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Nonalcoholic steatohepatitis and Fatty Liver Disease

*Liver manifestations of the
obesity epidemic...*

Changes in Food Industry

Transformation of local agriculture to “agri-business” of national and international scale

Correlates with rapid rise in obesity rates

Food, Inc (movie) based on two books:

***Fast Food Nation* by Eric Schlosser**

***The Omnivore’s Dilemma* by Michael Pollan.**

Obesity and Diabetes

1990-2008, as per CDC data:

- **Marked rise in obesity (BMI>30) incidence in USA to about 30% in many areas of the country**
- **Marked rise in diabetes to about 8% overall in adults**

Non-Alcoholic Fatty Liver Disease: Incidence in USA 2009-2011


*As per Centers of Disease
Control (CDC) website-*

NAFLD: 30-50% adults

13% children

NASH: 3-13% adults

Non-Alcoholic Fatty Liver Disease (NAFLD): Terminology



NAFLD

Steatosis
(>5%)

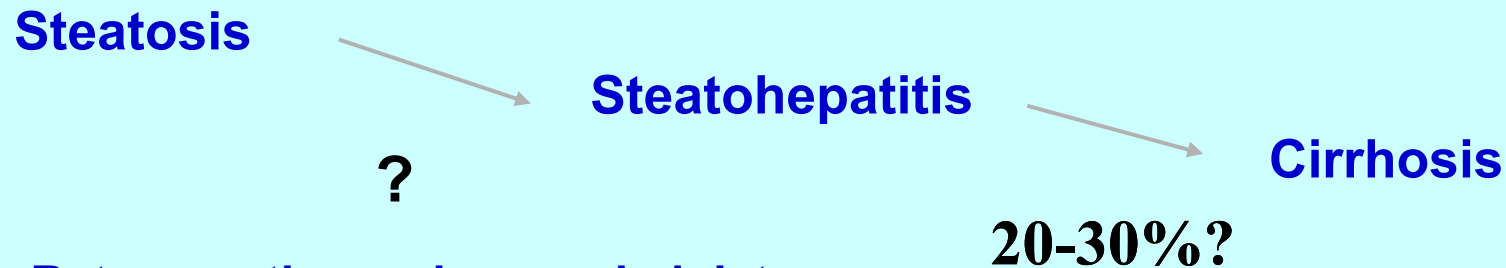
NASH

Steatosis
Ballooning
Inflammation
± Fibrosis

Cirrhosis

Fibrosis
± Inflammation
± Steatosis

NAFLD: Natural History



- Retrospective series, pooled data
 - Risk of progression of NASH
 - Increased fibrosis - 25%
 - Cirrhosis - 15%

Only few longitudinal studies done, which limits our understanding.

General concept for pathogenesis of NASH:

Consequence of over-supply of fatty acids in combination with defects in their metabolism (such as insulin resistance)

NASH: Associated Risks

- **Metabolic Diseases**
 - **Obesity**
 - **Diabetes type 2**
 - **Hyperlipidemia**
 - **Malnutrition**
 - **(Rapid weight loss?)**

NASH or NASH-like lesions: Other risks

- **Drugs**

- Amiodarone
- Perhexilene maleate
- **Tamoxifen**
- **Irinotecan (CASH)**

- **Possible or Questionable?**

- Risperidone (antipsychotic)
- Steroids
- Estrogens
- HAART, ART for HIV therapy
- Calcium channel blockers (ex: nifedipine)
- Methotrexate ??

- **Other**

- **HISPANIC ethnicity**
- Lipodystrophy
- Jejunioileal bypass or similar variants
- **Genetic metabolic disorders, ex: Wilson disease, tyrosinemia, abetalipoproteinemia**
- **Sudden decrease in liver size/volume??**

NASH: Diagnosis

- **Suspected:**
 - Unexplained elevation AST/ALT
 - Presence of NAFLD disease associations
- **Clinical:**
 - Non-alcoholic
 - Exclusion of other liver diseases
- **Histopathologic:**
 - Biopsy showing characteristic findings

NASH: Histologic Findings

FOUR BIG CRITERIA

- **Fat** (large and small droplet, microvesicular)
- **Ballooned hepatocytes**
- **Inflammation** (mononuclears predominate)
- **Centrizonal fibrosis** (pericellular, sinusoidal)

Other:

- **Glycogenated nuclei, apoptosis, pigmented macrophages, Mallory hyaline, giant mitochondria**

NASH: Histologic Findings

- Fat (large and small droplet, microvesicular)
- **Ballooned hepatocytes**
- **Inflammation**
- **Centrizonal fibrosis**

NASH: Histologic Findings

Problem: Definition of type of fat droplets**

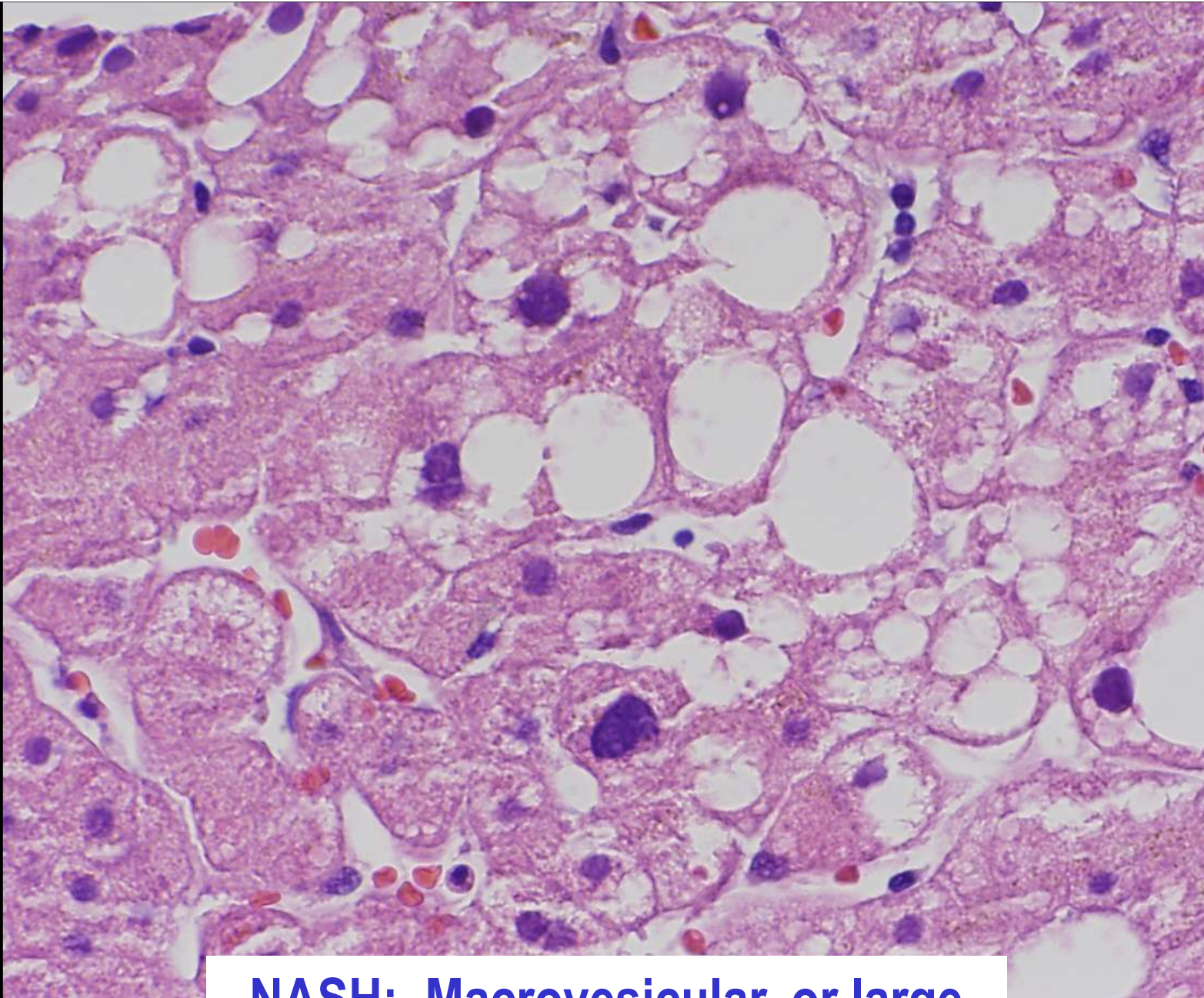
Macrovesicular

Small and large droplet

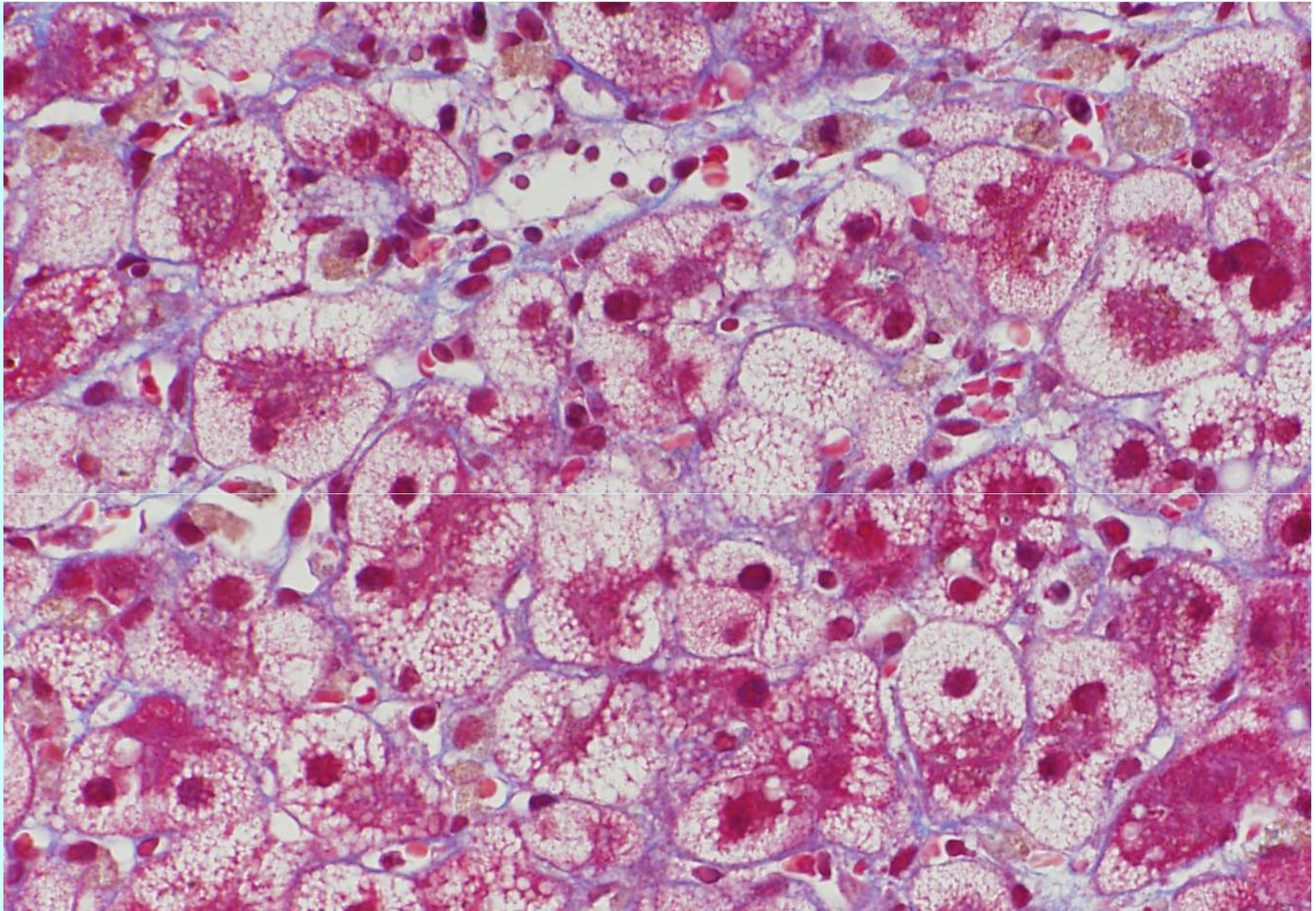
Microvesicular

****Note: Inconsistent usage of terms**

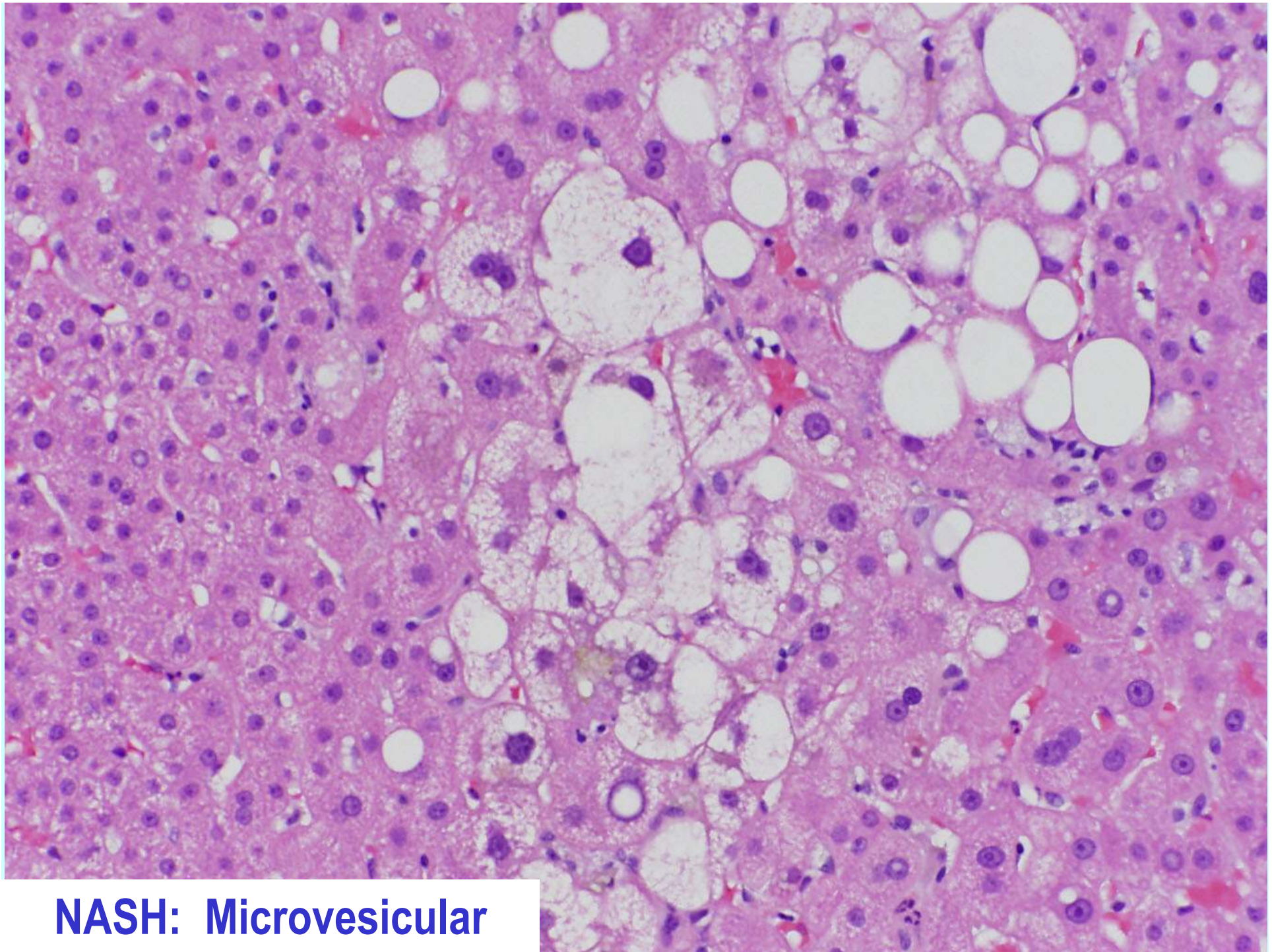
Kleiner, Brunt ... Ferrell...Yeh... et al: Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatol 41:1313, 2005



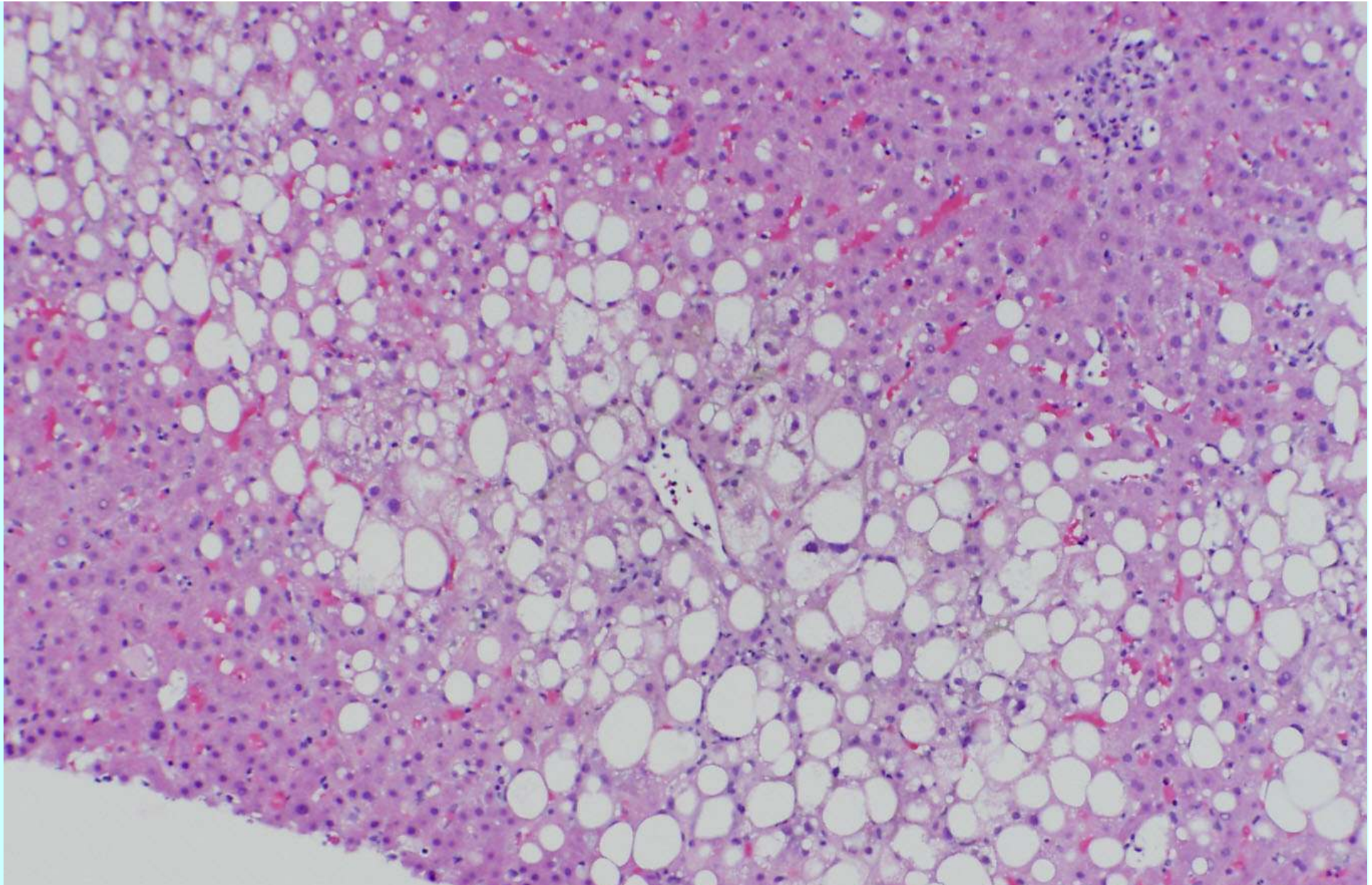
NASH: Macrovesicular, or large and small droplet fat



Microvesicular Fat (Fatty liver of Pregnancy)



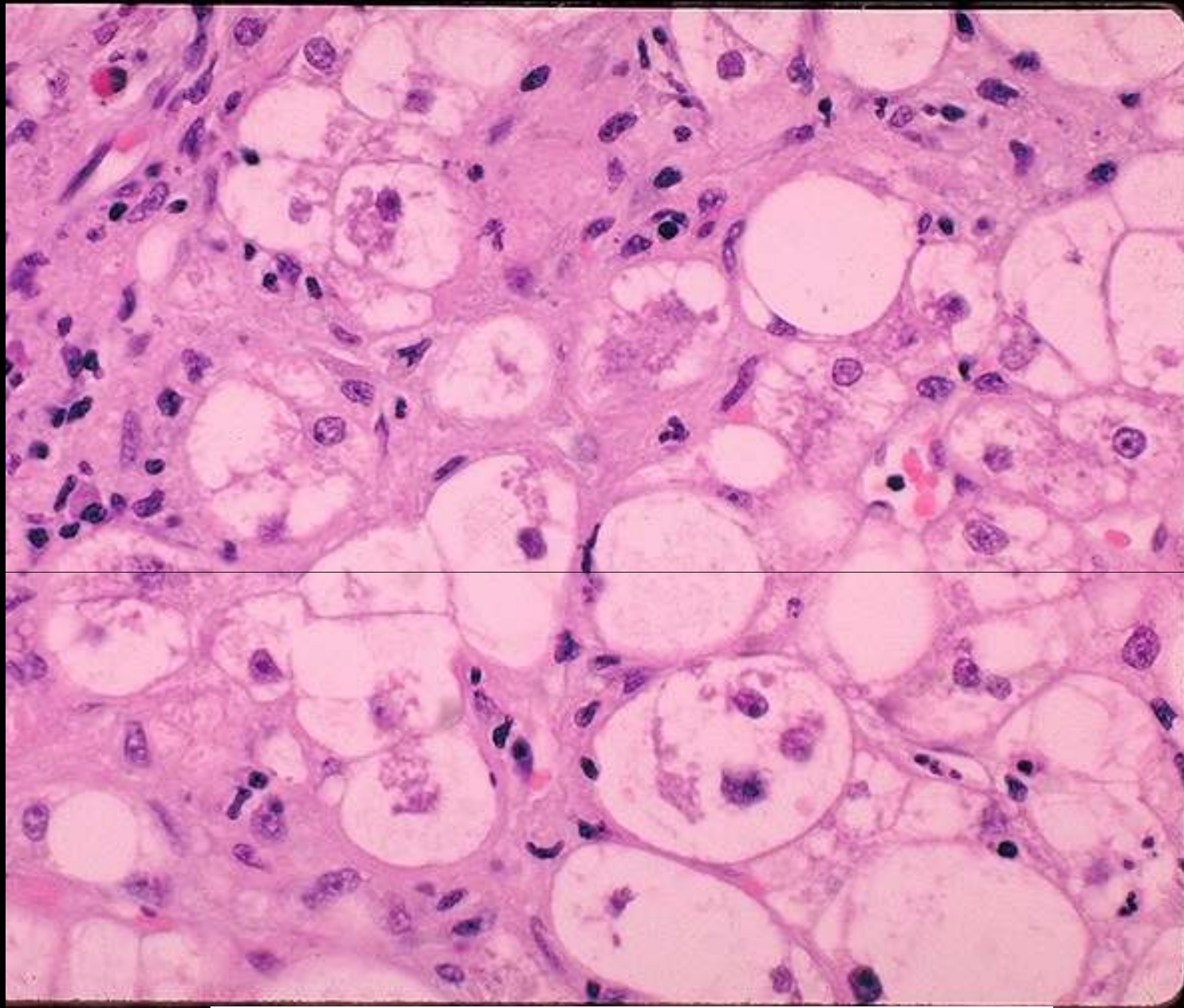
NASH: Microvesicular



NASH: Large and small droplet fat, typically noted in zone 3 (central zone)

NASH: Histologic Findings

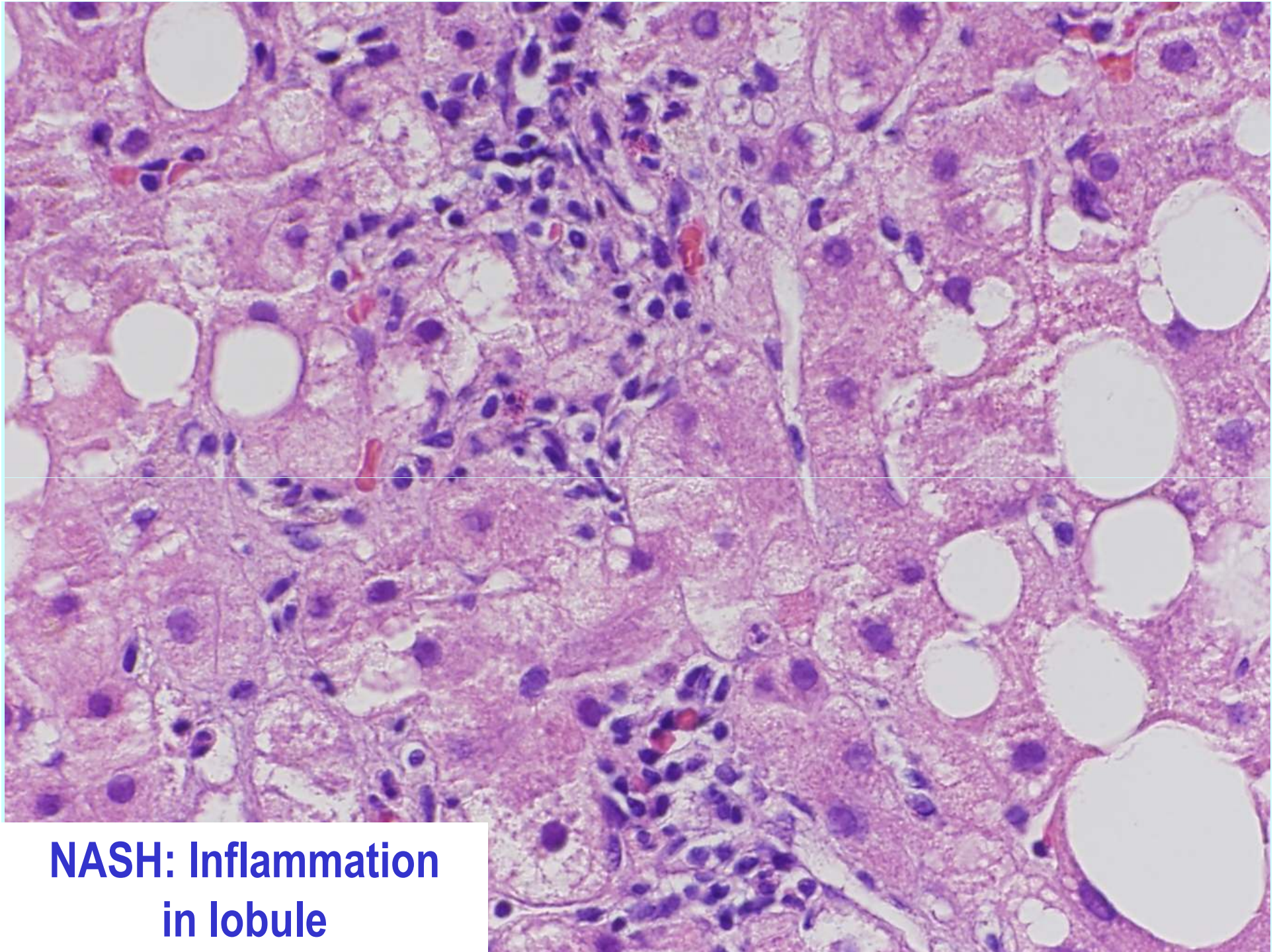
- Fat
- **Ballooned hepatocytes**
- Inflammation
- Centrizonal fibrosis



NASH: Ballooned Hepatocytes

NASH: Histologic Findings

- Fat
- Ballooned hepatocytes
- Inflammation (mononuclears predominate)
- Centrizonal fibrosis



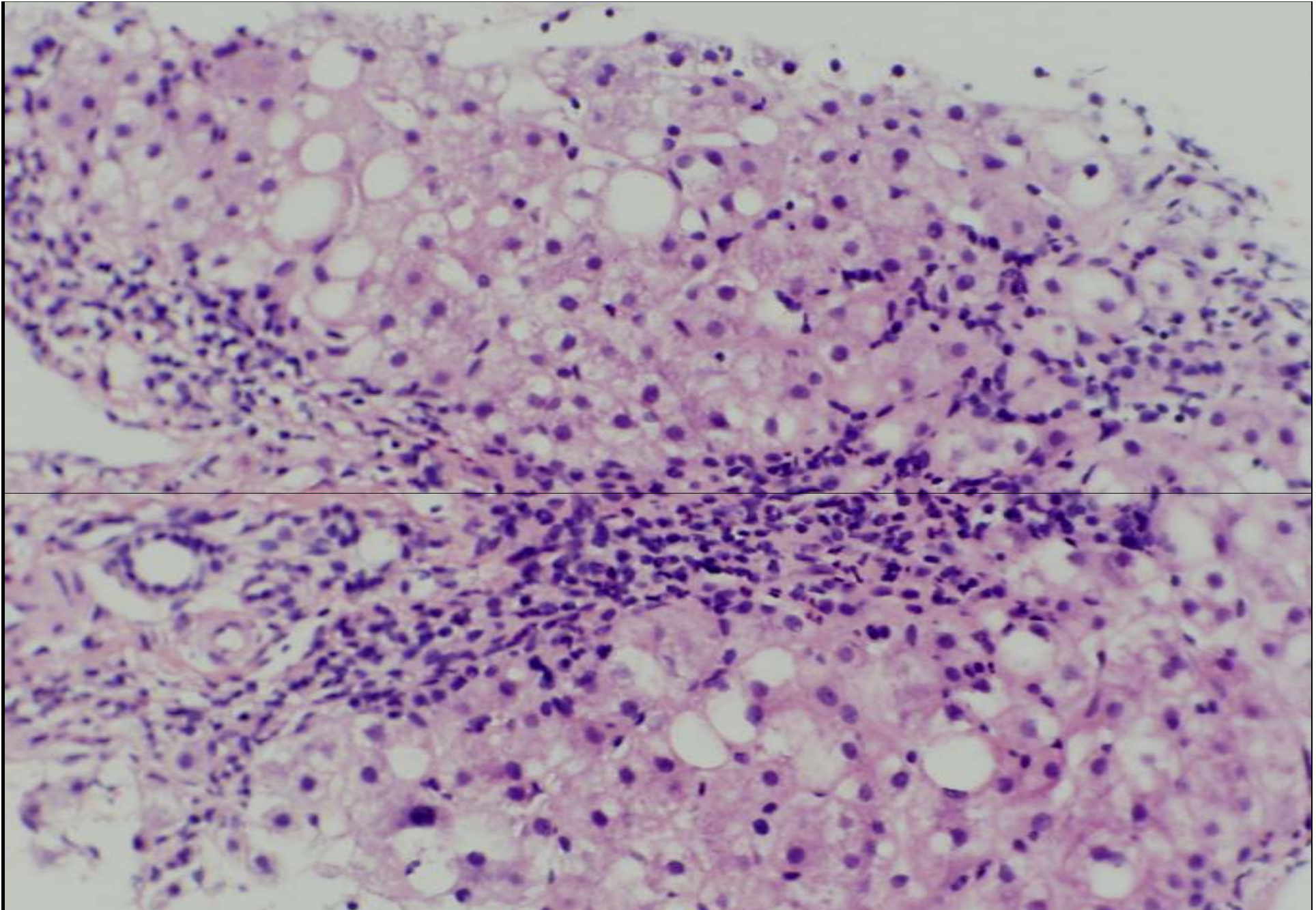
**NASH: Inflammation
in lobule**



Microlipogranuloma

This histological image shows a section of liver tissue stained with hematoxylin and eosin (H&E). The central feature is a microlipogranuloma, which is a small, well-circumscribed inflammatory lesion. It consists of a central core of lipid-laden macrophages (foam cells) surrounded by a ring of mononuclear inflammatory cells, including lymphocytes and plasma cells. The surrounding liver parenchyma shows signs of non-alcoholic steatohepatitis (NASH), with enlarged hepatocytes containing lipid droplets and some ballooning. The overall architecture is disrupted by the presence of these inflammatory foci.

NASH: Inflammation

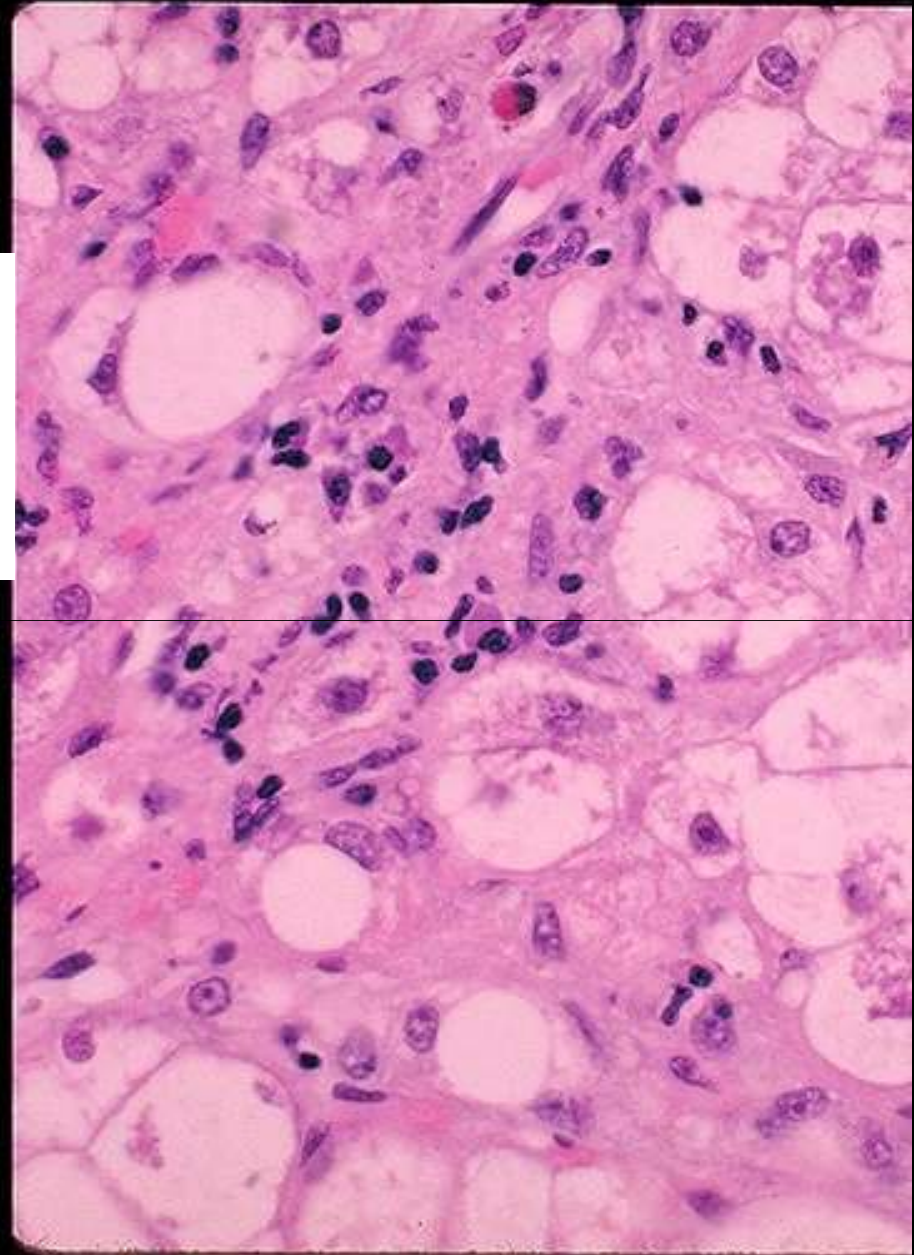


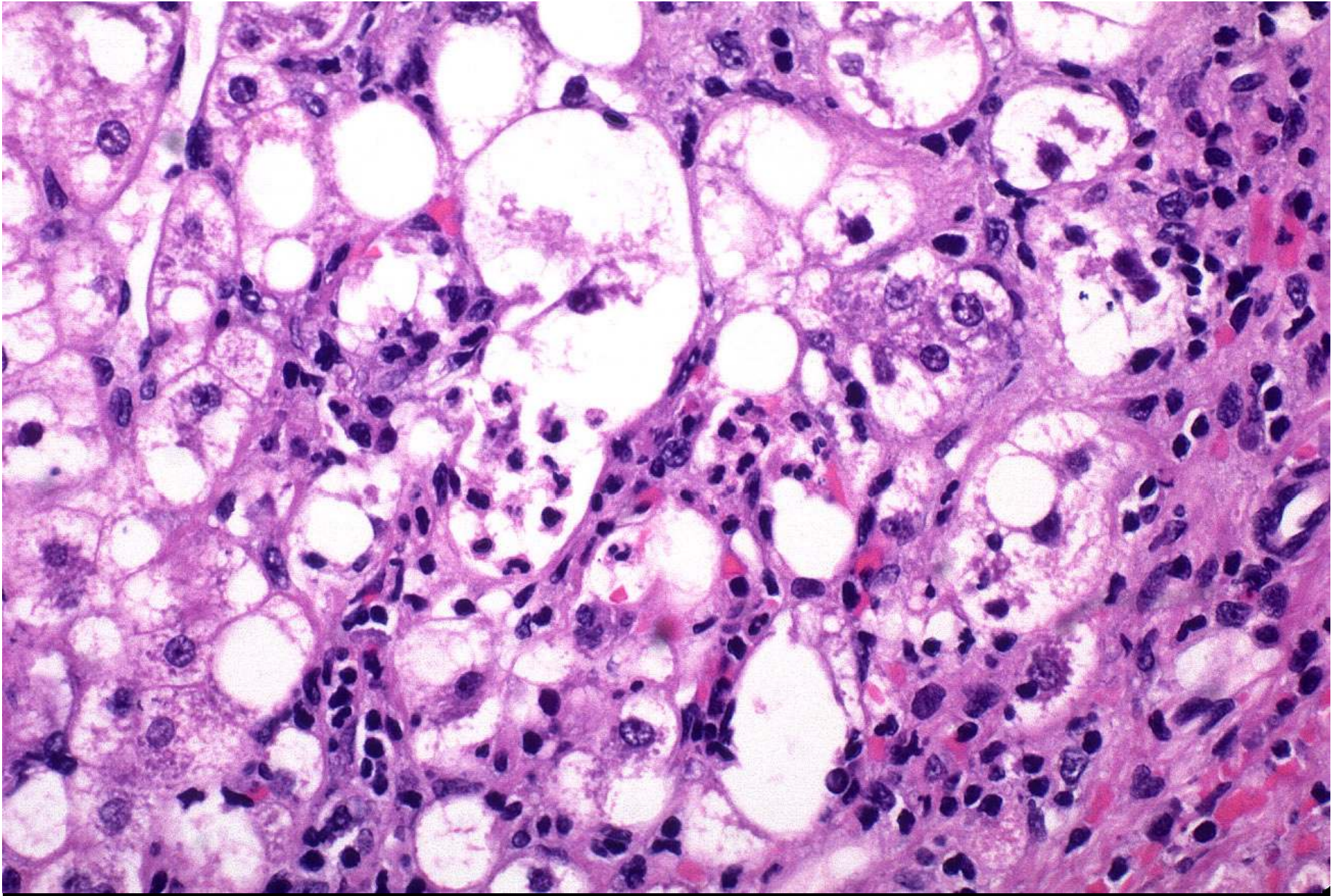
NASH: Portal inflammation typically minimal

NASH

Plasma cells

Eosinophils



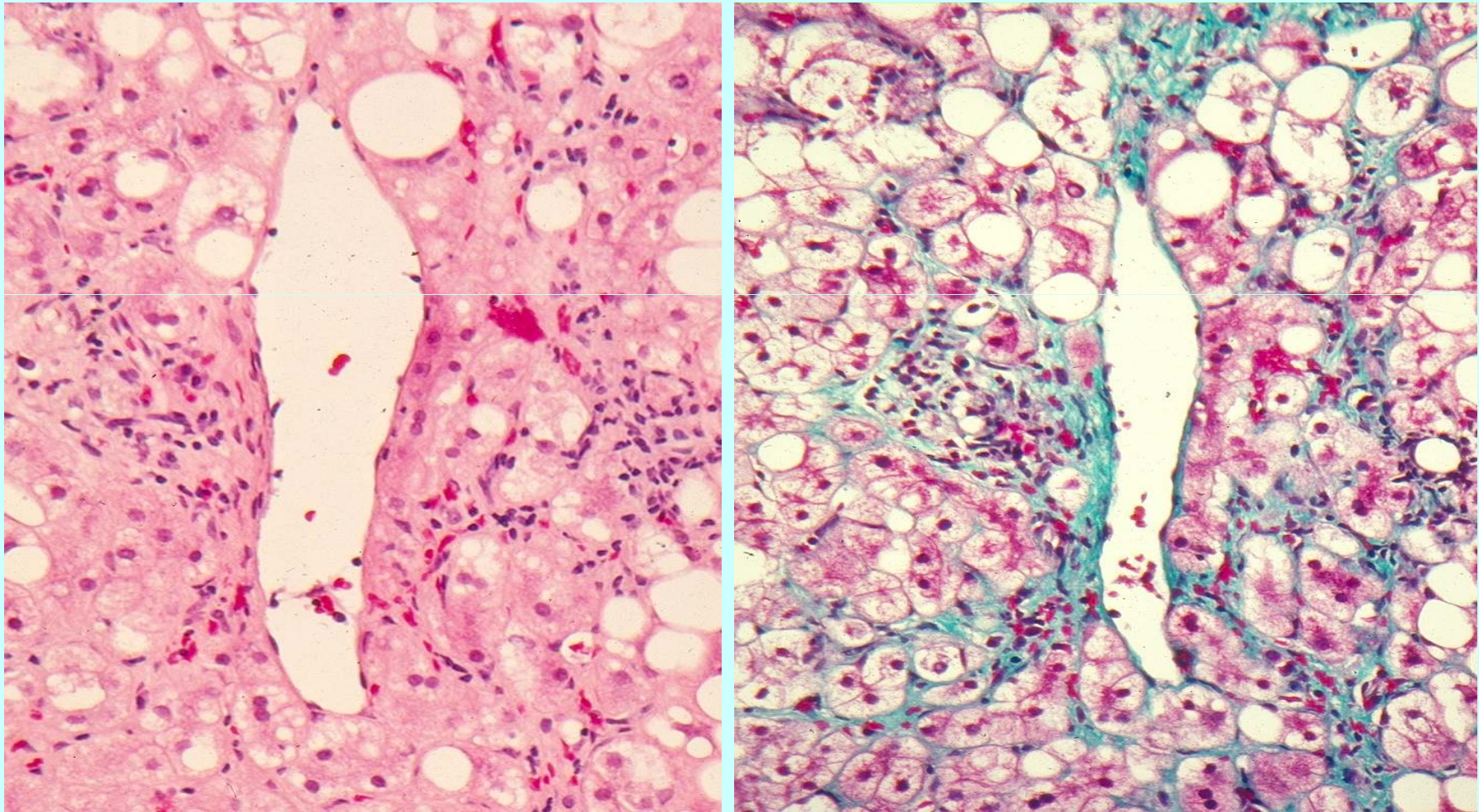


NASH: neutrophils

NASH: Histologic Findings

- Fat
- Ballooned hepatocytes
- Inflammation
- Centrizonal fibrosis (pericellular, sinusoidal)

Centrizonal Fibrosis: Trichrome stain



NASH: Histologic Findings

- Fat
- Ballooned hepatocytes
- Inflammation
- Centrizonal fibrosis

Other:

- Glycogenated nuclei, apoptosis, pigmented macrophages, Mallory hyaline, giant mitochondria (rare)

Focus on the Diagnosis
NASH: Histologic Findings

Active NASH

- **Fat**
- **Ballooned hepatocytes**
- **Inflammation**

Evidence for previous or chronic NASH

- **Centrizonal fibrosis**

The next step is...

Grading and Staging

....or how to make something appear objective
that is really subjective

NASH Grading/Staging

(NASH consortium 2005)

<u>Grade</u>	<u>Steatosis</u>
0	<5%
1	5 -33%
2	33-67%
3	>67%

Kleiner et al, Hepatol 41:1313-1321, 2005

NASH Grading/Staging

(NASH consortium 2005)

<u>Grade</u>	<u>Steatosis</u>
0	<5% (minimal)
1	5 -33% (< 1/3)
2	33-67% (close to 1/2)
3	>67% (> 2/3)

Kleiner et al, Hepatol 41:1313-1321, 2005

NASH

Staging Scheme (Brunt, 1999)

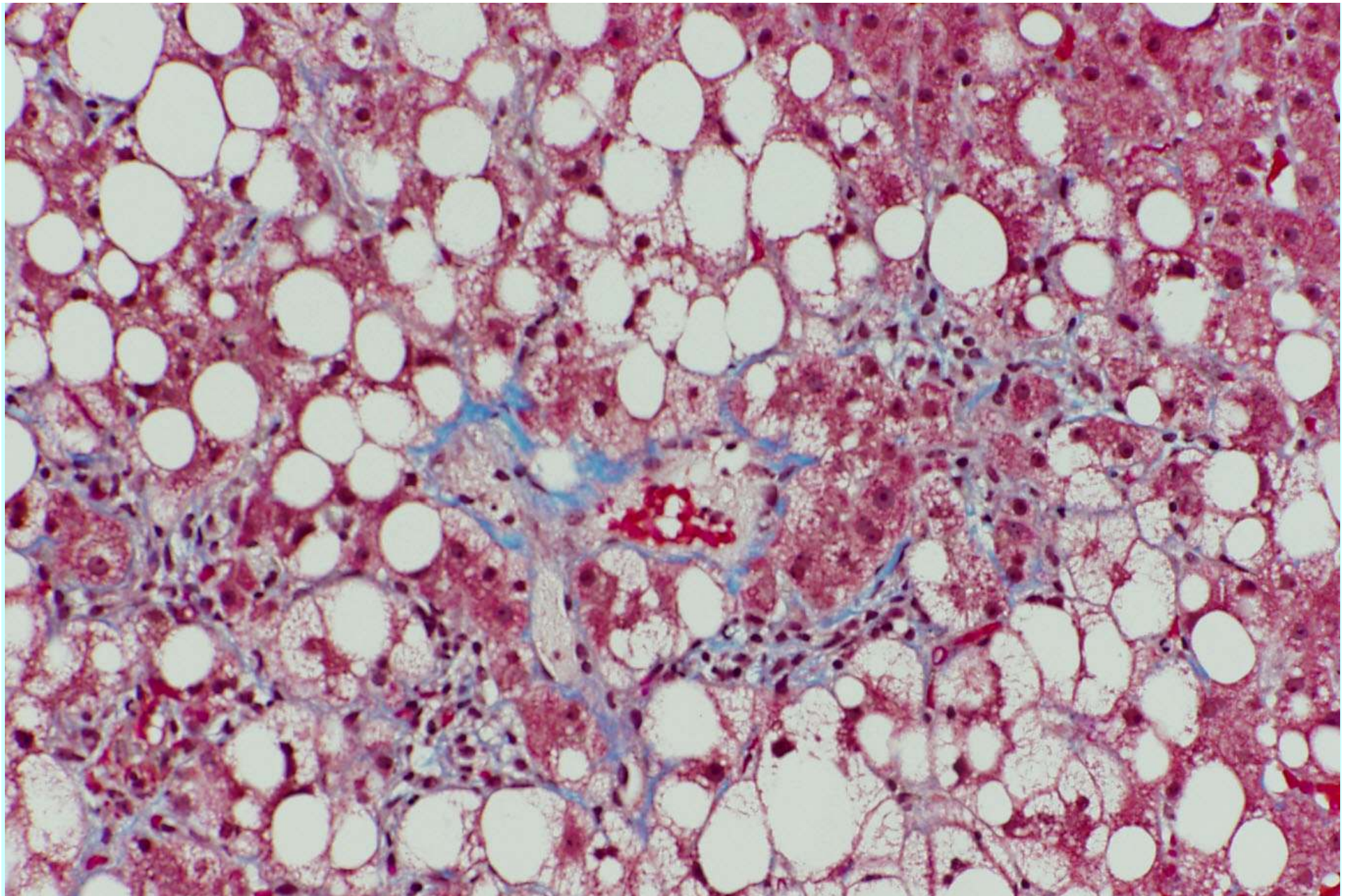
<u>Stage</u>	<u>Histologic Description</u>
0	No fibrosis
1	Zone 3 sinusoidal fibrosis, focal/extensive
2	Same as 1, plus focal/extensive periportal fibrosis
3	Same as 1, 2 plus focal/extensive bridging fibrosis zone 3-1 with nodular change
4	Cirrhosis

NASH

Staging Scheme (Kleiner, Brunt et al, including Ferrell and Torbenson, 2005)

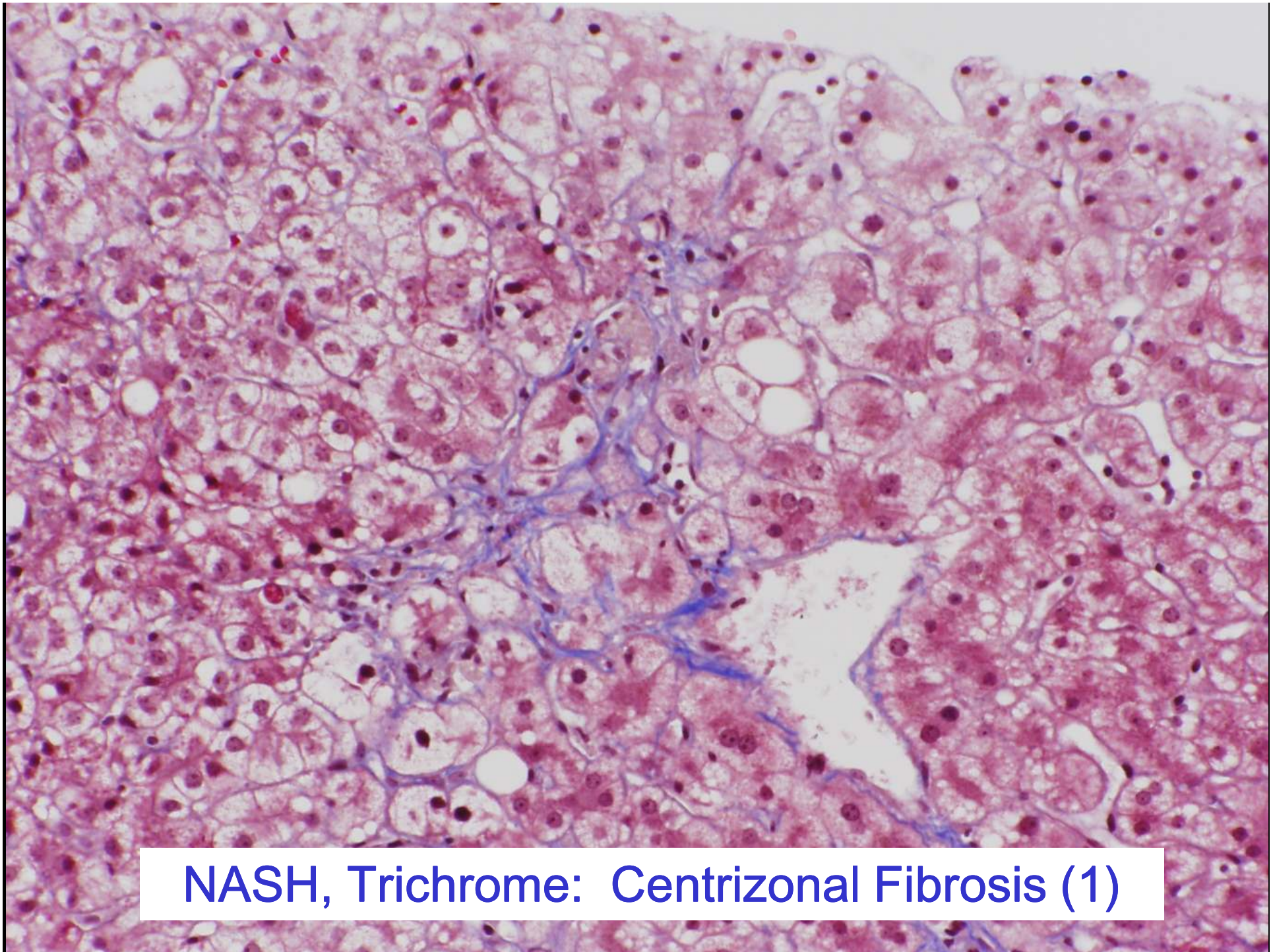
<u>Stage</u>	<u>Histologic Description</u>
0	No fibrosis
1a	Zone 3 sinusoidal, seen on trichrome
1b	Zone 3 sinusoidal, seen easily on
1c	H&E Portal/Periportal only
2	Zone 3 and periportal fibrosis
3	Bridging fibrosis
4	Cirrhosis

Kleiner et al, Hepatol 41:1313-1321, 2005

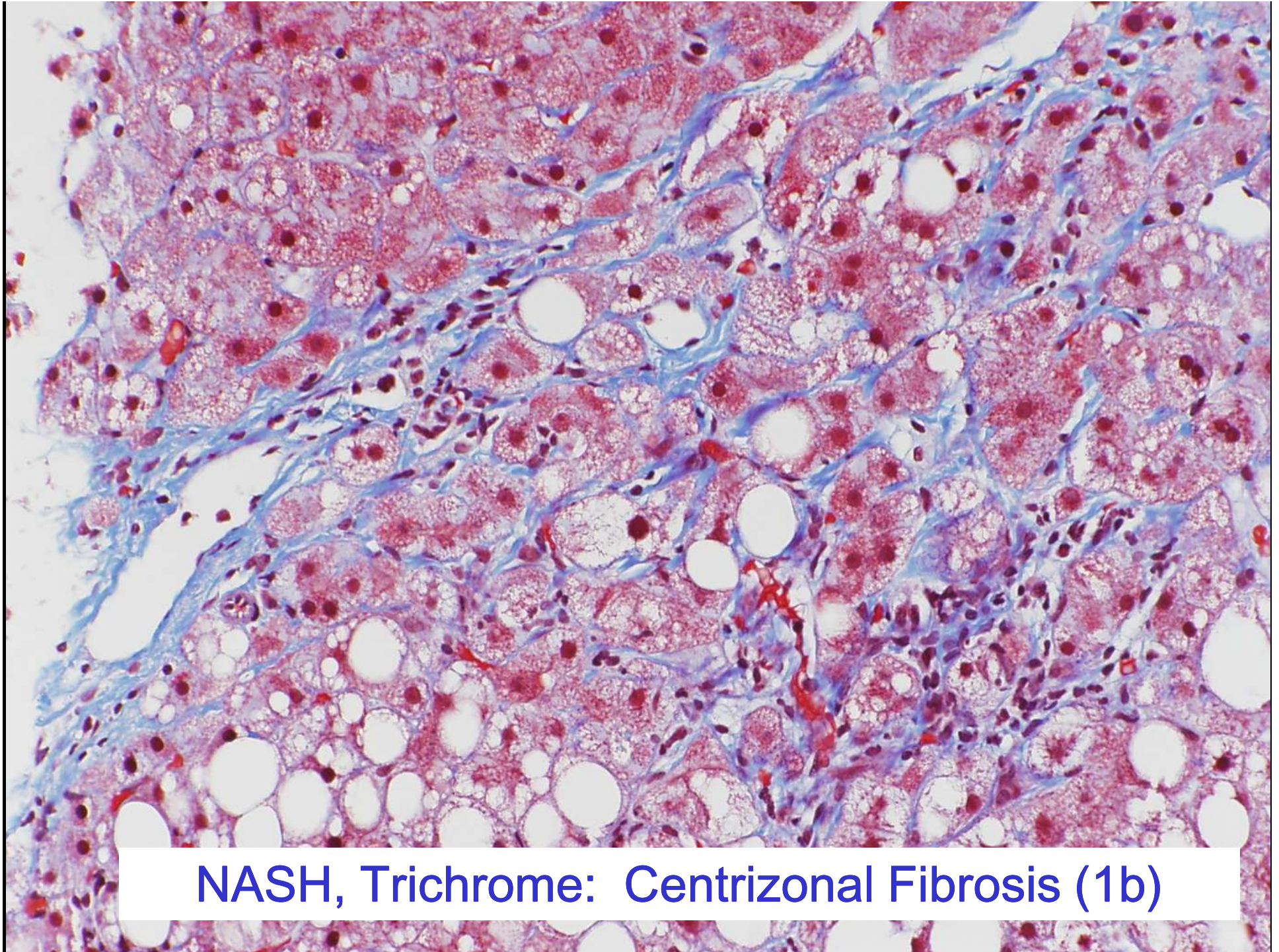


NASH, Trichrome: Centrilobular Fibrosis (1a)

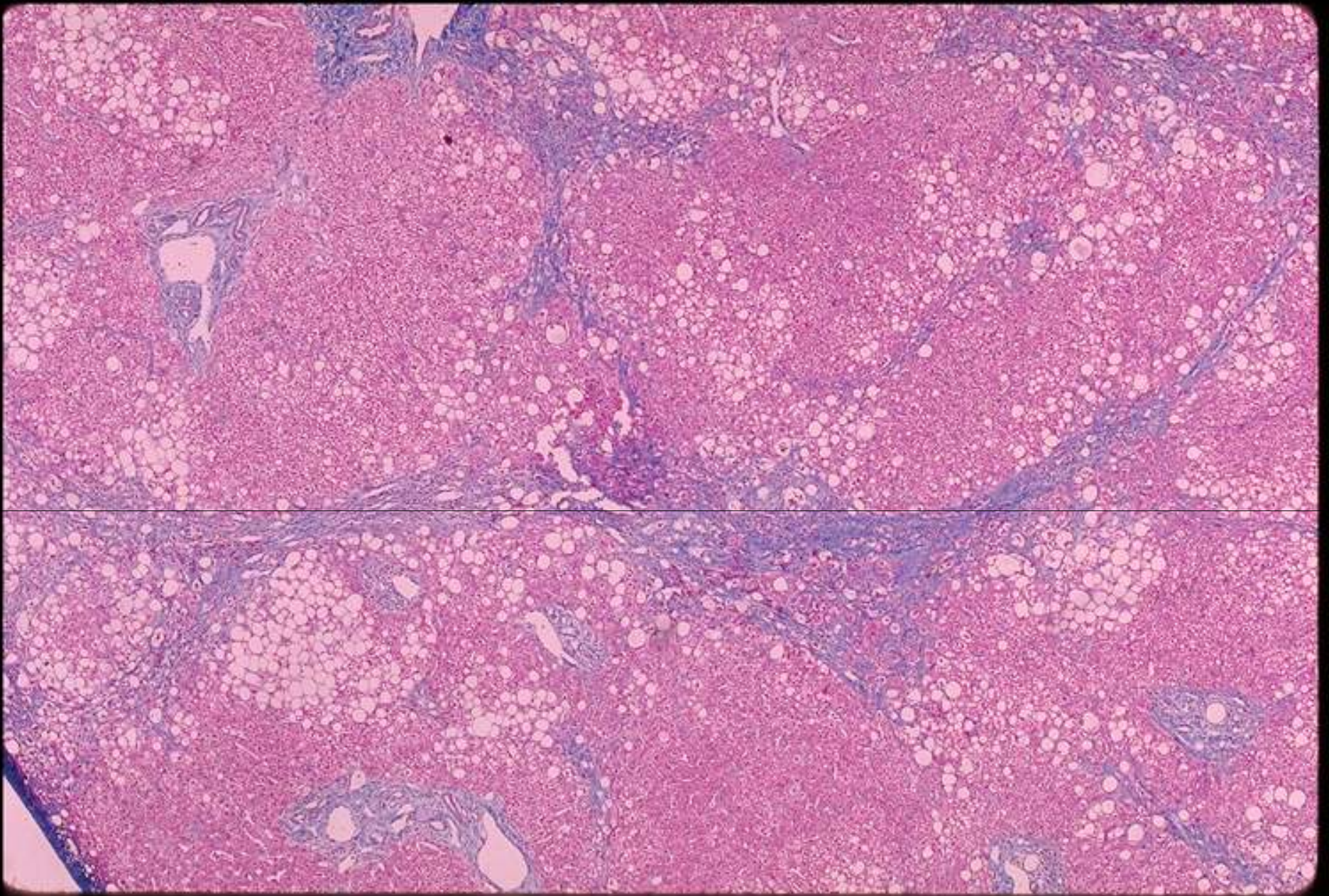




NASH, Trichrome: Centrilobular Fibrosis (1)



NASH, Trichrome: Centrizonal Fibrosis (1b)



NASH, Trichrome: Bridging Fibrosis (3)

NASH: Diagnosis Time

“My perspective”

Clinical Setting of elevated AST/ALT

- **Fat, inflammation only: steatosis, can't exclude steatohepatitis**
 - + fibrosis = steatohepatitis, chronic or remote
 - + ballooning = definite steatohepatitis
- **Stage (Brunt methodology), grade fat but not inflammation**

*And no entity is complete
unless it has variants*

- **Pediatric NASH**
 - “Type 2” NASH
 - But many/most still have typical NASH

Pediatric NASH

- Incidence increasing
 - Similar risk factors as adults
 - **BUT histology may show in subset:**
 - No zone 3 pattern of fat or fibrosis
 - Fibrosis may be periportal
 - Lack of ballooned hepatocytes
 - “Type 2 NASH”
- Minority of patients have typical NASH (“Type 1”)

Schwimmer, Behling, et al. Hepatol 2005;42:641-9

Pediatric NASH

“Type 2 NASH”

Occurs more commonly in:

- Younger patients
- Boys
- **Hispanic**, Asian, Native American ethnicity

Associated with more advanced fibrosis

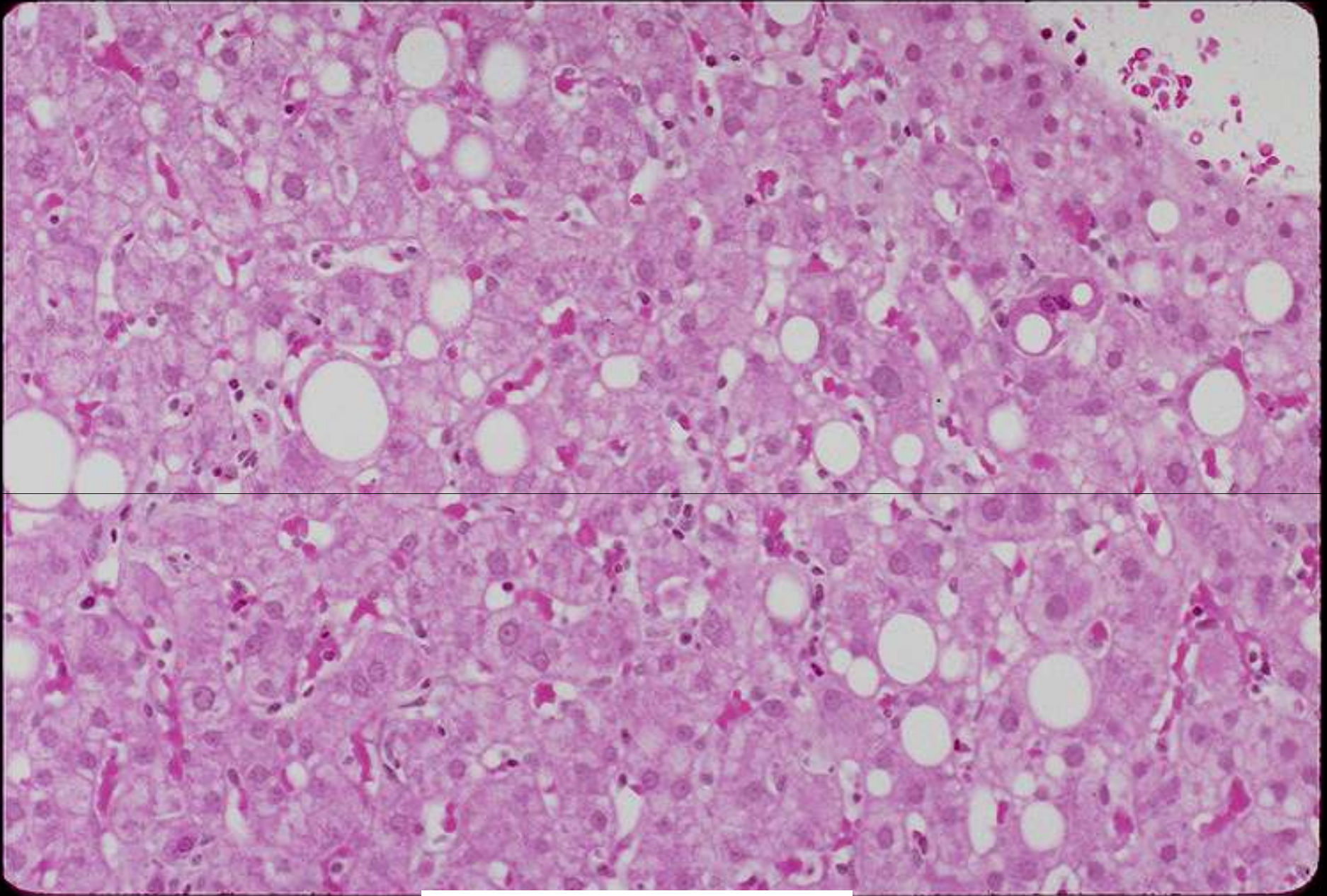
Schwimmer, Behling, et al. Hepatol 2005;42:641-9

NASH

- **Common diagnostic pitfalls:**
Fat is secondary finding to another disease - No NASH or alcoholic steatohepatitis (ASH)

Fat in hepatitis C

- randomly distributed
- grade 0-1
- genotype 3

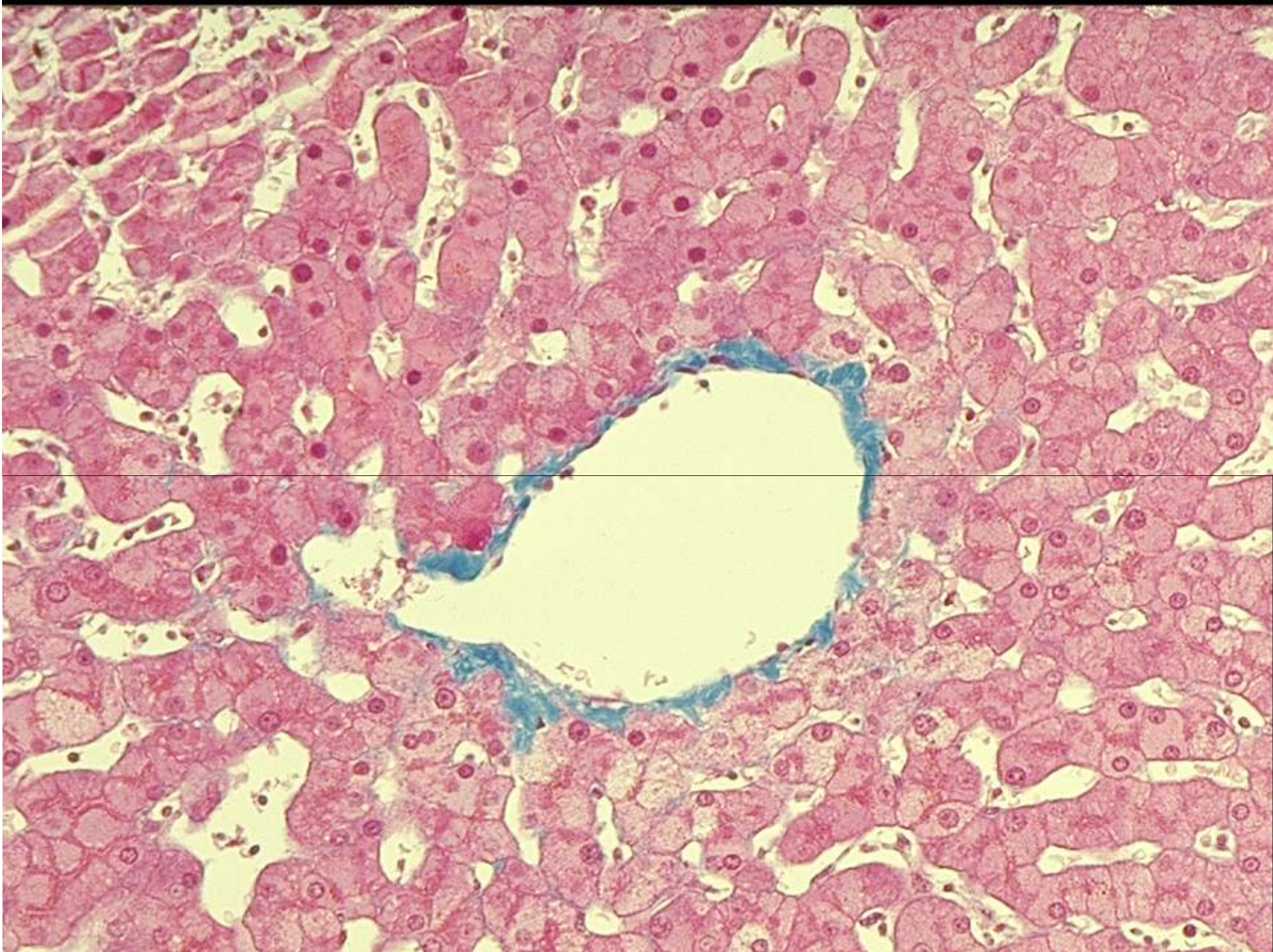


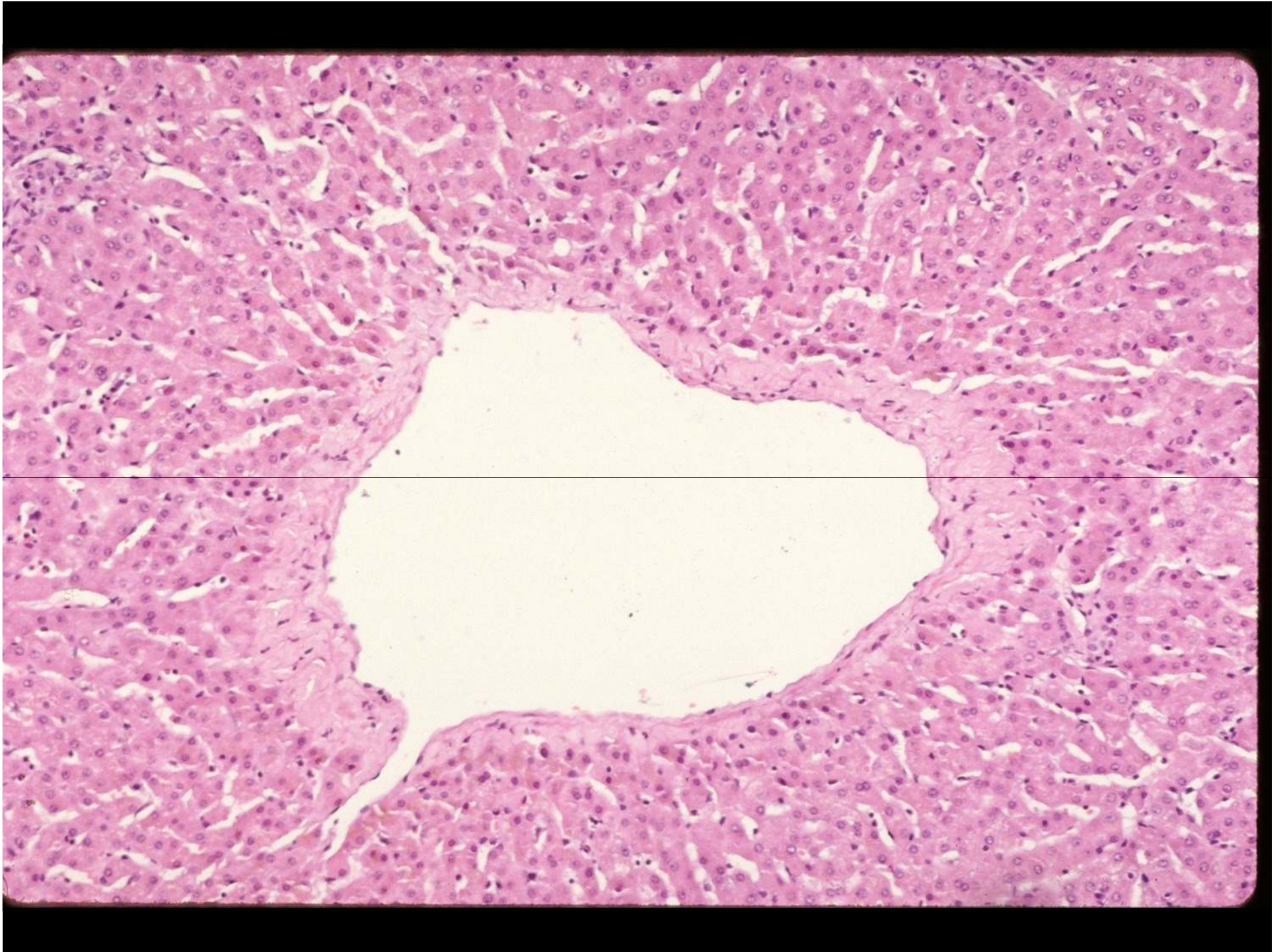
Hepatitis C

NASH

- **Common diagnostic pitfalls:**
 - *Identification of landmarks (overdiagnosis)*

Circumferential connective tissue around central veins is not diagnostic

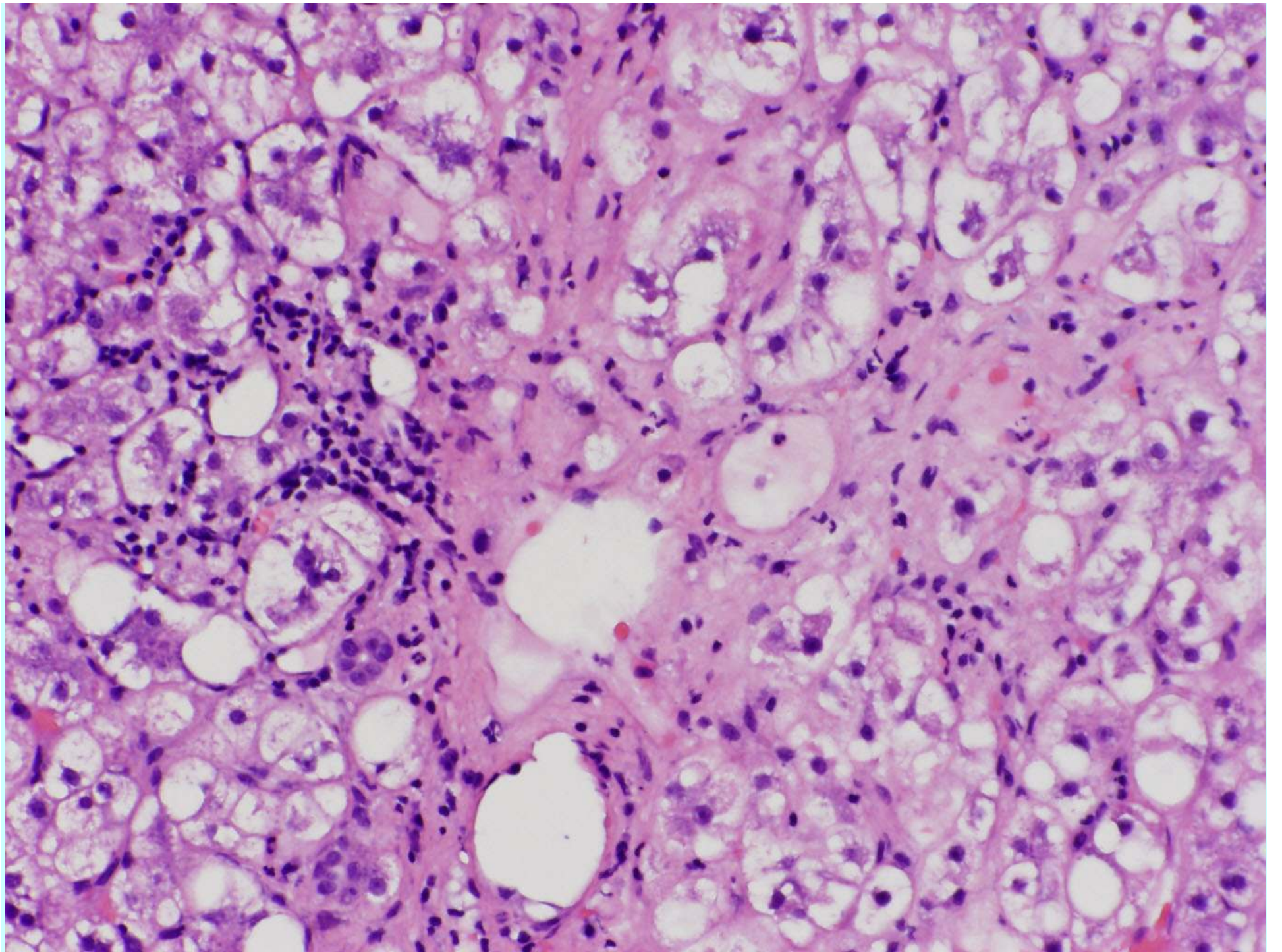


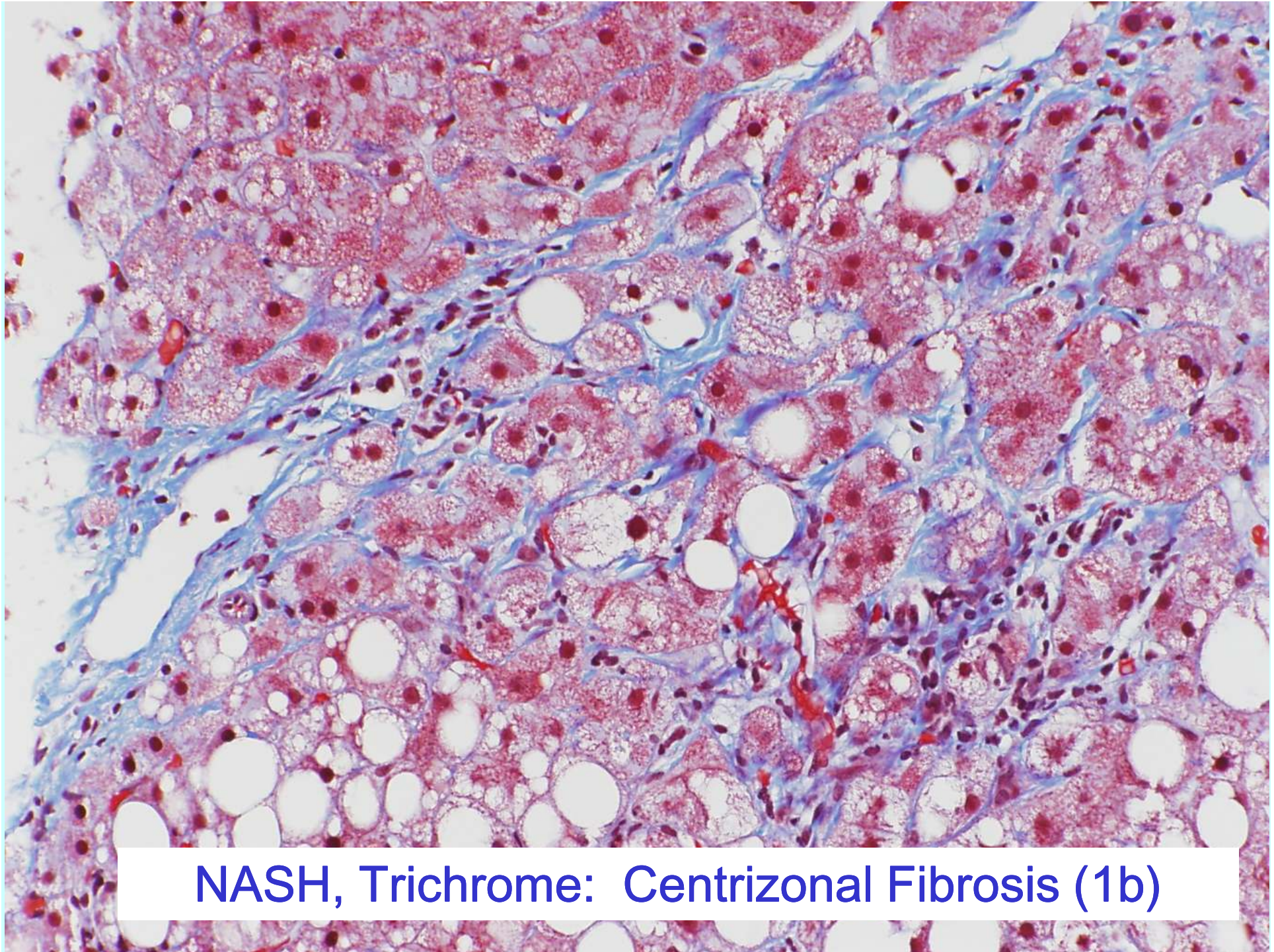


NASH

- **Common diagnostic pitfalls:**
 - *Identification of landmarks (underdiagnosis)*

Isolated ductular reaction and arteries in or near centrizonal scars: *DO NOT mistake these findings for portal areas and portal-based scarring*





NASH, Trichrome: Centrilobular Fibrosis (1b)

NASH + HCV or HBV

- **Common diagnostic pitfalls:**
 - *Too much of one thing*

Prominent chronic inflammation may suggest superimposed viral or other hepatitis/inflammatory process

(NASH can be admixed with HCV, HBV, or other)

NASH + HCV or HBV

NOTE Pattern of disease locations

PORTAL: favors chronic hepatitis

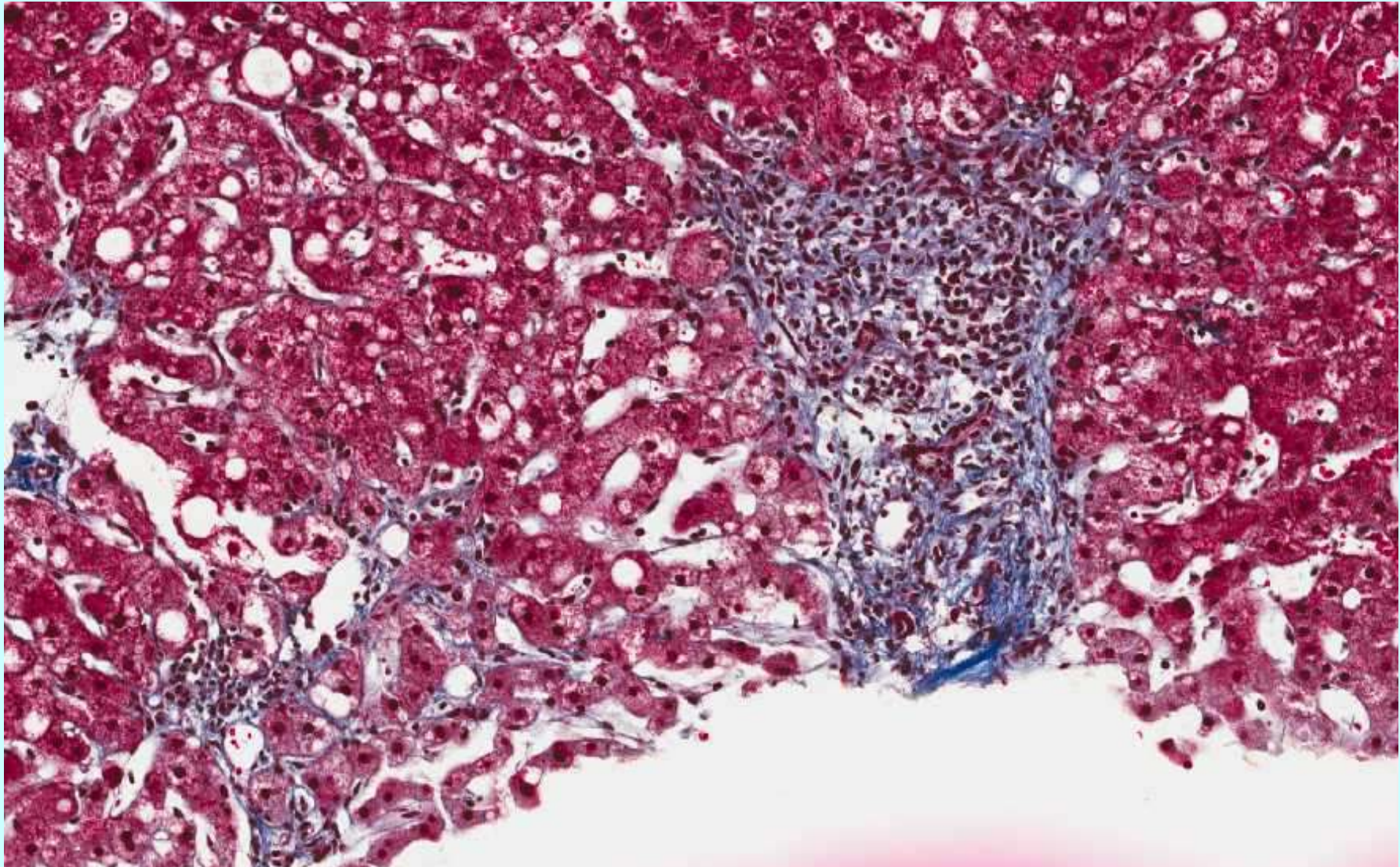
- Portal-based chronic inflammation, fibrosis, and interface hepatitis
- HBV or HCV markers

CENTRAL: favors steatohepatitis

- Centrizonal fat, fibrosis, ballooned cells, inflammation associated with fat
- Risk factors for NASH/ASH

NASH and HCV

Centrizonal and Periportal fibrosis



NASH and HCV

Centrizonal and Periportal fibrosis

How to stage?



NASH + HCV or HBV STAGING

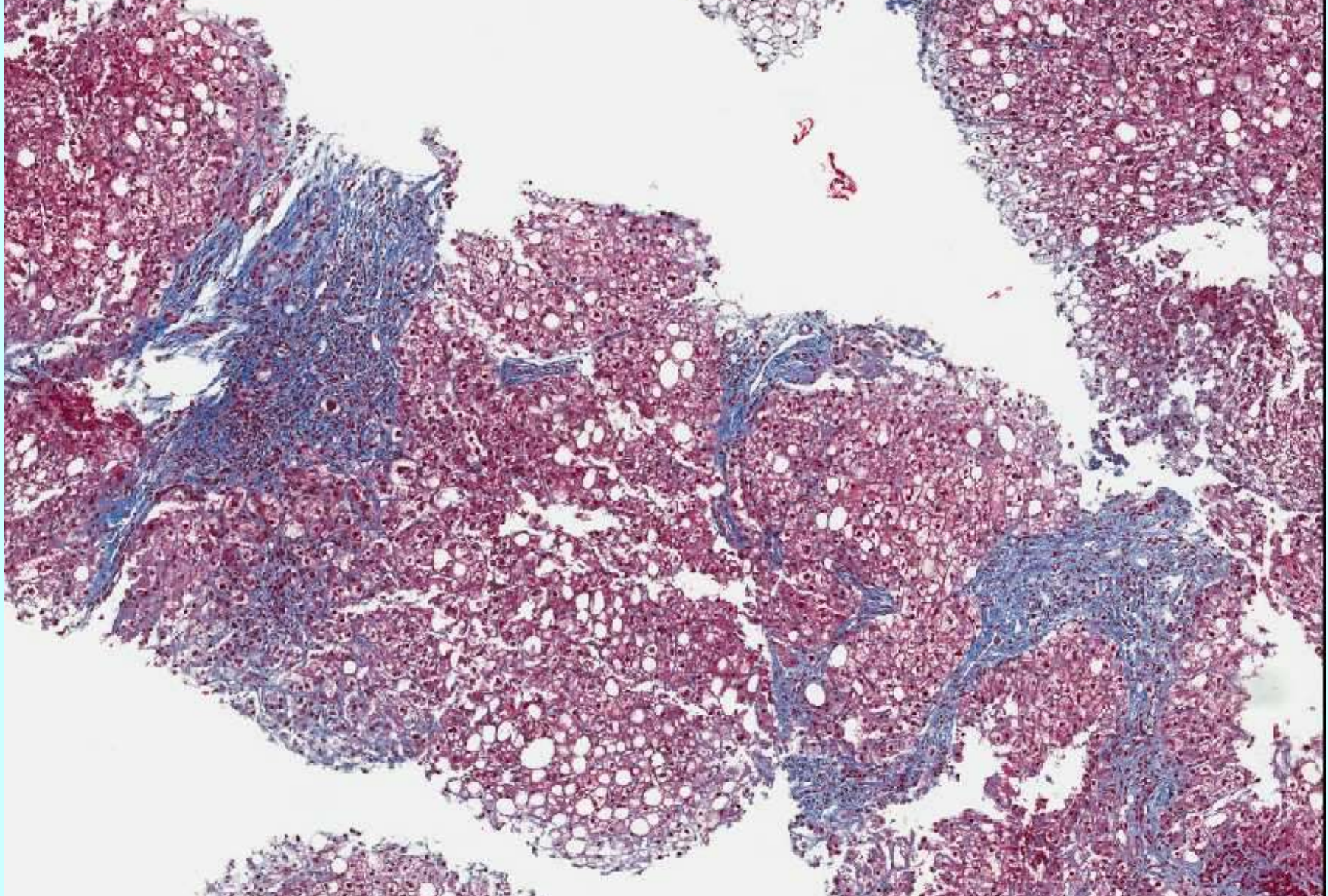
Stage separately for earlier stages if possible

- NASH: Brunt or Kleiner stage

Case example

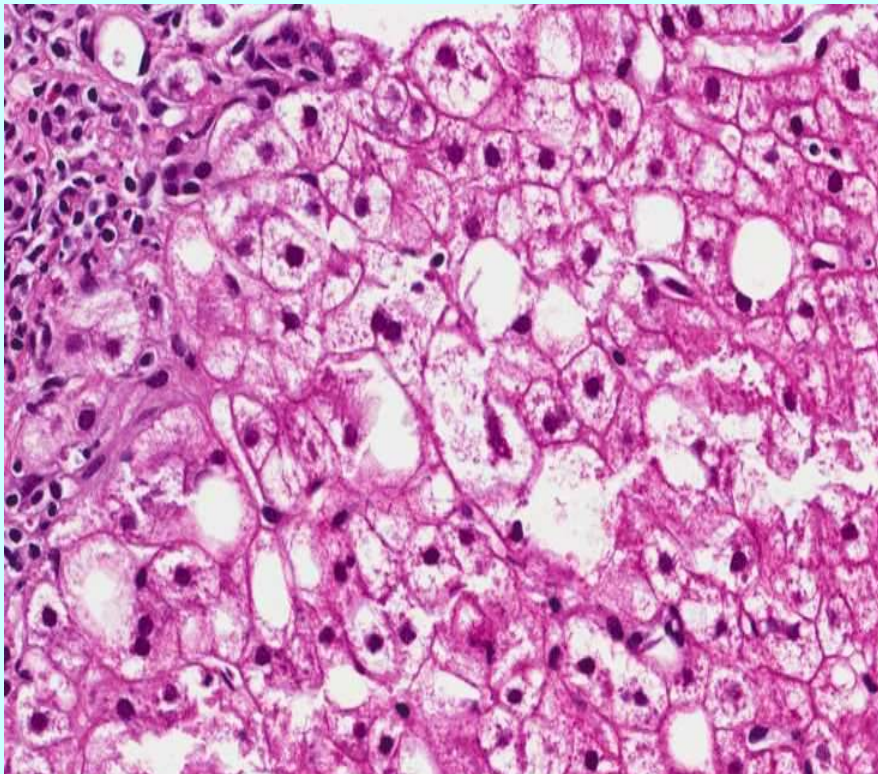
- if all fibrosis due to NASH, Stage 2 NASH
- If periportal likely due to HCV, then Stage 1 NASH
- Viral hepatitis: Do not include central fibrosis
 - Ishak stage 1 (or 2 if most portal areas have this fibrosis)
- Note prominent pattern or combination of patterns as centrizonal or portal if possible

NASH and HCV, Ishak St 5

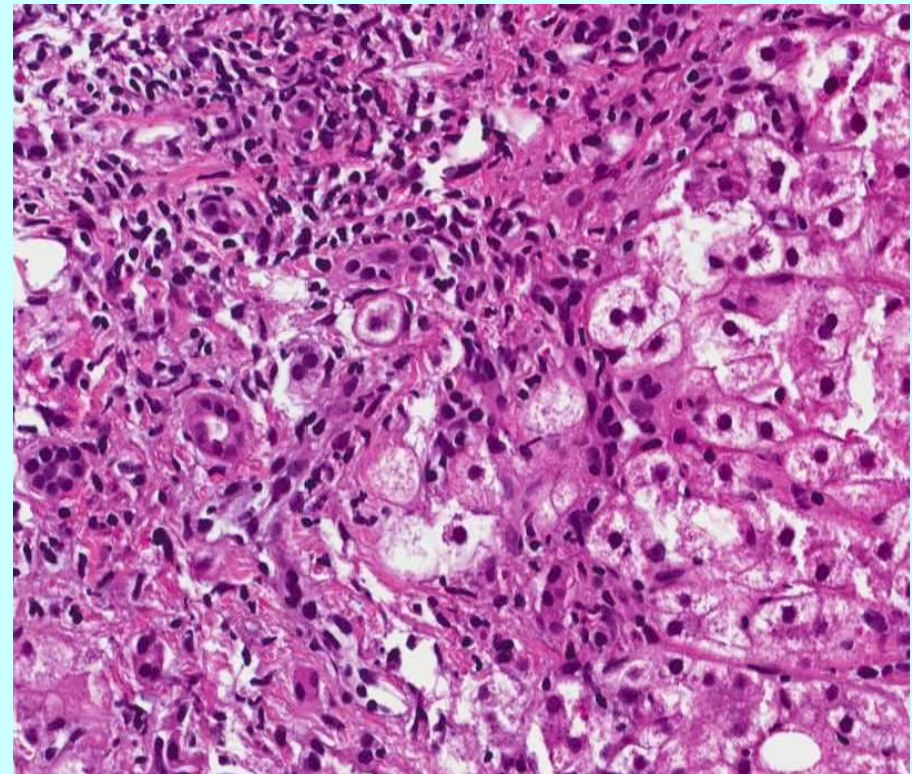


NASH and HCV

Ballooned hepatocyte, fat and glycogen

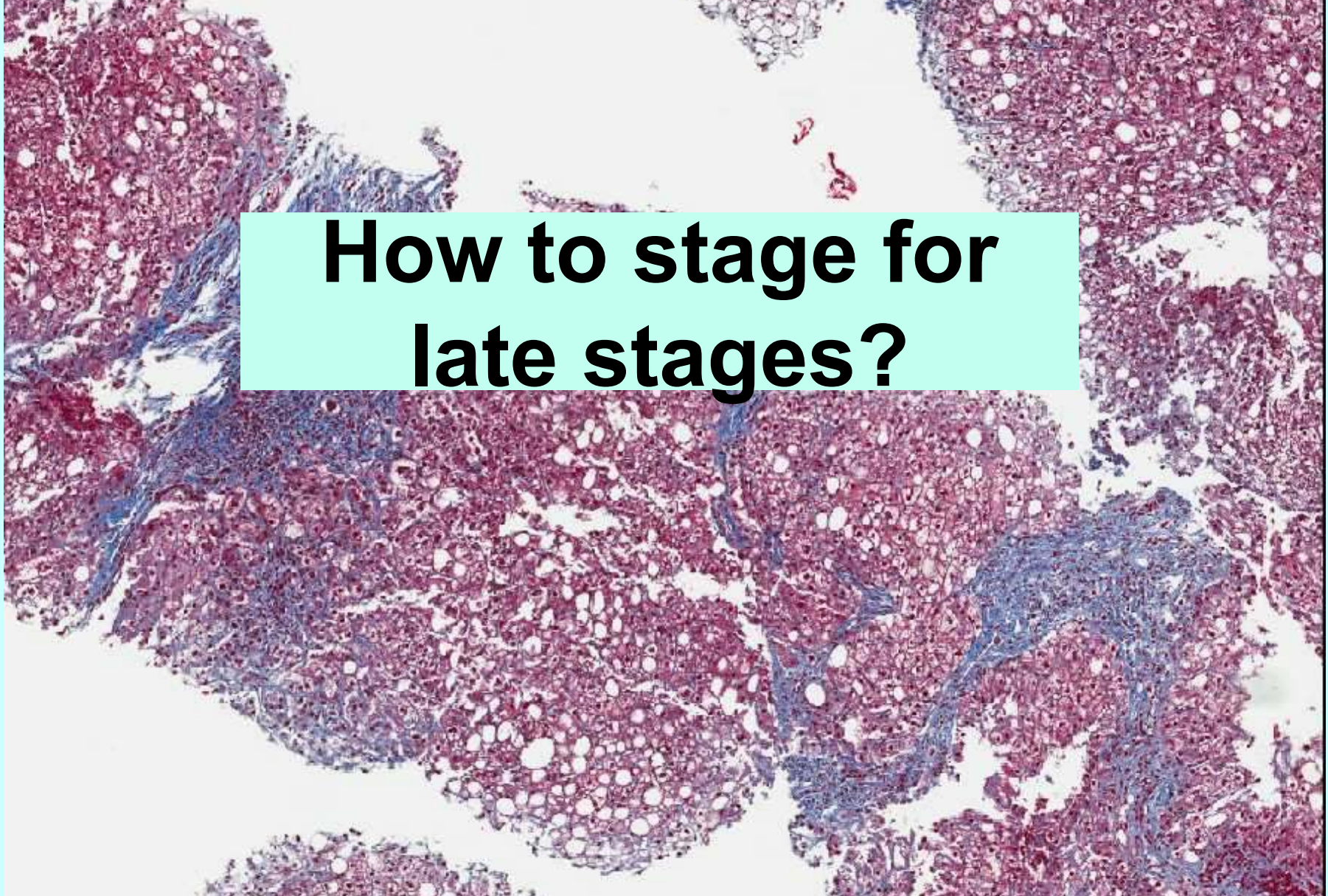


Ballooned hepatocyte with Mallory-Denk body



NASH and HCV, Ishak St 5

**How to stage for
late stages?**



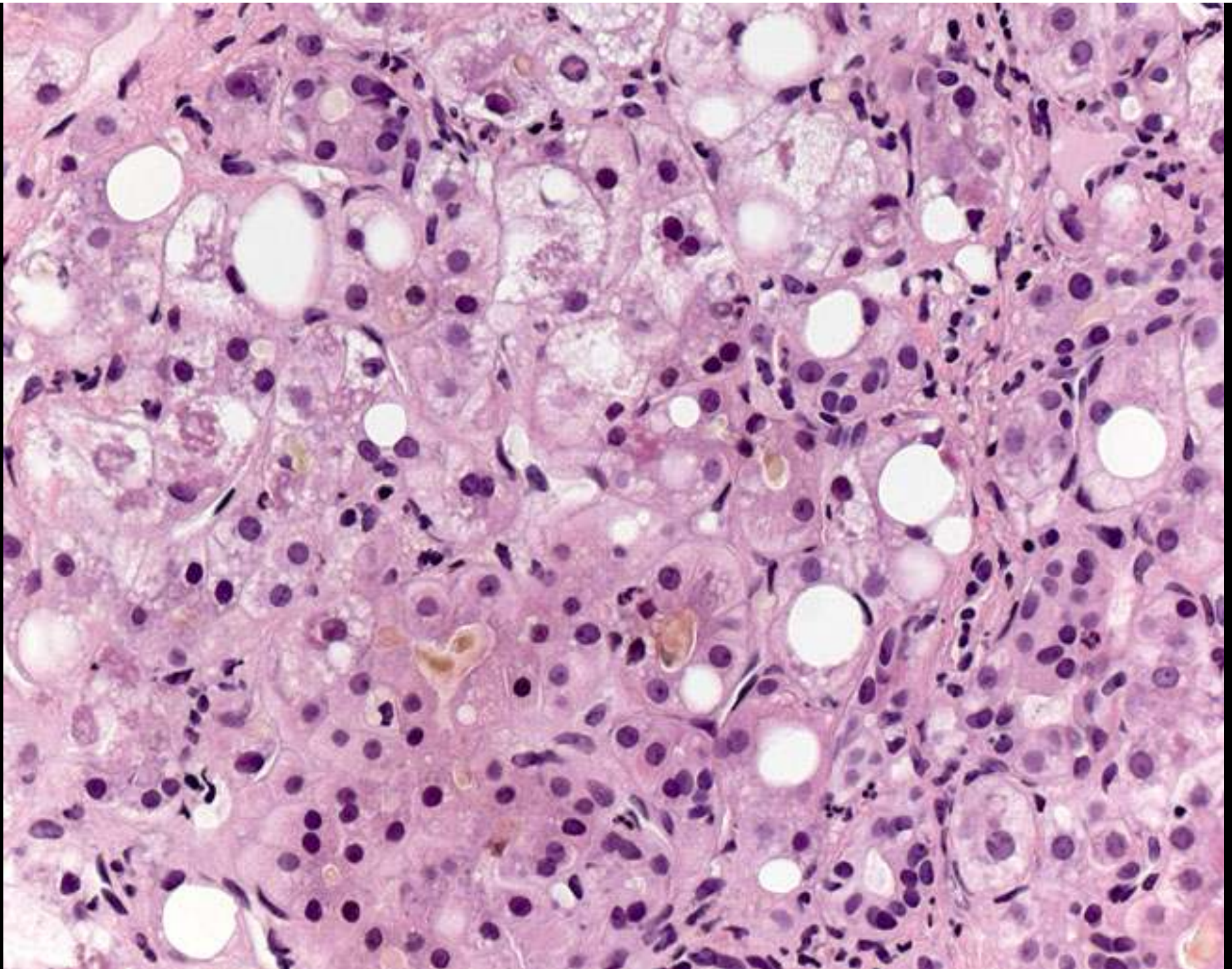
NASH + HCV or HBV STAGING

- **Later stages:** *Stage combined etiologic patterns as bridging or cirrhosis*
 - NASH stage 3 or 4 = Ishak stage 4-6
- Note if both centrizonal, portal patterns are present, and if possible, most prominent pattern
- Note any difficulties of determining etiologic cause of all fibrosis to communicate the message that both entities could have contributed to stage

NASH or Alcohol (ASH)?

- **Common diagnostic pitfalls:**
 - *Too much of one thing*

Prominent cholestasis, Mallory bodies, or neutrophils: alcoholic hepatitis??



NASH or Alcohol (ASH) ?

ASH may also demonstrate:

- More central vein sclerosis/obliteration**
- More extensive pericellular and sinusoidal fibrosis**
- Micronodular pattern of cirrhosis**

NASH, not Autoimmune

- **Common diagnostic pitfalls:**

Interpretation of plasma cells

Autoimmune hepatitis (AIH): More plasma cells and interface hepatitic changes

- NOTE: Autoimmune antibodies, including ANA, SMA, and even AMA may be elevated as nonspecific change in metabolic syndrome

NASH, not Drug

- **Common diagnostic pitfalls:**

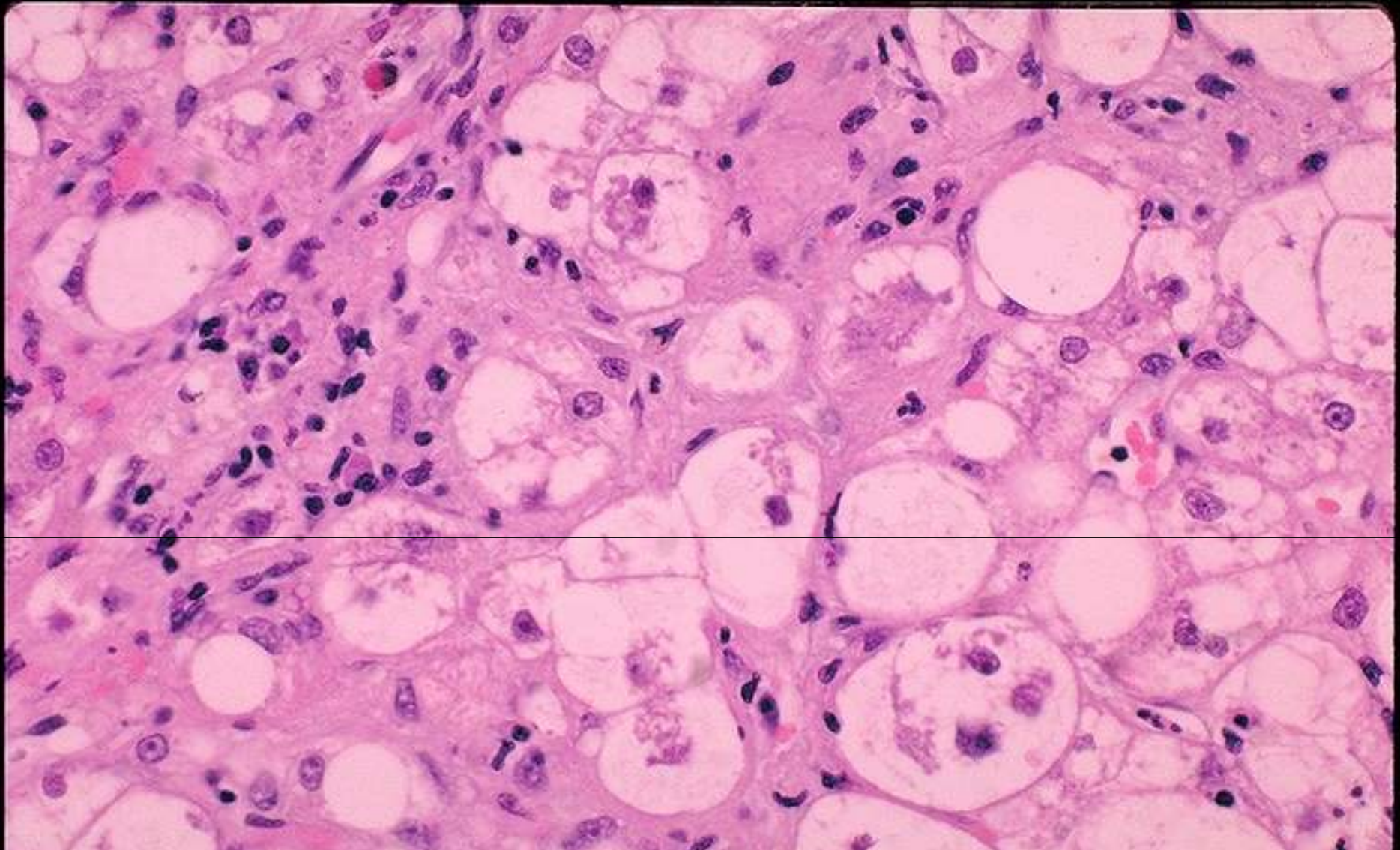
Interpretation of eosinophils

A few eosinophils common in NASH

Drug hepatitis, hypersensitivity type:

-LOTS (!) of eosinophils

-Also usually not fibrotic, especially in centrizonal pattern



**NASH: Inflammation can include some plasma cells
and eosinophils**

NASH

- **Common diagnostic pitfalls:**
 - *Absence of fat*

Minimal fat or no fat does not exclude NASH-related fibrosis/cirrhosis!

Fat can often be markedly decreased or absent in end-stage lesion

NASH and Cirrhosis

- **Relationship to cryptogenic cirrhosis**
 - **Absence of fat**
 - **Absence of steatohepatitis**
 - **Presence of risk factors for NAFLD**

Cryptogenic Cirrhosis: Risk Factors

- **Diabetes Mellitus or obesity**
 - 73% cryptogenic cirrhosis, 75% NASH
 - **DM only**
 - 53% cryptogenic cirrhosis, 42% NASH
 - **Marked obesity**
 - 47% cryptogenic cirrhosis, 64% NASH
- (From: Caldwell, 1999)**

NAFLD and Other Lesions

- **Hepatocellular Carcinoma (HCC)**
 - 18-27% incidence in cirrhosis, not quite as high risk as HCV
 - Related to insulin resistance?
- **Hepatocellular Adenoma (HCA)**
 - Inflammatory and HNF α 1 variants also increased in obesity/diabetes

Summary

- **Association: Metabolic Syndrome**
- **NASH vs steatosis only (NAFLD)**
 - **Ballooned hepatocytes: Active NASH**
 - **Centrizonal fibrosis: Active (chronic) or remote NASH**
- **Pediatric NASH variant: Portal-based**
- **NASH and cryptogenic cirrhosis**
- ***HCC/HCA may be the next manifestation of this epidemic...***