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# LIVER

## Update on Staging of Fibrosis and Cirrhosis

### Staging and Liver Fibrosis

Two important concepts for consideration:

- *Stage is more than histologic fibrosis*

An integrated clinical/pathophysiologic approach is needed to accurately stage the disease

- *Cirrhosis is not the “end” of the story:*

Histologic scoring may need to evolve to identify regression or remodeling of cirrhosis, and evaluate for very advanced nonreversible, or “end-stage” cirrhosis, based on degree of fibrosis

### Stage is more than liver fibrosis

**Clinical Modalities to Stage Chronic Liver Disease**

Measurements of liver function and pathophysiology include the following among others:

- *Transient elastography (Fibroscan ®)*
- *Clinical scores including Child-Pugh and MELD scores*
- *Serum markers and panels, such as Fibrotest ®, Hepascore®, FibroSpect ®, ELF score, AAR, APRI, etc.*
- *Hepatic venous pressure gradient (HVPG)*

## Going “Beyond Cirrhosis”

### Proposal from the International Liver Pathology Study Group

**Concept:** Cirrhosis has historically implied end-stage disease with the imminent death of patient as there was no cure and no treatment

**But now, many patients remain compensated, and function improves with therapy, particularly notable in chronic viral hepatitis**

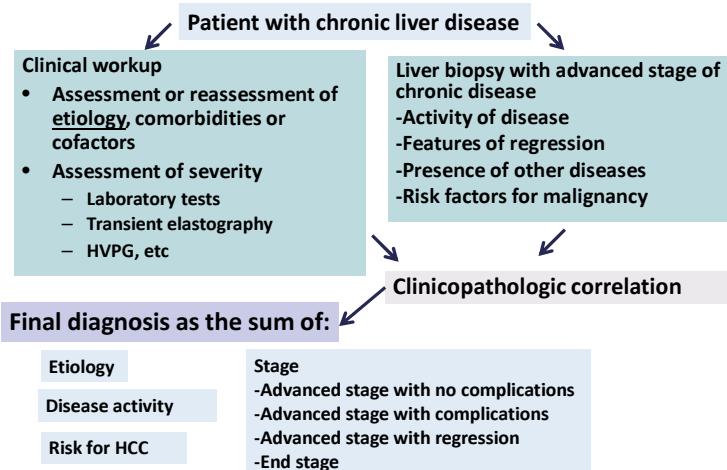
## Going “Beyond Cirrhosis”

**Proposal:** *It may be time to put aside the “one-term-fits-all” approach, and stage liver disease as related to etiology and pathophysiology*

*Should we drop the term cirrhosis or at least recognize different “degree’s of cirrhosis” for a better method of describing advanced liver injury based on etiology and patterns of injury??*

### Assessment of Advanced Chronic Liver Disease

Adapted from Figs 1, Beyond Cirrhosis (AJCP 2012) and Exploring Beyond Cirrhosis (Hepatol 2012, 56:779)



## Staging and Liver Fibrosis

Liver biopsy is still considered an important component of staging

### Questions:

- How do we use the liver biopsy in the best way?
- What are the histological aspects we need to consider?

## Staging and Liver Fibrosis

*An important starting point is the adequate biopsy!!*

## Adequacy of Biopsy for Grading/Staging

**Short summary (more details in syllabus)**

Current acceptable recommendations

- 5 portal areas minimum, probably >11 for optimal value
- And/or approx 2 cm core of reasonable width (17 gauge or larger)

## Staging and Liver Fibrosis: Other considerations

- Etiology of the injury
- Pattern and degree of histological injury
- Treatment effects resulting in remodeling, or regression, of fibrosis

*-What changes are reversible?*

## Staging: Histological Aspects

Etiology related to fibrosis degree and patterns

Etiology	HBV	HCV	AIH	NASH	ASH	PBC	PSC	HHC	WD	CVOO
Fibrosis ranking <sup>*13</sup>	3	3	3	NA	1	2	2	NA	NA	NA
Regression or remodel evidence <sup>15</sup>	++	++	+	++	+	+		++	+	NA
Centrilobular or sinusoidal fibrosis prominent pattern			+/-	++	+++					+++
Portal-based fibrosis prominent pattern	++	++	++			++	++	++	+	

**Fibrosis ranking on explanted liver, 1= most fibrosis, 3= least fibrosis**

AIH= autoimmune hepatitis; NASH= nonalcoholic steatohepatitis;  
ASH= alcoholic steatohepatitis; PBC= primary biliary cirrhosis;  
PSC= primary sclerosing cholangitis; HHC= hereditary hemochromatosis;  
WD= Wilsons disease; CVOO= primary types of chronic venous outflow obstruction

## Histological Aspects

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## Patterns of Fibrosis

Two major patterns for early scarring of the liver

Portal-based Fibrosis

Injury begins in periportal area

Central-based Fibrosis

Injury begins in centrilobular zone

## Portal-Based Fibrosis Pattern

### *Major associated lesions*

- Chronic hepatitis

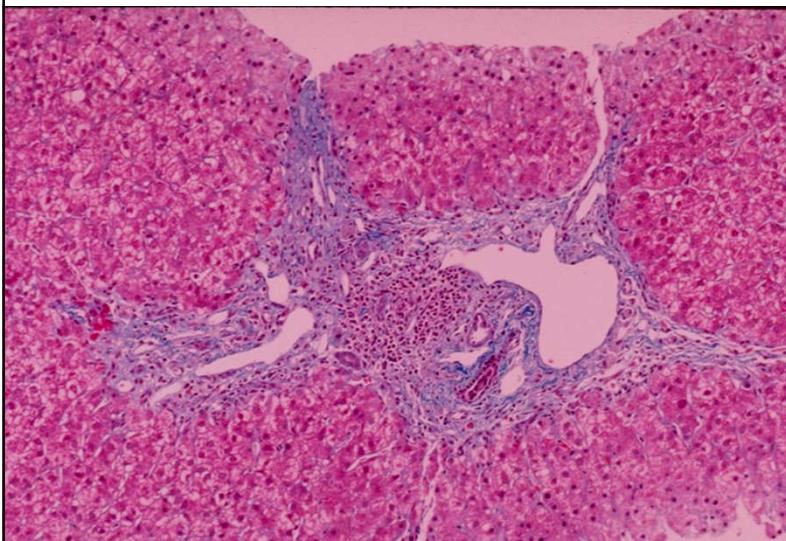
- Hepatitis B, C
- Autoimmune hepatitis
- Alpha-1-antitrypsin and Wilsons disease

- Biliary Disease

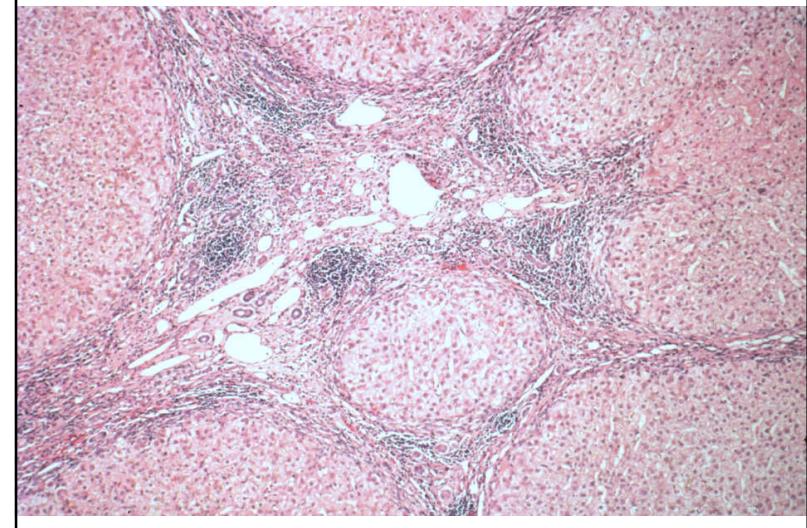
- PBC, PSC, Chronic obstruction

- Hemochromatosis

Portal-based Fibrosis: Chronic Hepatitis

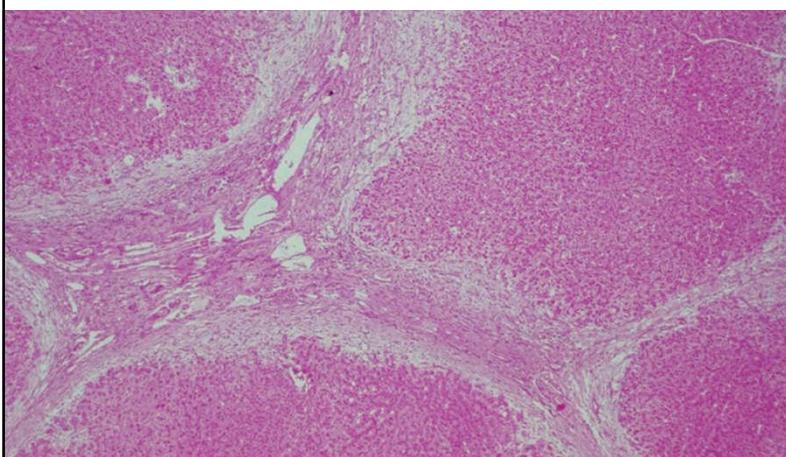


Chronic Hepatitis C: Cirrhosis, rounded nodules

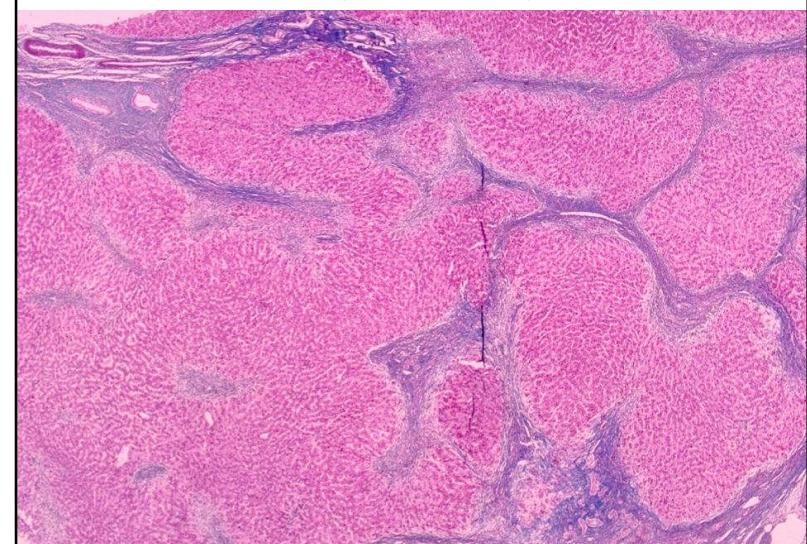


Chronic Biliary Disease

Wider fibrous bands with more ductular reaction  
can occur in comparison to chronic hepatitis B or C



Chronic Biliary Disease: Jigsaw fibrosis



## Fibrosis Scoring of Chronic Hepatitis

### Practical tips and common problems

- First step: Use a system that is
  - Simple
  - Reproducible
  - Useful in clinical setting

### Commonly used Grading/Staging systems

- Scheuer/Batts-Ludwig/Tsui:
  - Grade and Stage on scale 0-4
  - Simple, reproducible, validated clinically
- METAVIR:
  - Grade 0-3, Fibrosis 0-4
  - Simple, reproducible, validated clinically
- Ishak, et al:
  - Grades four categories of activity/necrosis, 0-4 or 0-6
    - Generally considered too complex, not necessary
  - Staging 0-6
    - Preferred in many clinical trials
    - Still reproducible and validated clinically

### Scheuer / Batts-Ludwig / Tsui Grading and Staging

- Simple, reproducible, validated
- Essentially same methodology so interchangeable for the most part
- Most commonly used day-to-day in USA and validated for studies as well
- #1 Recommended for typical usage for grading

### Scheuer/Batts,Ludwig/Tsui Fibrosis scoring for Chronic Hepatitis

Stage	Description
0	No fibrosis, normal amount of connective tissue
1	Portal/periportal fibrosis
2	Septal fibrosis
3	Bridging fibrosis with architectural distortion.
4	Cirrhosis, probable cirrhosis

## METAVIR

2-letter, 2-number system similar to Scheuer  
Used extensively in France

F = fibrosis

- F0 = no fibrosis
- F1 = portal fibrosis without septa
- F2 = portal fibrosis with rare septa
- F3 = numerous septa, not cirrhosis
- F4 = cirrhosis

## Ishak, et al: Fibrosis Scoring System

J Hepatol 1995;22:696-9

(Grading system typically not used due to complexity)

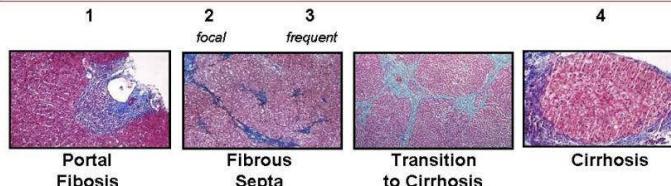
<b>0</b>	No fibrosis
<b>1</b>	Expansion of some portal areas with or without septa
<b>2</b>	Expansion of most portal areas with or without septa
<b>3</b>	Expansion of most portal areas with occasional portal to portal bridging
<b>4</b>	Expansion of portal areas with marked bridging (portal-portal and/or portal-central)
<b>5</b>	Marked bridging with occasional nodules (incomplete cirrhosis)
<b>6</b>	Cirrhosis, probable or definitive

### Stages of Fibrosis

Modified Ishak ↔ Batts-Ludwig



Metavir



From Theise ND, Mod Pathol 2007, 20(supple 1):S3-14;  
Also published in MacSween's Pathology of the Liver

## Portal-Based Fibrosis: *Which scoring system to use?*

- All three systems are reasonable
- Scheuer and Batts/Ludwig 0-4 scales works well for chronic hepatitis B and C and is simple
  - Validated by many studies

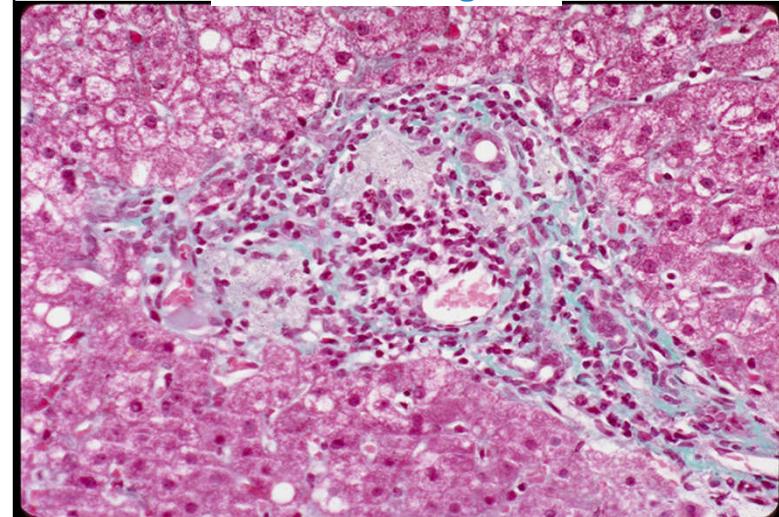
### Limitations:

- Doesn't apply to centrilobular liver disease
- Mixed etiologies (Example: Alcohol + HBV)
- Doesn't go "beyond cirrhosis"
  - No differentiation between early, compensated versus advanced, end-stage decompensated cirrhosis)
- Doesn't evaluate for remodeling/regression

## CASE EXAMPLES

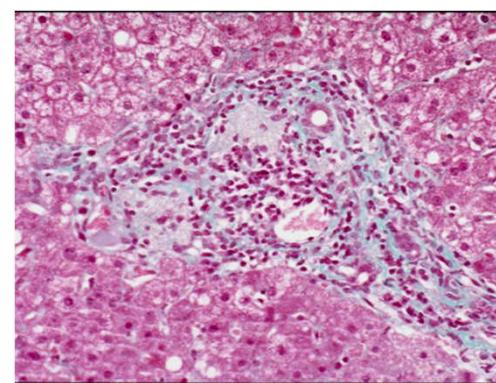
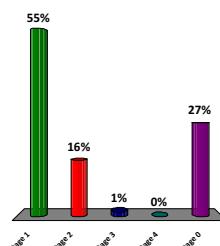
Practice staging using Scale 0-4

Fibrosis: Stage ?

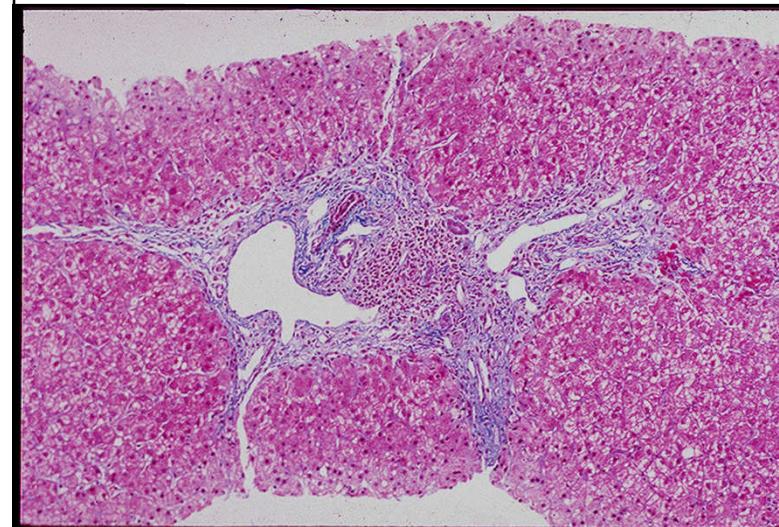


Fibrosis Stage?

- 1. Stage 1
- 2. Stage 2
- 3. Stage 3
- 4. Stage 4
- 5. Stage 0

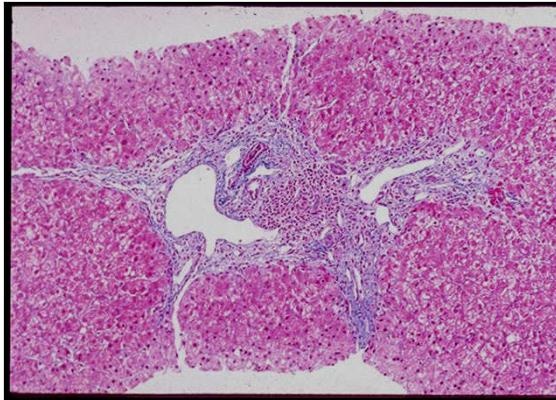


Fibrosis: Stage ?



Fibrosis stage?

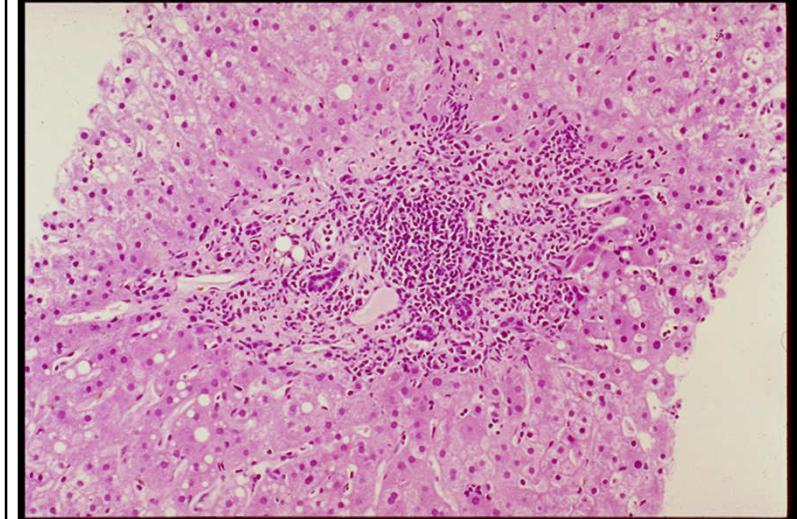
- 1. Stage 1
- 2. Stage 2
- 3. Stage 3
- 4. Stage 4
- 5. Stage 0



Bar chart showing the distribution of fibrosis stages:

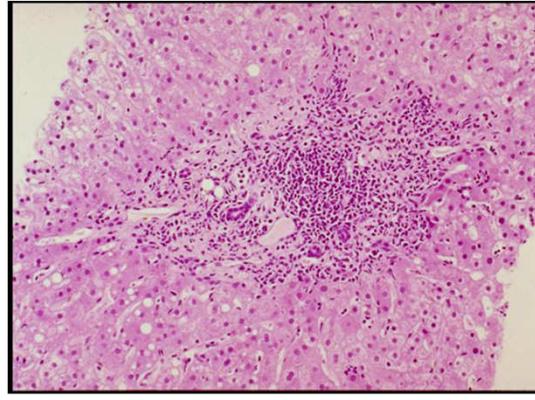
Stage	Percentage
Stage 1	23%
Stage 2	55%
Stage 3	22%
Stage 4	0%
Stage 0	0%

Fibrosis: Stage ?



Fibrosis stage?

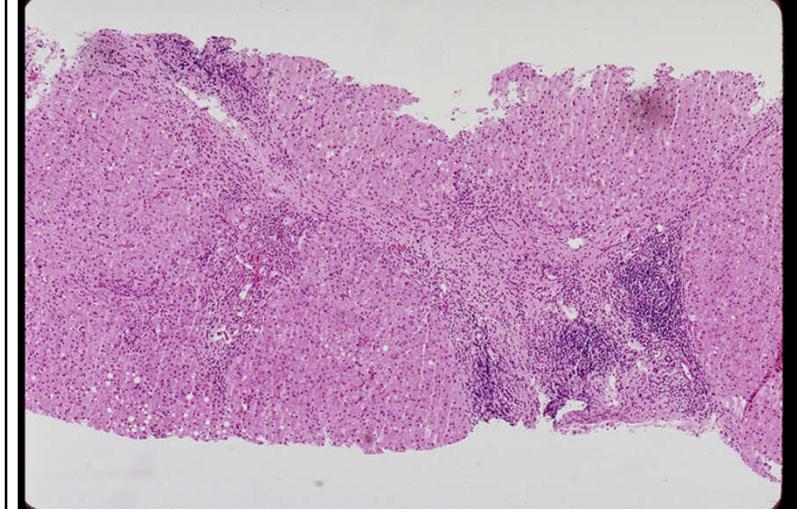
- 1. Stage 1
- 2. Stage 2
- 3. Stage 3
- 4. Stage 4
- 5. Stage 0

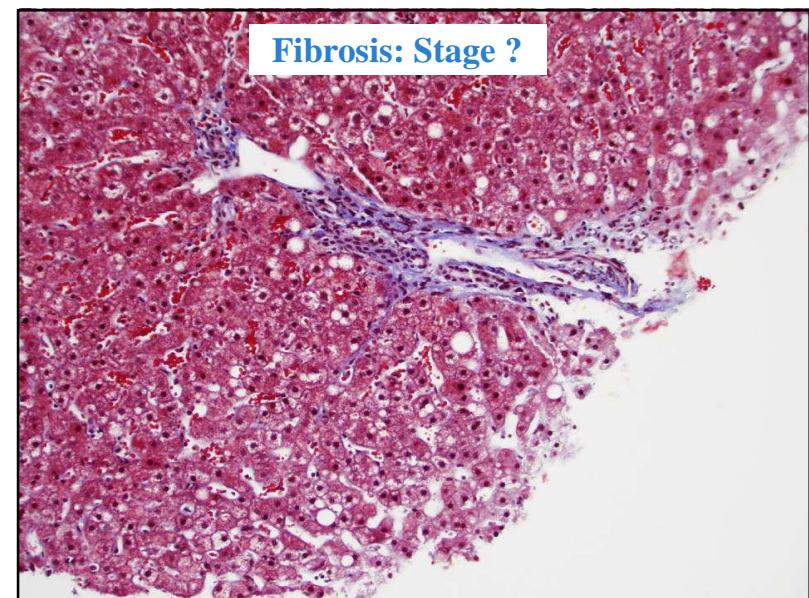
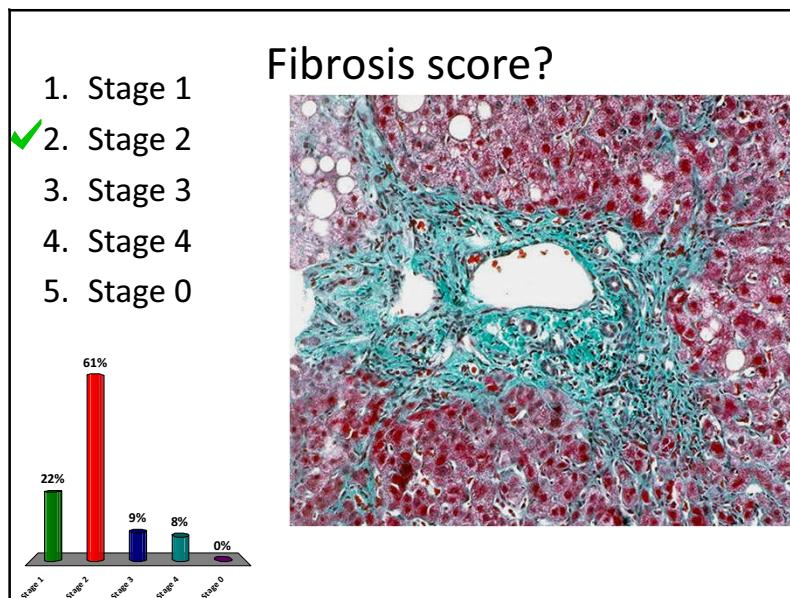
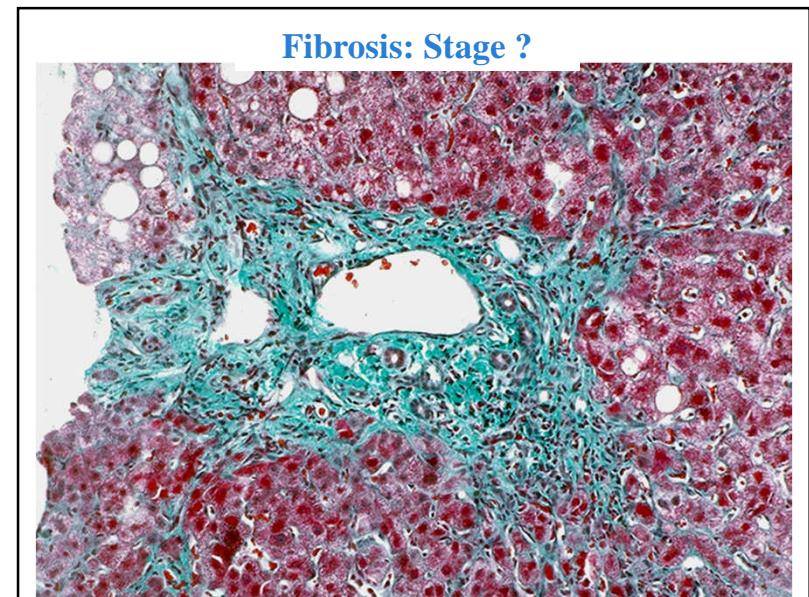
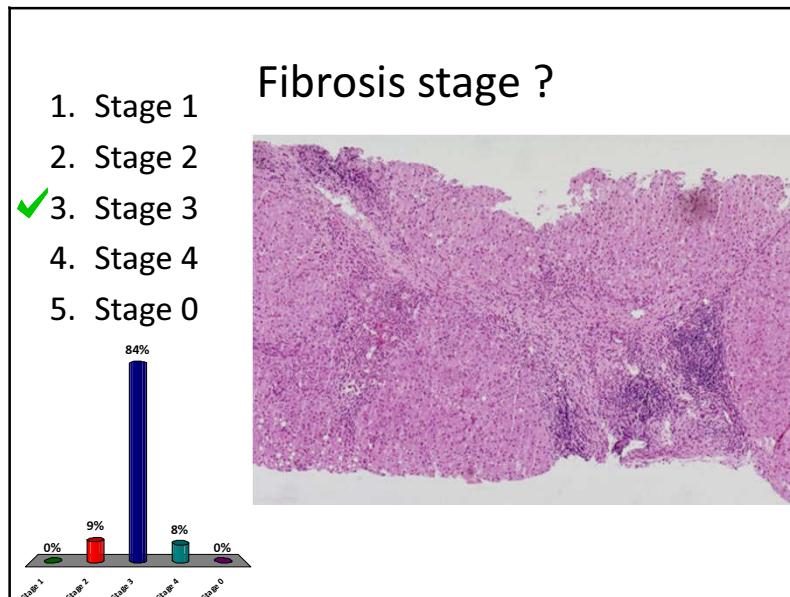


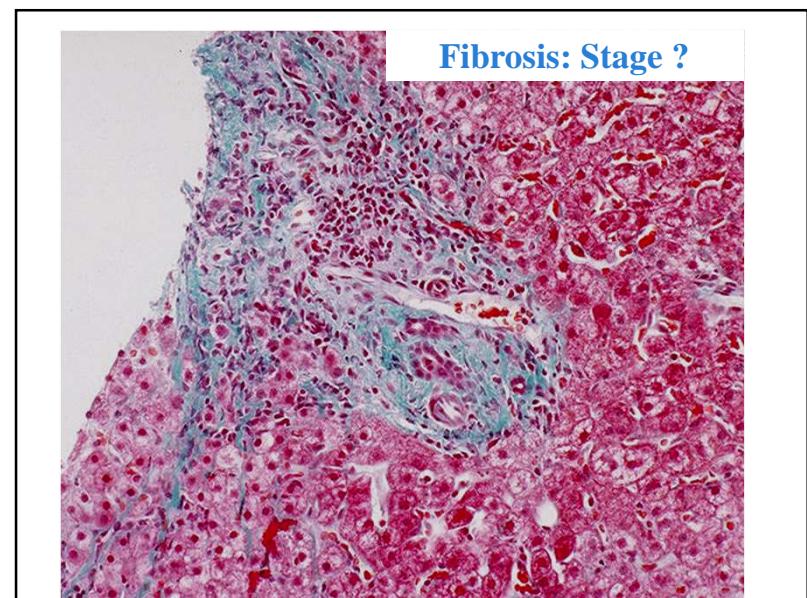
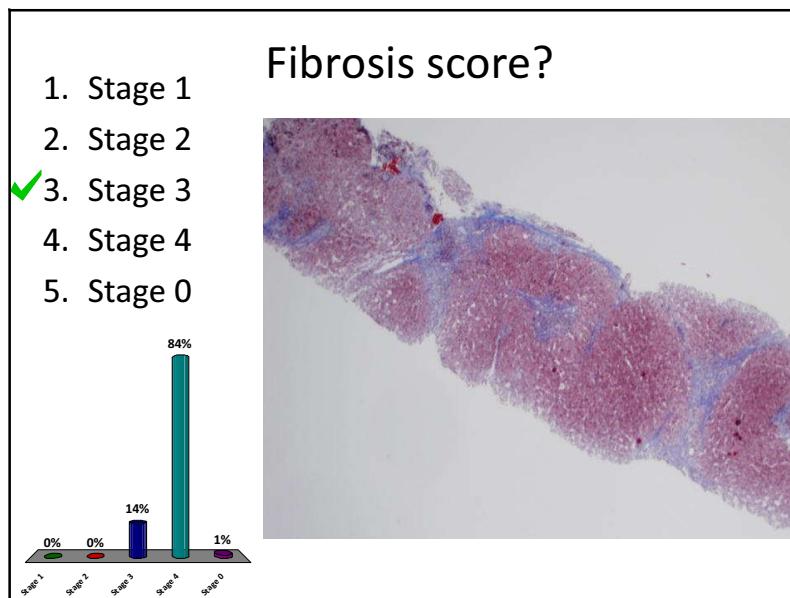
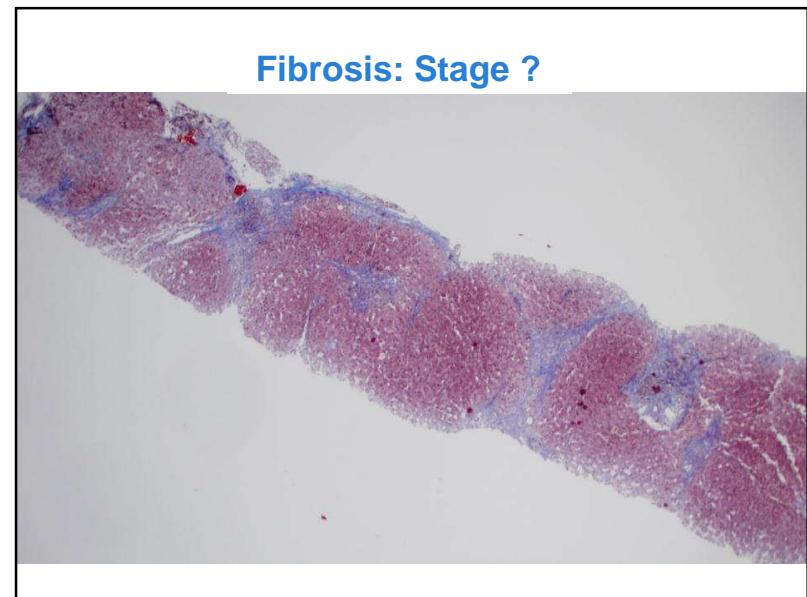
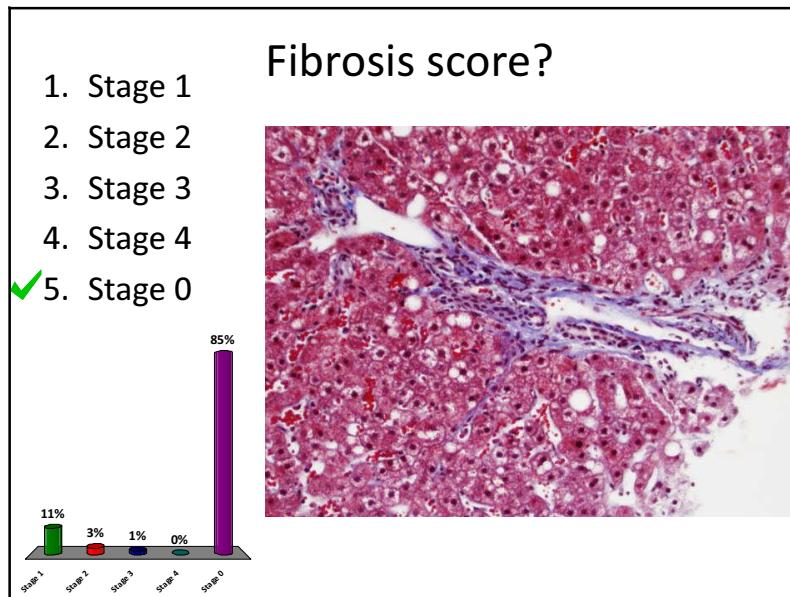
Bar chart showing the distribution of fibrosis stages:

Stage	Percentage
Stage 1	52%
Stage 2	0%
Stage 3	0%
Stage 4	0%
Stage 0	48%

Fibrosis: Stage ?

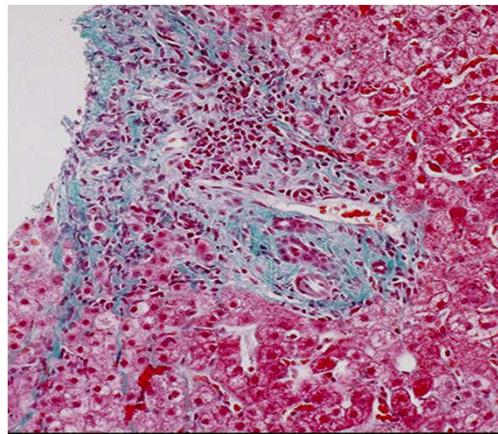
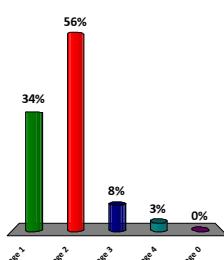






## Fibrosis score?

- ✓ 1. Stage 1
- ✓ 2. Stage 2
- 3. Stage 3
- 4. Stage 4
- 5. Stage 0

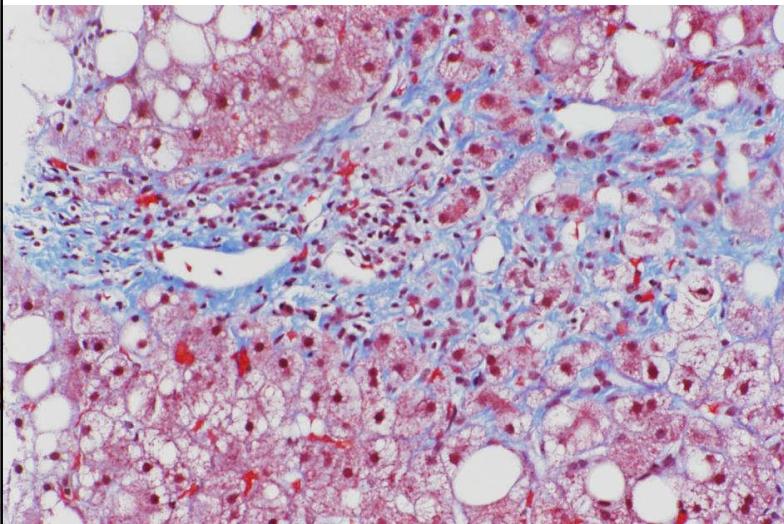


## Centrilobular Fibrosis Pattern

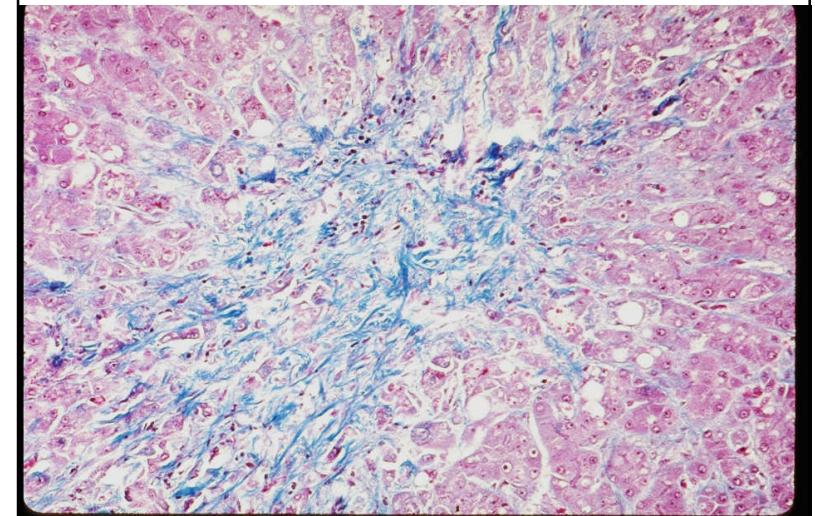
### *Major associated lesions*

- Chronic steatohepatitis
  - Nonalcoholic types (NASH)
  - Alcoholic types (ASH)
- Chronic venous outflow obstruction

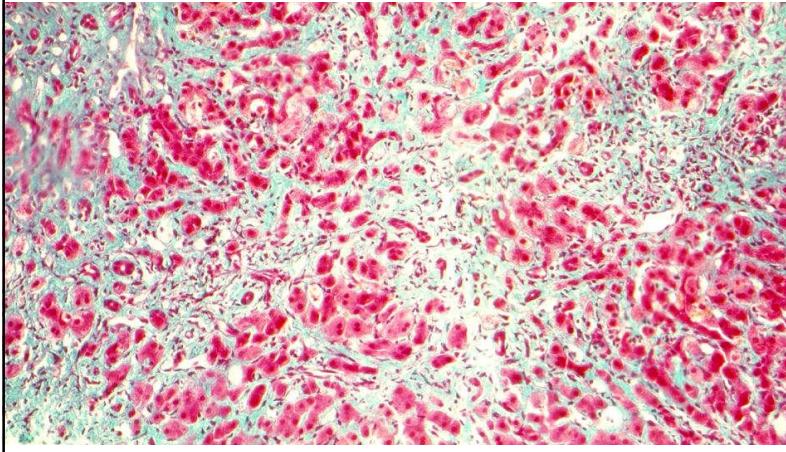
### NASH: Centrilobular Fibrosis with focal dense scarring



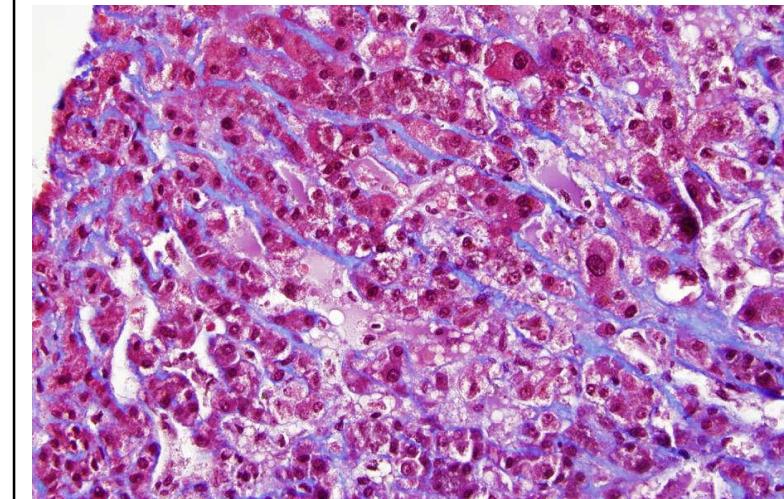
### Alcohol: Central vein obliteration



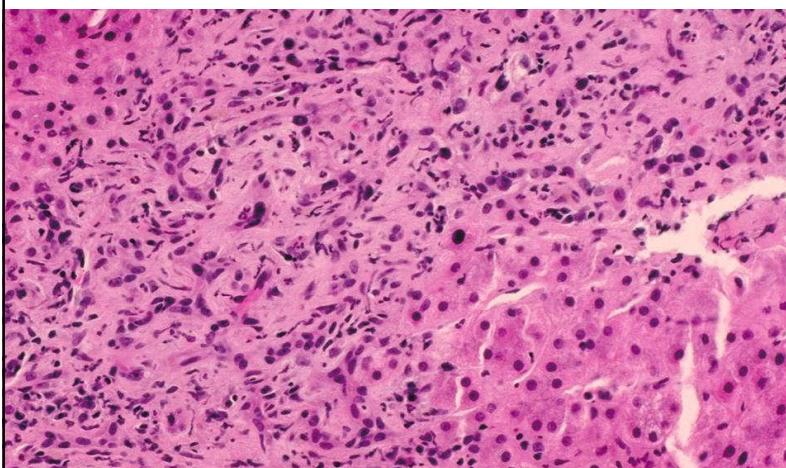
Alcohol: Central vein and extensive sinusoidal obliteration



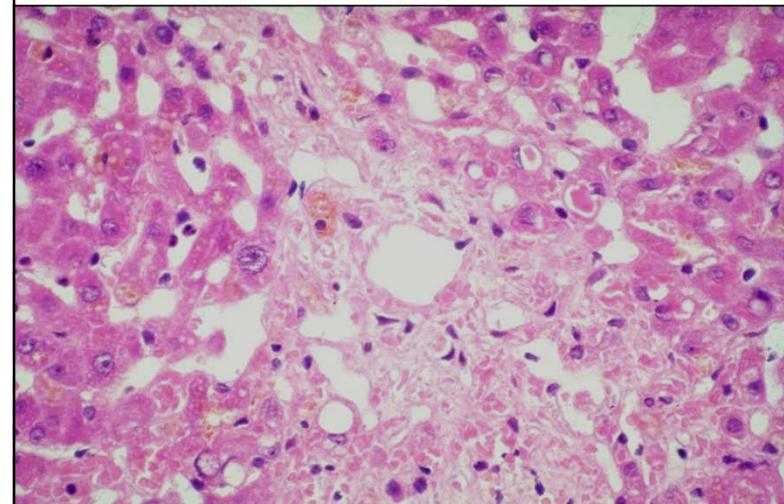
Sinusoidal Fibrosis in chronic venous outflow obstruction (chronic heart failure), Trichrome



Budd-Chiari Syndrome:  
Centrilobular Fibrosis and Ductular Metaplasia of hepatocytes (probably an ischemic effect)



Chronic Heart Failure: Centrilobular Fibrosis



## Fibrosis Scoring (Brunt E, et al, 1999) Designed for NASH

Score	Histologic Description
0	No fibrosis
1	Zone 3 sinusoidal, focal or extensive
2	Zone 3 as above and focal/extensive periportal fibrosis
3	Same as 1 or 2 with bridging fibrosis from zone 3-1 with nodular change
4	Cirrhosis

## Fibrosis Scoring - NASH (Kleiner, Brunt et al, including Ferrell, 2005)

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

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

### Central-based Fibrosis

#### *Which scoring system to use?*

- Kleiner (NASH CRN) system covers broader spectrum for Stage 1 than older Brunt methodology but both cover most current demands

#### Limitations

- Problems with stage 2 with only early centrilobular scarring combined with periportal scarring: many stage 1 lesions may be higher stage clinically
- Doesn't account for mixed portal/central lesions
- Doesn't go "beyond cirrhosis"
- Doesn't evaluate for remodeling

### Problem areas: Mixed etiologies could mean mixed patterns

- Could use combination of Kleiner and Scheuer or Batts/Ludwig and Kleiner for early stages 1 and 2

#### Limitations

- Doesn't account for more advanced lesions scored in 3-4 range or "beyond cirrhosis"

## NASH + HCV or HBV

**NOTE Pattern of disease locations**

**PORTAL: favors chronic hepatitis**

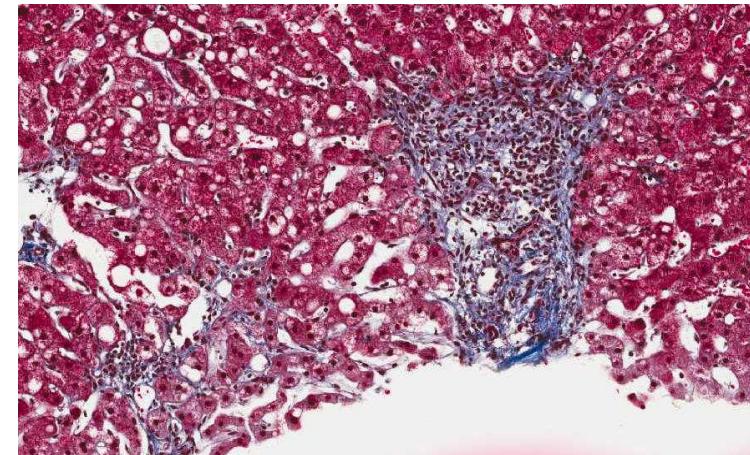
- Portal-based chronic inflammation, fibrosis, and interface hepatitis
- HBV or HCV markers

**CENTRAL: favors steatohepatitis**

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

## NASH and HCV

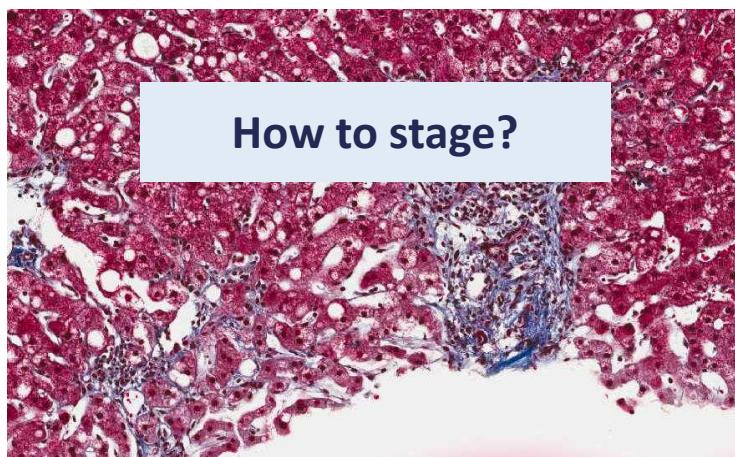
Centizonal and Periportal fibrosis



## NASH and HCV

Centizonal and Periportal fibrosis

How to stage?

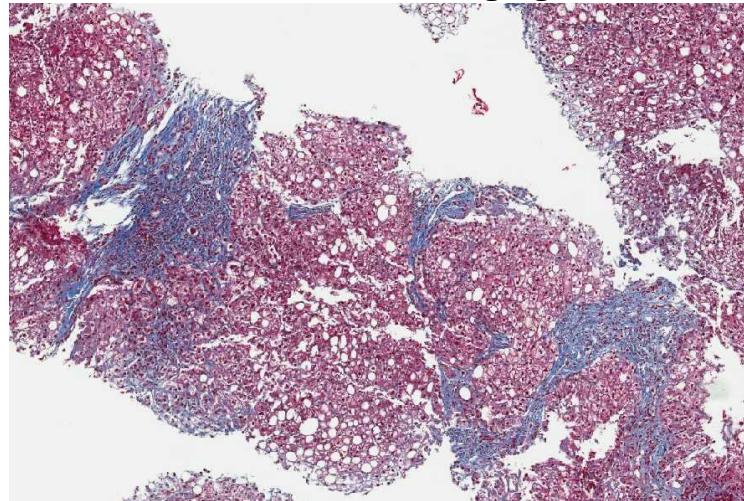


## NASH + HCV or HBV STAGING

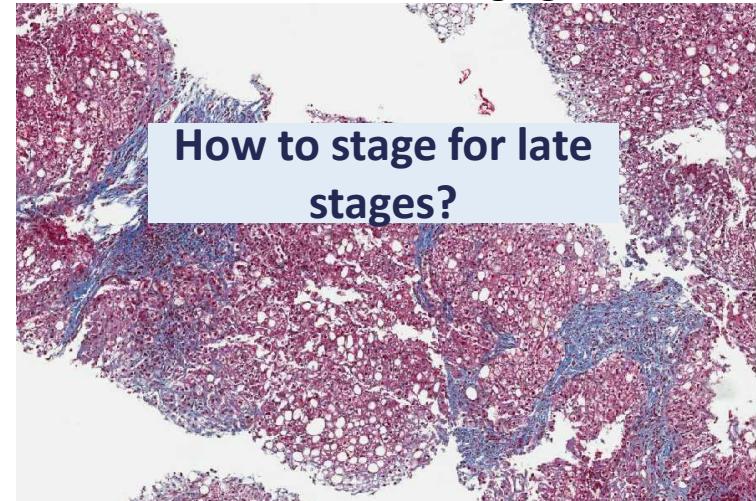
Stage separately for earlier stages if possible

- 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
    - Scheuer or Batts/Ludwig stage 1 or 2
- Note prominent pattern or combination of patterns as centizonal or portal if possible

NASH and HCV with bridging fibrosis



NASH and HCV with bridging fibrosis



### NASH + HCV or HBV STAGING

- **Later stages:** Stage combined etiologic patterns as bridging or cirrhosis
  - NASH stage 3 or 4 or Scheuer 3 or 4
- Note if both centrilobular, 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

### NEW: Modified Laennec Scoring System

#### Features:

- Does not use portal-based versus central-based pattern of scarring as a primary definition so could be used for mixed lesions
- 6 stages and 6 scores
  - 3 for pre-cirrhotic conditions as in the 0-4 methodologies
  - Adds 2 more stages and scores for cirrhosis.
- Makes a distinction between stage and score

## Modified Laennec Scoring System

Stage	Name	Criteria (as slightly modified by LF)	Score
0	No fibrosis	No definite fibrosis	0
1	Minimal fibrosis	No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis	1
2	Mild fibrosis	Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis	2
3	Moderate fibrosis	Moderate thin septa; up to incomplete cirrhosis (thin bridging OK)	3
4A	Cirrhosis, mild definite, or probable	Marked septation with rounded contours or visible nodules Most septa are thin (1 broad septum allowed)	4
4B	Cirrhosis, moderate	At least 2 broad septa, but no very broad septa and <1/2 of biopsy length composed of minute nodules (micronodules)	5
4C	Cirrhosis, severe	At least 1 very broad septum or >1/2 of biopsy length composed of micronodules	6

Adapted from Table 2 in: Kim, et al on staging reference list

## Modified Laennec Scoring System

- Recognizes that all cirrhoses are “not equal” in that the degree of fibrosis may be related to clinical stage

### Limitations

- Newest methodology: validated only on limited basis for cirrhosis scores
- Doesn’t address etiology
- Doesn’t evaluate remodeling/regression
- Problem with the 3-4 scale as overlapping features of focal thin or thicker septa could be seen in 3 or 4b

## Problems universal to all fibrosis scoring systems

- Limitation by sample size
- Mixed ETIOLOGIC lesions not addressed directly (which may relate to therapy)
- No system recognizes remodeling changes

### QUESTIONS

- What lesions are potentially reversible and can remodel /regress?
- What lesions suggest remodeling/regression?

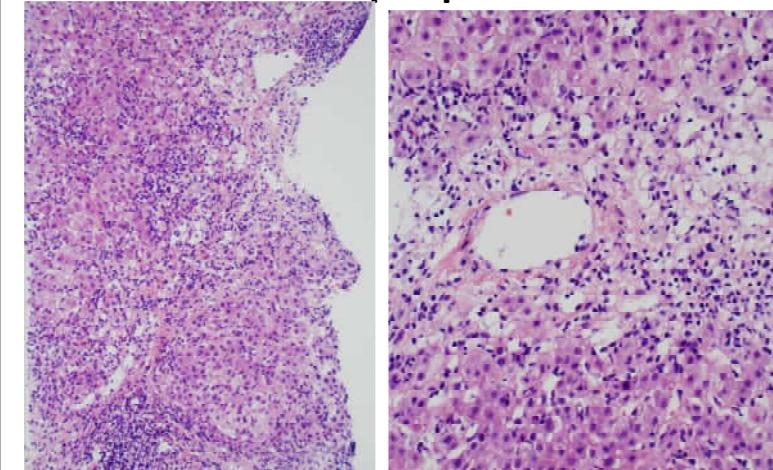
## Remodeling/Regression changes

- Remodeling could be the sequelae of necrosis, so is a broader concept than regression
- Regression is noted by decrease in fibrous tissue, so can include remodeling patterns
  - Regression is usually associated with improvement of clinical status, but can be variable in degree of improvement depending on reversibility of the liver damage

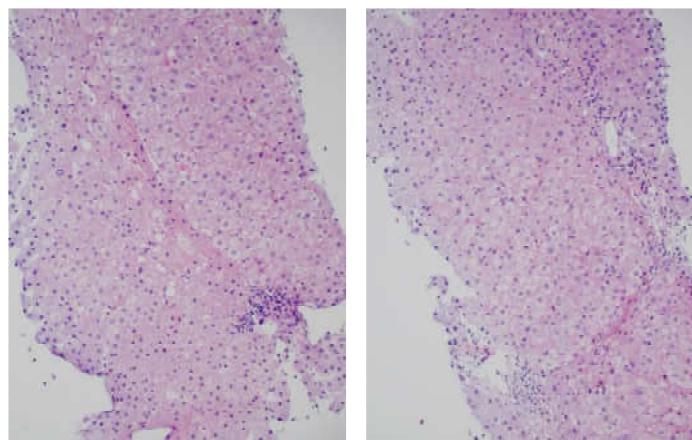
### Case Example of Remodeling in Setting of Necrosis to Fibrosis

- Acute necrosis followed by fibrosis and chronic hepatitis
- Patient was later shown to have LKM antibody, thought to be type 2 AIH
- Responded to steroids and azothioprine
- Liver biopsy 15 months later: shows features of thin septa

### Biopsy in acute stage with confluent centrilobular and periportal necrosis



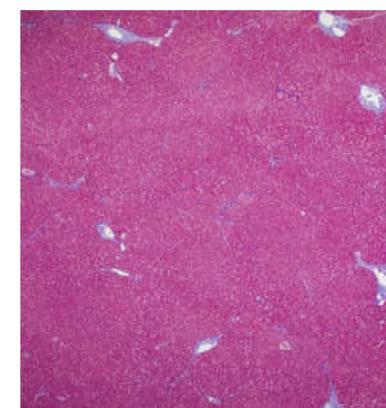
### Followup biopsy 15 months later with minimal inflammation and thin septa



### Case Example of Regression

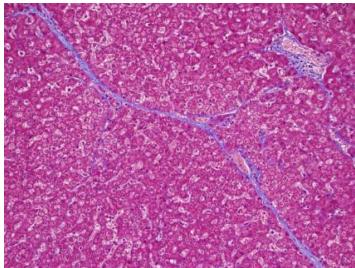
#### 73 year old woman

- History of Hepatitis B cirrhosis by history
- Had received antiviral therapy
  - No evidence of active viral hepatitis

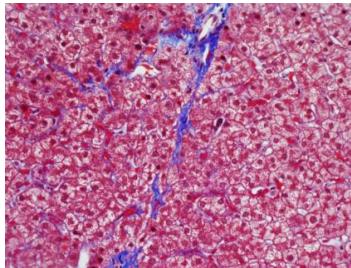


## Example of Regression

Trichrome: Thin septa  
Can be difficult to identify without collagen stain



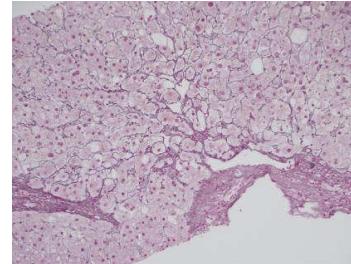
Trichrome: Perforated septa  
Plates lined up irregularly



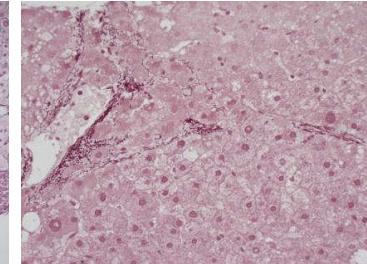
*Should we develop a scoring system for these changes?*

## Example of Regression

Reticulin: irregular architecture includes sinusoidal changes



Orcin for Elastic: remnants of remote dense scarring



Regression occurs if changes are reversible.

**What is not reversible?**

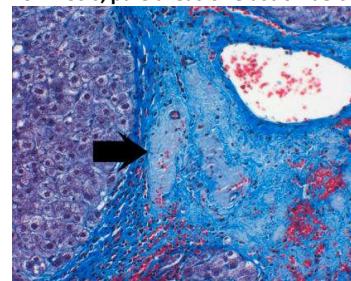
- Extensive scar with elastosis and/or parenchymal extinction is unlikely to regress
  - Elastosis occurs in later stages of scarring
  - Often seen with nondegradable forms of highly-complexed collagen (such as Type III)
  - Nondegradable forms of collagen and elastosis seen in parenchymal extinction
- Extensive vascular remodeling may limit reversibility of liver function regardless of regression of fibrosis

**Irreversible lesions: What is Elastosis?**

Elastosis = extensive deposits of elastic fibers

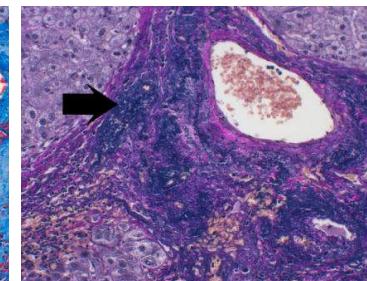
Trichrome Stain:

Cirrhosis, pale areas of elastic fibers



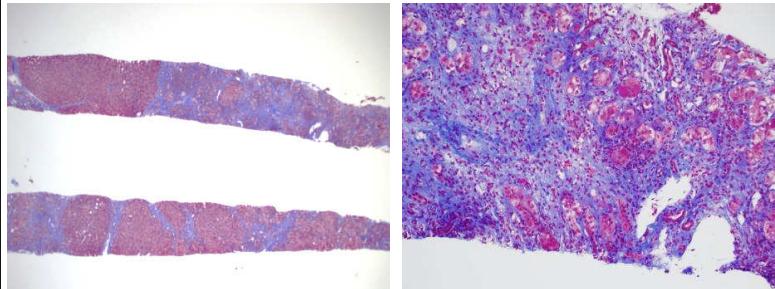
EVG Stain:

Cirrhosis, bundles of elastic fibers



## What is Parenchymal Extinction?

Parenchymal Extinction = Extensive scar

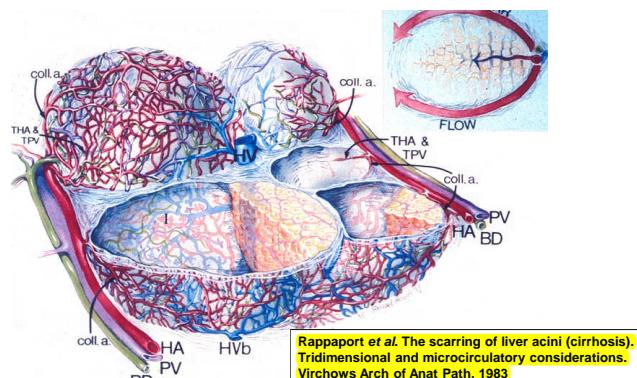


## What is Parenchymal Extinction?

Parenchymal Extinction = Extensive scar

- Dark, dense fibers predominate = highly complexed collagen
- Indicates a late stage in the fibrotic process as in Laennec stage 4c
- Much of the extensive scarring probably related to either venous outflow or arterial inflow alterations and chronic ischemic effects in advanced “end-stage” cirrhosis

## Vascular Alterations in Cirrhosis



Vascular collaterals/modifications develop in fibrosis and cirrhosis.

Fibrosis leads to intraparenchymal vascular resistance

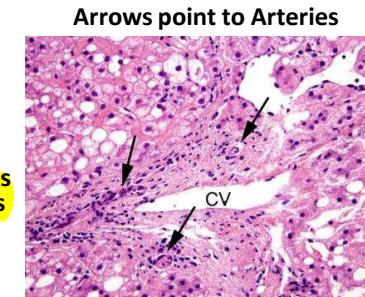
Micro- and Macrocirculatory changes occur in conjunction with alterations in hepatic flow dynamics

## Microcirculatory Remodeling

Example: Arterialization of Centrilobular Scars

Gill R...Ferrell L: AJSP, 35, 1400-04, 2011.

- Increased arteries and microvessels in centrilobular scars
- Increased CD34 staining of sinusoidal endothelial cells as effect of loss of fenestrations (“capillarization”)
- Occurs prior to cirrhosis, but most prevalent in fibrosis score 4-6 by ISHAK

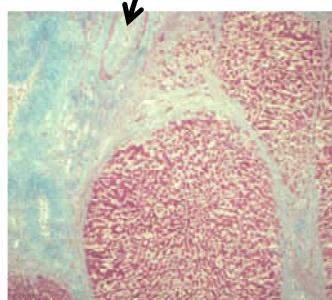


## Vascular Alterations in Cirrhosis

### Vascular thrombosis secondary to cirrhosis

- Commonly seen in decompensated cirrhosis
- *Organized, obliterative lesions likely not reversible!*

Obliteration of portal vein



## Conclusions:

- Fibrosis score requires an adequate biopsy
- Current 0-4 systems of fibrosis scoring good for chronic viral hepatitis and fatty liver when used for single etiology
- Recognize limitations of current scoring systems for mixed lesions and advanced stage of cirrhosis
- Correlate biopsy scores with clinical findings

### Questions:

- *Should we consider findings of advanced cirrhosis? (parenchymal extinction, elastosis)*
- *Should we consider identification of remodeling, or regression changes?*

The real  
Tom Sawyer  
was from  
San  
Francisco

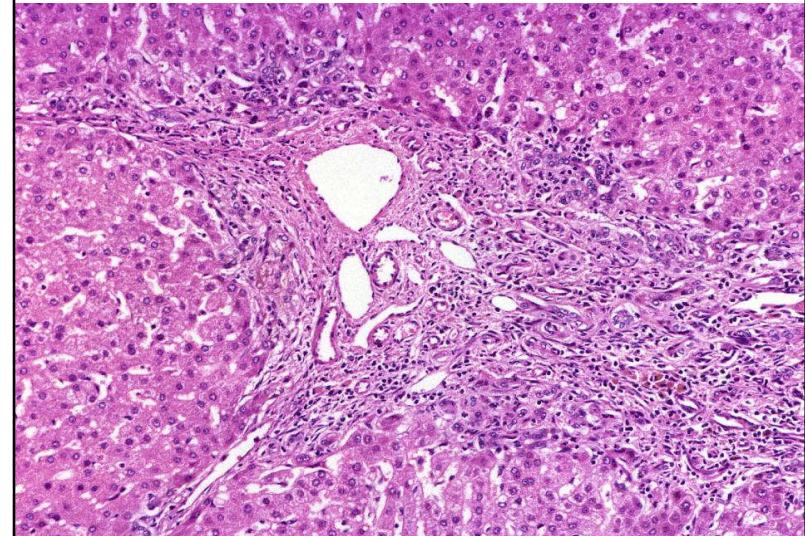
*Reference:  
Smithsonian  
Magazine, Oct  
2012, pg 51-7.*



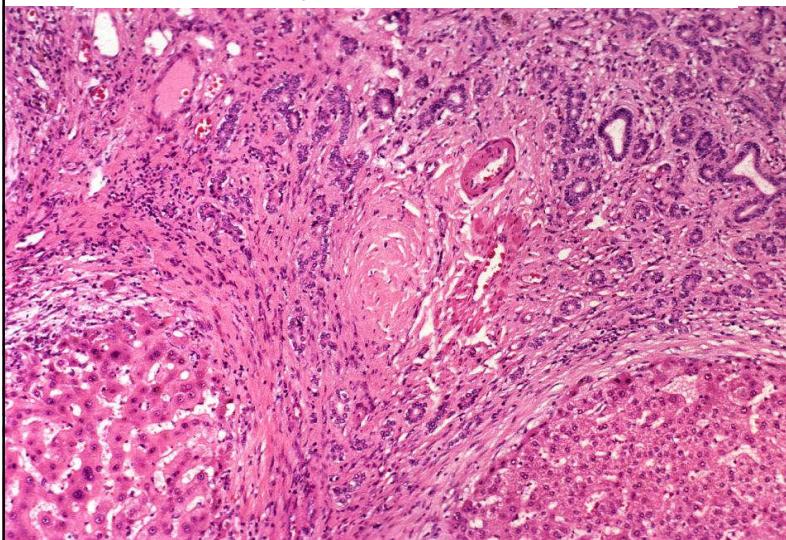
## Other complications

- Ductopenia
  - PBC
  - PSC

PBC: Portal area with interface hepatitis and ductopenia



PSC: Hyaline scar at duct site



PSC: Sclerosis of large duct in hilum resulting in a large circular scar at the site of the former bile duct

