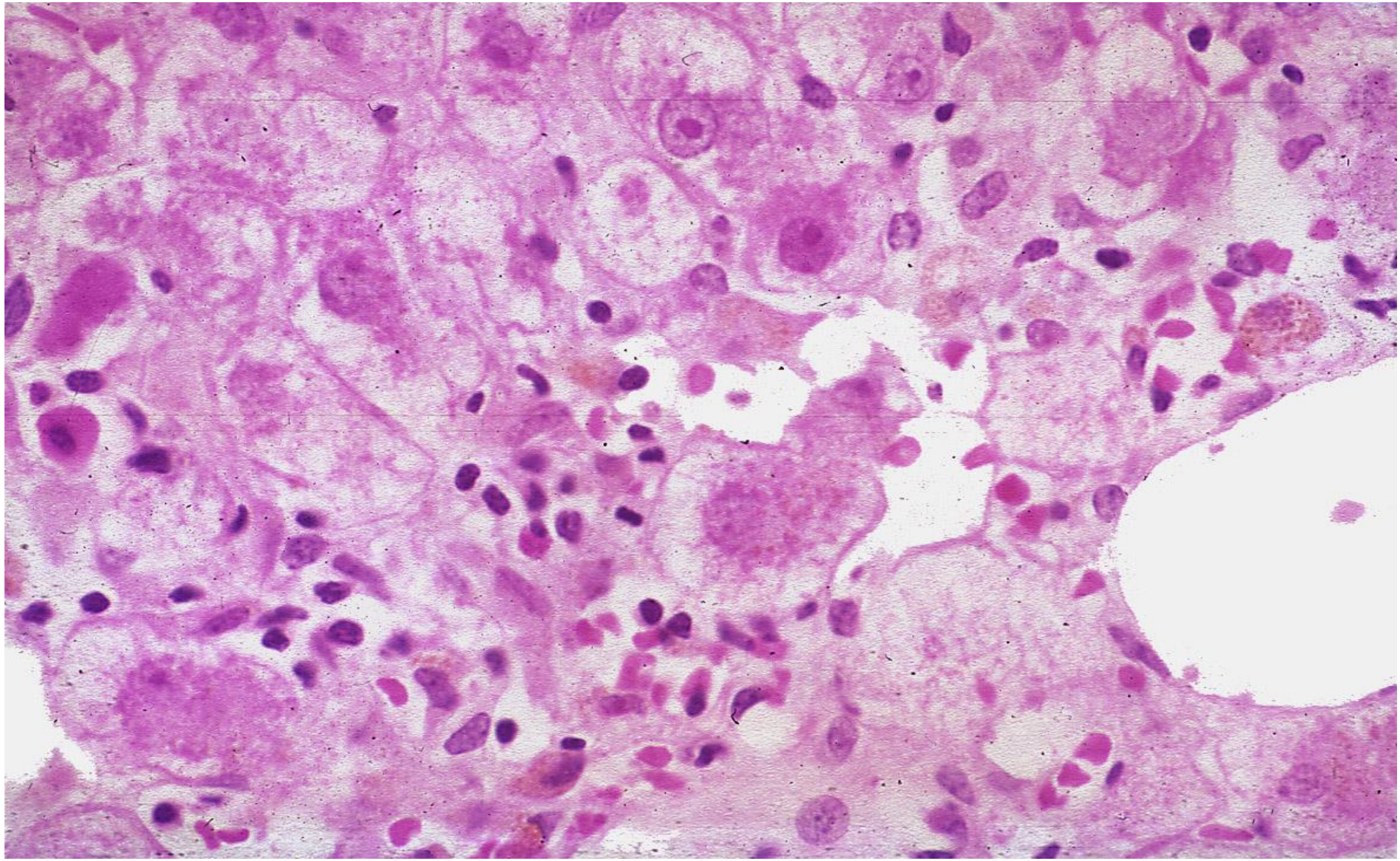
Acute hepatitis: Lobular disarray



Apoptotic bodies („Councilman bodies“)



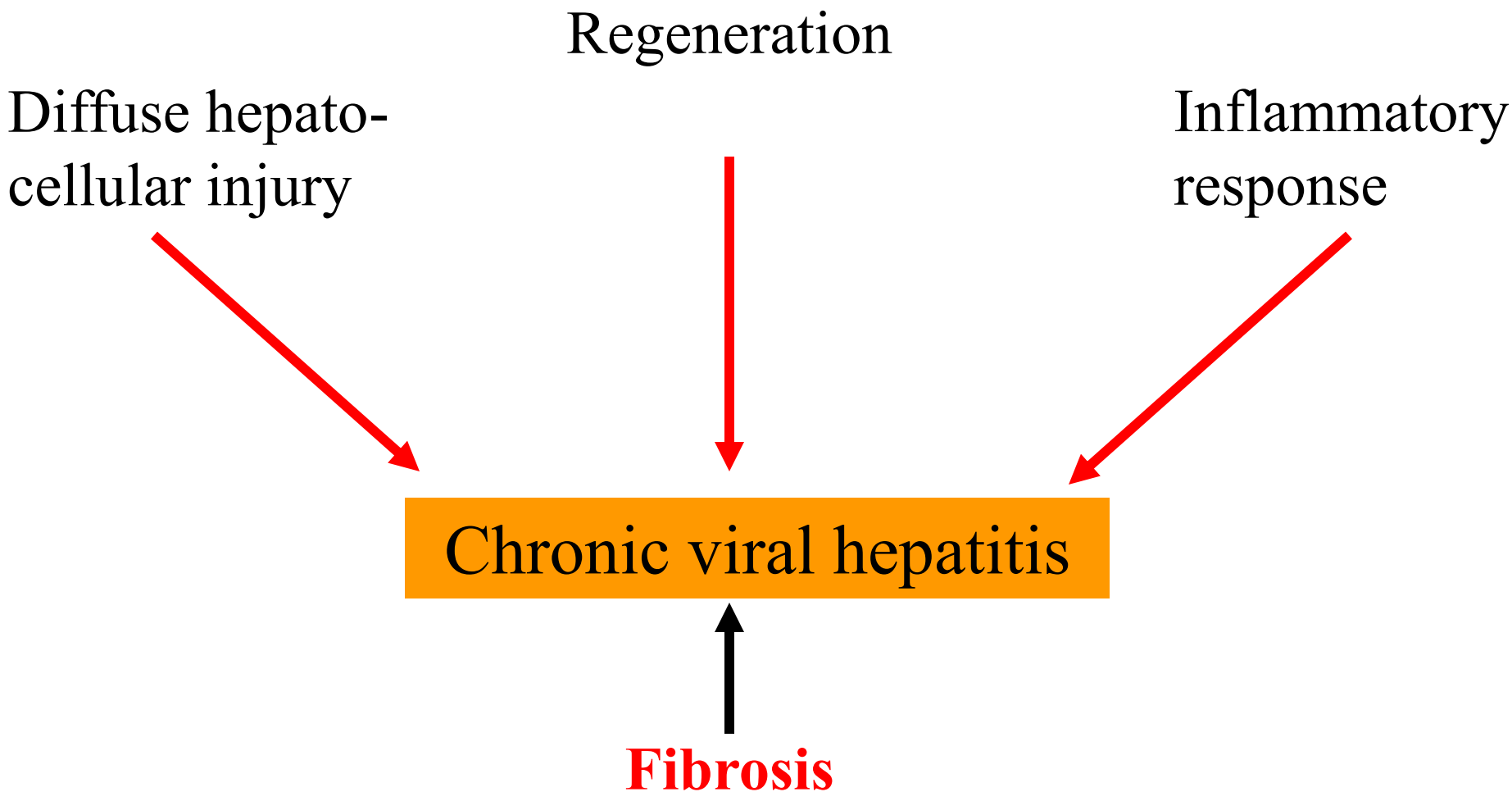
Ballooning degeneration



Classical Causes of Chronic Hepatitis

- Hepatitis B, with or without HDV superinfection
- Hepatitis C
- Autoimmune hepatitis
- Drug-induced hepatitis
- Chronic hepatitis of unknown cause

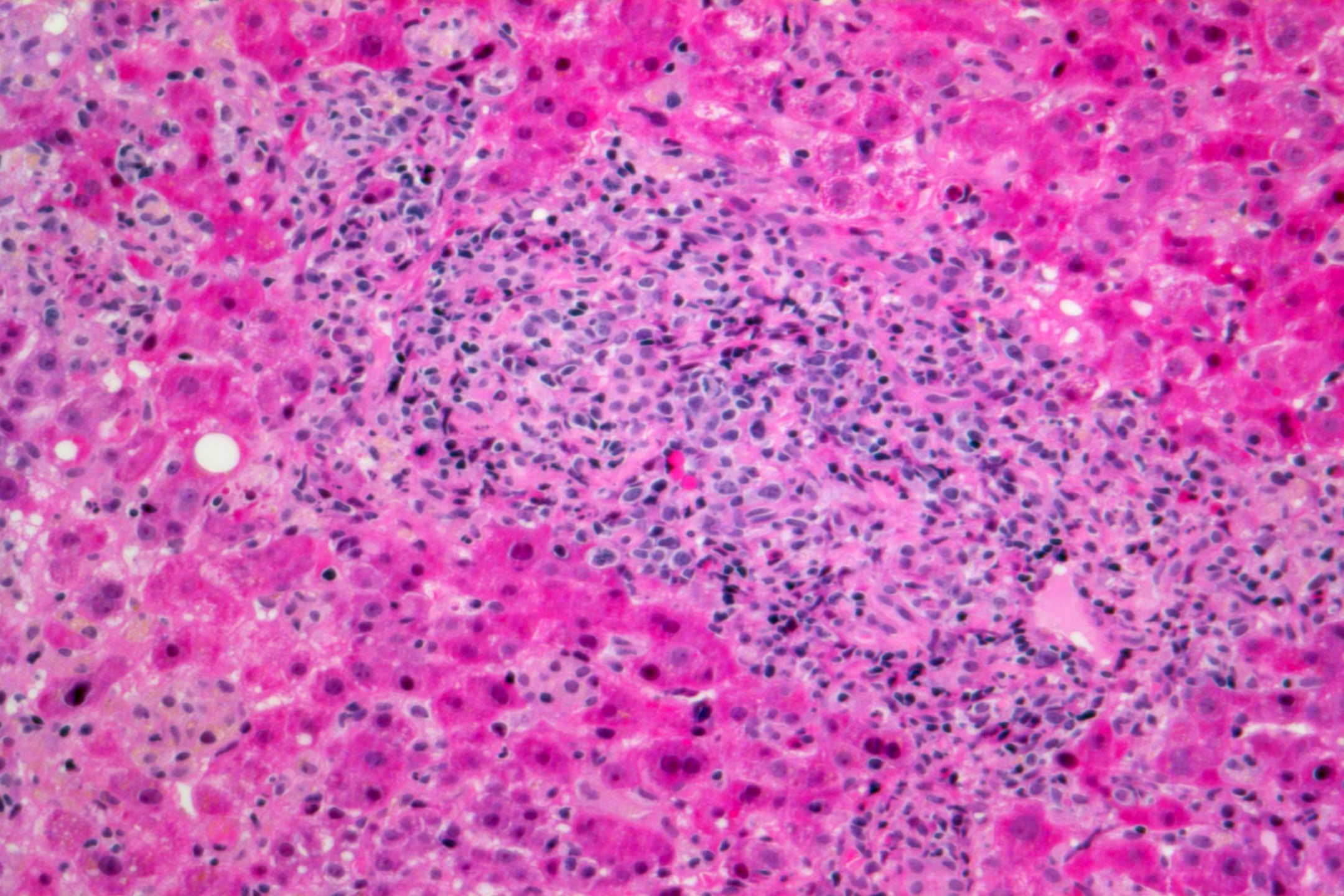
Chronic Viral Hepatitis
Histologic Findings



Chronic Viral Hepatitis B

Histology

- Portal inflammation: CD4+ helper / inducer T-lymphocytes
- Interface hepatitis („piecemeal necrosis“): CD8+ suppressor / cytotoxic T cells
- Lobular and Confluent necrosis
- HBs-containing ground-glass hepatocytes
- HBc-containing „sanded“ nuclei
- Portal tracts with maple-leaf configuration



Chronicity

Morphological Criteria:

- Portal fibrosis (facultatitive)
- Predominance of portal inflammation
- „Piecemeal„ („interface“) Hepatitis

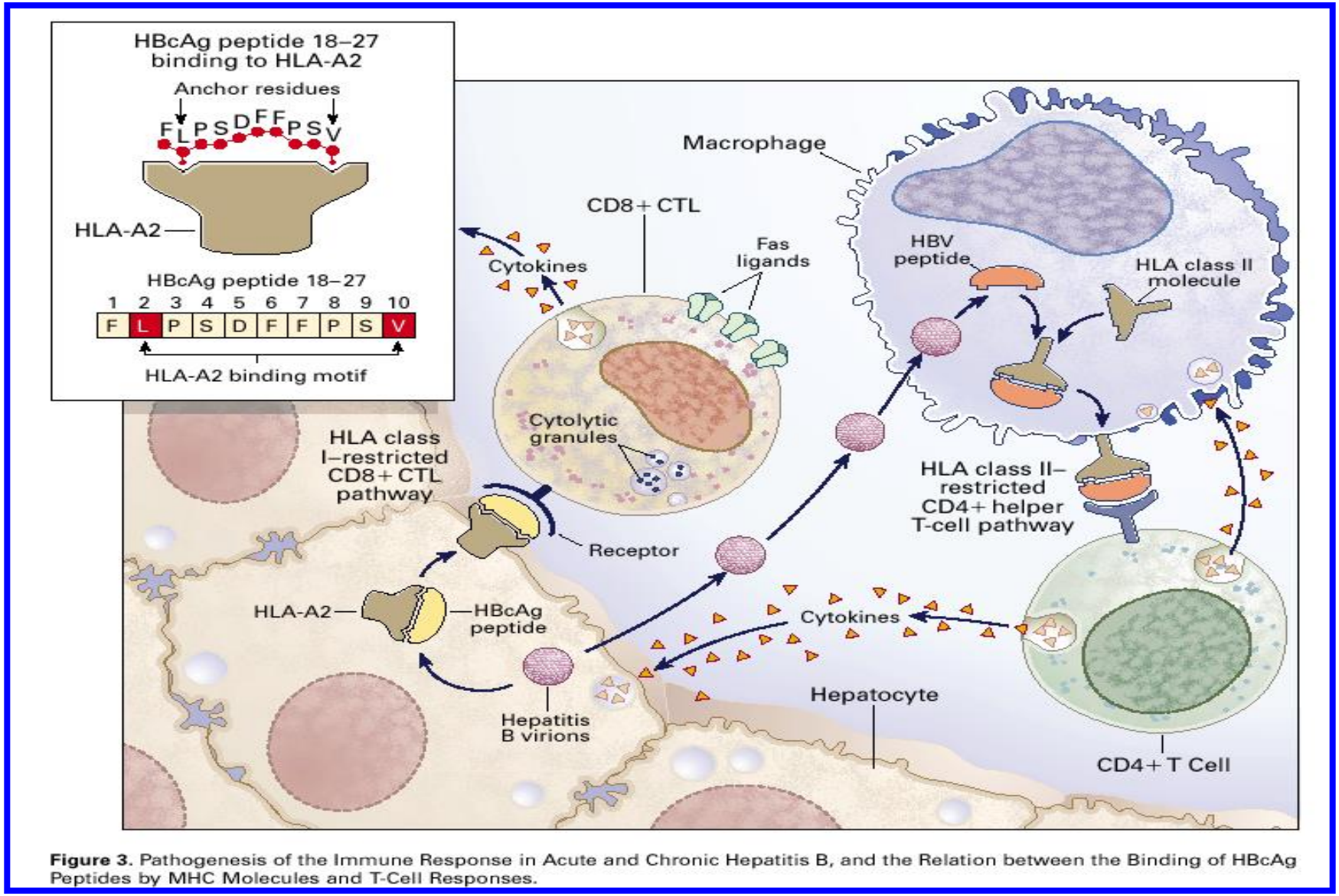
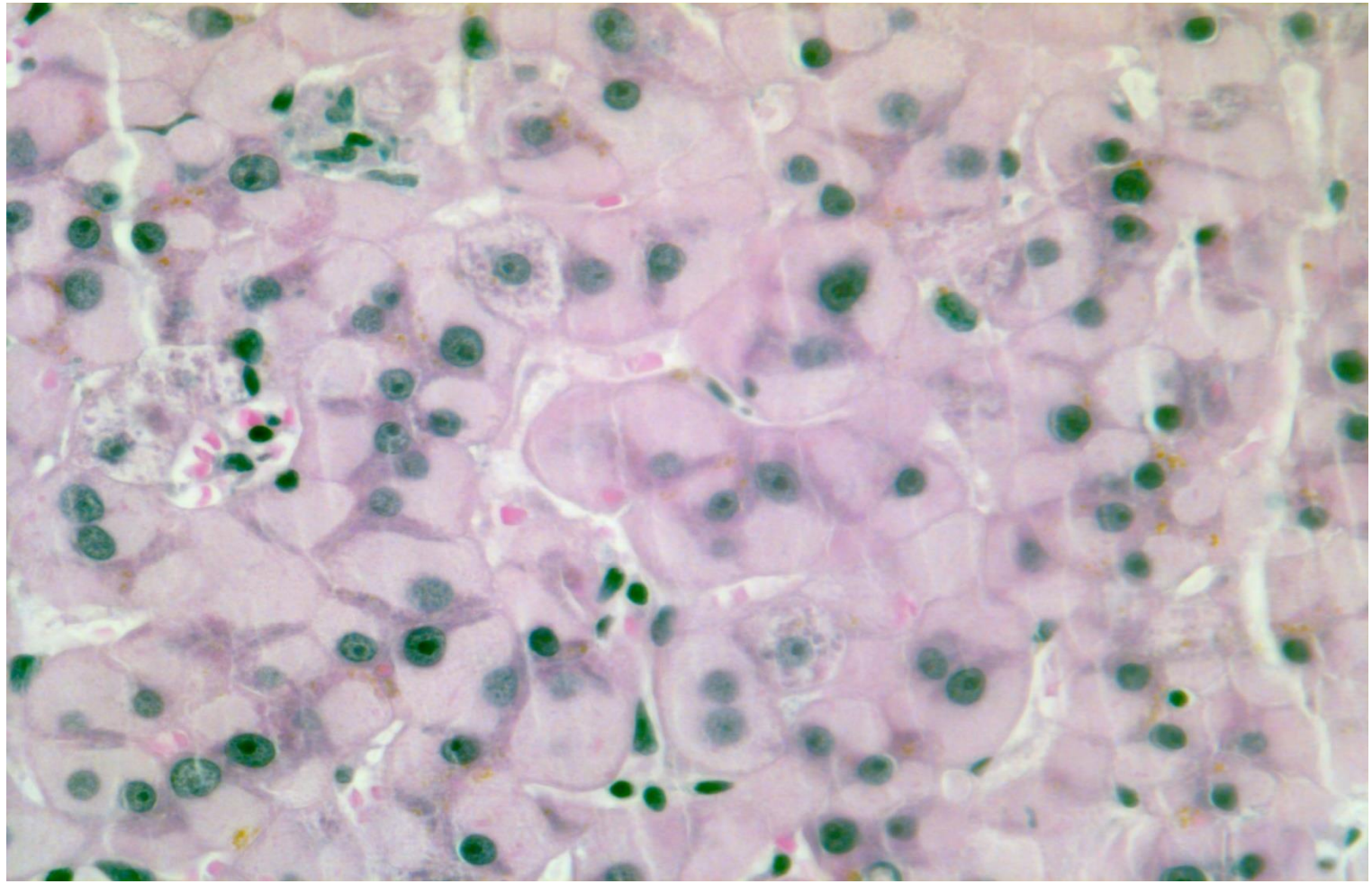


Figure 3. Pathogenesis of the Immune Response in Acute and Chronic Hepatitis B, and the Relation between the Binding of HBcAg Peptides by MHC Molecules and T-Cell Responses.

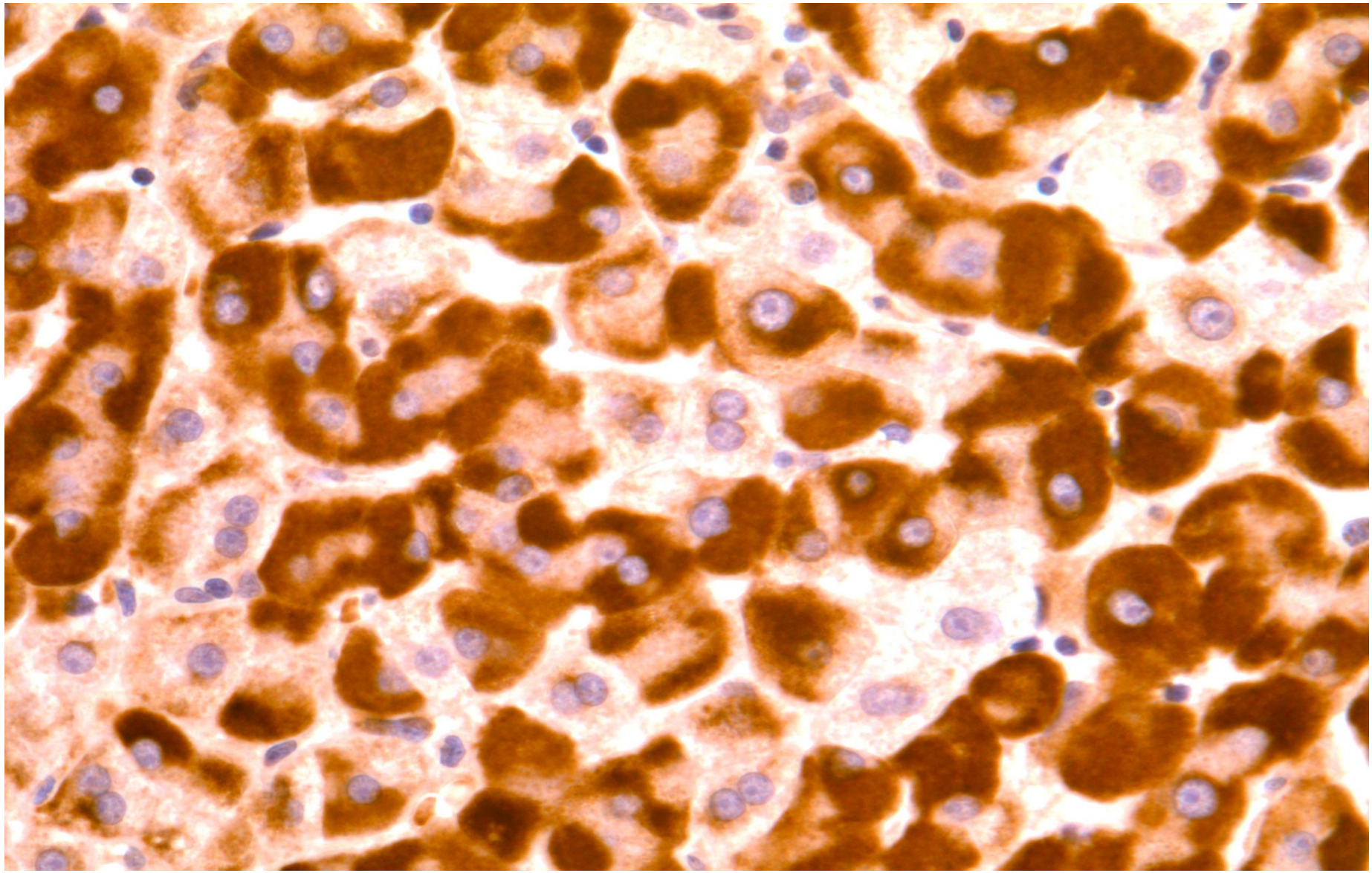
The host‘s immune attack against HBV is the cause of the liver injury, mediated by a cellular response to small epitopes of HBV proteins, especially HBcAg, presented on the surface of the hepatocyte

HBV Infection

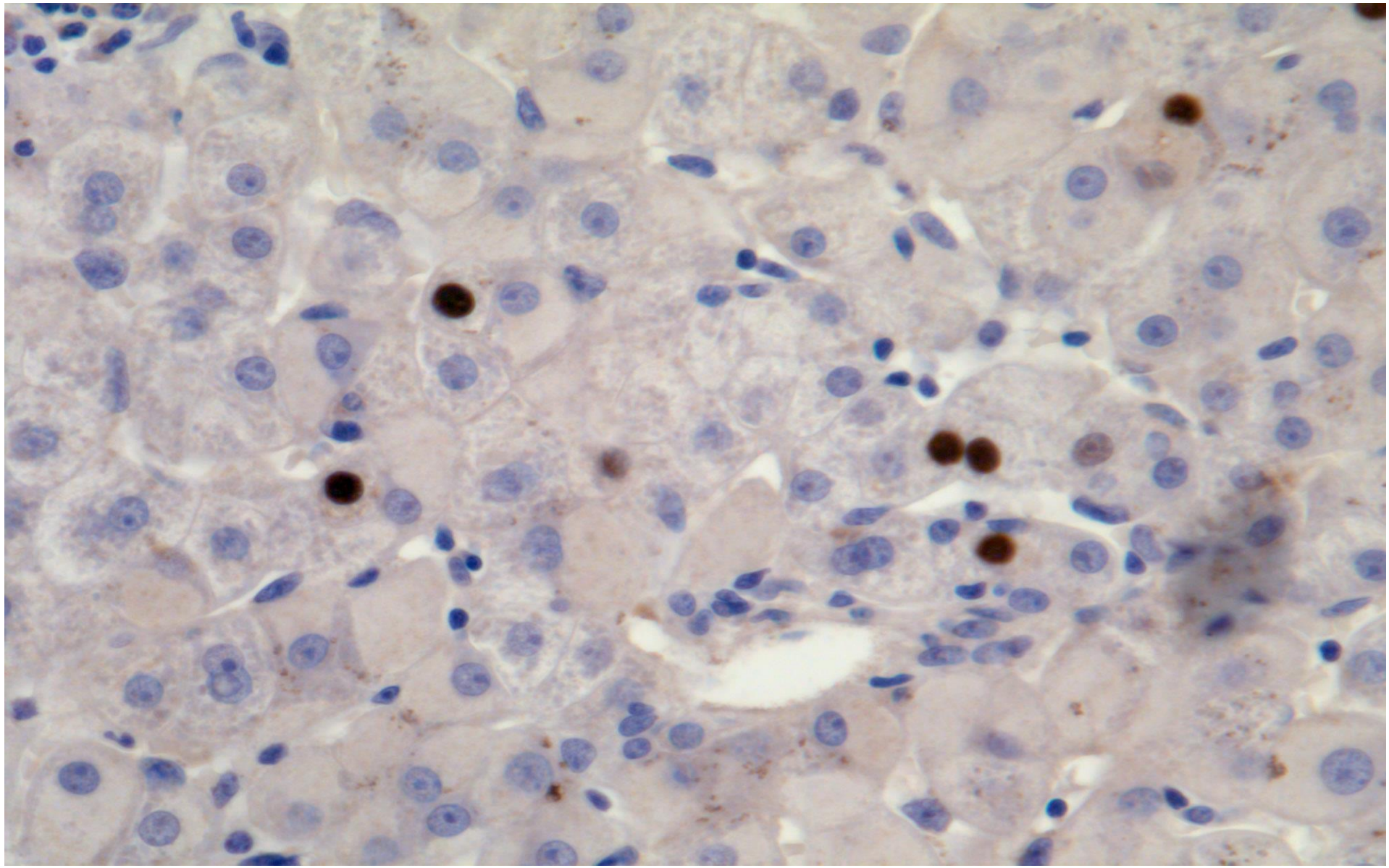


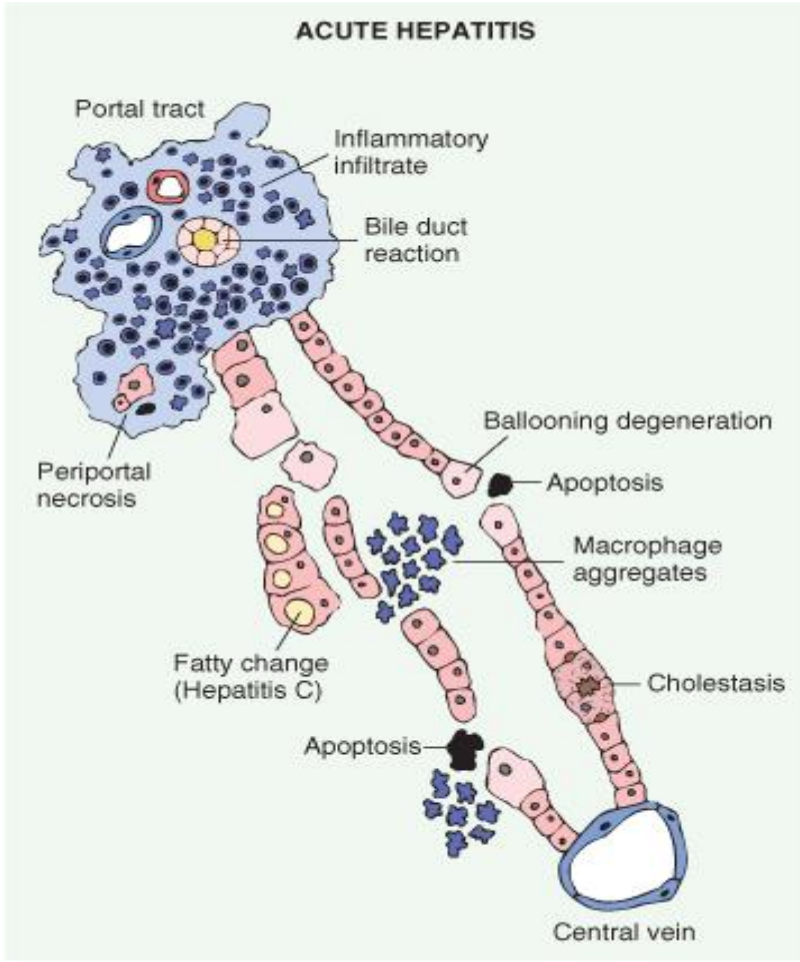
„ground-glass“ hepatocytes

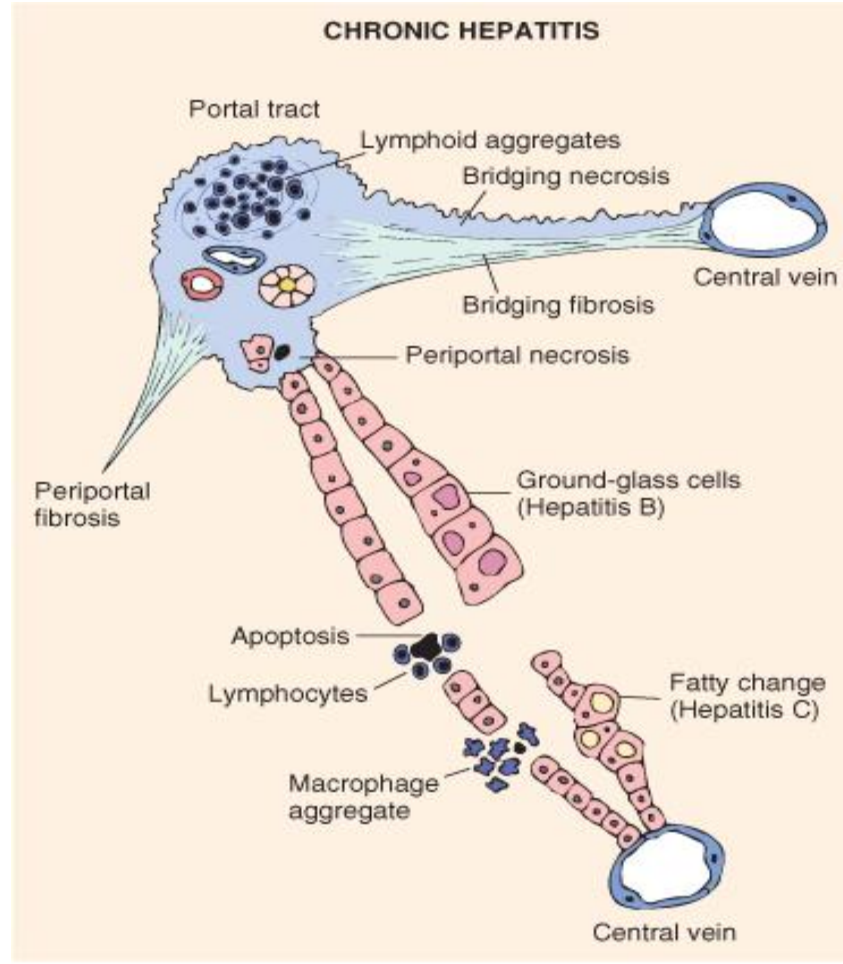
HBV chronic infection: Surface antigen (HBsAg)



HBV infection: Core Antigen





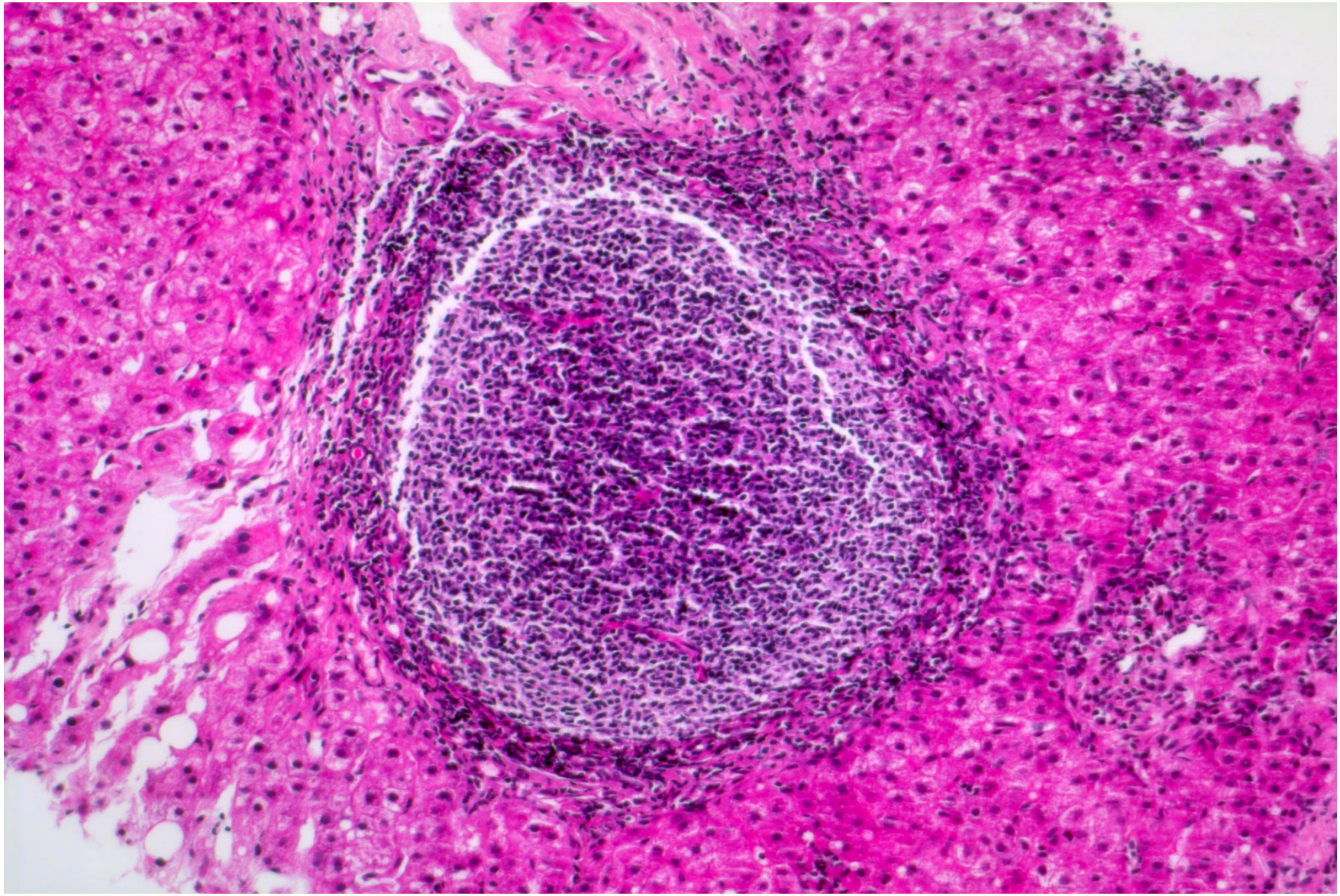


Diagrammatic representations of the morphologic features of acute and chronic hepatitis. Bridging necrosis (and fibrosis) is shown only for chronic hepatitis; bridging necrosis may also occur in acute hepatitis (not shown).

Histopathology of Chronic Hepatitis C
Characteristic but not specific features!

- Prominent lymphoid aggregates in portal tracts
- Bile duct damage
- Steatosis

Chronic Hepatitis C: Lymphoid follicle



Chronic Viral Hepatitis

The Role of Liver Biopsy

- Grading
- Staging
- Confirming the diagnosis of viral hepatitis
- Confirming or excluding concurrent disorders such as alcoholic steatohepatitis or hemocromatosis
- Assess response to therapy

Chronic Hepatitis

Grading = Severity of necroinflammatory changes

(Portal, periportal and lobular activity)

Staging = Extent of fibrosis / architectural distortion

V. Desmet, 1994

Metavir Score

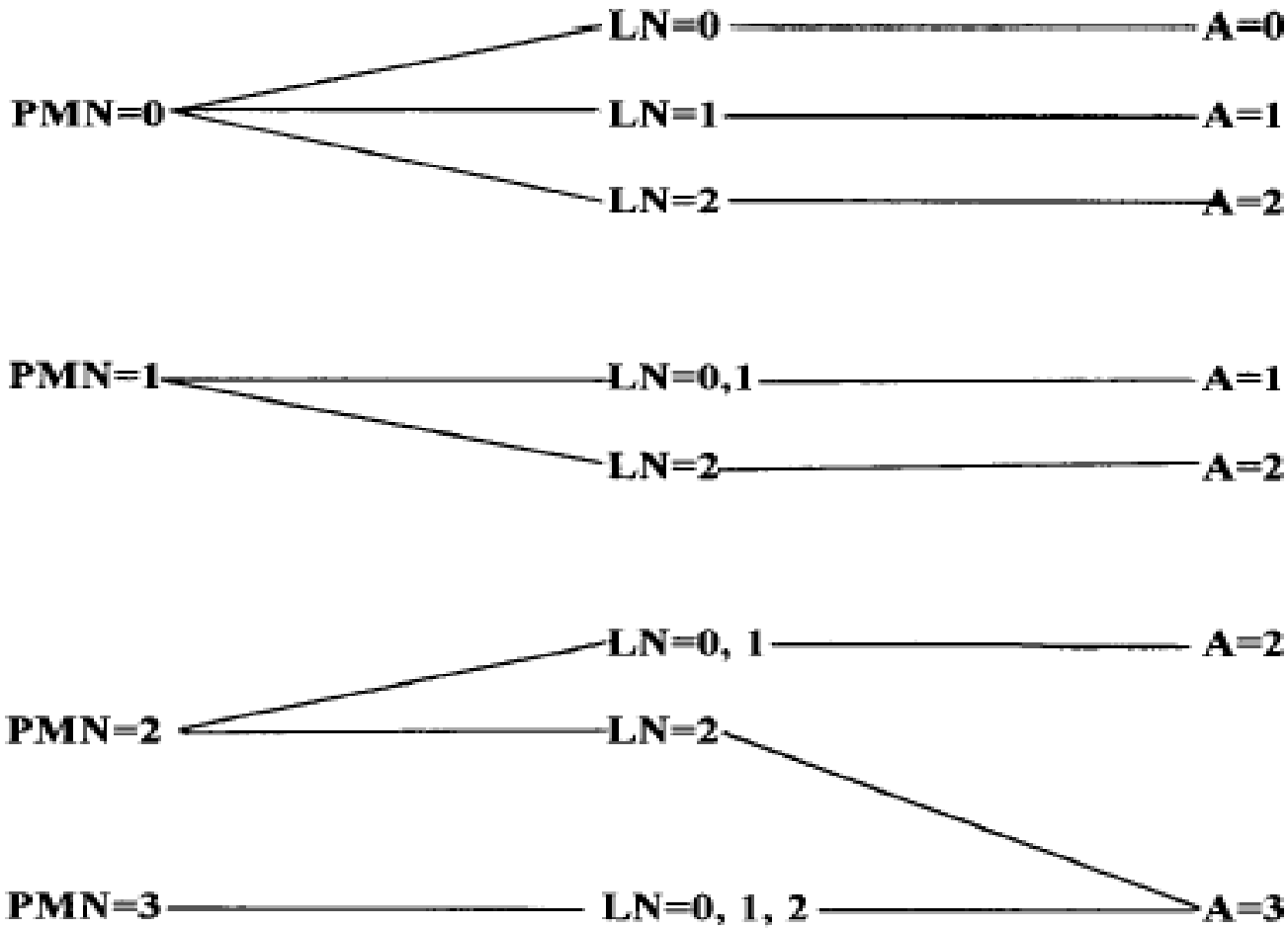


FIG. 2. Algorithm for the evaluation of histological activity. PMN, piecemeal necrosis; 0, none; 1, mild; 2, moderate; 3, severe; LN, lobular necrosis; 0, no or mild; 1, moderate; 2, severe; A, histological activity; 0, none; 1, mild; 2, moderate; 3, severe.

Metavir Scoring System

A two letter and two number system

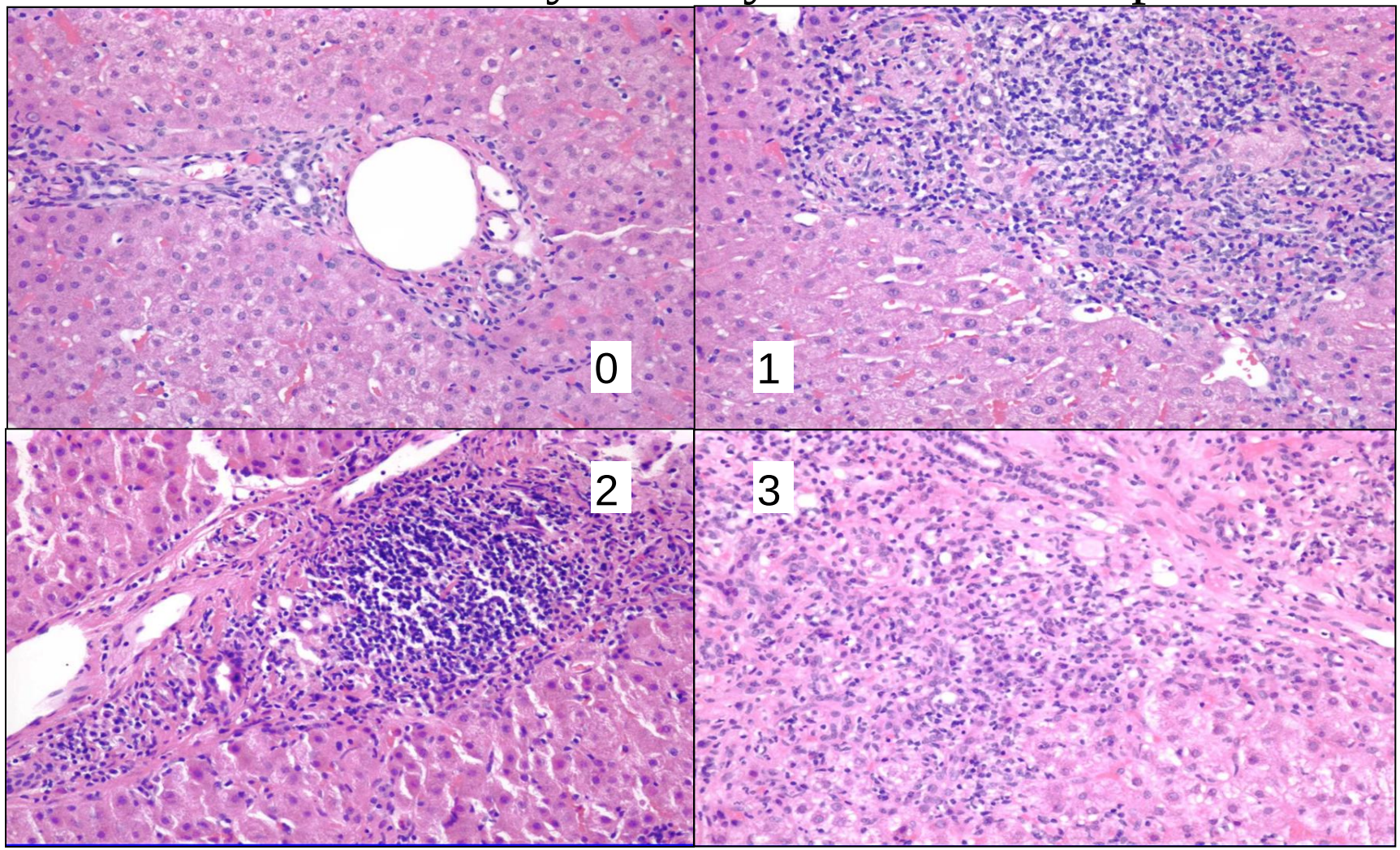
A = Histological activity
- A0 - no activity
- A1 - mild activity
- A2 - moderate activity
- A3 - severe activity

F = Fibrosis
- F0 - no fibrosis
- F1 - portal fibrosis, no septa
- F2 - portal fibrosis, rare septa
- F3 - numerous septa, no cirrhosis
- F4 - cirrhosis

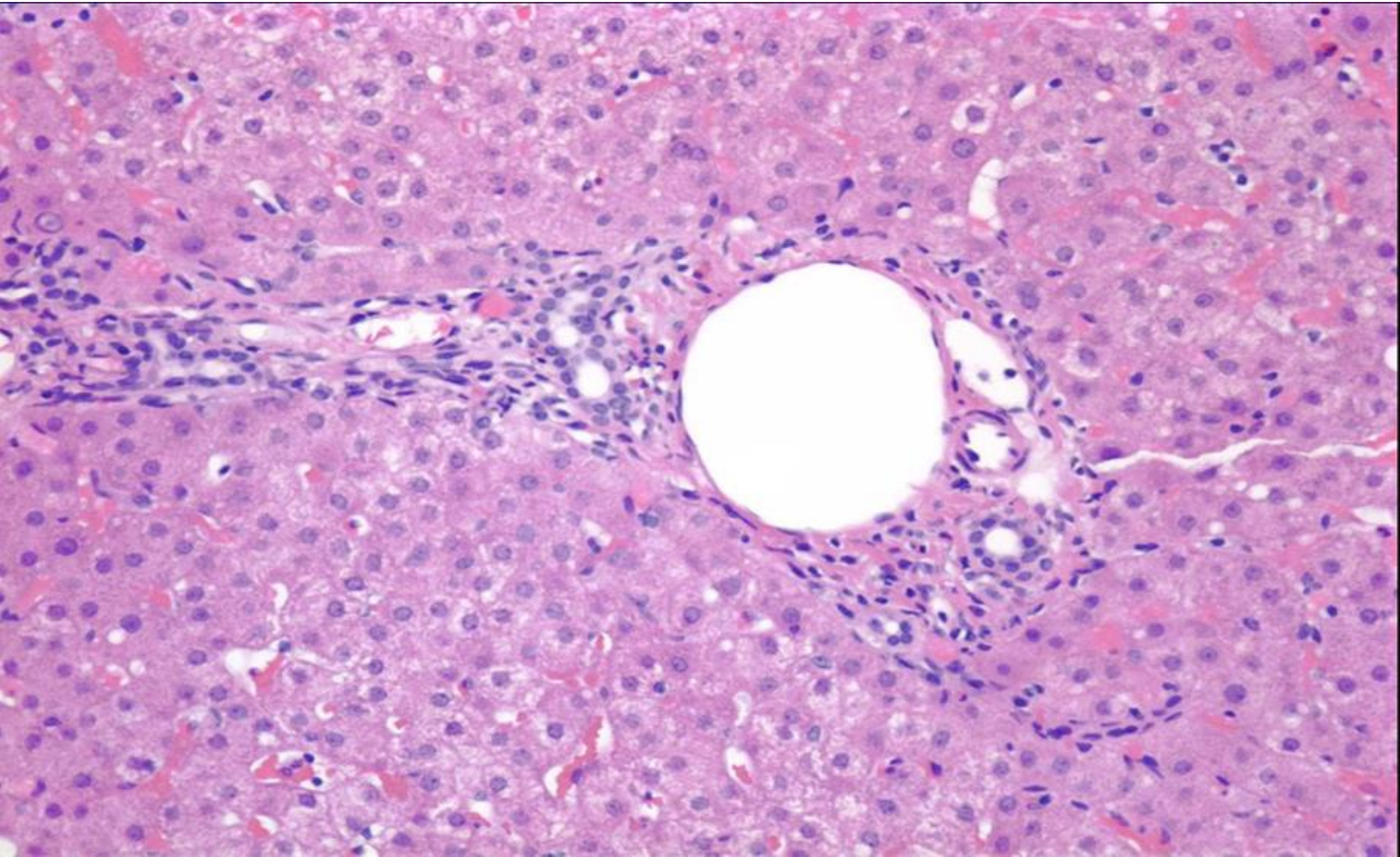
Bedossa P, Poynard T, Hepatology 1996; 24:289

HCV - Natural History

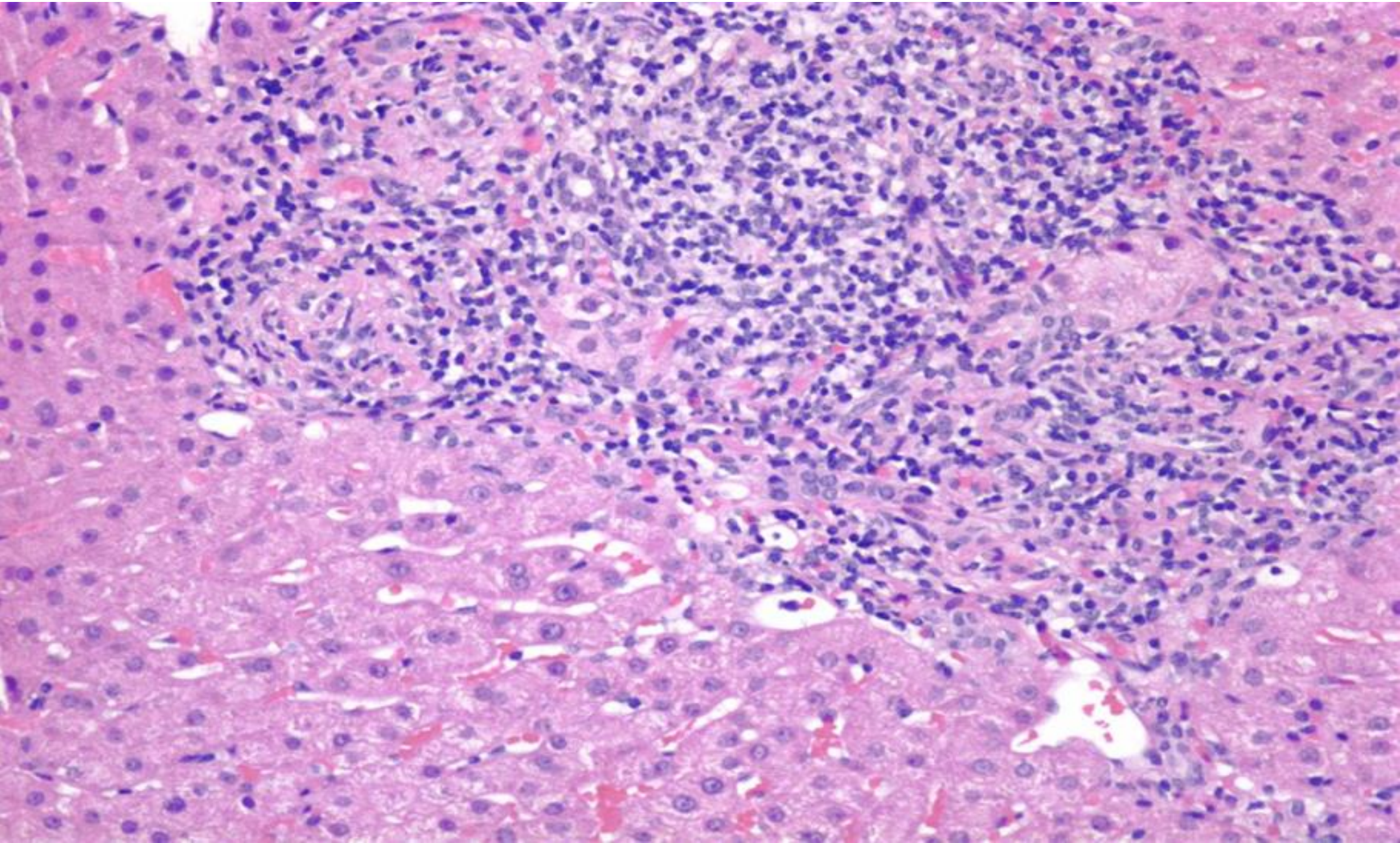
Grade of inflammatory activity in Chronic Hepatitis



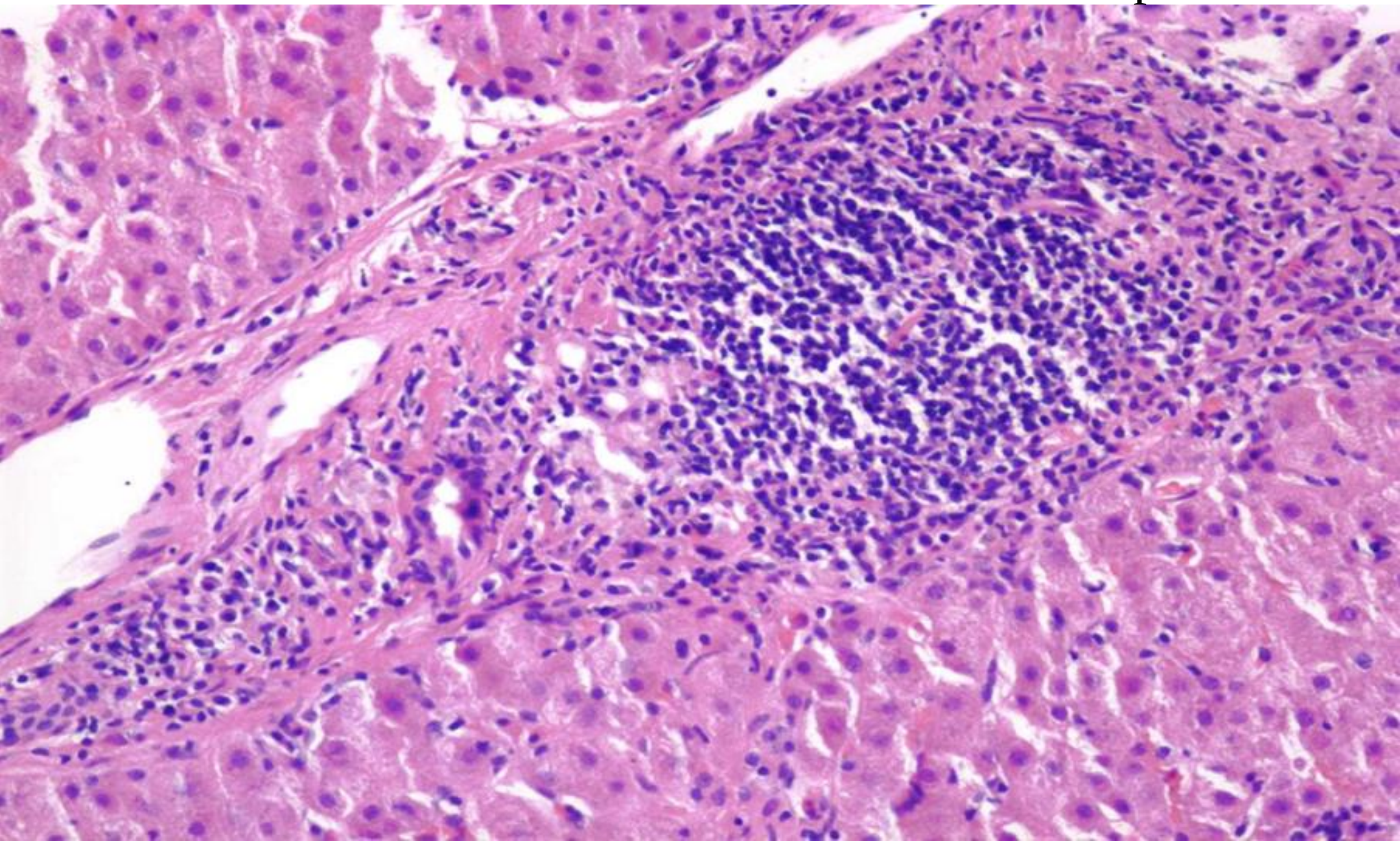
HCV - Grade 0 Inflammation in Chronic Hepatitis



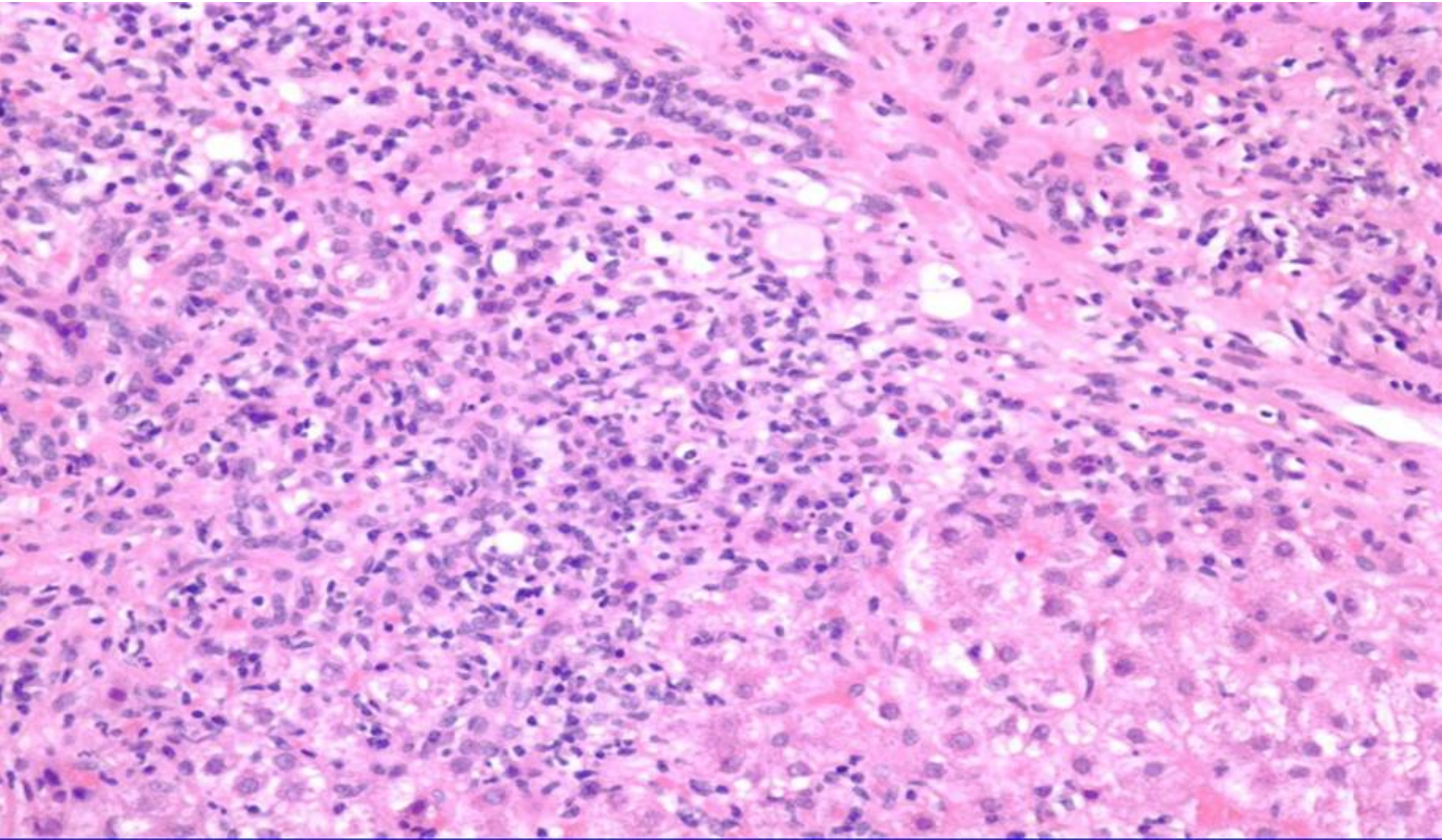
HCV - Grade 1 Inflammation in Chronic Hepatitis



HCV - Grade 2 Inflammation in Chronic Hepatitis

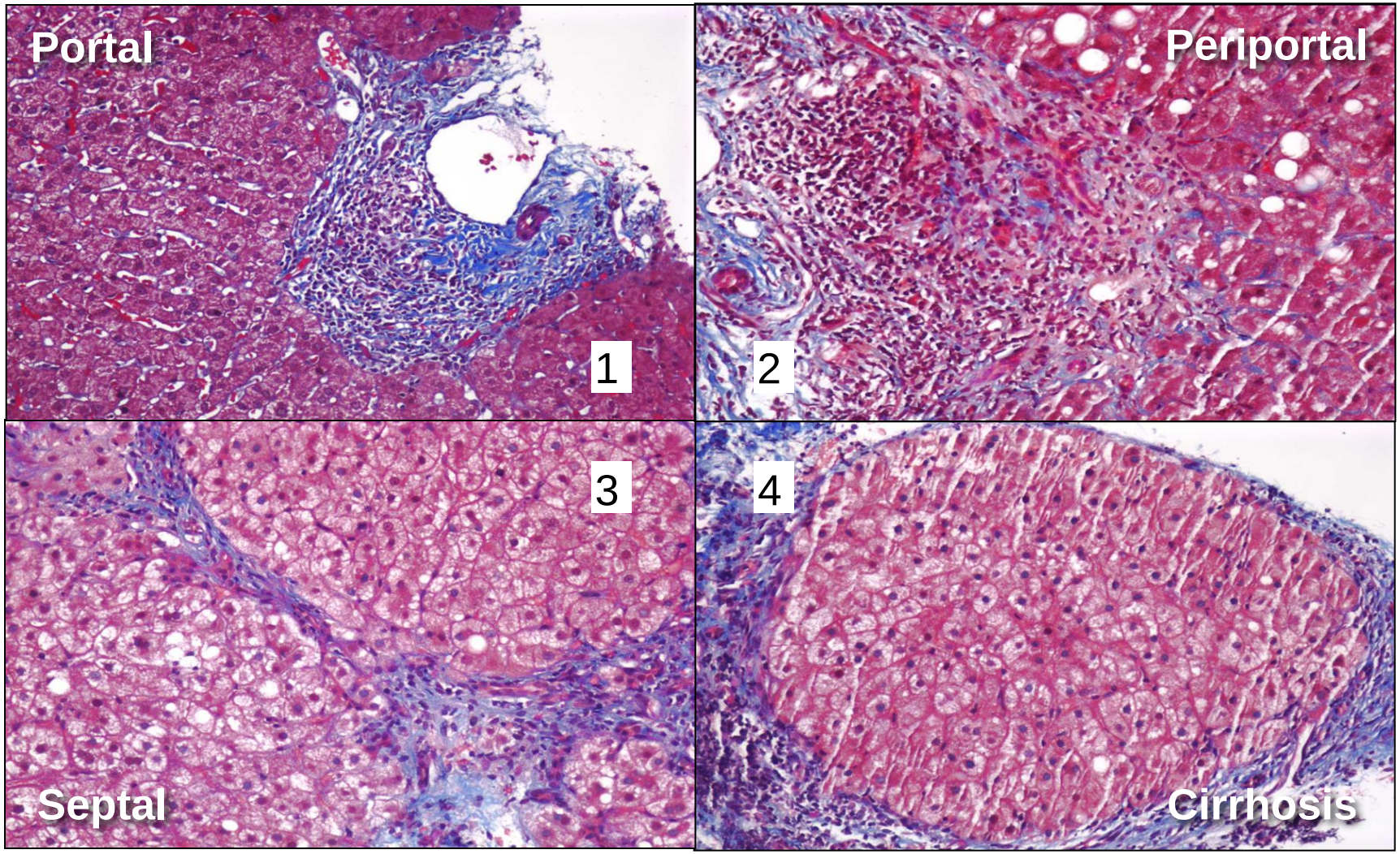


HCV - Grade 3 Inflammation in Chronic Hepatitis

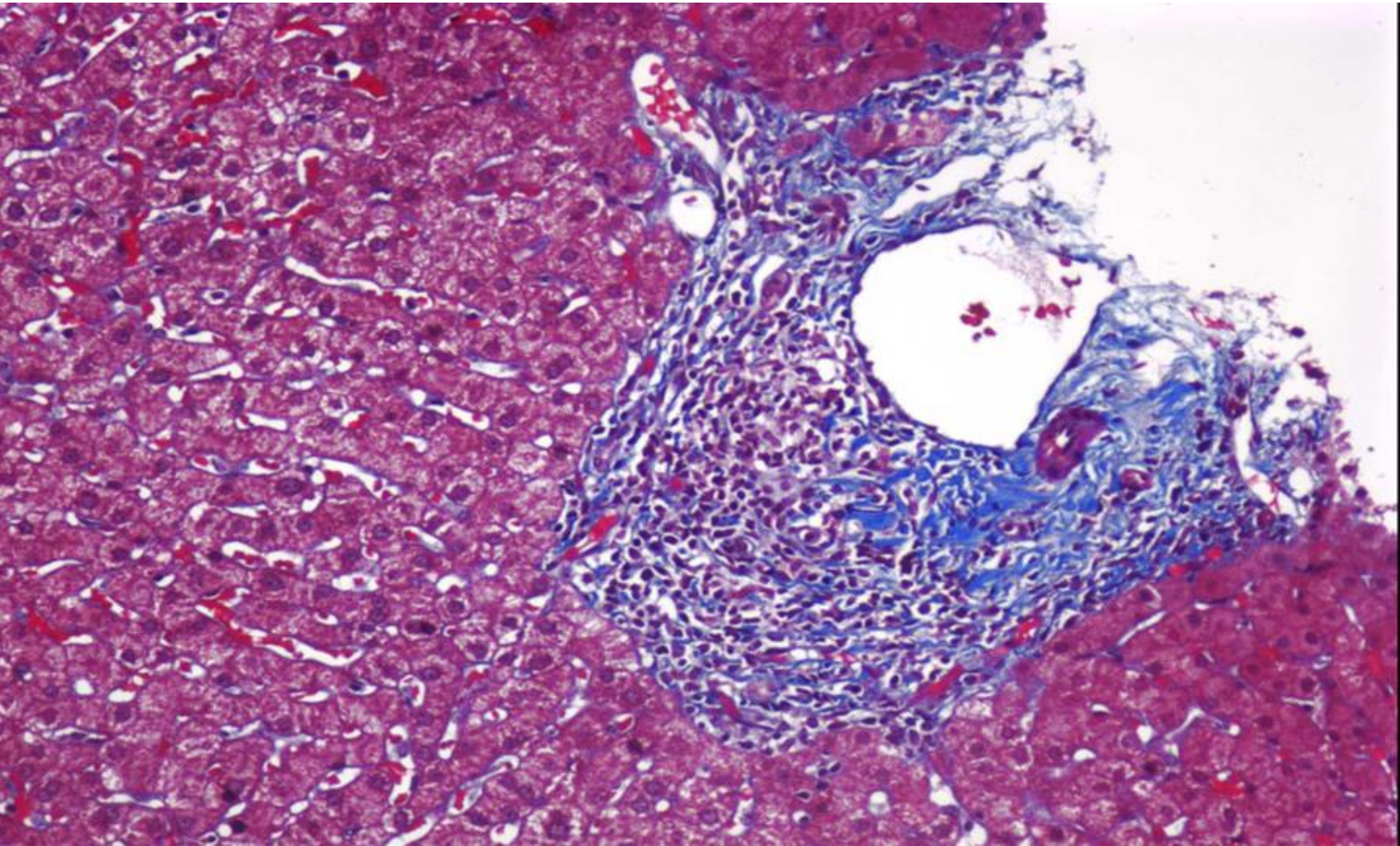


HCV - Natural History

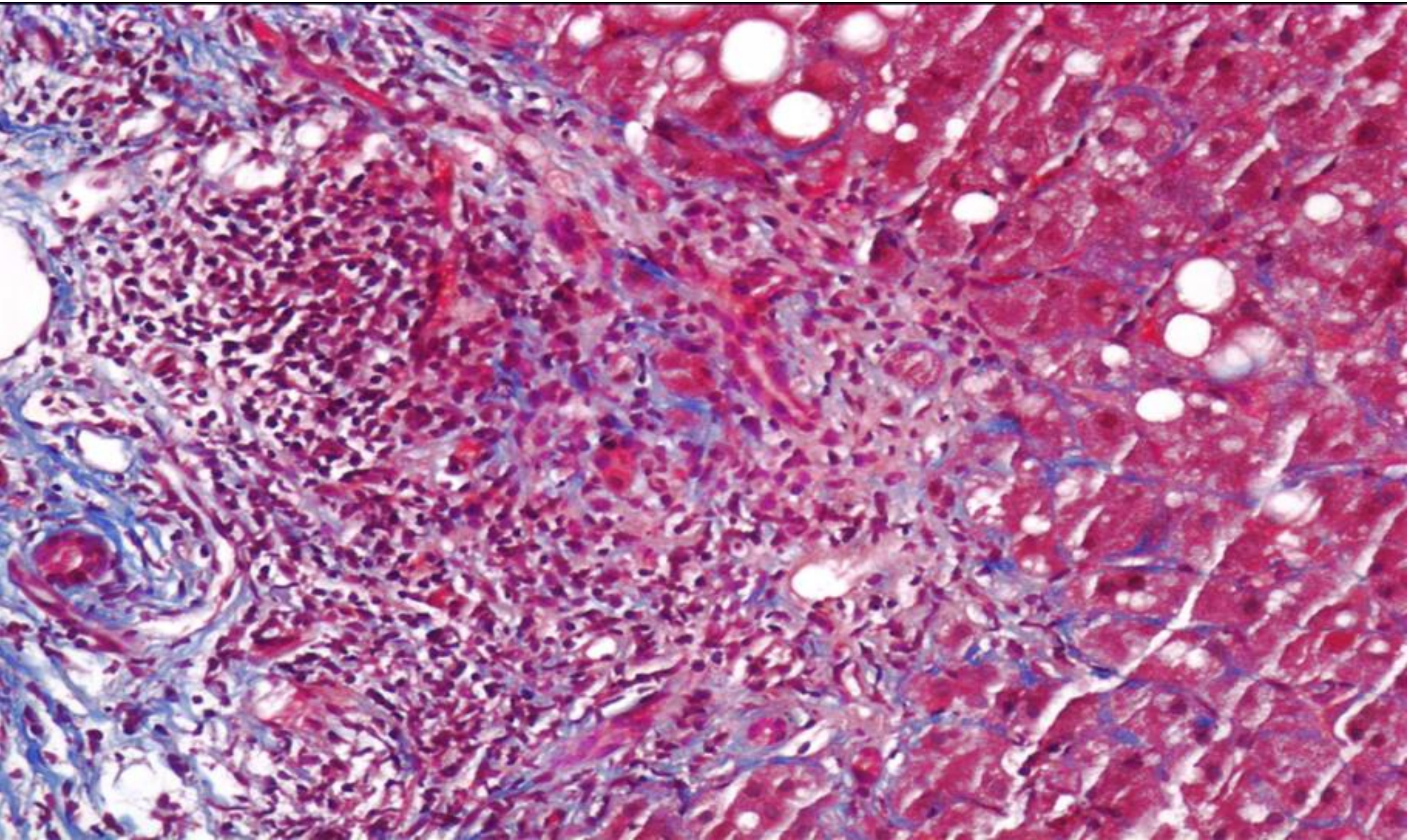
Stages of Fibrosis in Chronic Hepatitis



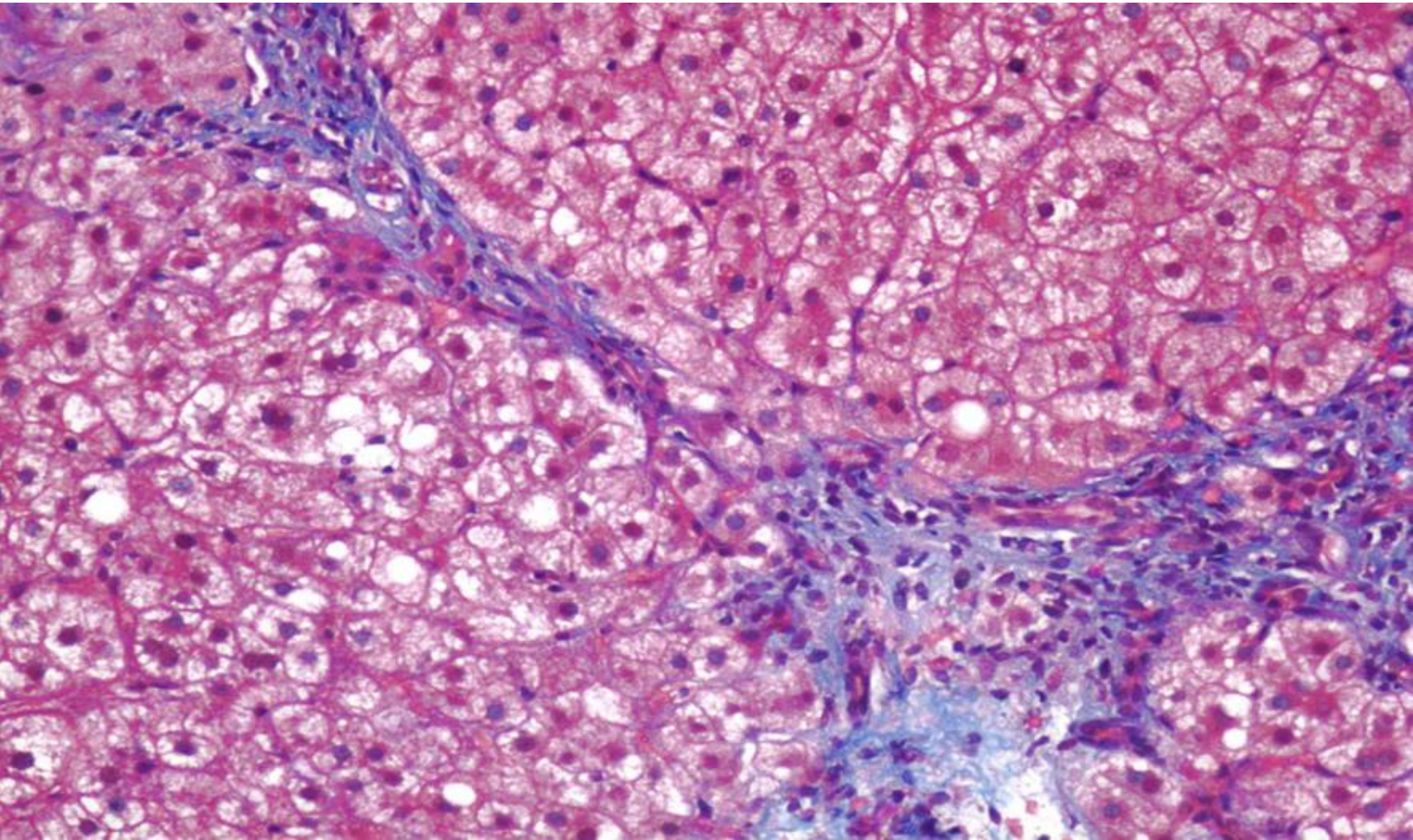
HCV - Stage 1 Fibrosis (Portal)



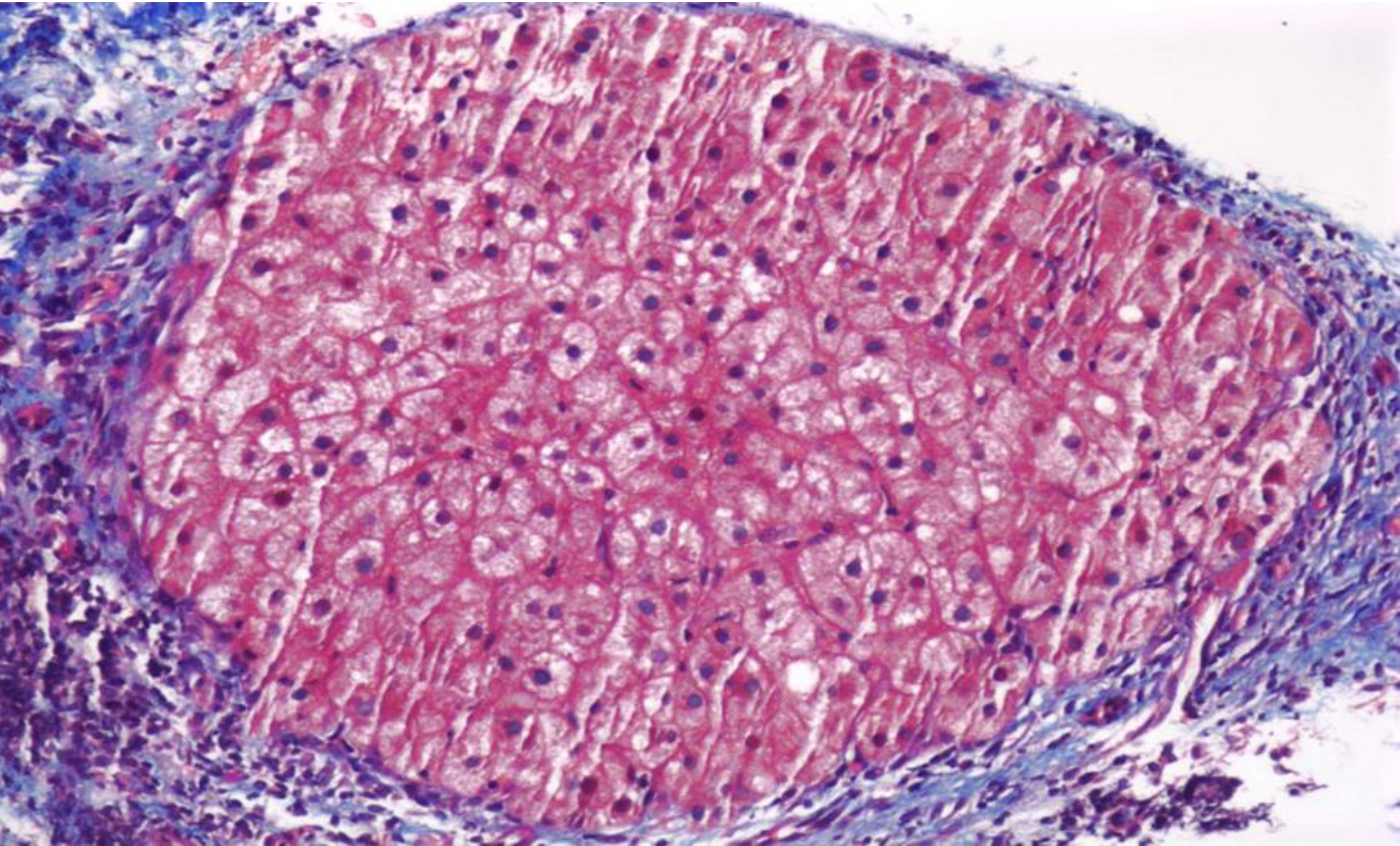
HCV - Stage 2 Fibrosis (Periportal)



HCV - Stage 3 Fibrosis (Septal)



HCV - Stage 4 Fibrosis (Cirrhosis)



Chronic Viral Hepatitis (II)

Luigi Terracciano
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University Hospital Basel

Basel, 2016

Preview

Each biopsy report should convey

- The cause of the hepatitis when known
- The amount of inflammation
- The amount of fibrosis
- Any other biopsy findings, eg fat

Preview

Each biop **nvey**

- Th n
-
-
- Any

Key point 1:

Do this accurately:

Your biopsy report will be perfect in >99% of all cases

Typical reasons for liver biopsy

The primary diagnosis of chronic

hepatitis C or

hepatitis B

is already known in most cases

before the liver biopsy is performed

Typical reasons for liver biopsy

- Determine amount of fibrosis (stage of liver disease)
- Evaluate fibrosis progression
- Evaluate degree of inflammation (grade)
- Evaluate for concomitant liver disease

Typical reasons for liver biopsy

- Determine amount of fibrosis (stage of liver disease)
- Evalu
- Eva (grade)
- Evalua disease

<u>Key point 2</u>:
This is the main reason for biopsy in most cases of HCV and HBV

Liver Fibrosis Assessment

- Trichrome stain commonly used
- Acceptable but not perfect reproducibility
- Fibrosis variability more likely when:
  - Small biopsy (less than 15 mm)
  - Old inactive cirrhotic livers with large macronodules
  - Biliary tract disease

Liver Fibrosis Assessment

- Reporting fibrosis in a liver biopsy
  - Narrative vs number vs both
    - Mild portal fibrosis
    - MHAI fibrosis stage: 1/6
    - Mild portal fibrosis, MHAI stage 1/6.

Liver Fibrosis Assessment

- Many different staging and grading schemas
  - Most are quite similar
  - None clearly better than the rest
  - Make sure **YOU** know the system well
  - Make sure the clinicians understand the system
    - In the pathology report, it's helpful to indicate the system you're using (and the scale), for example:
    - MHAI fibrosis stage = 2/6

Liver Fibrosis Assessment

- Many different staging and grading schemas
  - Most a
  - No
  - M system
    - – icate the
      sy example:
    - – MHA

Key point 3:
Make sure you don't get so caught up in filling out numbers that you forget to carefully study the biopsy !

Staging schemas are similar

- Essentially all are fibrosis staging is based on the following conceptual stages and differ only in how they are subdivided:
  - No fibrosis
  - Portal fibrosis
  - Bridging fibrosis
  - Cirrhosis

General Comparison of the Most Commonly Used Staging Systems

MHAI	HAI	METAVIR	DESMET	SCHEUER	BATTS
0	0	0	0	0	0
1	1	1	1	1	1
2	1	1	1	1,2	1,2
3	***3****	***2***	***2,3***	***2***	***2***
4	3	3	2,3	3	3
5	3	3	2,3	3	3
6	4	4	4	4	4

Inflammation and fibrosis

are a NON-LINEAR continuum:

Giving a number doesn't change that

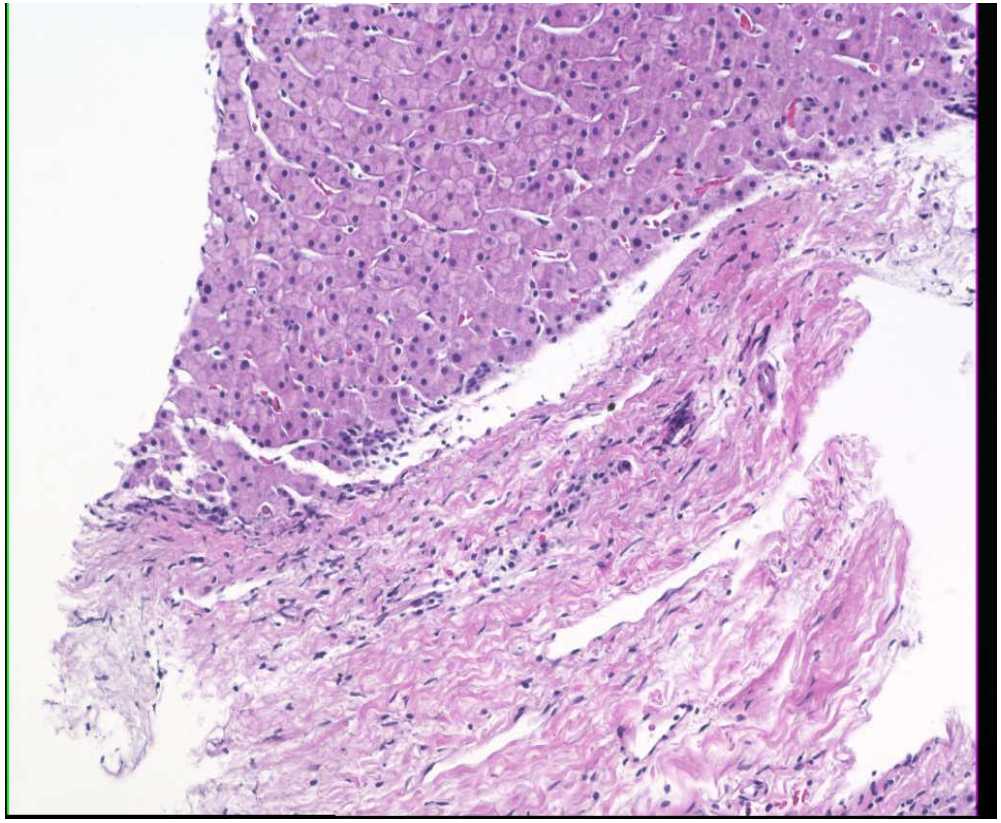
The numbers in staging and grading systems are not equidistance

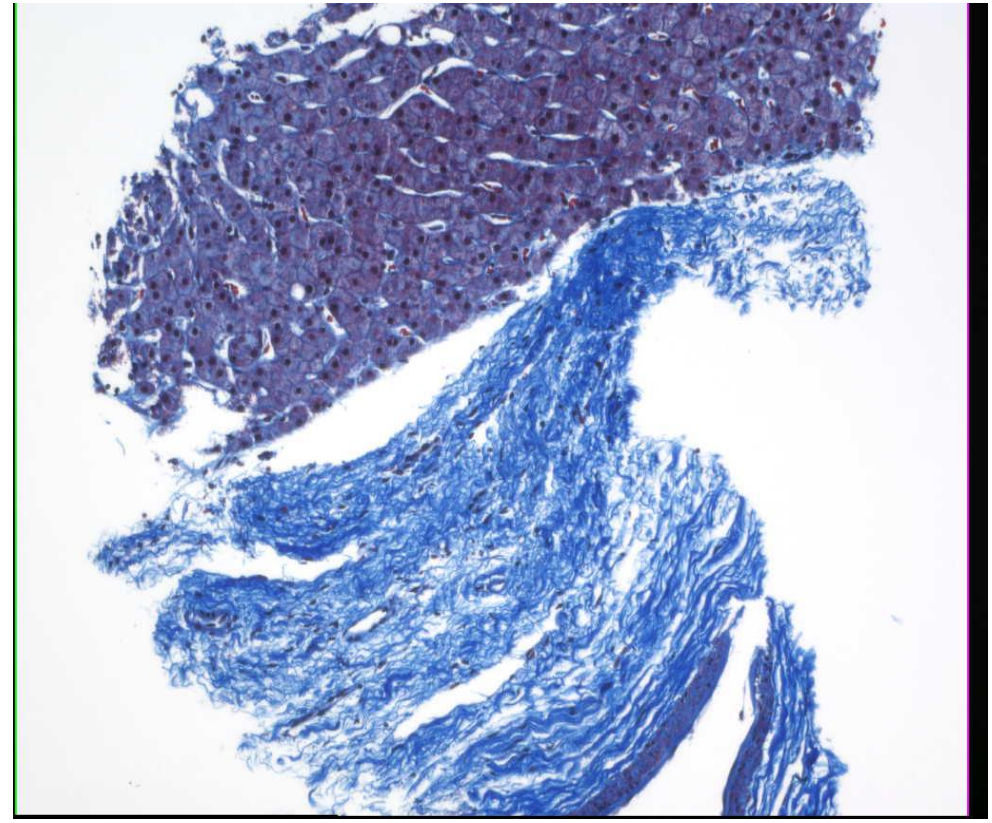
A stage 2 liver bx **does not** have twice as much fibrosis as stage 1

A grade 4 bx **does not** have ½ as much inflammation as grade 8.

Staging pitfalls

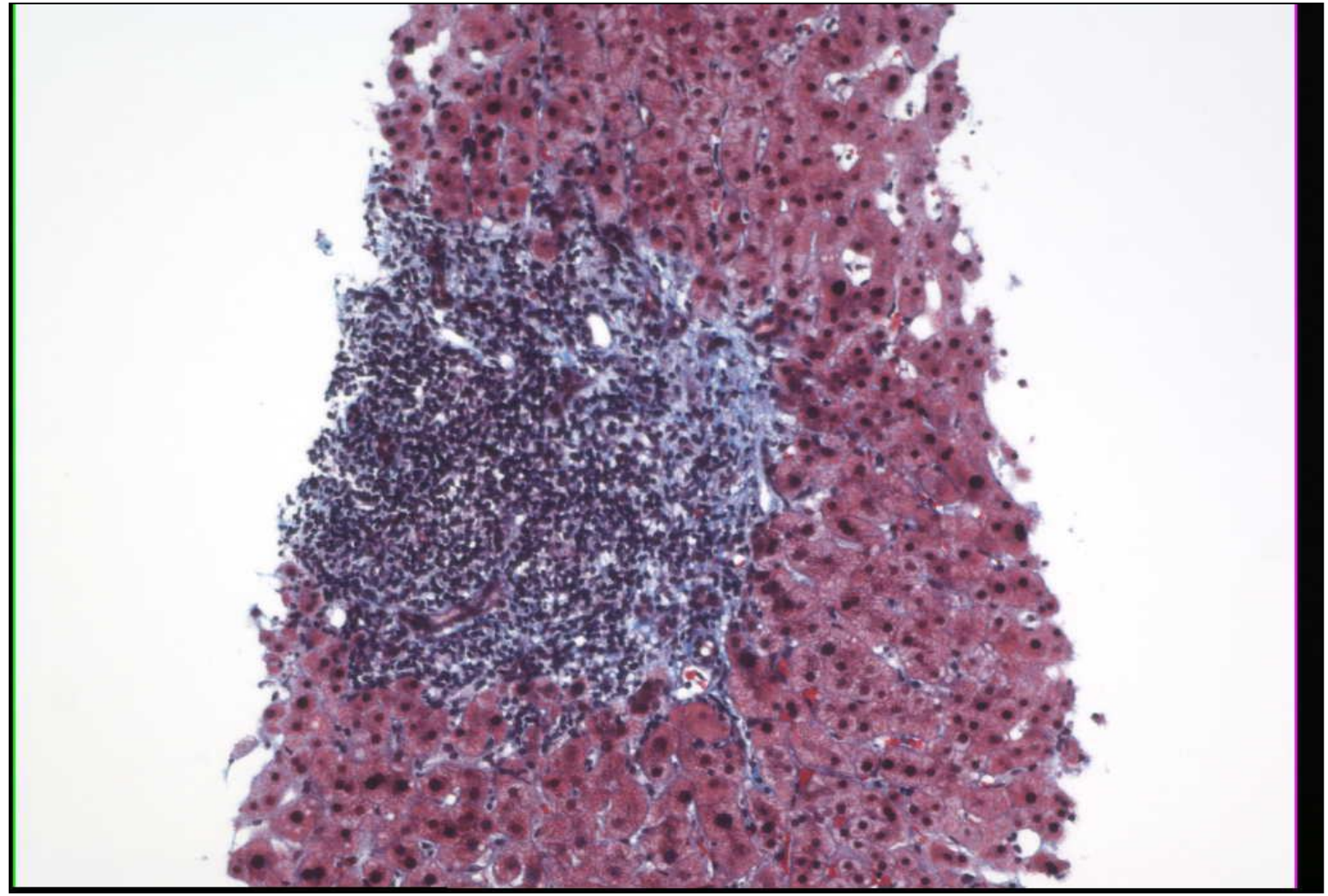
- Large portal tracts





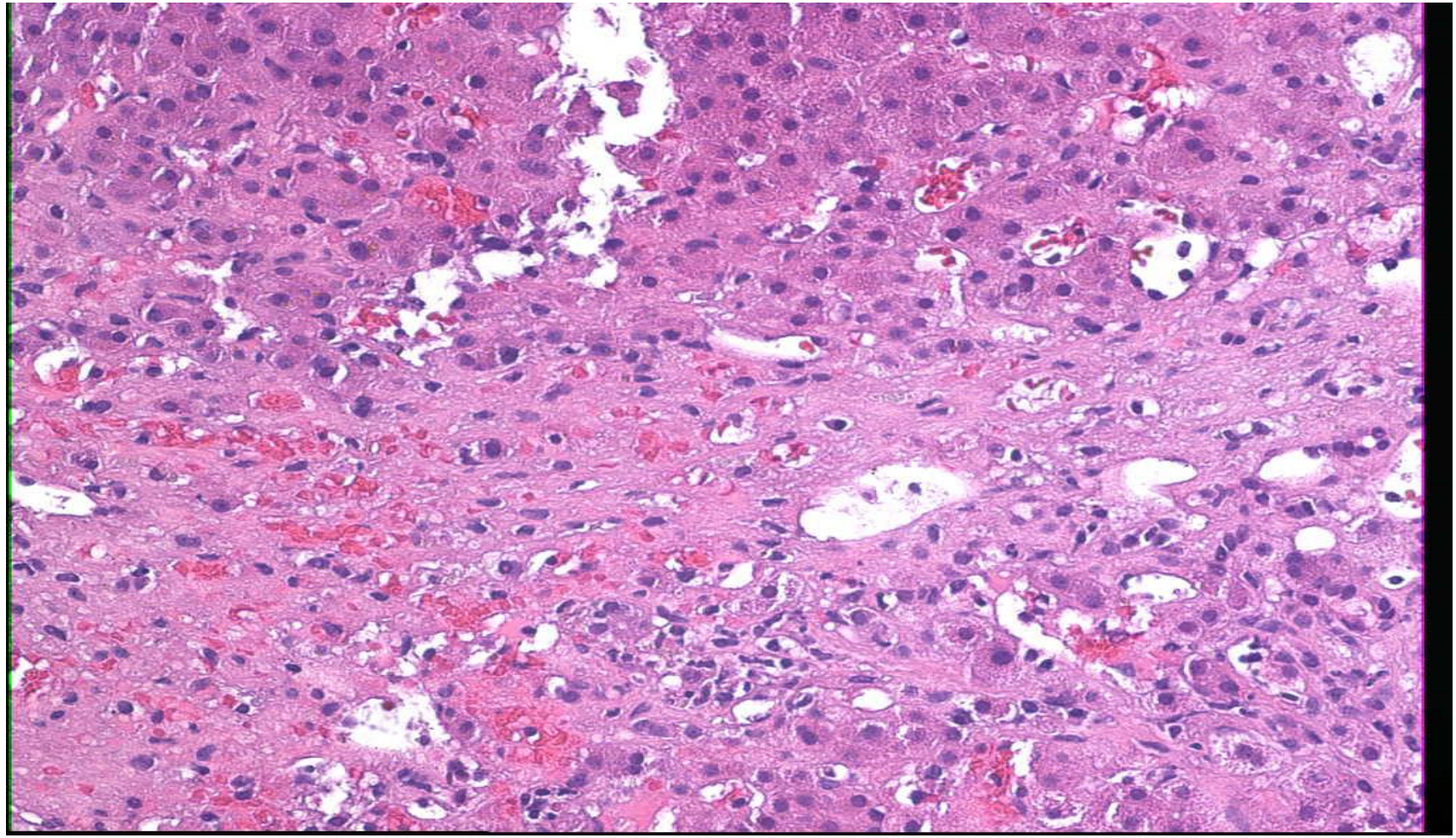
Staging pitfalls

Marked portal inflammation



Staging pitfalls

Bridging necrosis

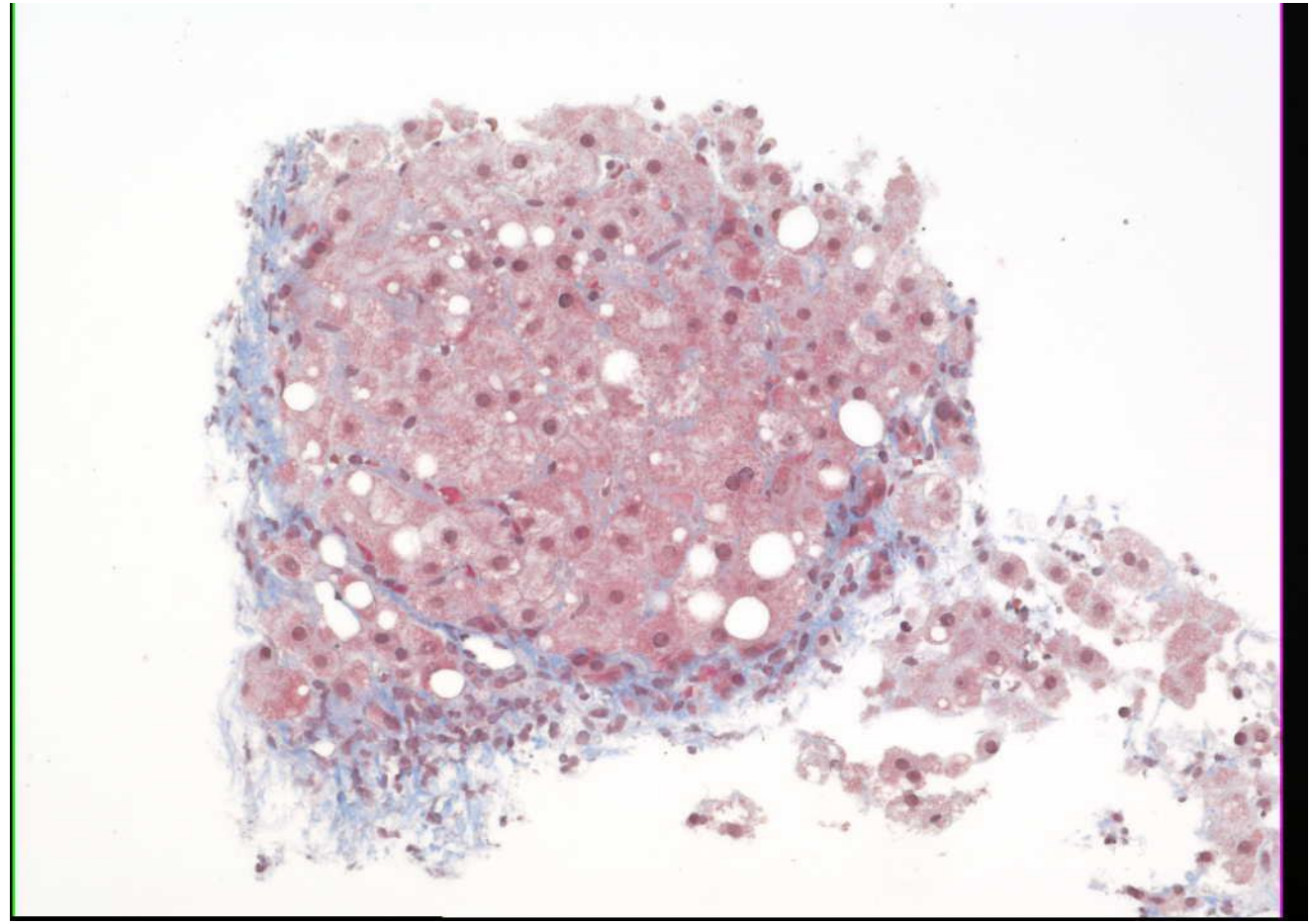


Staging pitfalls

- If the biopsy specimen is too small or fragmented, *please* say so in the report.
  - “The biopsy is too small to adequately stage but there does appear to be at least mild portal fibrosis”.

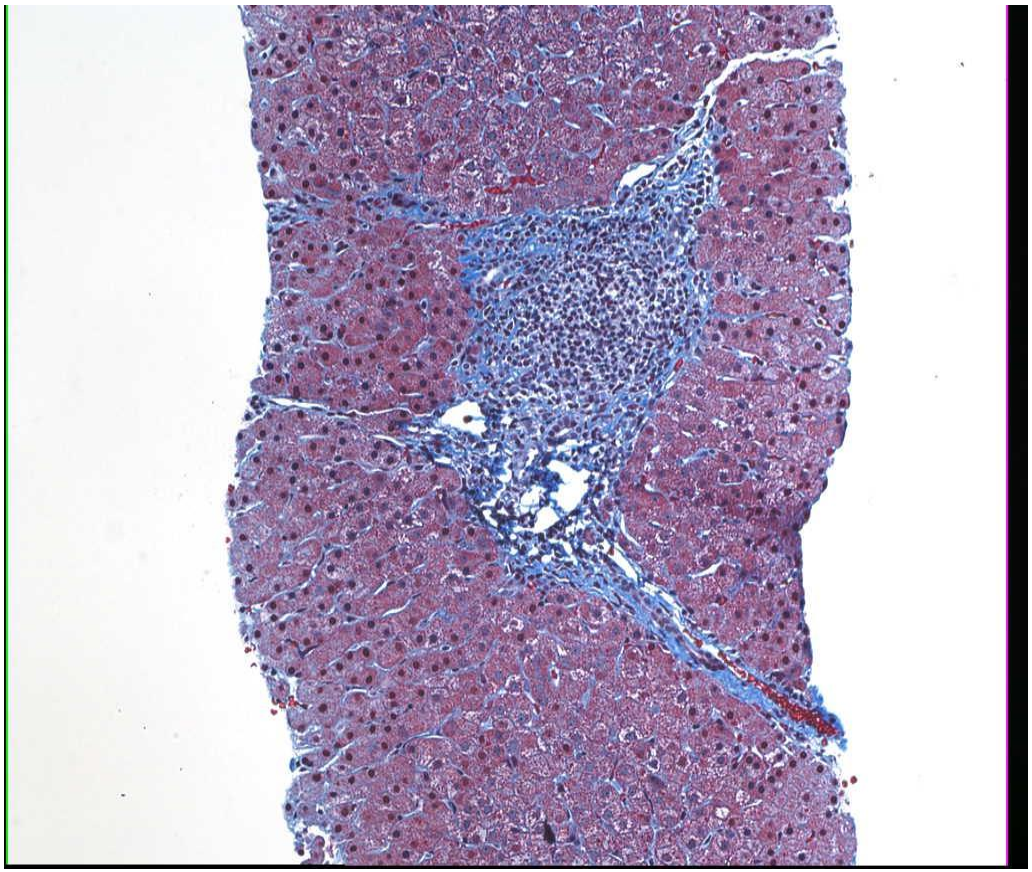
Staging pitfalls

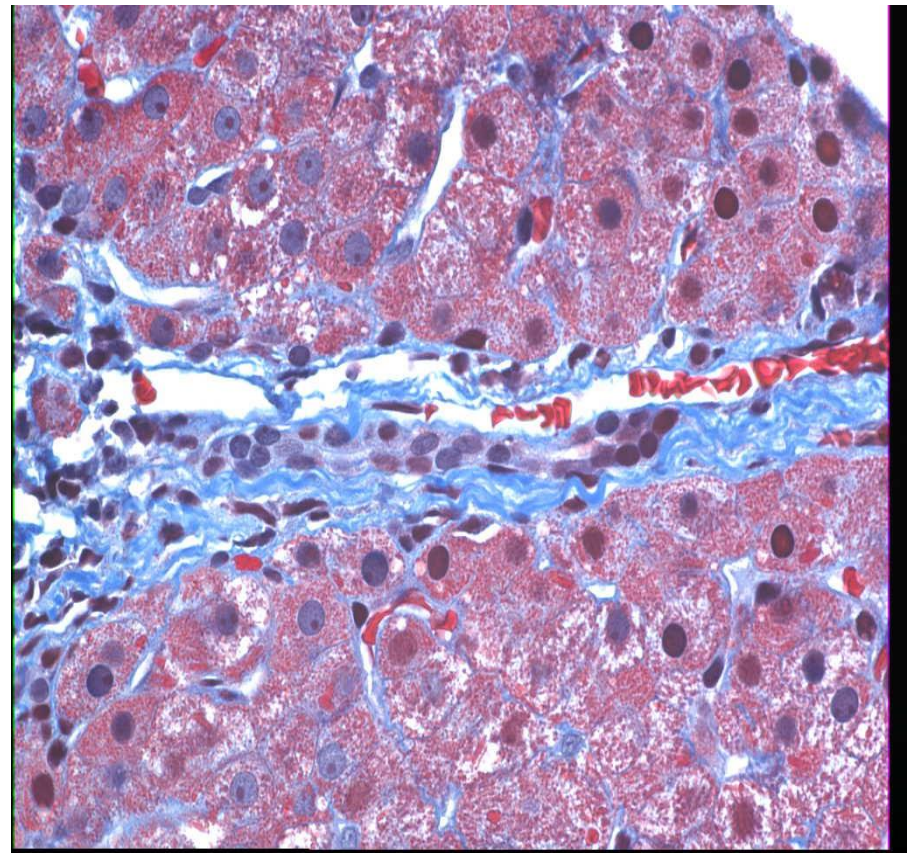
“Fibrous caps”



Staging pitfalls

Focal fibrous bridging vs longitudinal section of portal tract





Typical reasons for liver biopsy

- Determine amount of fibrosis (stage of liver disease)
- Evaluate fibrosis progression
- Evaluate degree of inflammation (grade)
- Evaluate for concomitant liver disease

Fibrosis progression

- Fibrosis progression poorly understood
- Overall, 20% of those with HCV are cirrhotic in 20 yrs.
- Determining fibrosis progression is best performed by comparing two trichrome stains directly.
  - Comparing current case to report of old case is less desirable

Findings on Liver Biopsy That May Increase Risk for Fibrosis Progression

- Fibrosis
- Steatosis
- Steatohepatitis
- Coinfection with HBV or HIV
- Iron overload
- (not a complete list, but some of the more common findings)

Typical reasons for liver biopsy

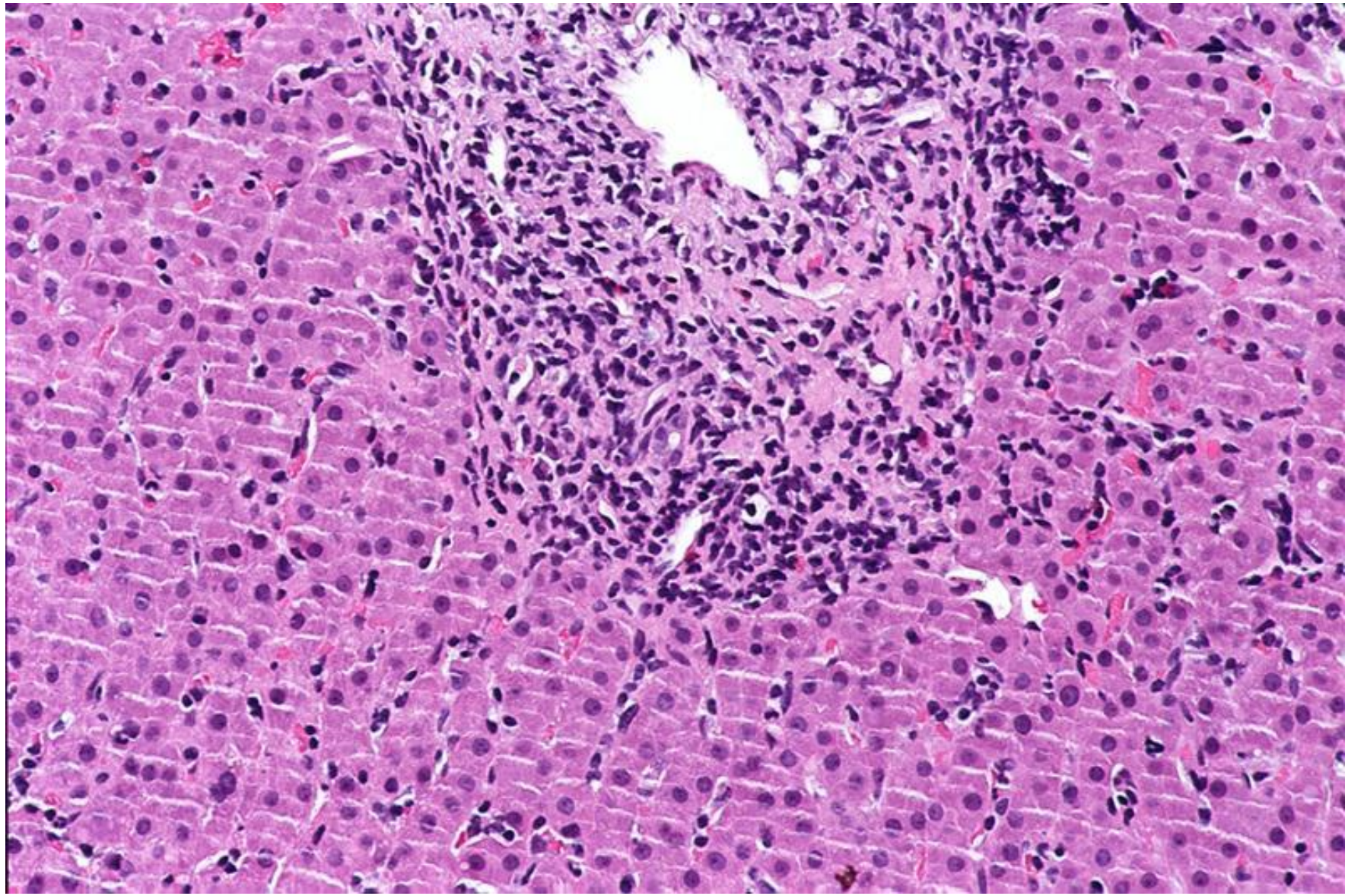
- Determine amount of fibrosis (stage of liver disease)
- Evaluate fibrosis progression
- Evaluate degree of inflammation (grade)
- Evaluate for concomitant liver disease

Inflammation (grade)

- Three “compartments” to inflammation
  - Portal inflammation
  - Interface activity/periportal hepatitis/piecemeal necrosis
  - Lobular hepatitis/spotty necrosis

  Most staging systems accompanied by grading systems.
  - For clinical purposes, probably doesn't add much to pathology report over descriptive diagnosis

Inflammation



Inflammation

- In greater than 90% of cases of HCV liver biopsies
- **Portal inflammation** is
  - Either mild or moderate
- **Lobular inflammation** is
  - Either mild or moderate

Inflammation

- In greater than 90% of cases of HCV
- **Porta**
  - Eit
- **Lobular**
  - Either mild or moderate

Key point 4:
If the inflammation in your biopsy for HCV *doesn't* look like this, think some more

Inflammation

- If your biopsy shows marked lobular inflammation in particular
  - Start thinking!
  - Check the history
  - Check the liver enzymes

Inflammation

- Chronic HCV **does not have enzyme "flares"**
- This is in contrast to chronic HBV
- If your biopsy shows marked lobular hepatitis and there has been enzyme flare,
  - Strong possibility of another liver injury superimposed on chronic HCV (could be drug, HBV, etc)

Typical reasons for liver biopsy

- Determine amount of fibrosis (stage of liver disease)
- Evaluate fibrosis progression
- Evaluate degree of inflammation (grade)
- Evaluate for concomitant liver disease

Are liver biopsies helpful in finding Co-existing Diseases?

- Yes
- Yield is much higher when there is clinical suspicious for another disease process.
- The yield is low in patients biopsied solely for staging/grading HCV
  - In a study of 535 Italian patients with HCV or HBV, 3.7% of biopsies yielded additional diagnoses (Dig Dis Sci 2001 Jul;46(7):1409-15)

Steatosis and HCV

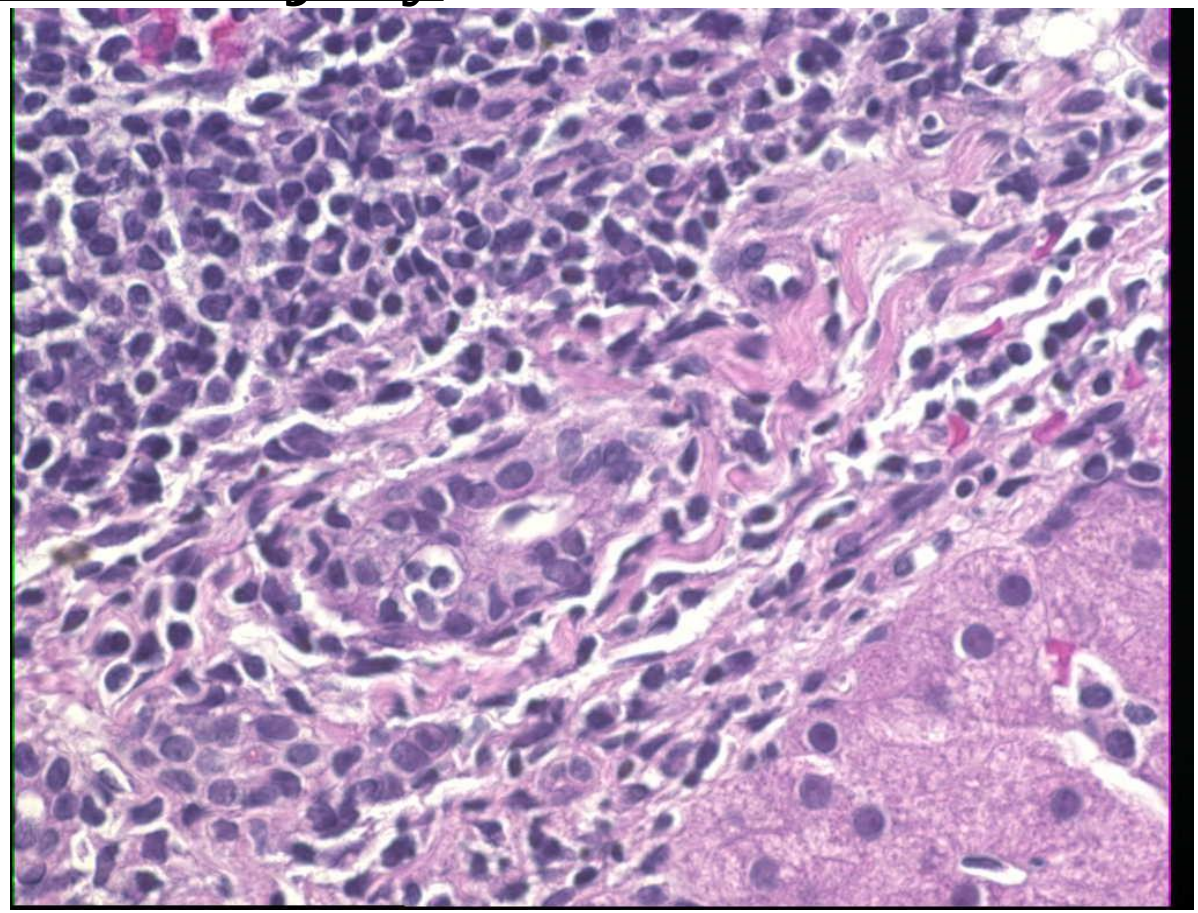
Causes

- NAFLD
- HCV Genotype 3
- Drug effect, including some anti retrovirals
- Etoh

HCV-Other findings

Bile duct lymphocytosis and injury

- Up to 1/3 of cases in Some studies
- No clear direct clinical relevance
- Not assoc with higher Alk phos

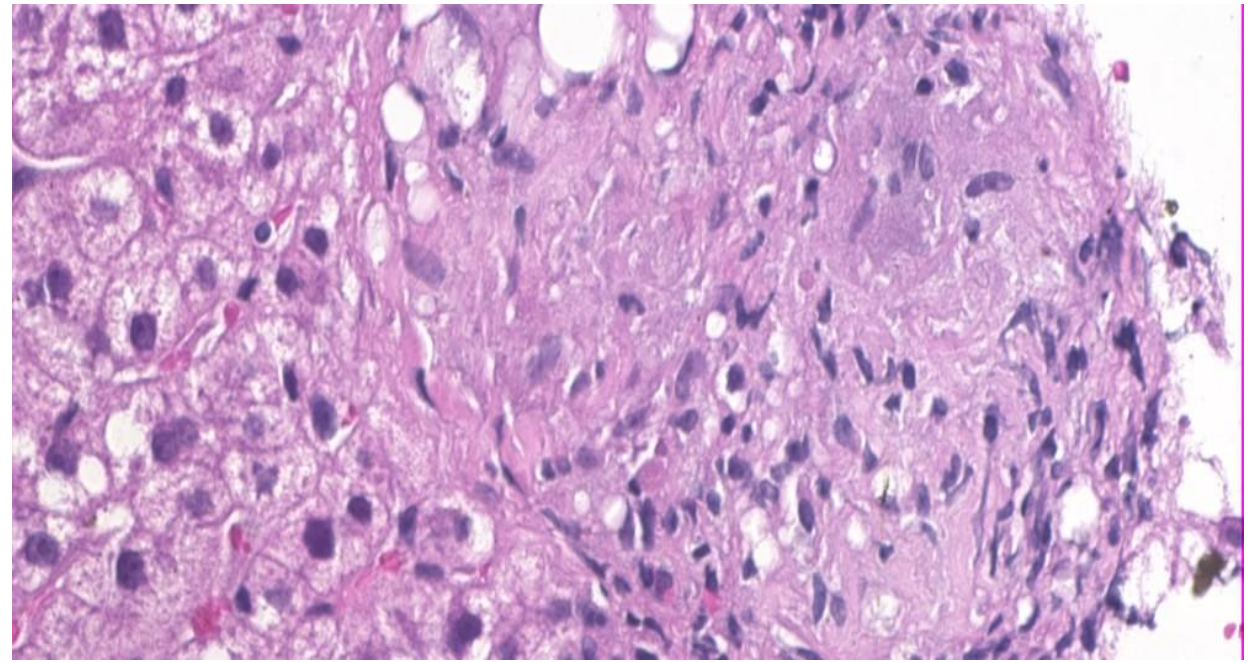


Mod Pathol. 1994 Dec;7(9):937-45

HCV-Other findings

Portal granulomas

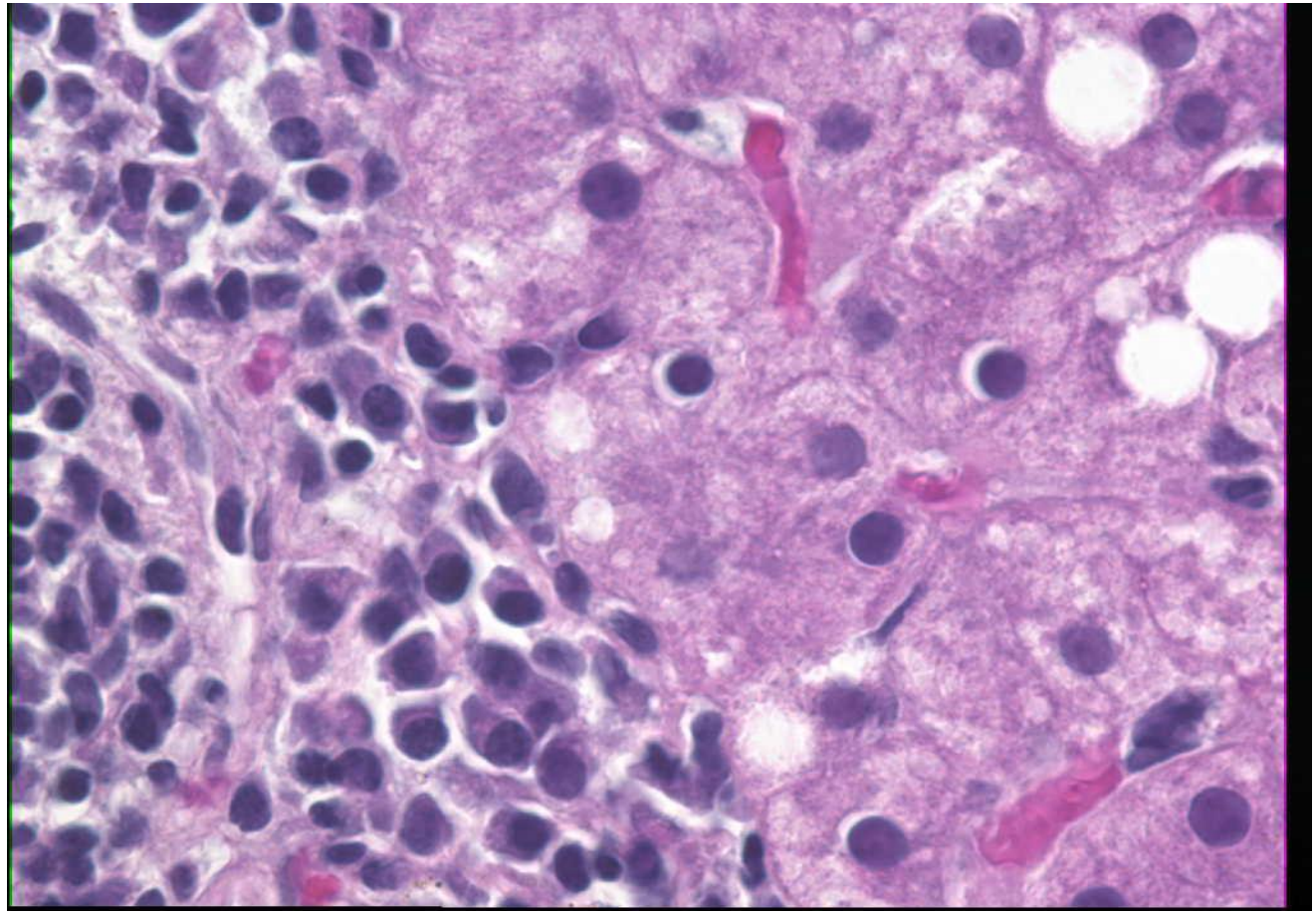
- 1.3% of 605 pts.
- No association with TB, IFN therapy
- Often present on repeat bx
- Significance??



Clin Gastroenterol. 2004 May-Jun;38(5):449-52

HCV-Other findings

- Increased portal plasma cells
- More frequent in those with elevated serum ANA



HCV-Elevated serum ANA

ANA positive in 8% of 605 cases of chronic HCV

- 1:40 = 22
- 1:80 = 20
- 1:160 = 8

- ANA positivity associated with
  - Female gender
  - Geographic location
  - Portal plasma cells

J Viral Hepat. 2004 Sep;11(5):459-64

HCV-Elevate serum ANA

No association with:

- Age
- Route of infection
- Genotype
- Fibrosis stage
- Inflammatory grade

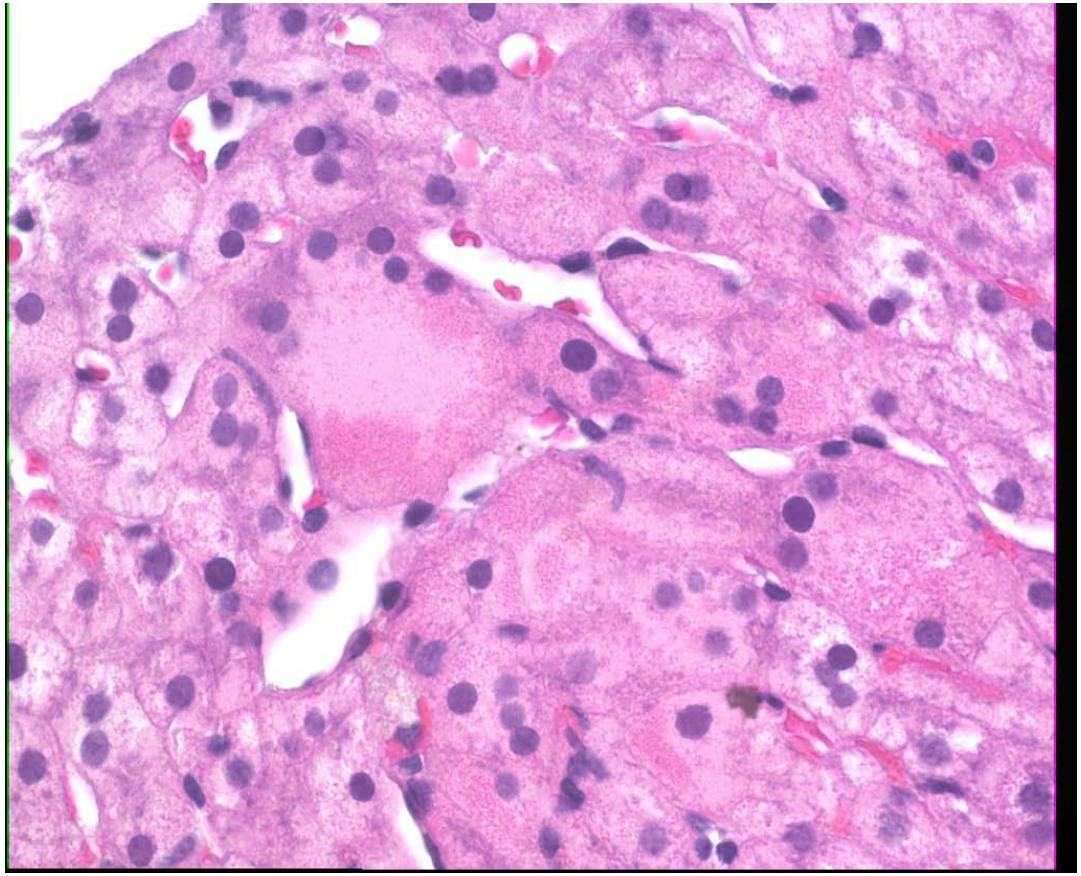
J Viral Hepat. 2004 Sep;11(5):459-64

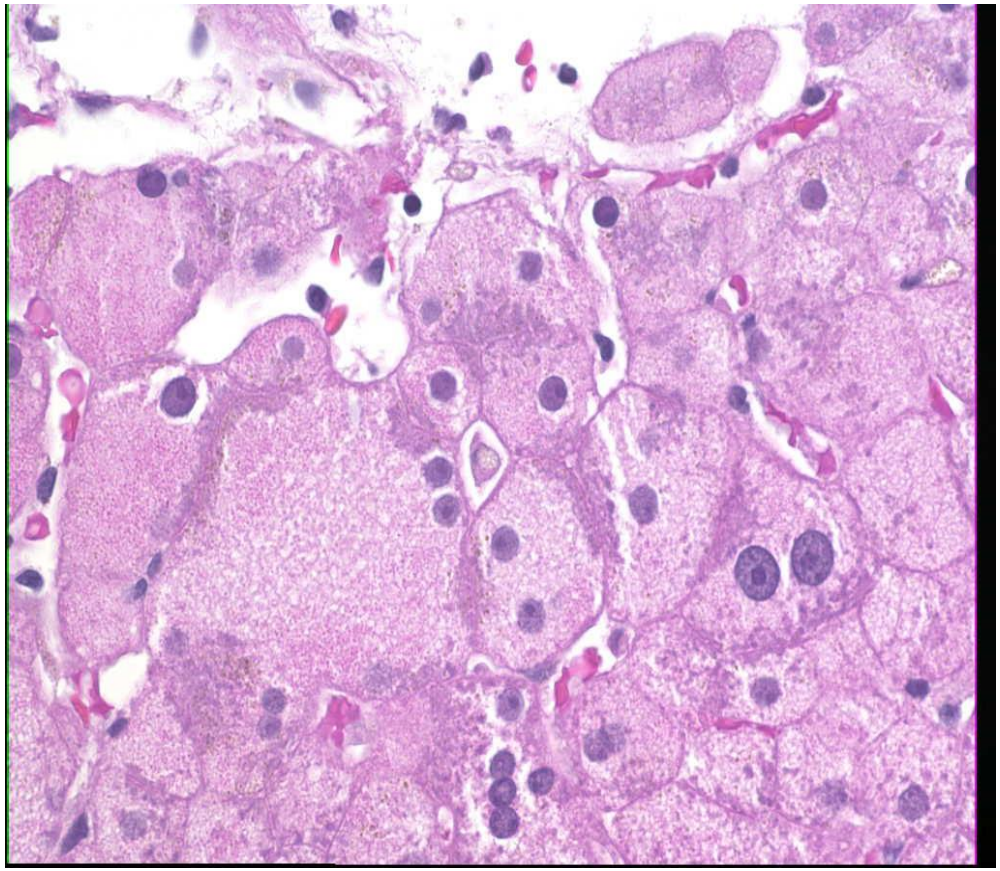
HCV-Other findings

- **Giant cell change** in hepatocytes
- Always limited to zone 3
- Can be focal or involve most lobules
- Approx 1% of bxs in our case material
- Much more common in HCV/HIV coinfection
- Often present on repeat bxs taken several yrs later
- ??clinical correlates

J Clin Pathol. 2008 Sep;61(9):1058-61

HCV-Other findings

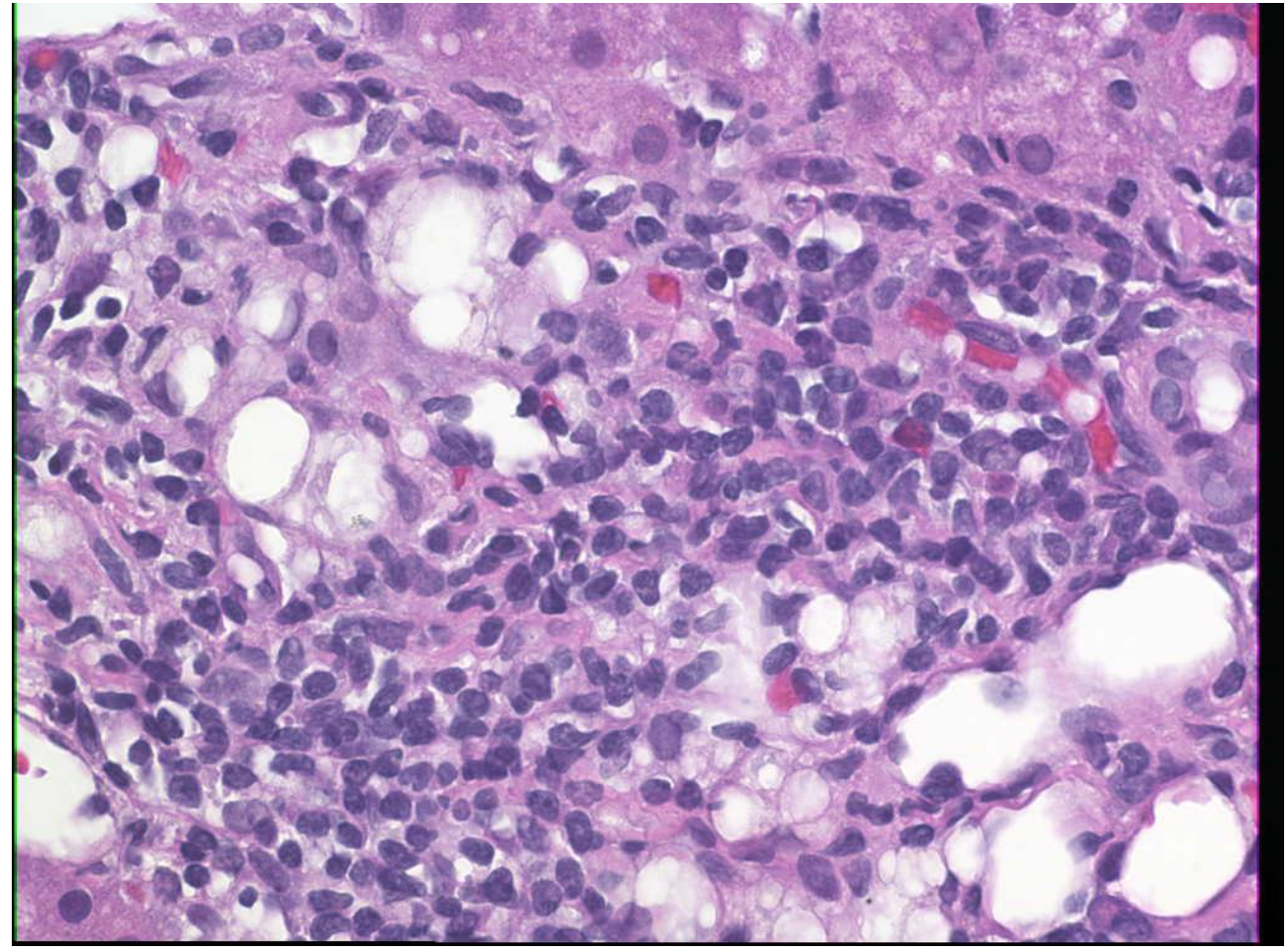




HCV-Other findings

“lipid” granulomas

- Actually mineral oil
- No clinical correlate

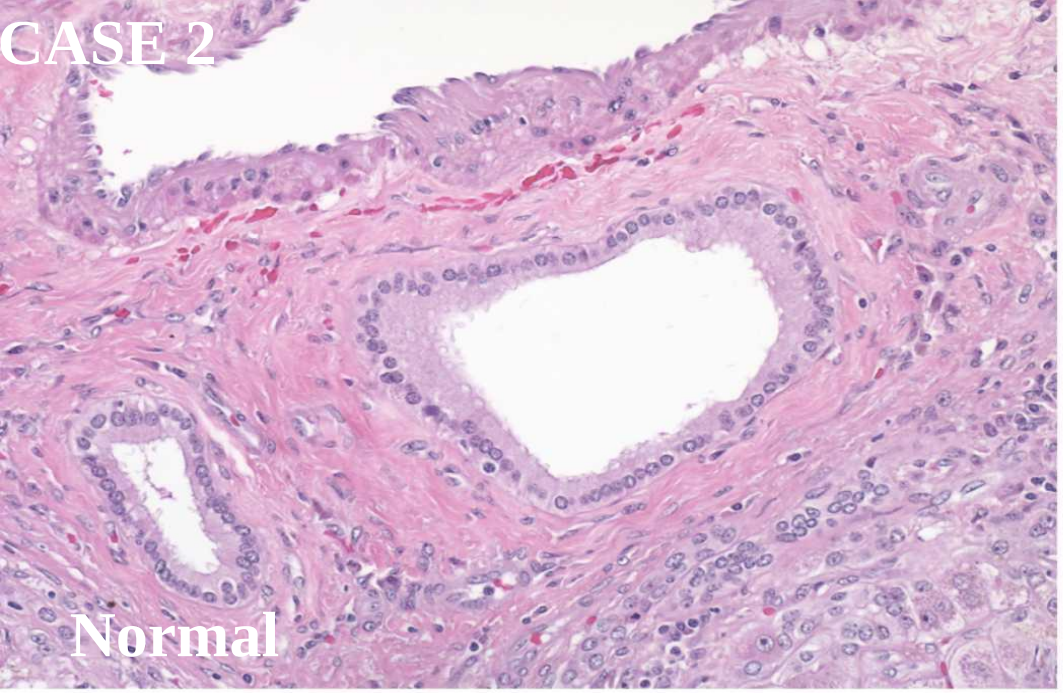


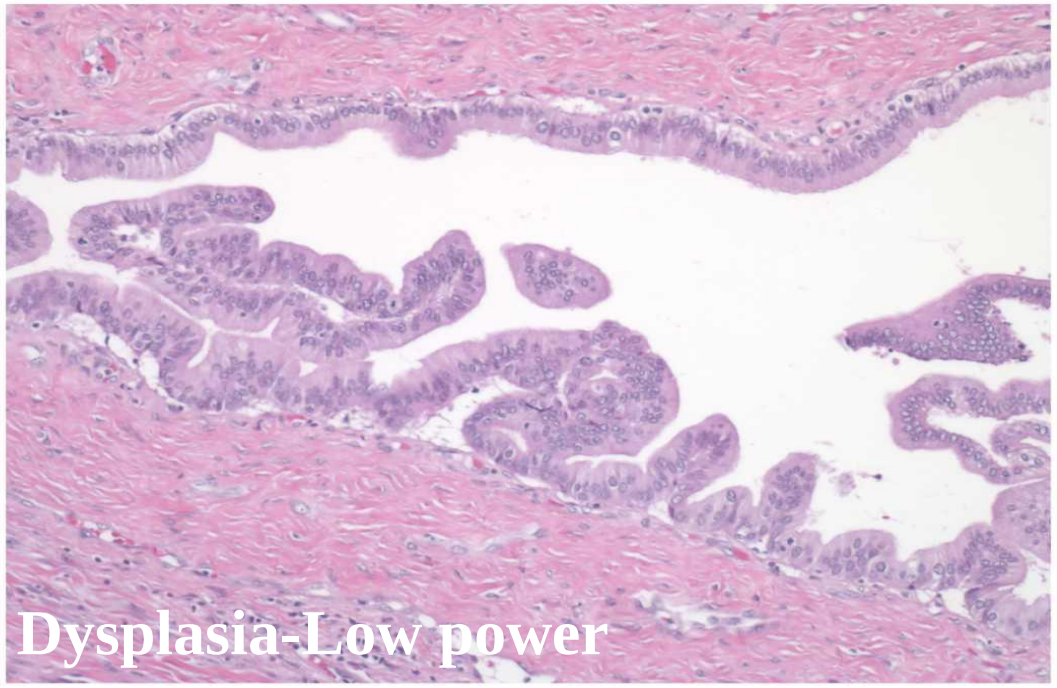
HCV is a risk factor for intra-hepatic cholangiocarcinoma

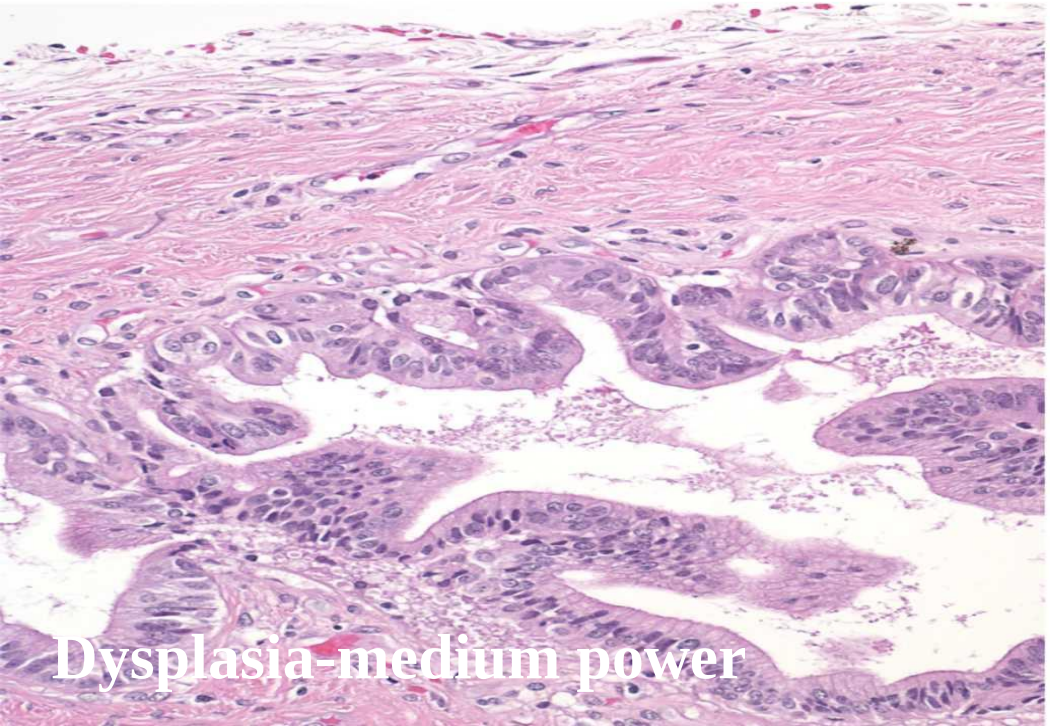
Surgical specimens and explants from HCV occasionally show bile duct dysplasia

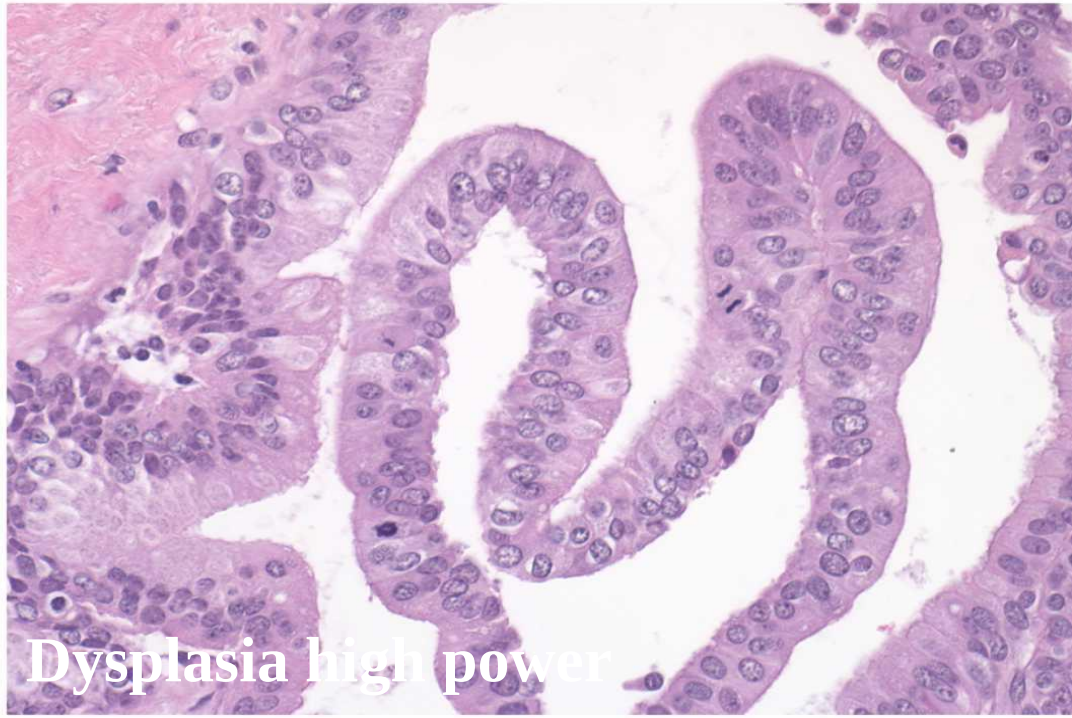
Am J Surg Pathol. 2007 Sep;31(9):1410-3

CASE 2


Normal


Dysplasia-Low power


Dysplasia-medium power


Dysplasia high power

Summary

Summary

Each biopsy report should convey

- The cause of the hepatitis when known
- The amount of inflammation
- The amount of fibrosis
- Any other biopsy findings, eg fat

Summary

Each biops[illegible]nvey

- [illegible]

Key Pnt 1. Do this accurately:
Your biopsy report will be
perfect in >99% of all cases

- [illegible]
- Any [illegible]

Summary

2. **Fibrosis staging is the main reason for biopsy in most cases of HCV and HBV**
   - Take your time; get it right
   - Beware of pitfalls
3. **If you want to use a numerical system**
   - Take the time to really master it.
   - Don’t get so caught up in filling out the sheet that you miss other histological findings.

Summary

4. **The inflammation in chronic HCV biopsies is generally mild to moderate and associated with mild but stable elevations in liver enzymes**
    - Your biopsy doesn't look like this?
    - Has there been a flare in liver enzymes?
    - If so, there is a strong probability that there is a second source of liver injury