Viral Hepatitis Biopsy Assessment in the Treatment Era:

The Beijing Classification

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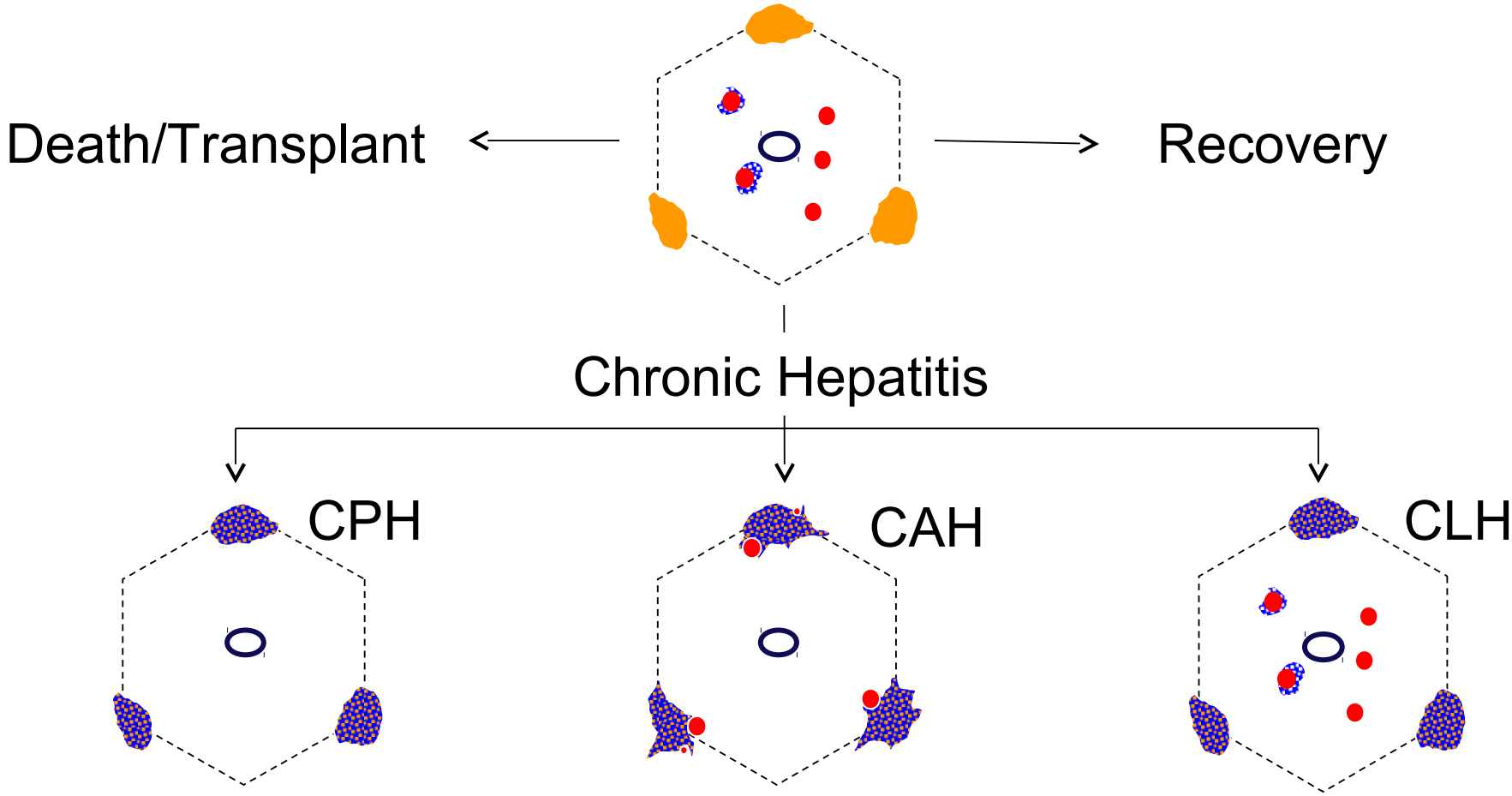
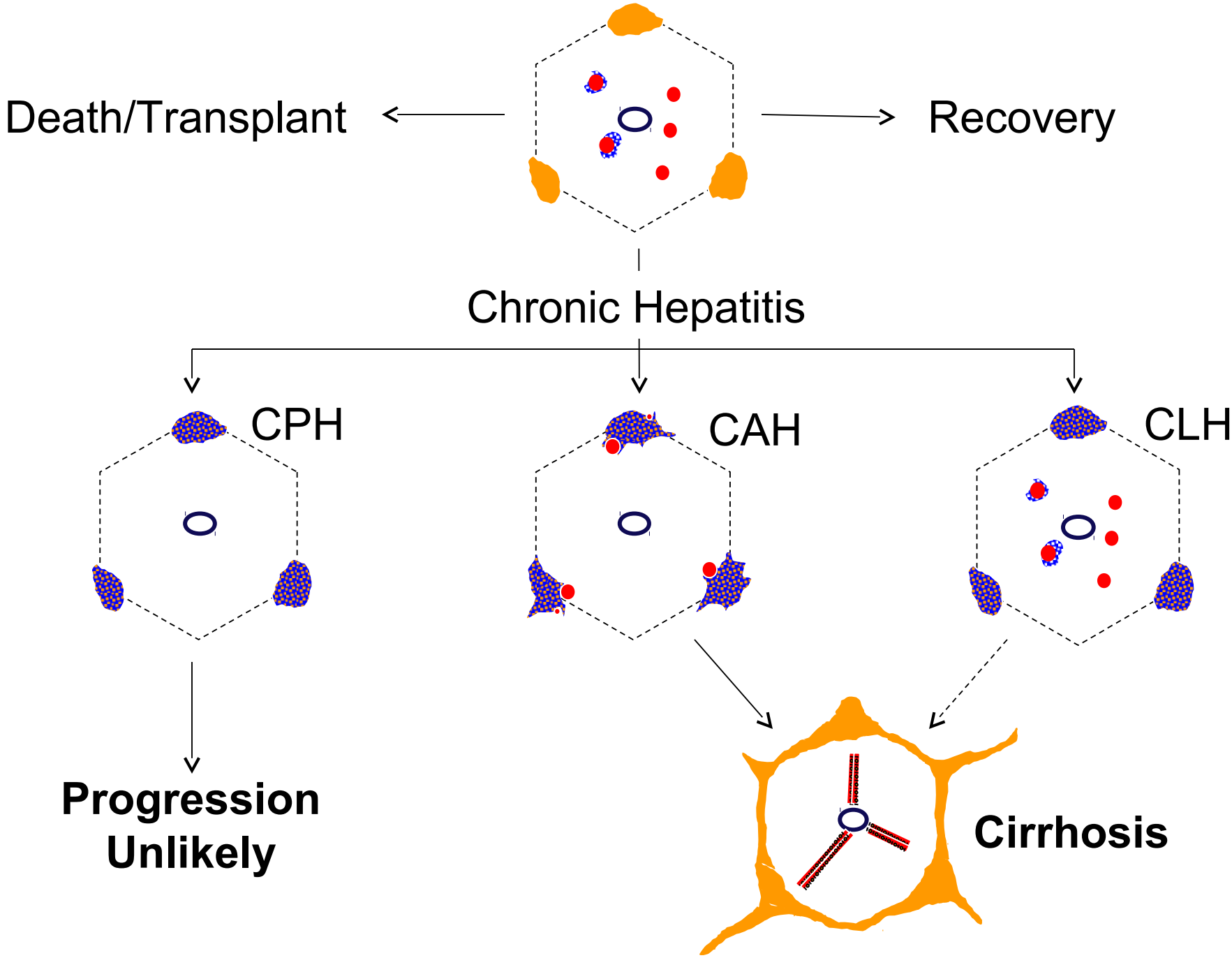
Department of Pathology
New York University School of Medicine
New York City

Clinical problems, 1968:

- Hepatitis B
- Autoimmune hepatitis

=> Biopsy for assessment of prognosis: CAH


Death/Transplant
Recovery
Chronic Hepatitis
CPH
CAH
CLH


Death/Transplant
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CPH
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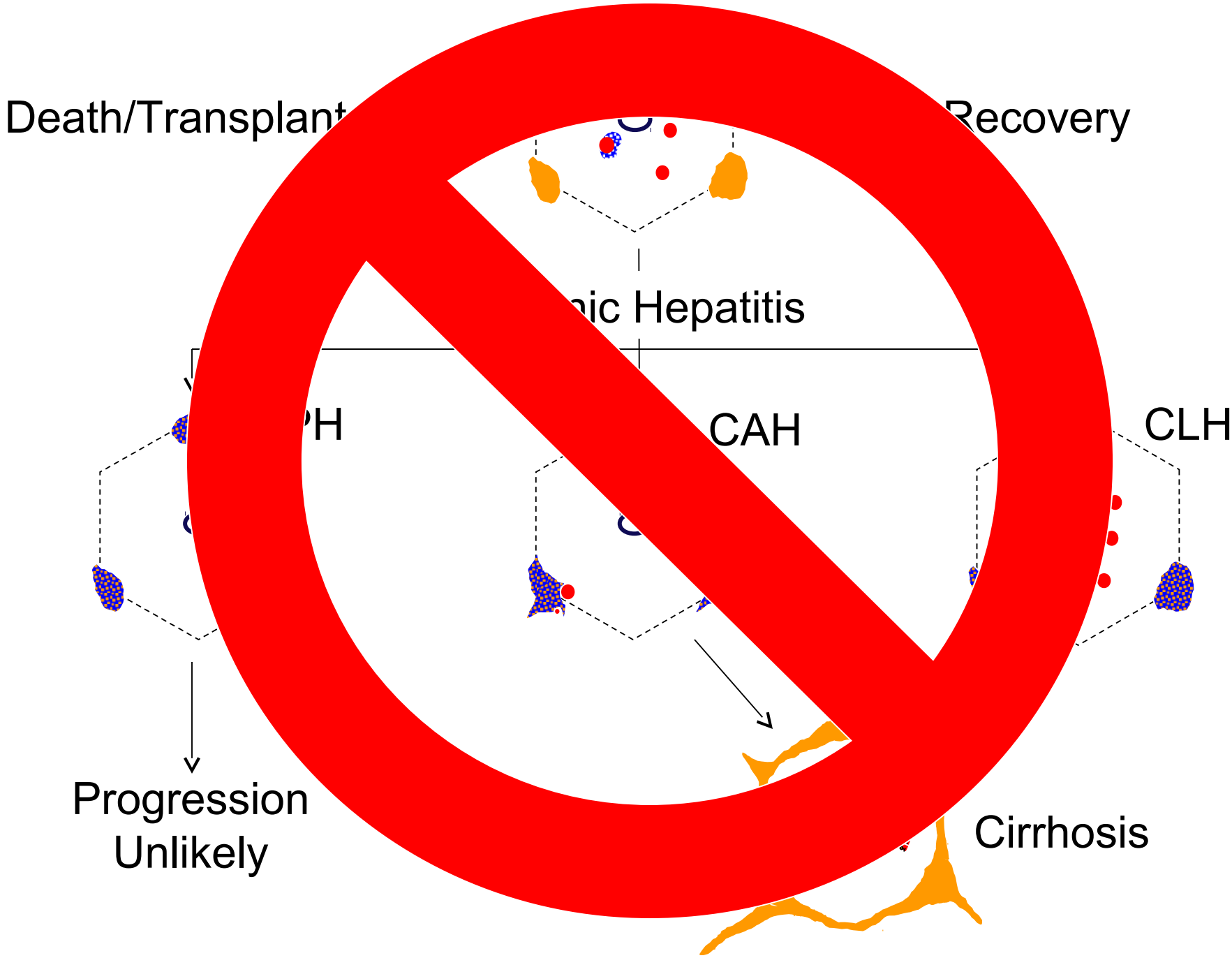
Progression Unlikely
Cirrhosis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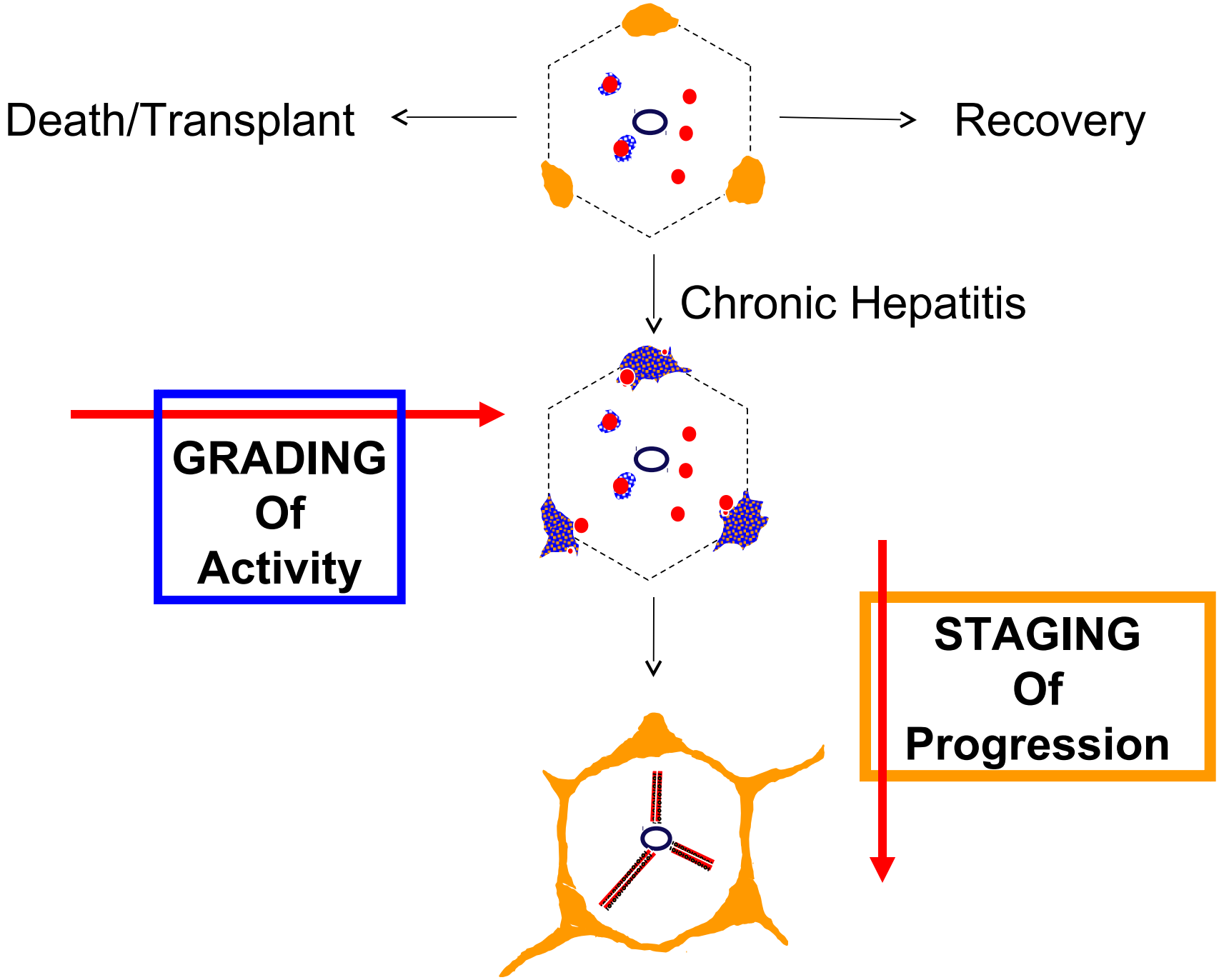
=> Biopsy for assessment of Tx needs:
Ishak, modified Ishak, Batts-Ludwig, Metavir


Death/Transplant
Recovery
Chronic Hepatitis
GRADING
Of
Activity
STAGING
Of
Progression

Stages of Fibrosis

Modified Ishak ⇔ Batts-Ludwig

Ishak

1 2 3 4

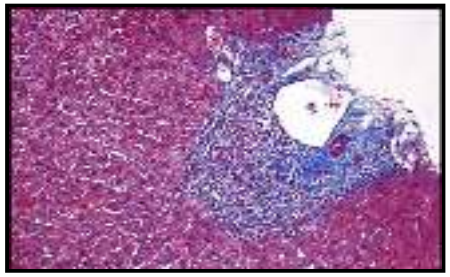
1 2 3 4 5 6

focal *frequent* *focal* *frequent*

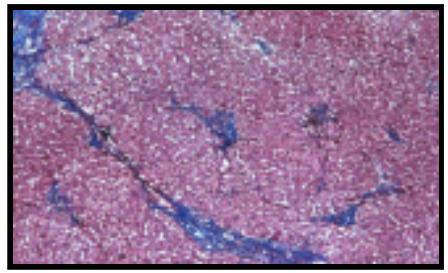
Metavir

1 2 3 4

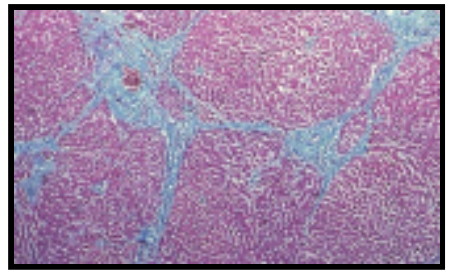
focal *frequent*



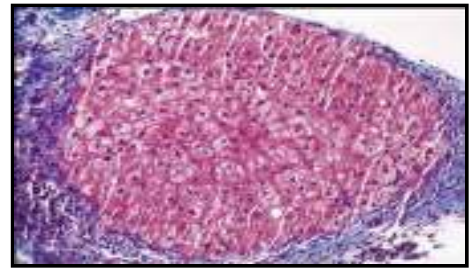
Portal Fibosis



Fibrous Septa



Transition to Cirrhosis



Cirrhosis

Theise ND. Human Pathology 2007

Sta is

Modified Ishak ⇔ Batts-Lud

1 2 3 4

Ishak

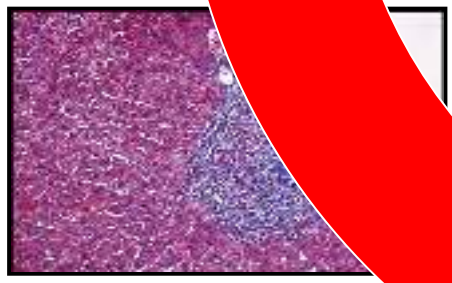
1 3 5 6

focal *ent* *focal* *nt*

Metavir

2 3 4

focal *frequent*



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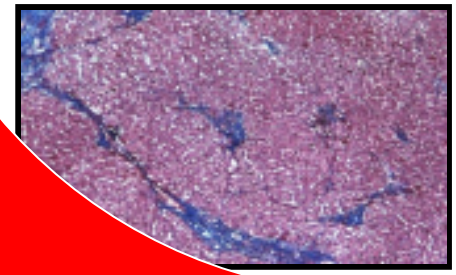

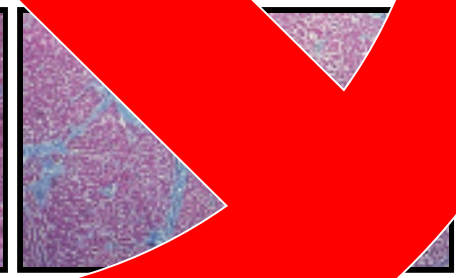

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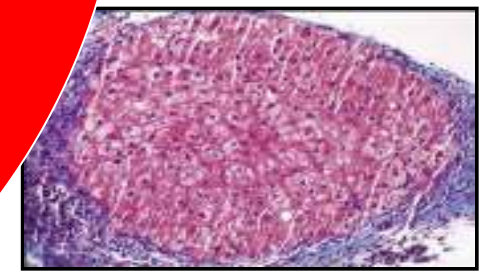

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Clinical problems, 2016:

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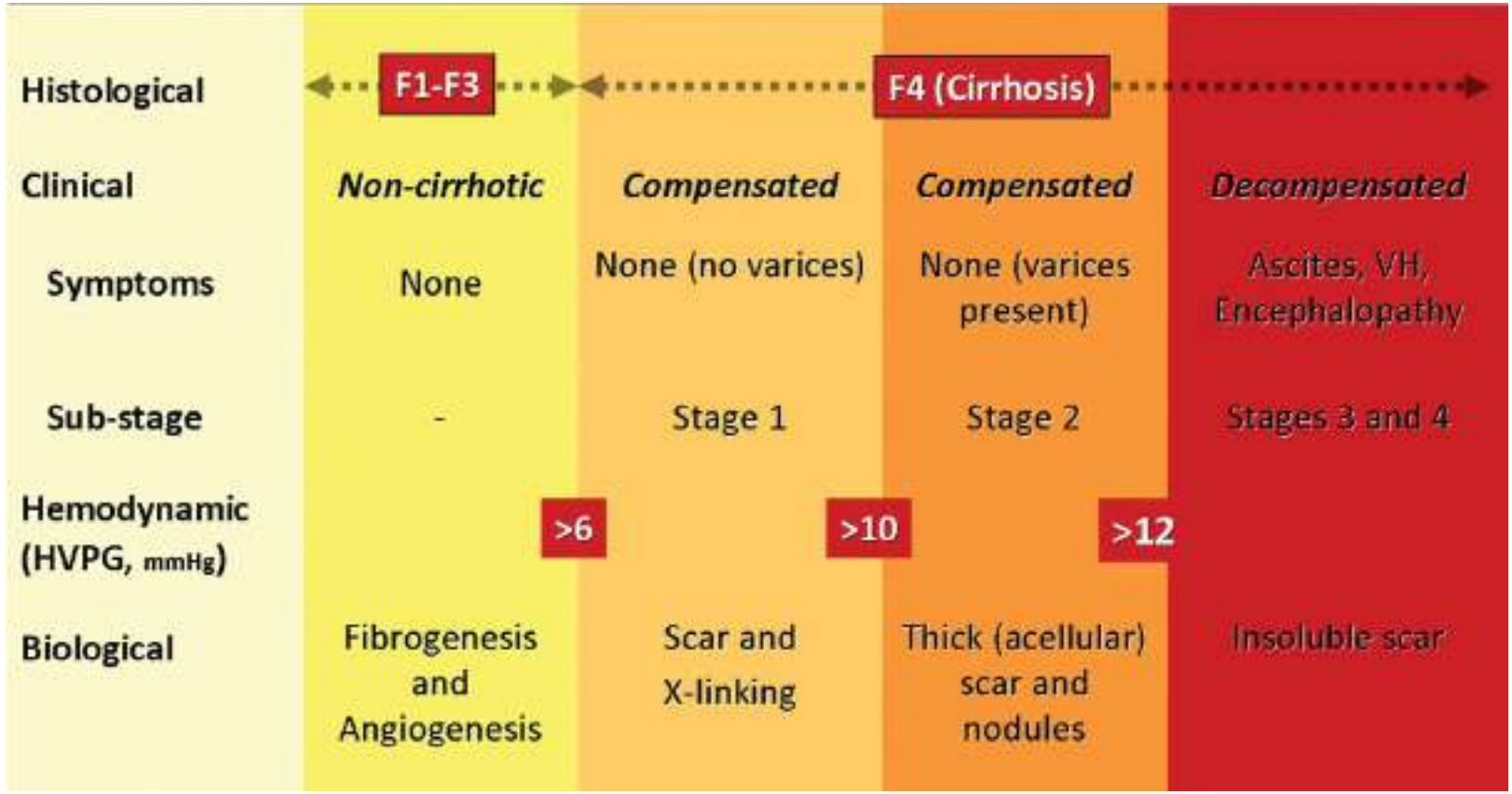
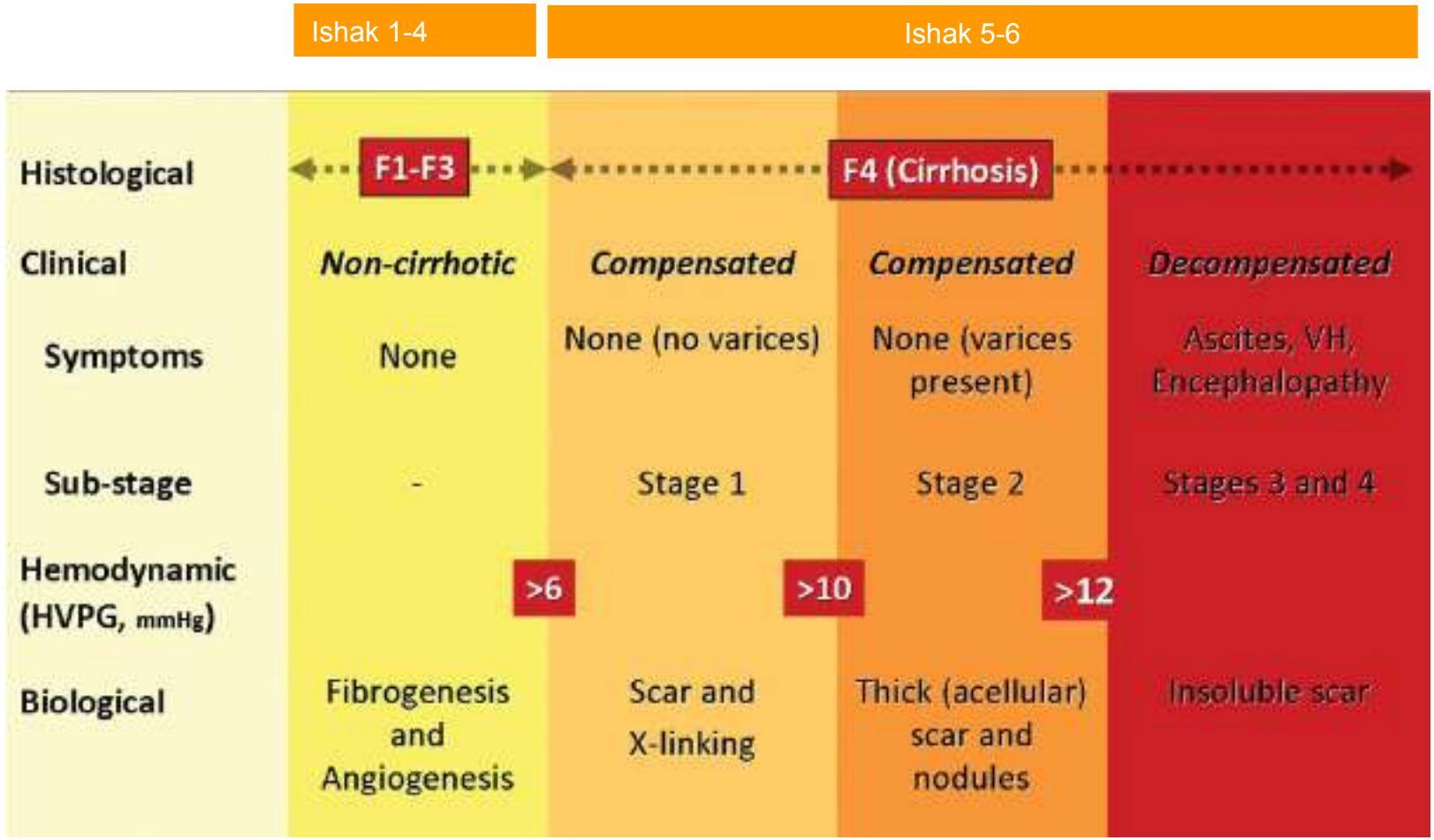
=> Biopsy of advanced (cirrhotic) stage liver
for assessment of prognosis

…but not all cirrhosis is the same…



Garcia-Tsao, Friedman, Iredale and Pinzani.
Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis.
Hepatology 2010: 51(4):1445-49



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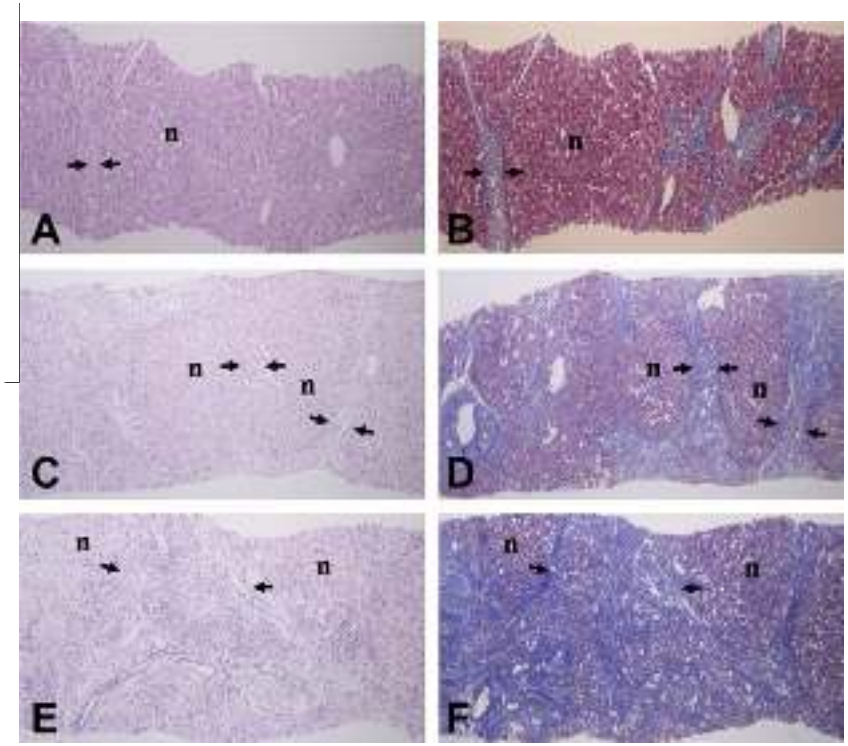
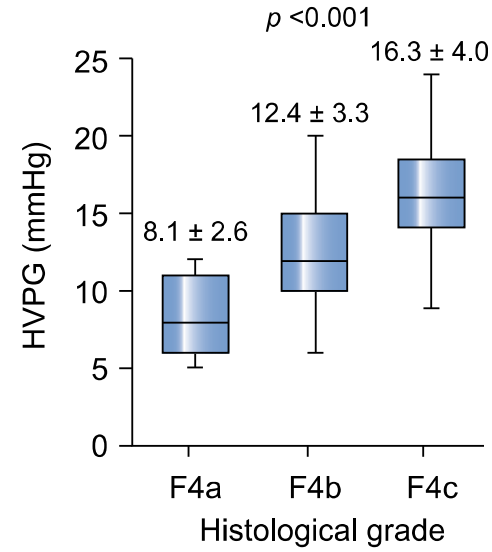
The Laennec Staging System





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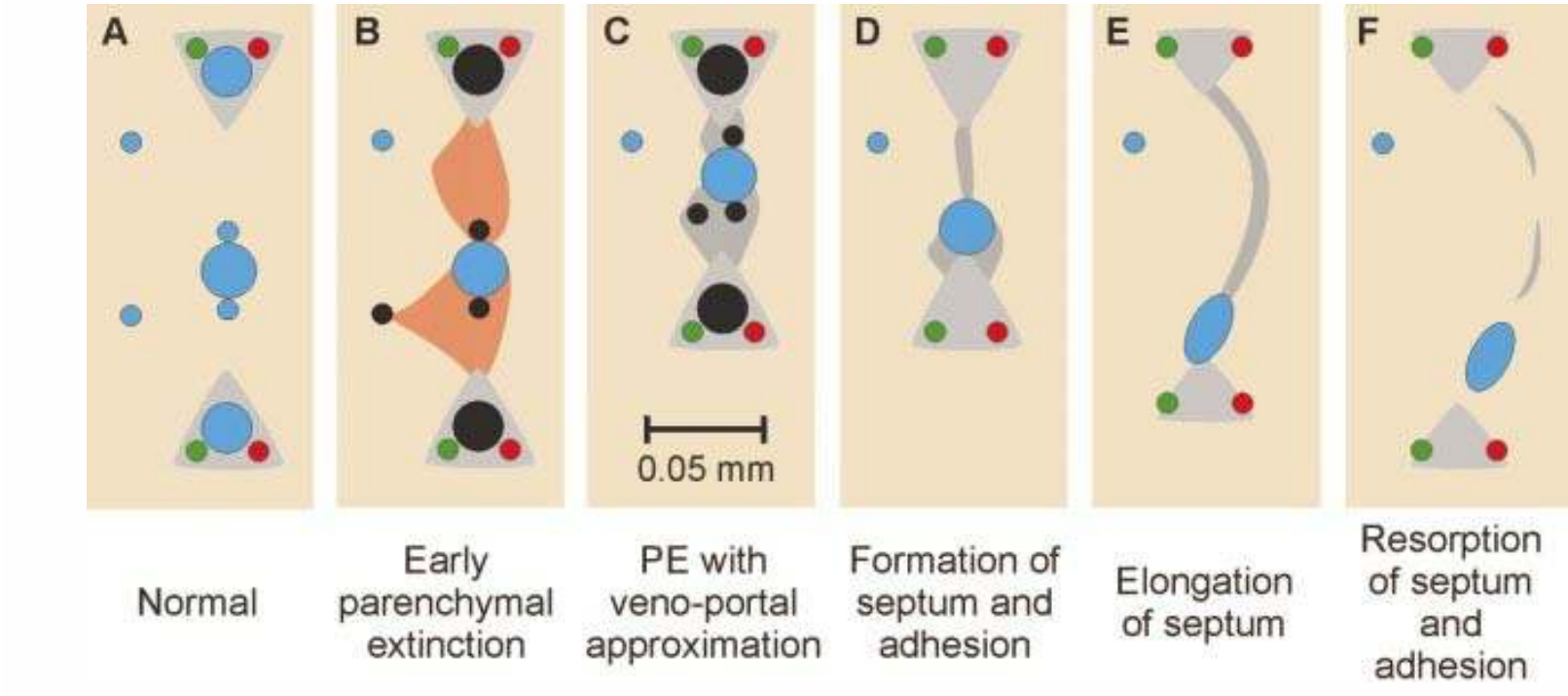
What about *regression* of cirrhosis?



Wanless, Nakashima and Sherman.
Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis.
Arch Pathol Lab Med 2000;124:1599

Hepatic Repair Complex

1. Fragmentation and regression of scar

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B. isolated thick collagen fibers
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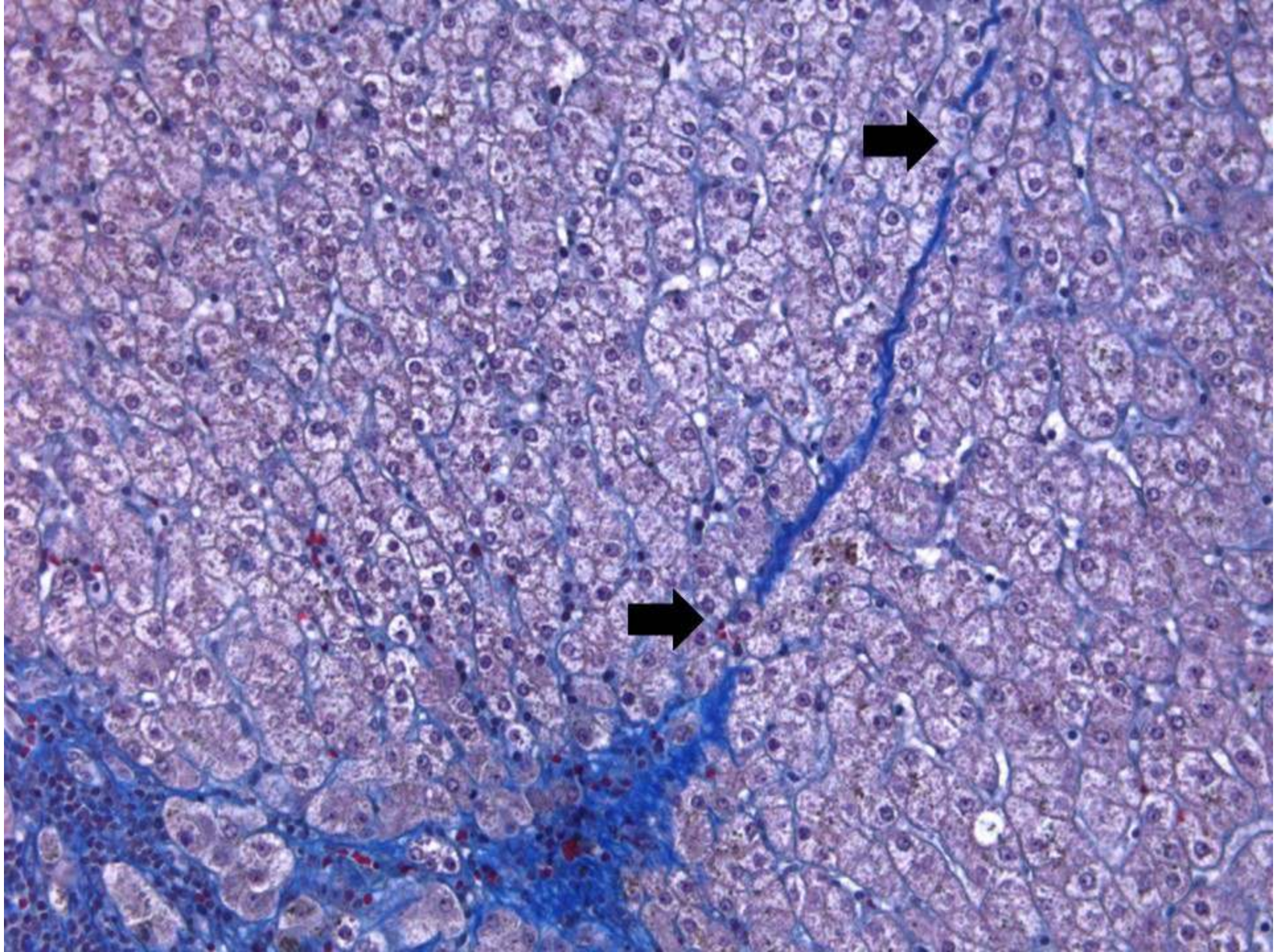

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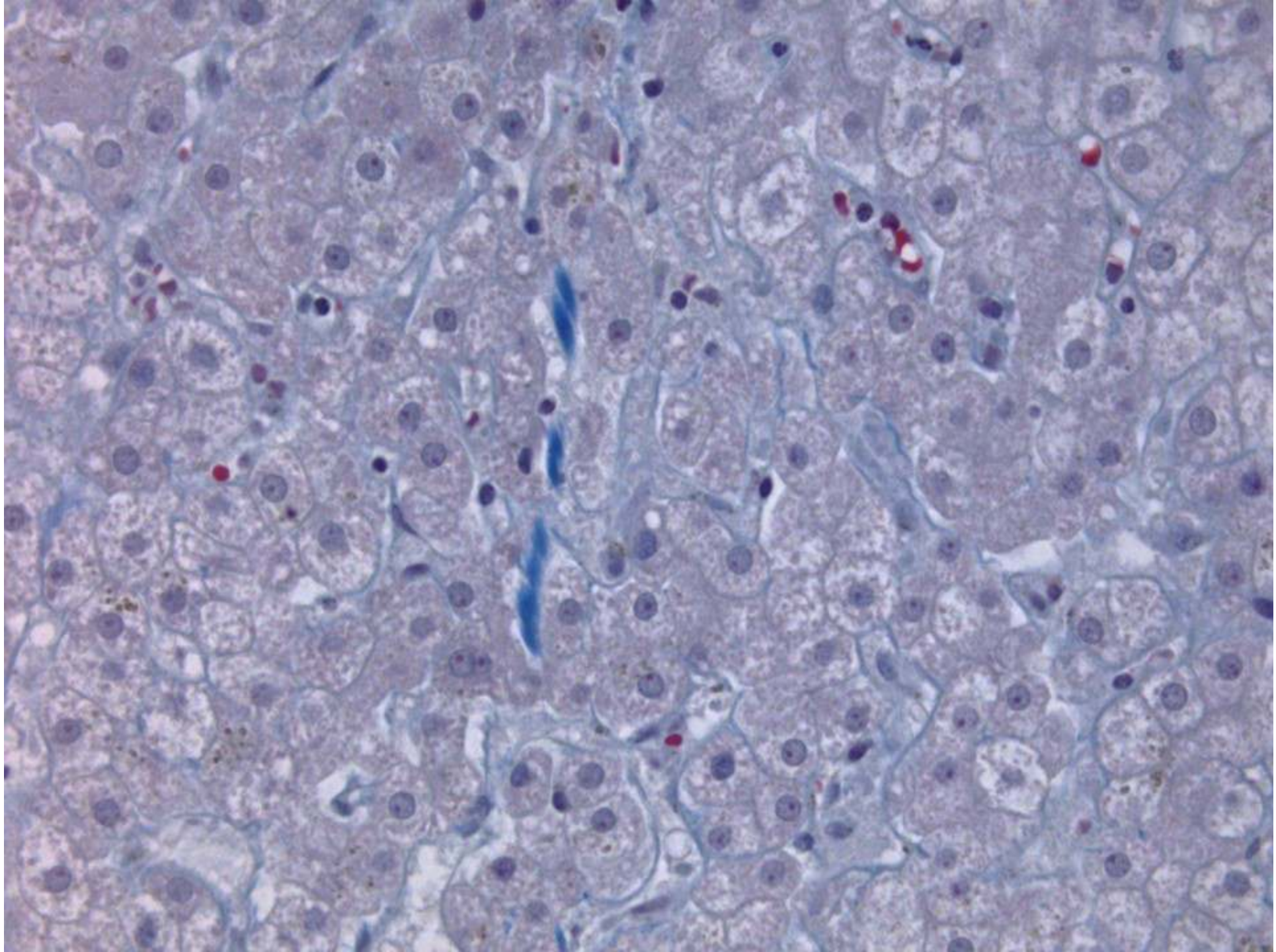

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A. portal tract remnants
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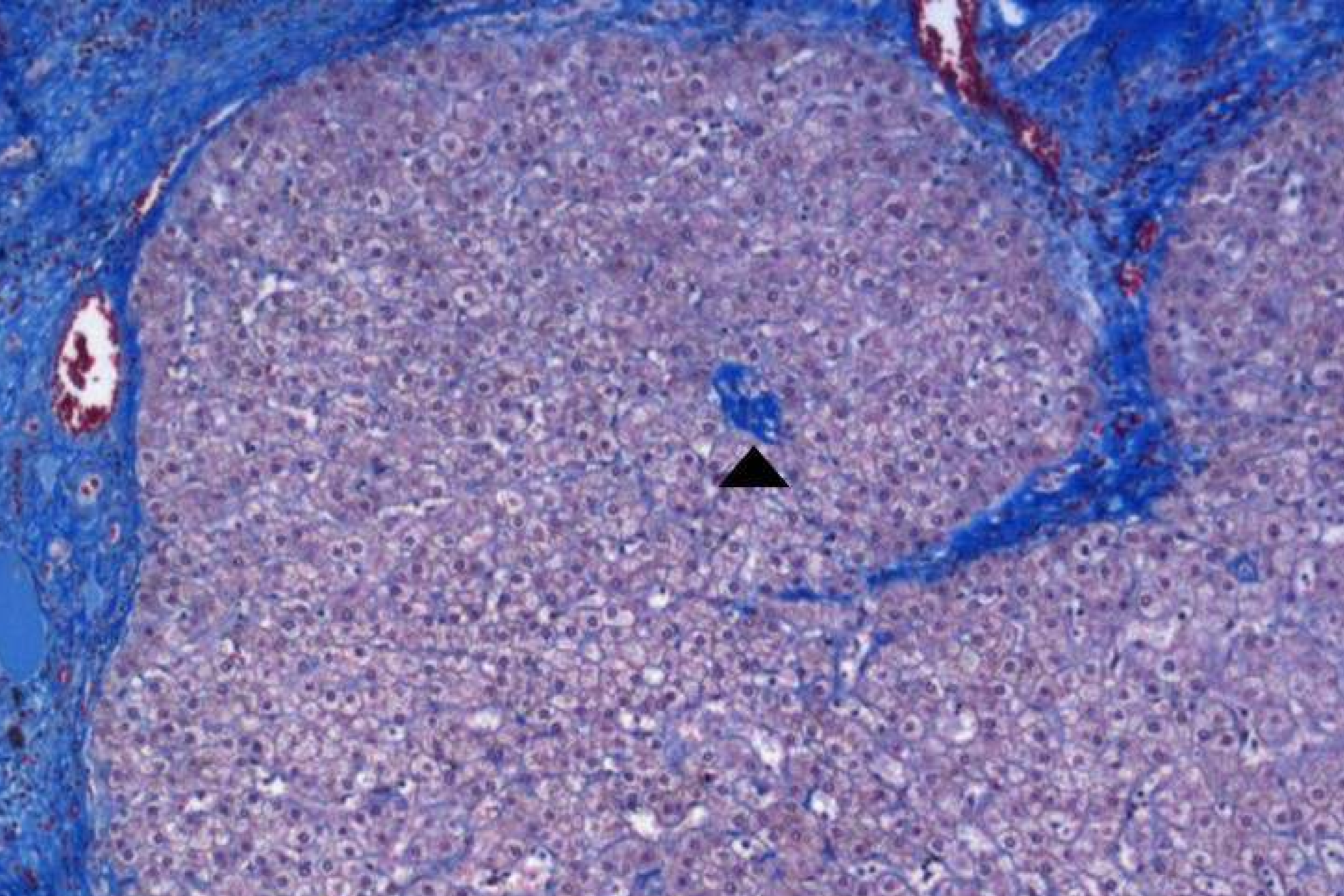

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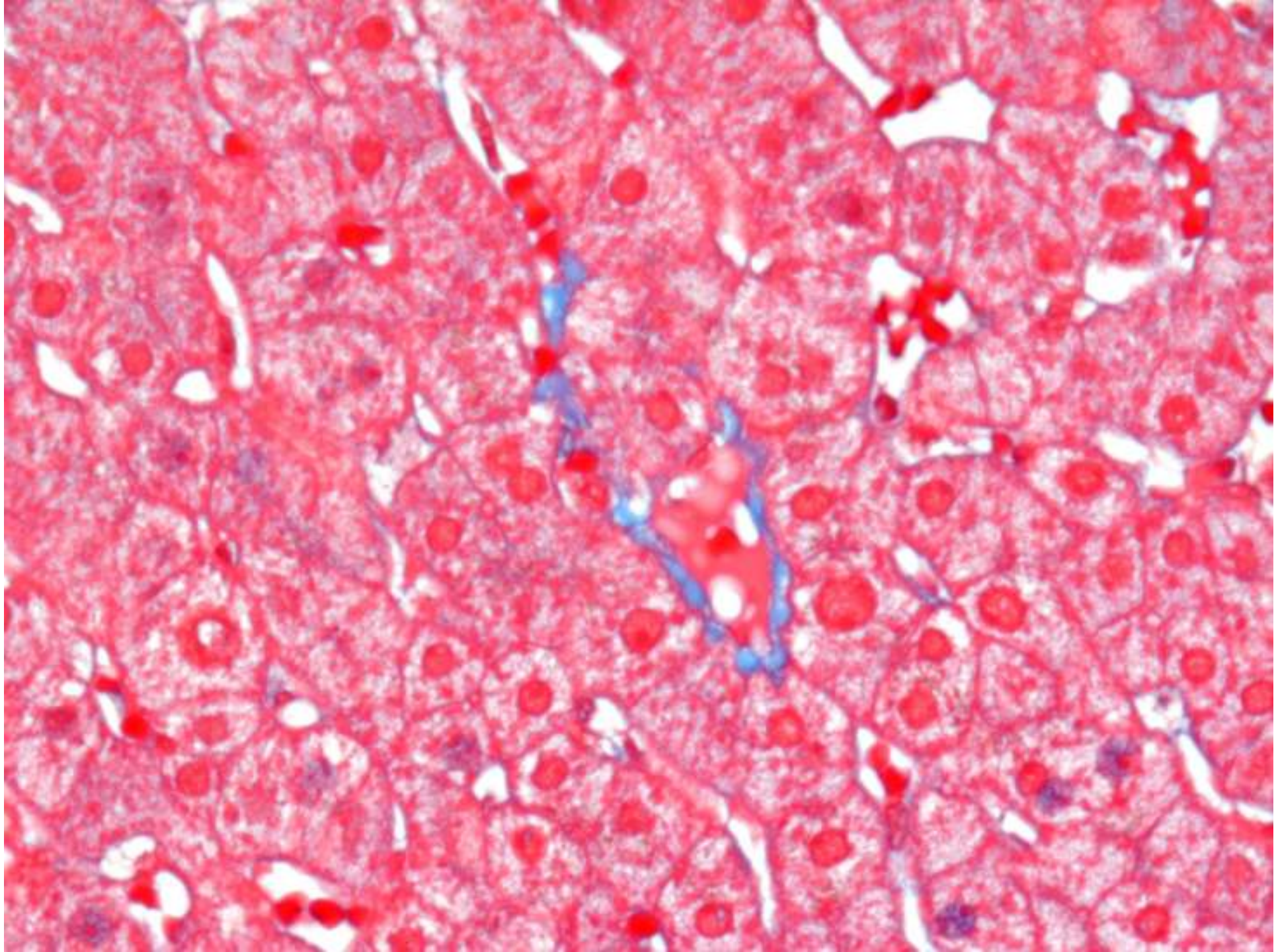

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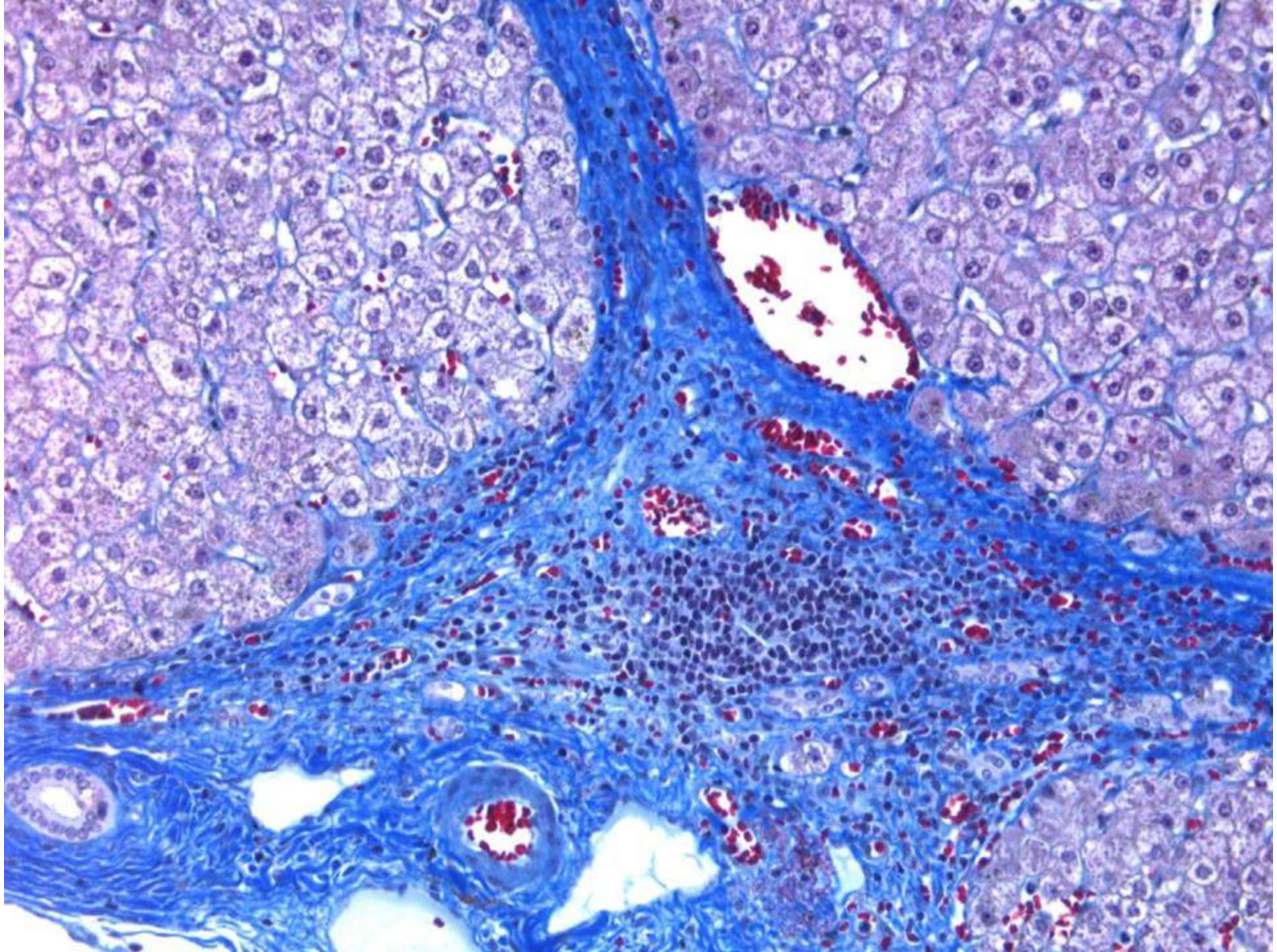

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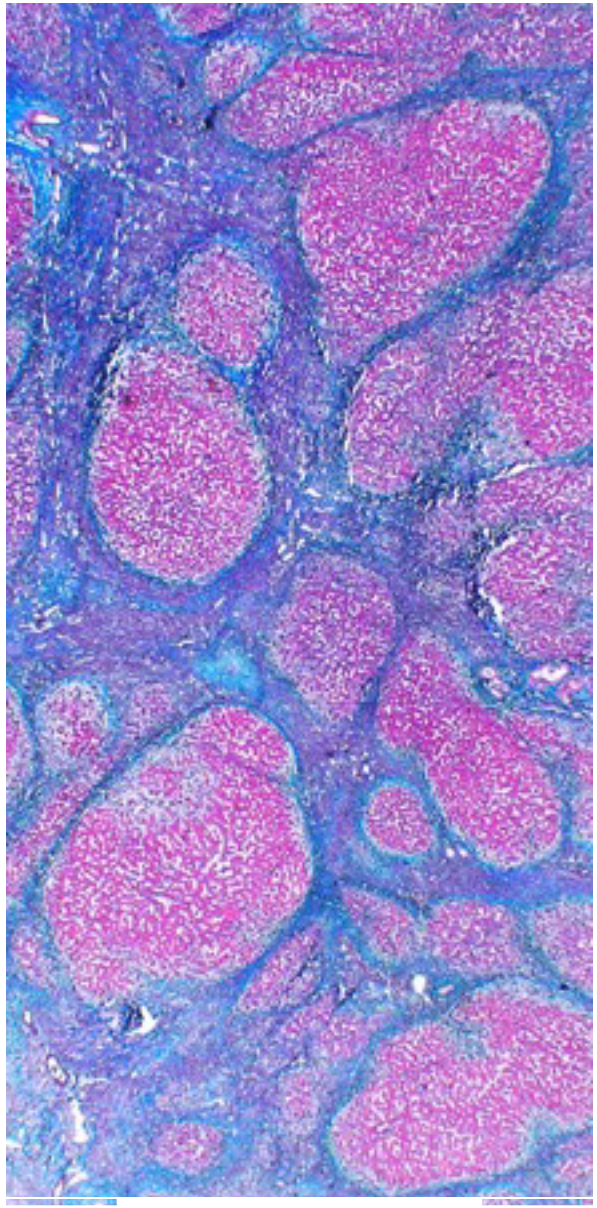
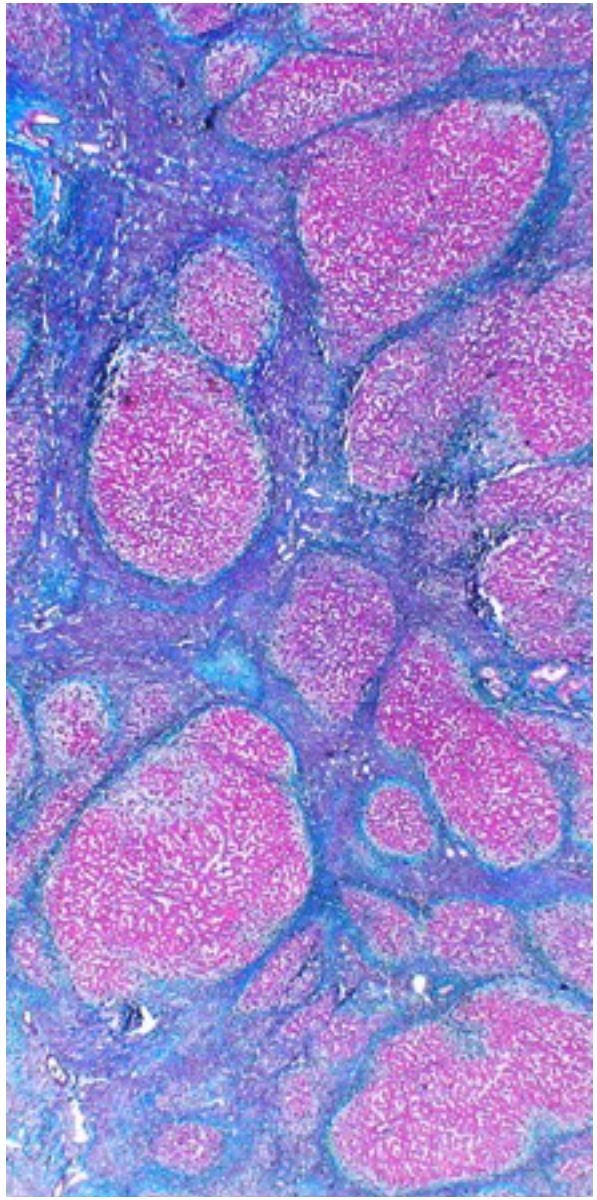
3. Parenchymal regeneration, i.e. “hepatocyte buds”



Active
Alcohol Use



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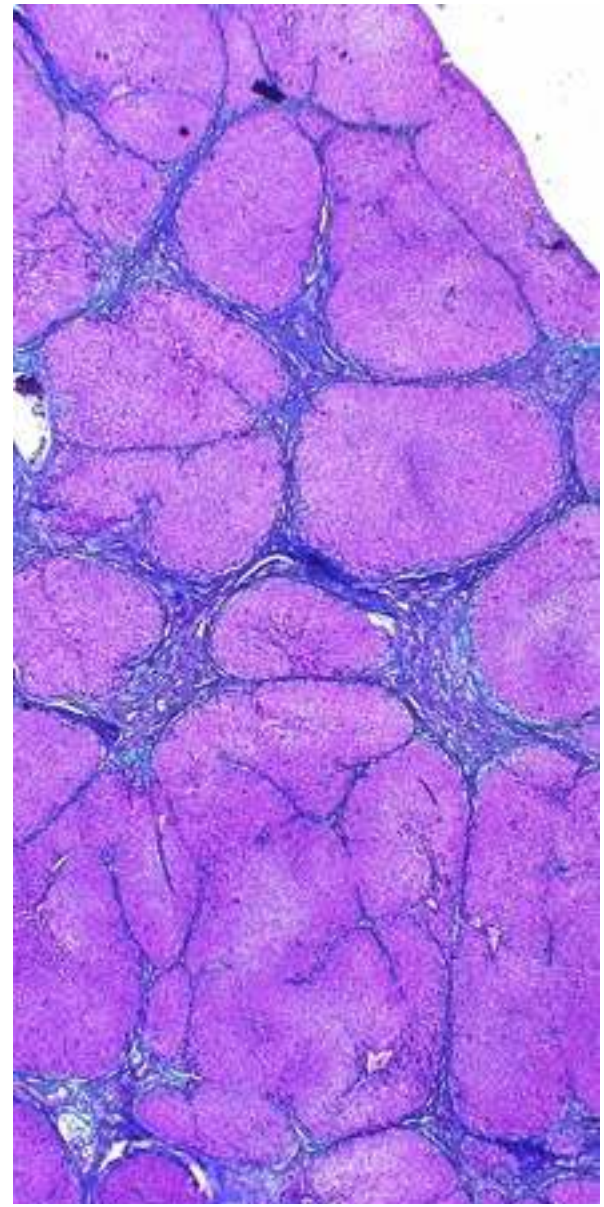
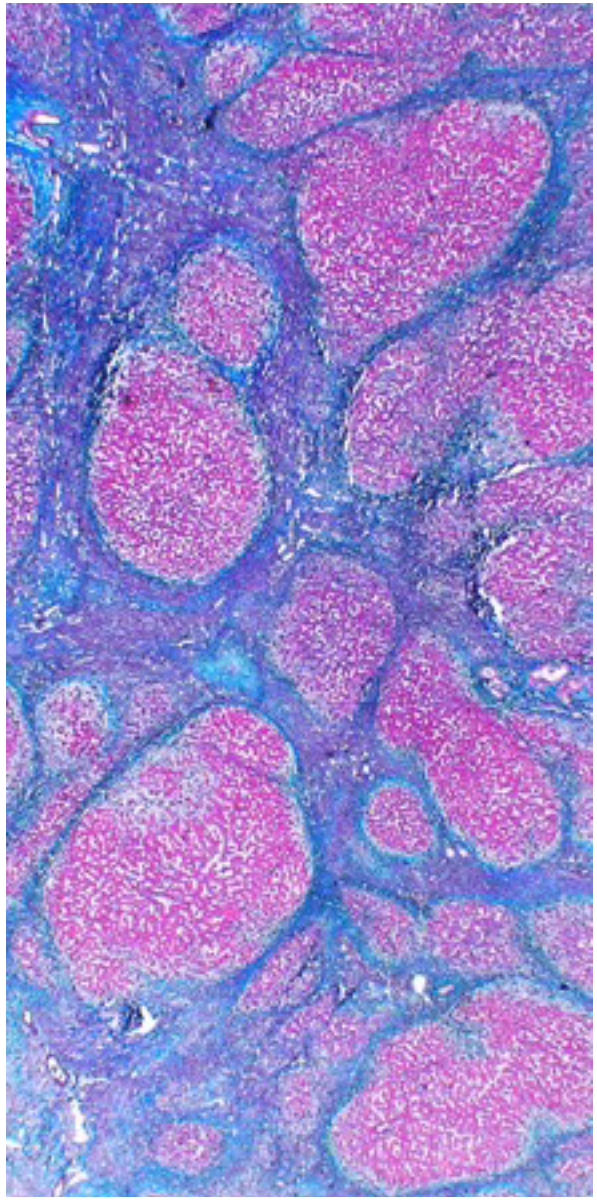


> 6 months abstinence



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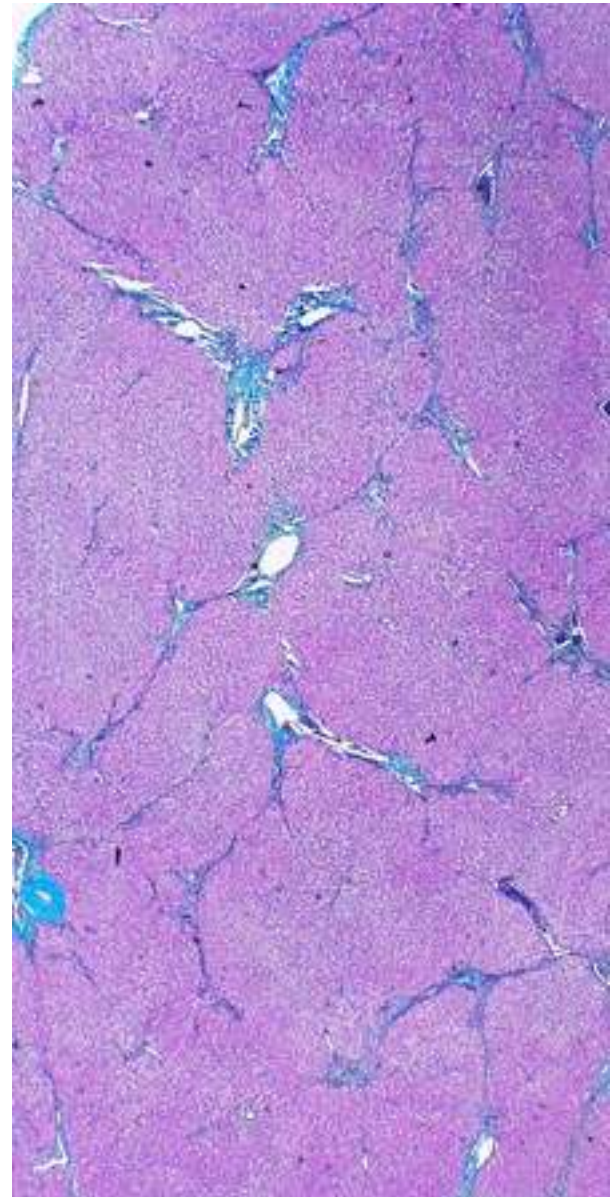
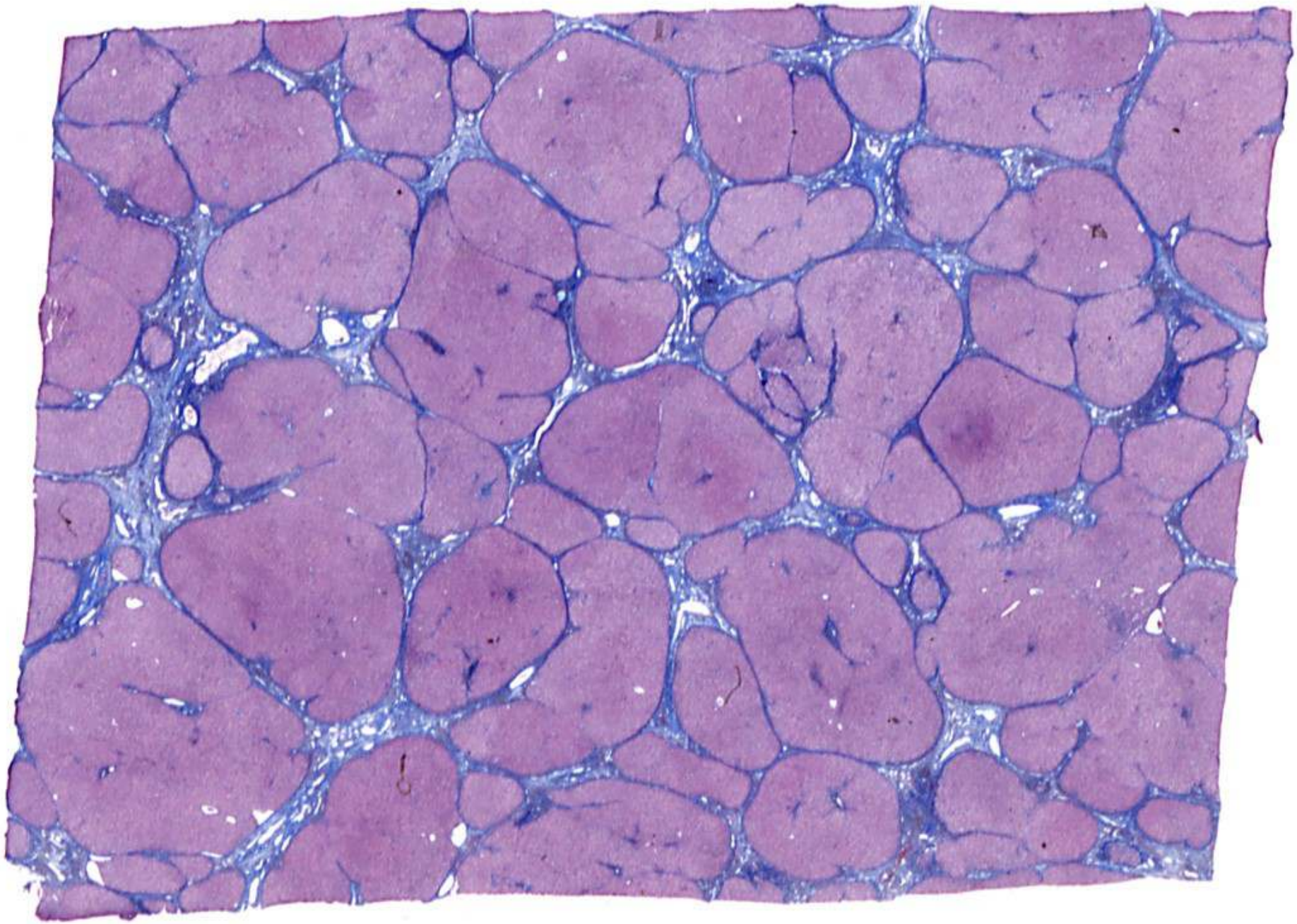
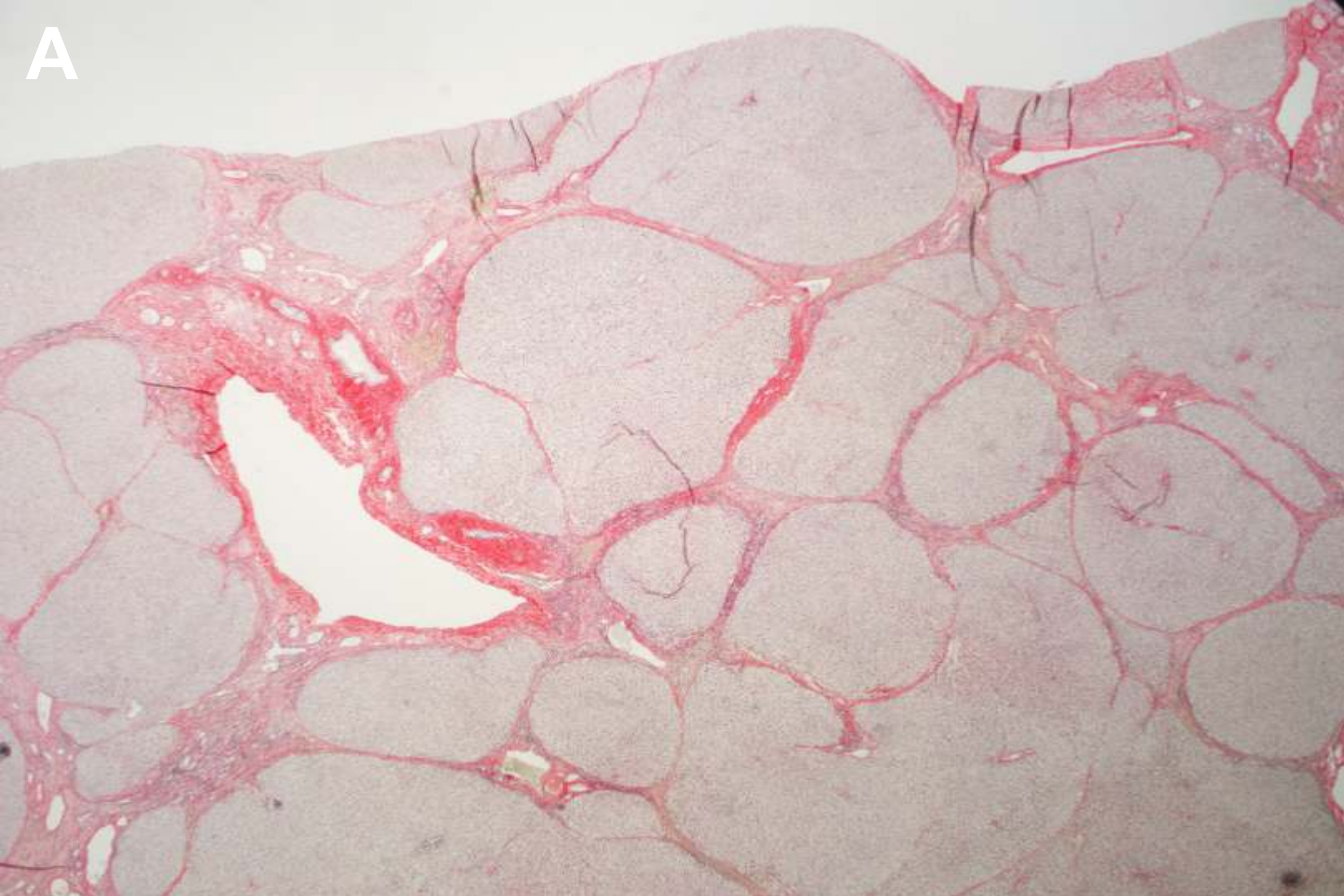
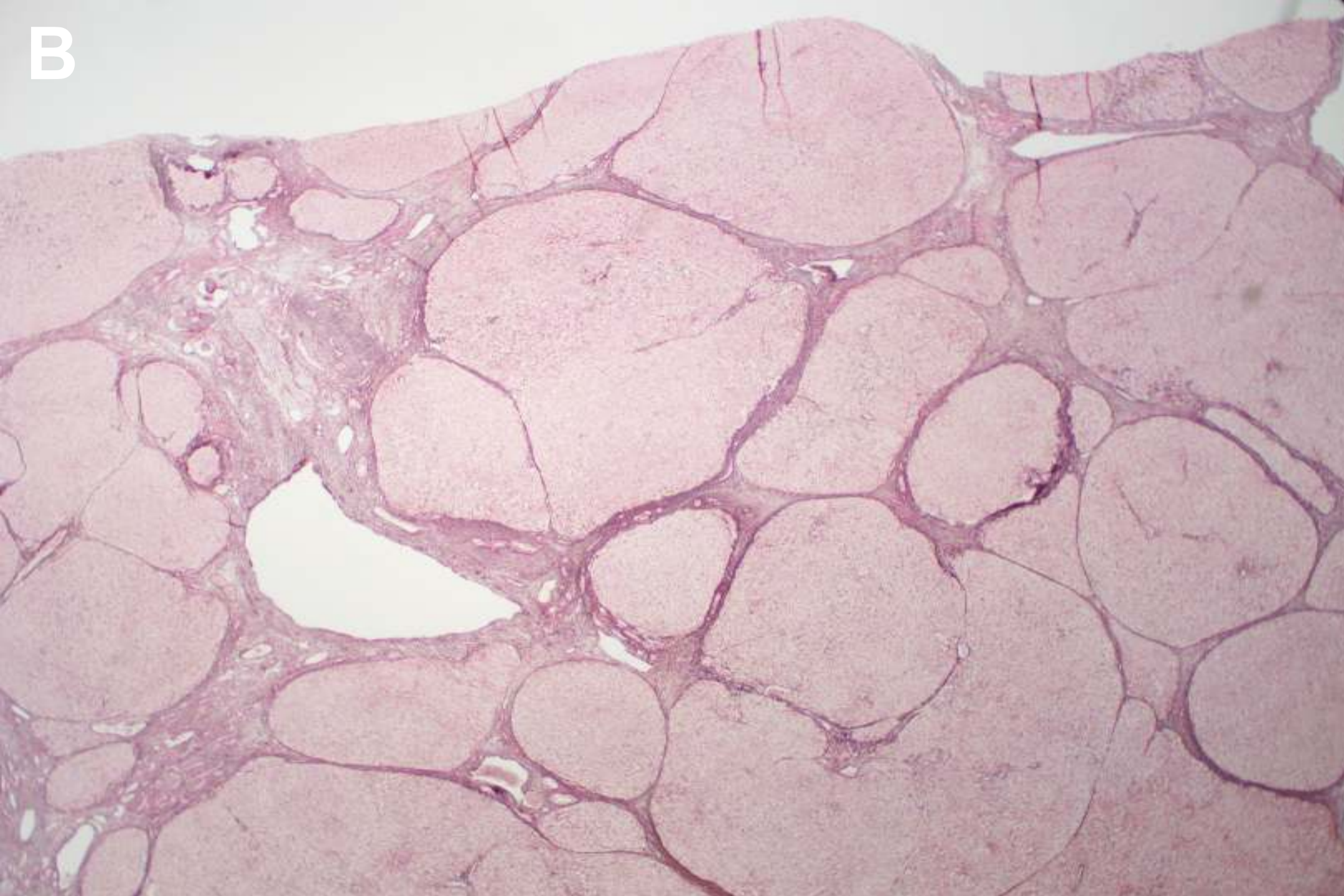
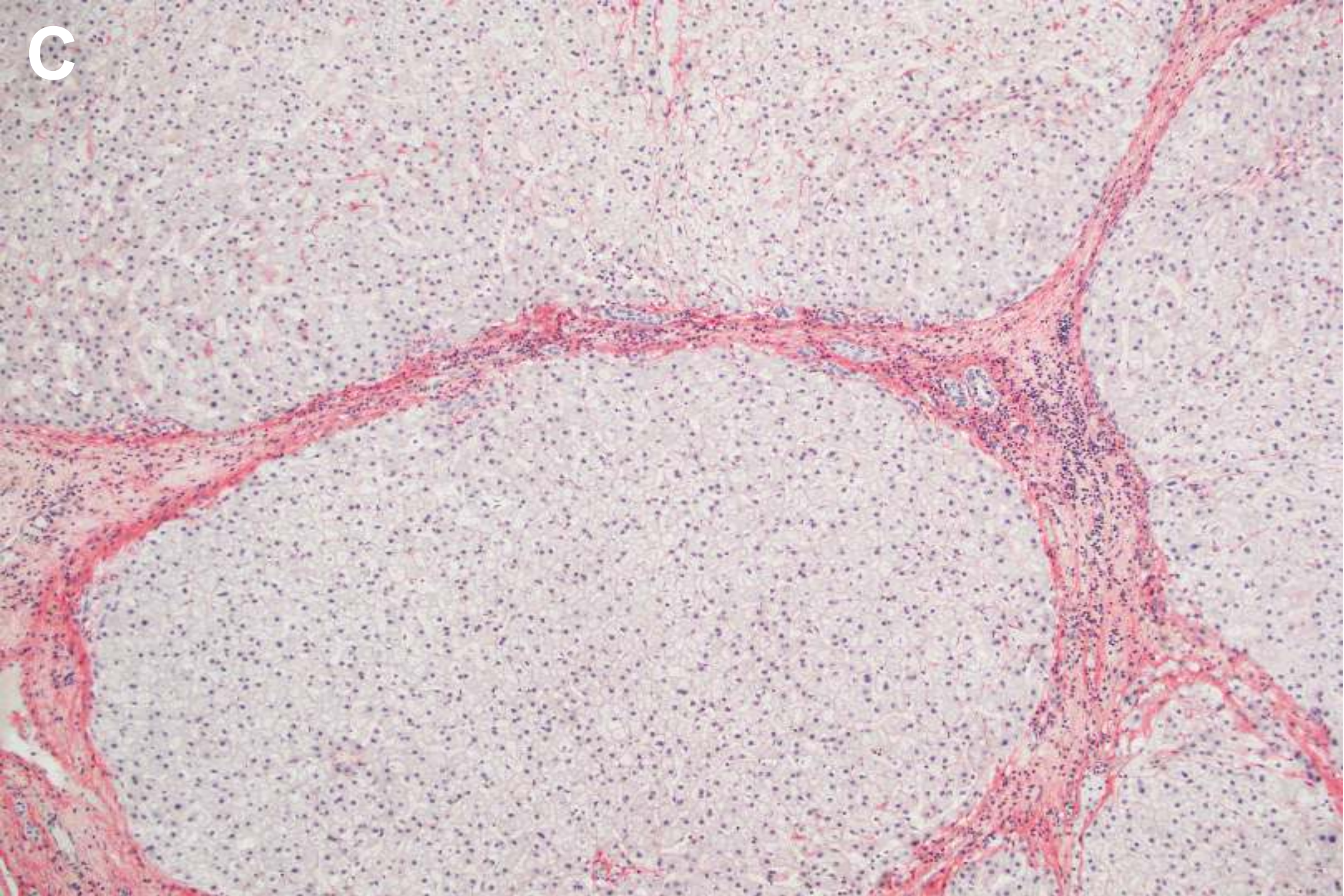


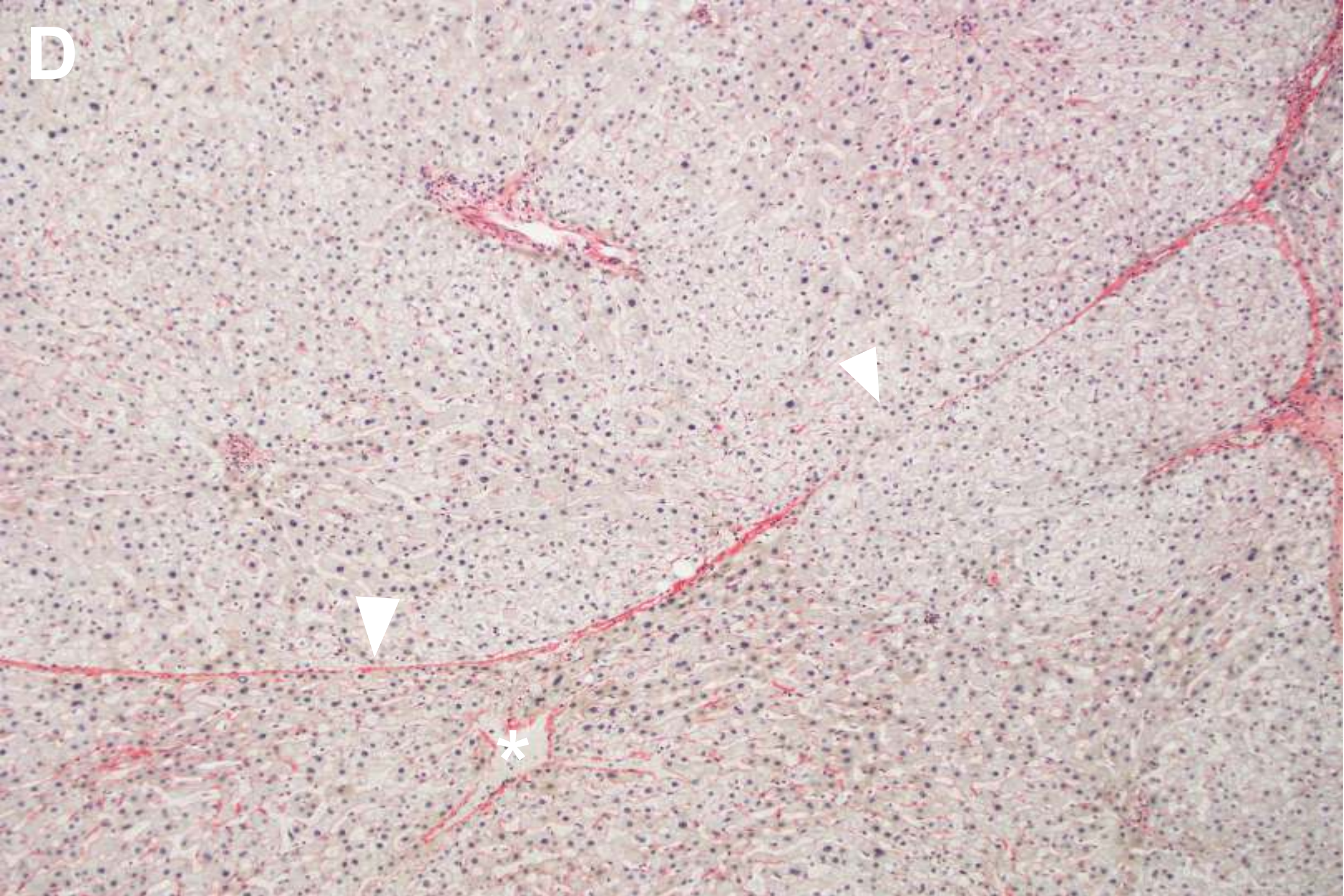
4 years abstinence




A


B


C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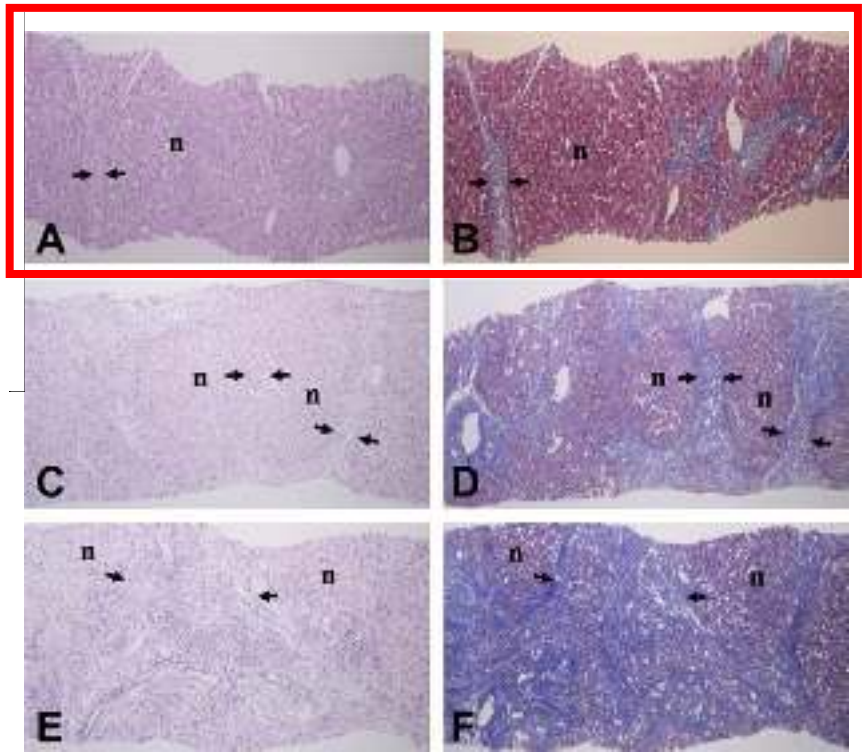

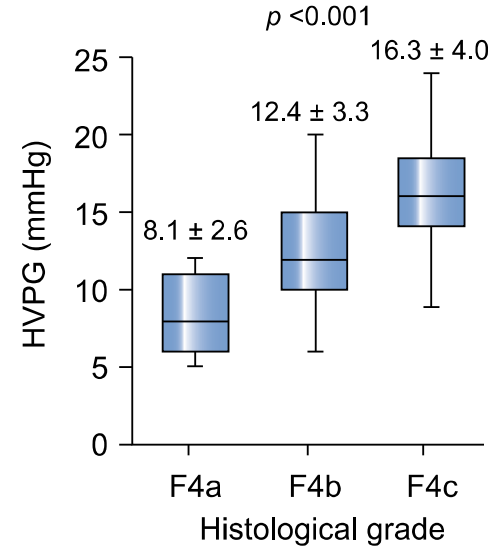

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- The new system must be *prognostic*, predicting who will resolve back to a normal liver after successful curative treatment or long term disease suppression.


民共和国万岁
世界人民大团结万岁

HEPATOLOGY

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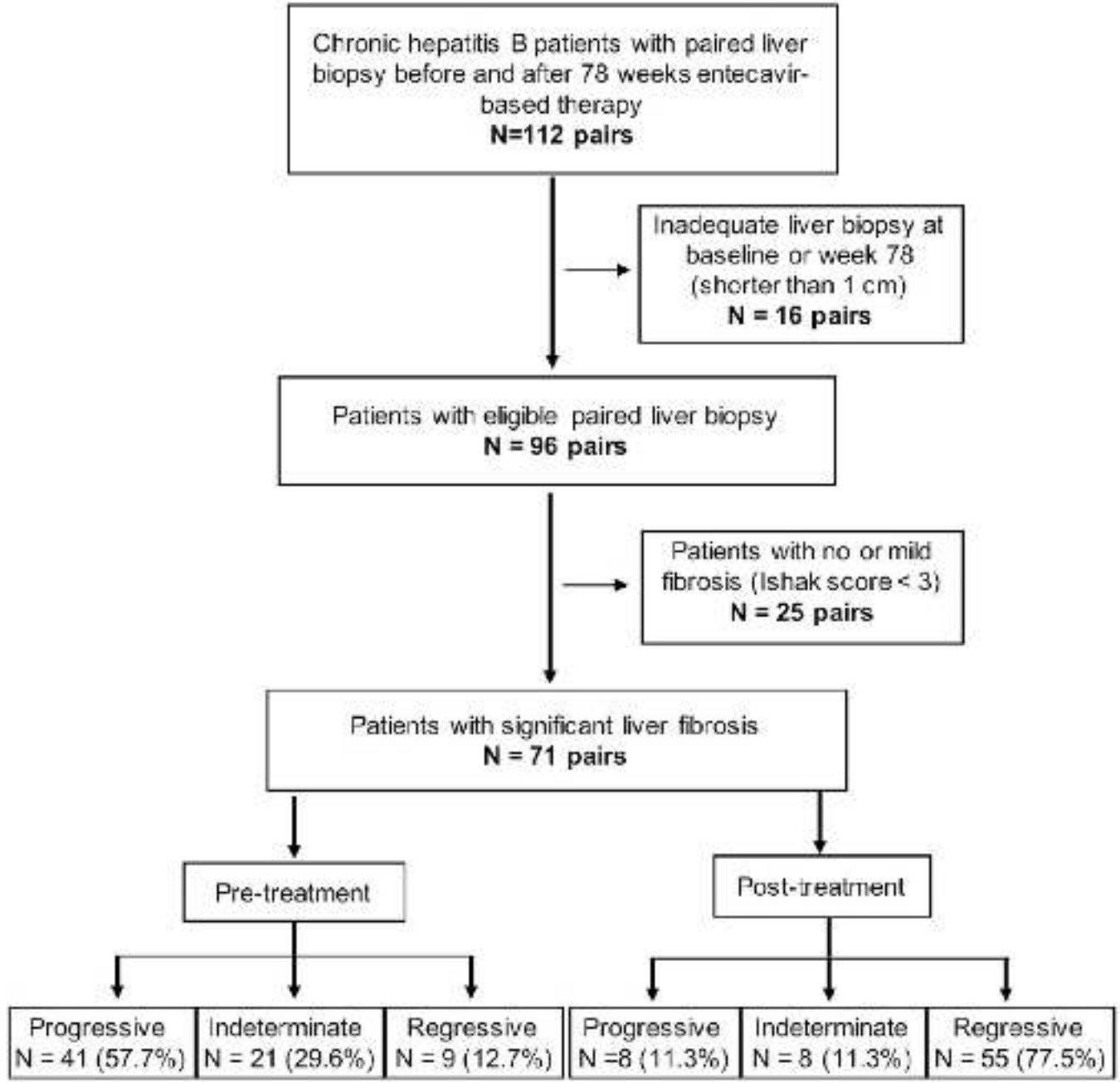
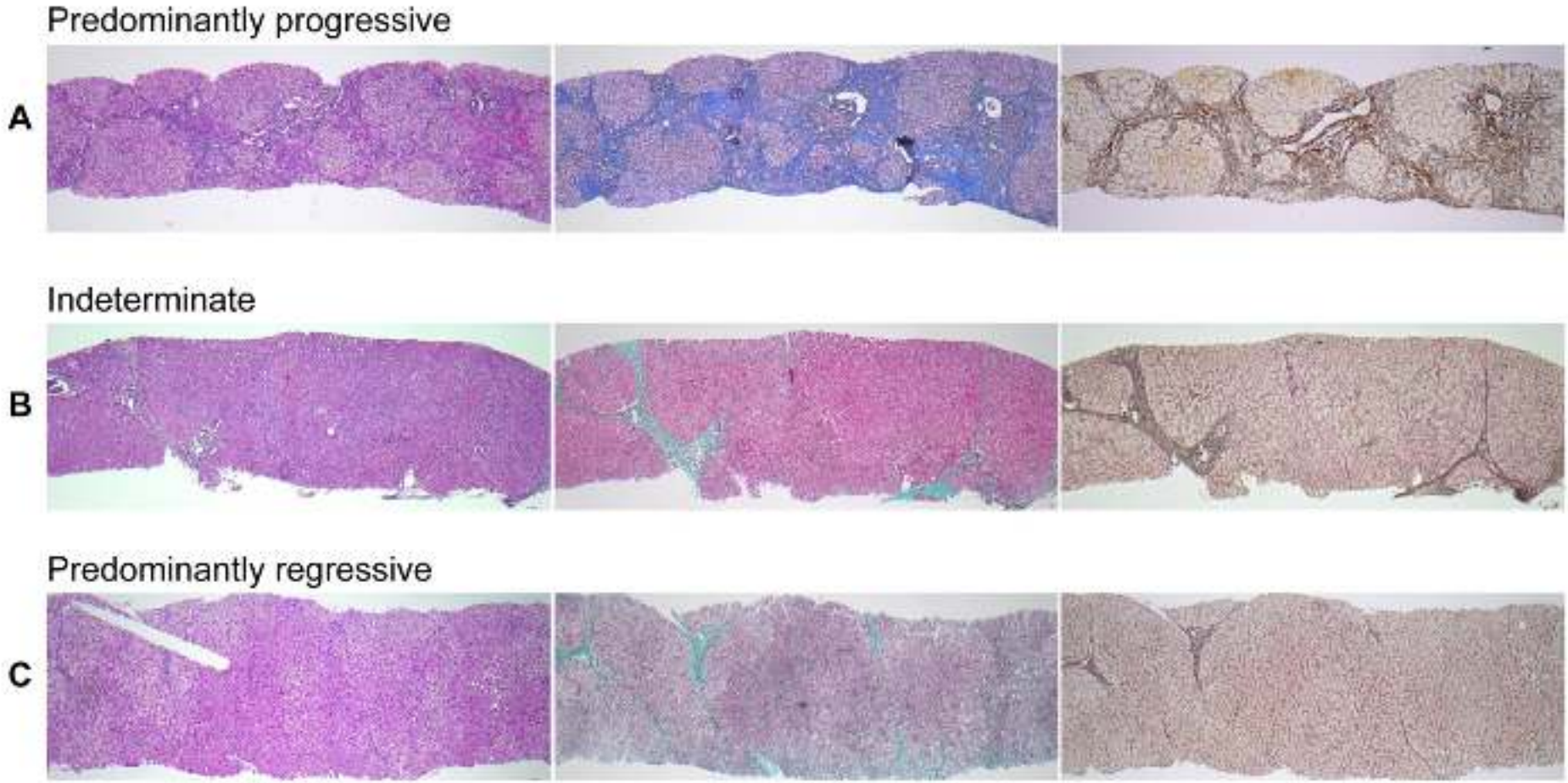
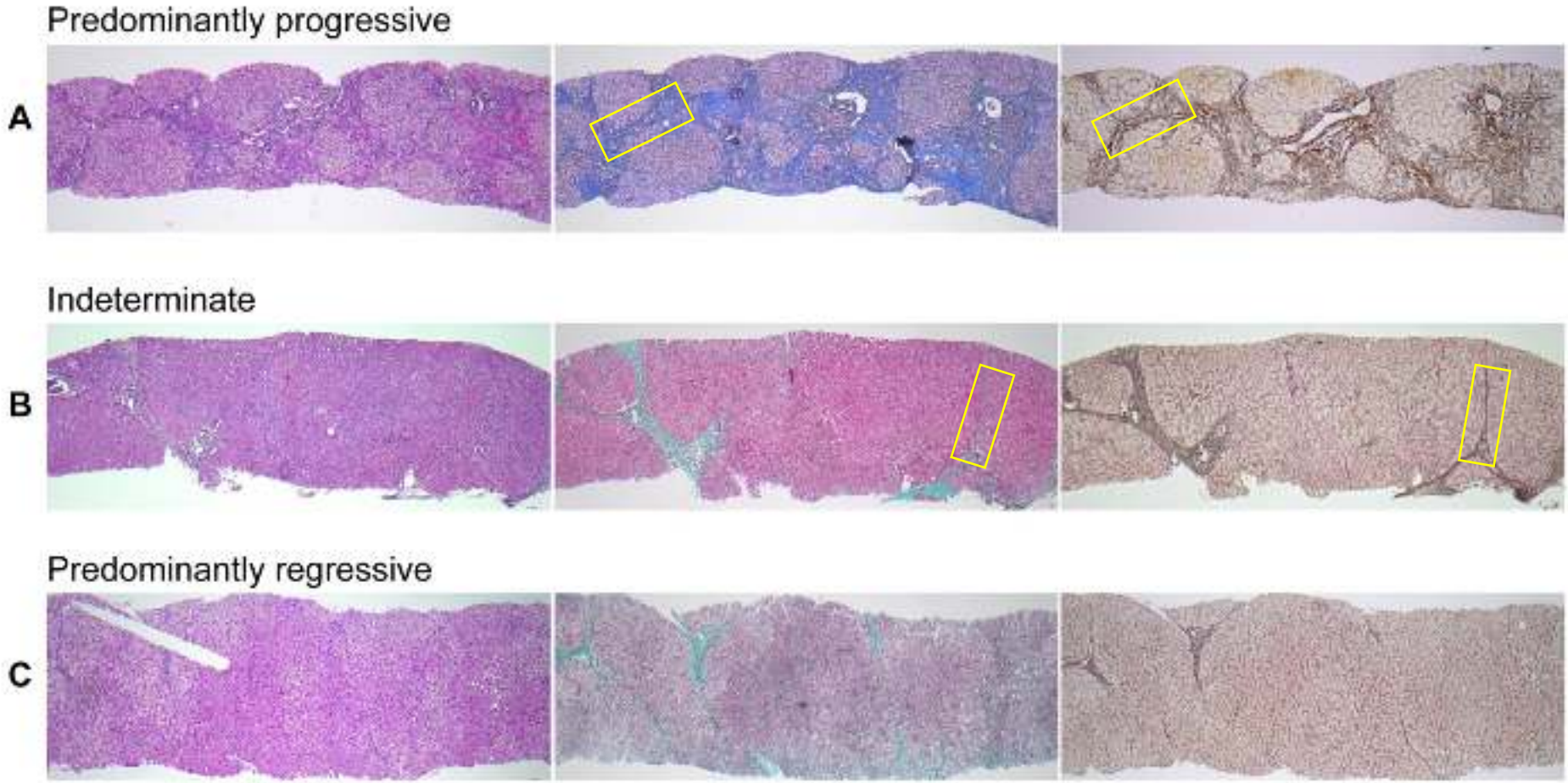
VIRAL HEPATITIS

New Classification of Liver Biopsy Assessment for Fibrosis in Chronic Hepatitis B Patients Before and After Treatment

Yameng Sun,[1] Jialing Zhou,[1] Lin Wang,[1] Xiaoning Wu,[1] Yongpeng Chen,[2] Hongxin Piao,[3] Lungen Lu,[4] Wei Jiang,[5] Youqing Xu,[6] Bo Feng,[7] Yuemin Nan,[8] Wen Xie,[9] Guofeng Chen,[10] Huanwei Zheng,[11] Hai Li,[12] Huiguo Ding,[13] Hui Liu,[14] Fudong Lv,[14] Chen Shao,[15] Tailing Wang,[15] Xiaojuan Ou,[1] Bingqiong Wang,[1] Shuyan Chen,[1] Aileen Wee,[16] Neil D. Theise,[17]* Hong You,[1]* and Jidong Jia[1]*


Chronic hepatitis B patients with paired liver biopsy before and after 78 weeks entecavir-based therapy
N=112 pairs
Inadequate liver biopsy at baseline or week 78 (shorter than 1 cm)
N = 16 pairs
Patients with eligible paired liver biopsy
N = 96 pairs
Patients with no or mild fibrosis (Ishak score < 3)
N = 25 pairs
Patients with significant liver fibrosis
N = 71 pairs
Pre-treatment
Post-treatment
Progressive
N = 41 (57.7%)
Indeterminate
N = 21 (29.6%)
Regressive
N = 9 (12.7%)
Progressive
N =8 (11.3%)
Indeterminate
N = 8 (11.3%)
Regressive
N = 55 (77.5%)


Predominantly progressive
A
Indeterminate
B
Predominantly regressive
C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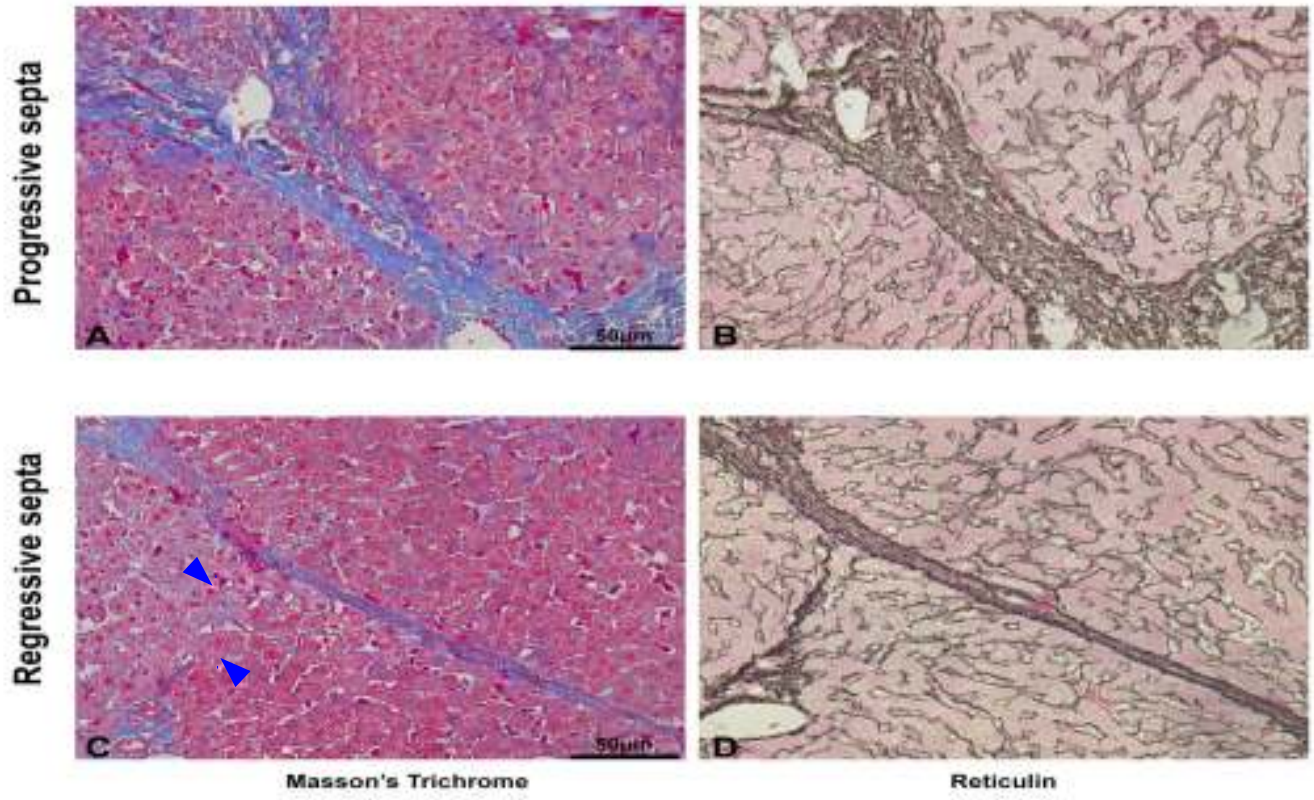
Progressive septa
A
50µm
B
Regressive septa
C
50µm
D
Masson's Trichrome
Reticulin

Table 4. Beijing classification for histologic assessment of chronic viral hepatitis.

Hepatitis Assessment:	**Description**	**Prior classifications**
Inactive	Portal inflammation only or rare foci of interface or lobular hepatitis; no confluent necrosis	Chronic persistent hepatitis Ishak HAI 1-5 Metavir A1
Active, non-severe	Varying degrees of interface and lobular hepatitis easily identified at low power; no confluent necrosis	Chronic active (aggressive) hepatitis Ishak HAI 5-12 Metavir A1-A2
Active, severe*	Confluent necrosis (perivenular drop out or bridging necrosis or parenchymal collapse) NOTE: This definition of severe activity raises the question of possible concomitant diseases (e.g. AIH, DILI) or immunosuppression (e.g. untreated HIV).	Chronic active (aggressive) hepatitis Ishak HAI 13-18 Metavir A3
Fibrosis Stage:		
Early	No fibrosis or portal fibrosis	Ishak 1-2 Metavir F1
Intermediate	Fibrous septa, focal or frequent	Ishak 3-4 Metavir F2-F3
Advanced	Fibrous septa with focal or diffuse nodularity (developing or established "cirrhosis")	Ishak 5-6 Metavir F3-F4
P-I-R Score:		
Predominantly **Progressive** features	Most of specimen shows progressive forms of stroma	Laennec 4A** or 4B or 4C
Indeterminate	Uncertain mix/balance between progressive and regressive stroma	Laennec 4B
Predominantly **Regressive** features	Most of specimens regressive forms of stroma	Laennec 4A
Not applicable	Not used in biopsies with "early stage" fibrosis, i.e. without fibrous septa	

For Peer Review

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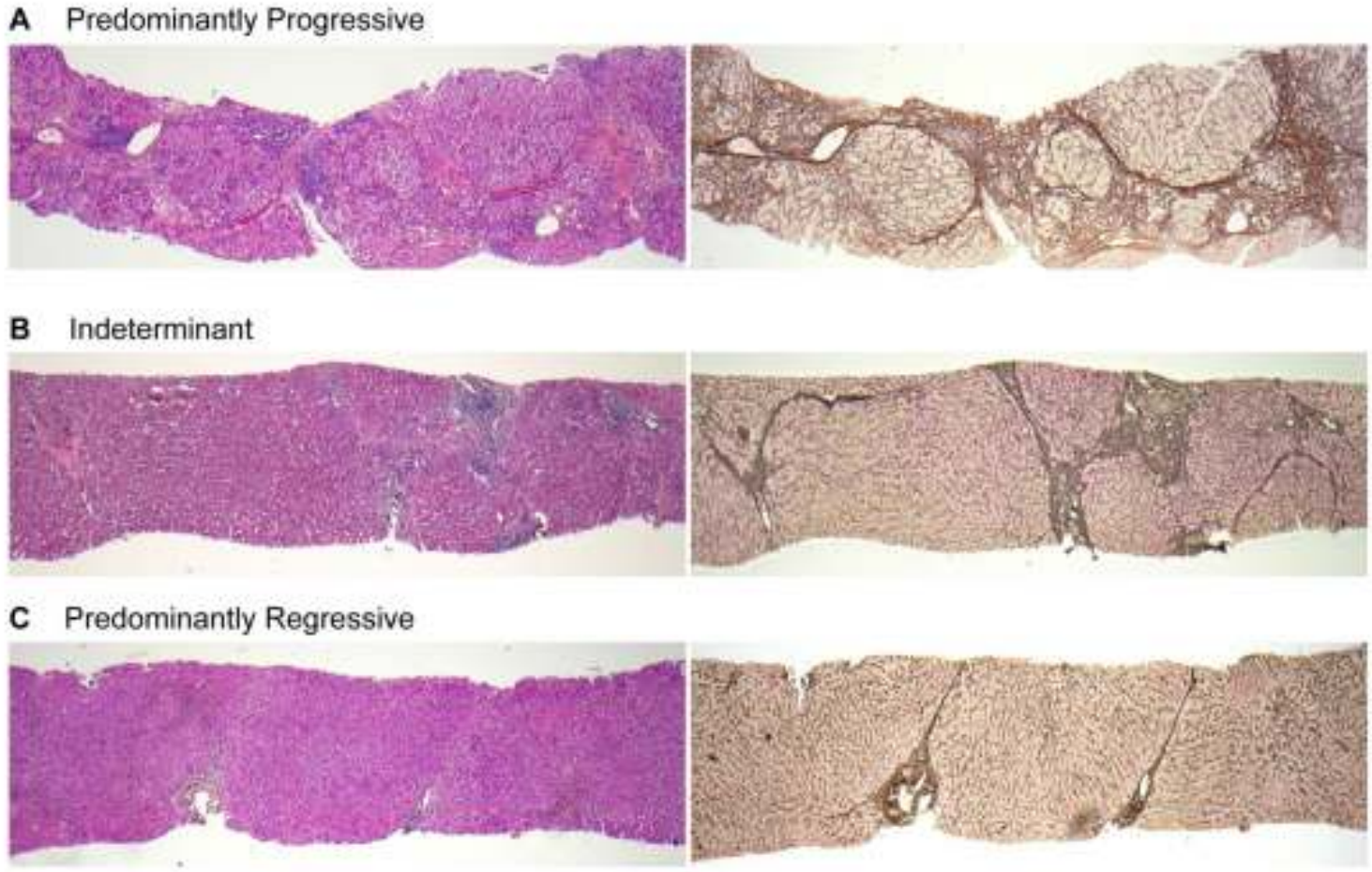
A Predominantly Progressive
B Indeterminant
C Predominantly Regressive
H&E
Reticulin

Table 1. Patient characteristics according to P-I-R classification pre- and post-treatment

	Progressive	Indeterminate	Regressive	*P* value
Pre-treatment				
N (%)	41 (57.7)	21 (29.6)	9 (12.7)	-
Age, year	40 ± 10	39 ± 9	38 ± 9	0.739
Gender (male), n (%)	34 (82.9)	15 (71.4)	8 (88.9)	0.523
PLT, $\times 10^9$/L	160.0 ± 55.9	168.5 ± 68.7	160.6 ± 45.8	0.859
ALT, U/L	94.7 (54.8, 167.5)	75.0 (40.2, 116.5)	35.0 (31.6, 45.1)	0.001
AST, U/L	66.0 (44.3, 140.5)	46.0 (34.5, 72.1)	33.6 (27.5, 37.6)	<0.001
ALB, g/L	41.6 (38.8, 44.1)	44.0 (41.9, 46.3)	47.2 (44.9, 50.9)	0.004
HBeAg (+), n (%)	37 (90.2)	14 (66.7)	5 (55.6)	0.013
HBV DNA, Log IU/mL	7.1 ± 1.3	6.9 ± 1.2	5.4 ± 1.6	0.003
LSM, Kpa	14.1 (11.5, 18.0)	8.9 (6.4, 11.8)	7.3 (6.8, 11.6)	<0.001
CPA	5.3 (3.3, 8.8)	3.3 (2.4, 4.5)	2.6 (1.9, 4.5)	0.001
Necroinflammation score, n (%)				<0.001
0-3, n=2	0	1 (4.8)	1 (11.1)	
4-6, n=29	9 (22.0)	13 (61.9)	7 (77.8)	
7-9, n=23	17 (41.5)	5 (23.8)	1 (11.1)	
≥10, n=17	15 (36.6)	2 (9.5)	0	
Ishak score, n (%)				0.134
3, n=11	4 (9.8)	5 (23.8)	2 (22.2)	
4, n=9	3 (7.3)	3 (14.3)	3 (33.3)	
5, n=23	14 (34.1)	6 (28.6)	3 (33.3)	
6, n=28	20 (48.8)	7 (33.3)	1 (11.1)	

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A

Progressive
Ishak 6, Laennec 4C
Fibroscan, 17.2Kpa

Regressive
Ishak 6, Laennec 4A
Fibroscan, 8.2Kpa

B

Progressive
Ishak 6, Laennec 4C
Fibroscan, 35.3Kpa

Regressive
Ishak 6, Laennec 4A
Fibroscan, 10.0Kpa

Table 2. Post-treatment P-I-R score versus changes of Ishak stage to evaluate disease progress or reverse.

Ishak (pre-post)	**Post-treatment P-I-R score n=71**		
	Progressive n=8	**Indeterminate n=8**	**Regressive n=55**
Increase, n=3	Absolutely advancing 67% (2/3)	0	33% (1/3)
Stable, n=35	Probably advancing 17% (6/35)	11% (4/35)	Probably reversing 72% (25/35)
Decrease, n=33	0	12% (4/33)	Absolutely reversing 88% (29/33)

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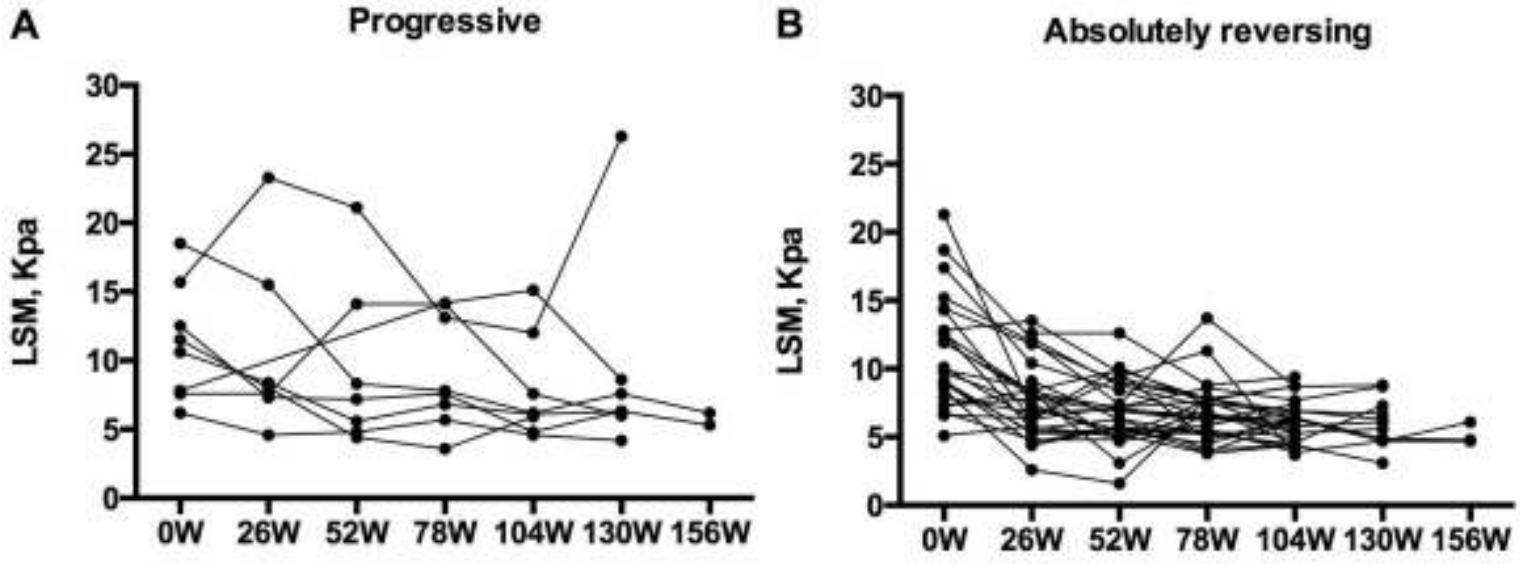
A
Progressive
LSM, Kpa
30
25
20
15
10
5
0
0W
26W
52W
78W
104W
130W
156W
B
Absolutely reversing
LSM, Kpa
30
25
20
15
10
5
0
0W
26W
52W
78W
104W
130W
156W

Supplementary Table 4. Inter-observer variation of P-I-R score.

	Kappa value	Strength of agreement*
P-I-R score	0.71	Substantial
Interpretation of Kappa value*	<0	Poor
	0.01-0.20	Slight
	0.21-0.40	Fair
	0.41-0.60	Moderate
	0.61-0.80	Substantial
	0.81-1.00	Almost perfect

**Landis JR, et al. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.*

epted

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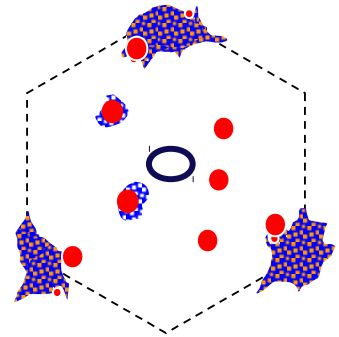
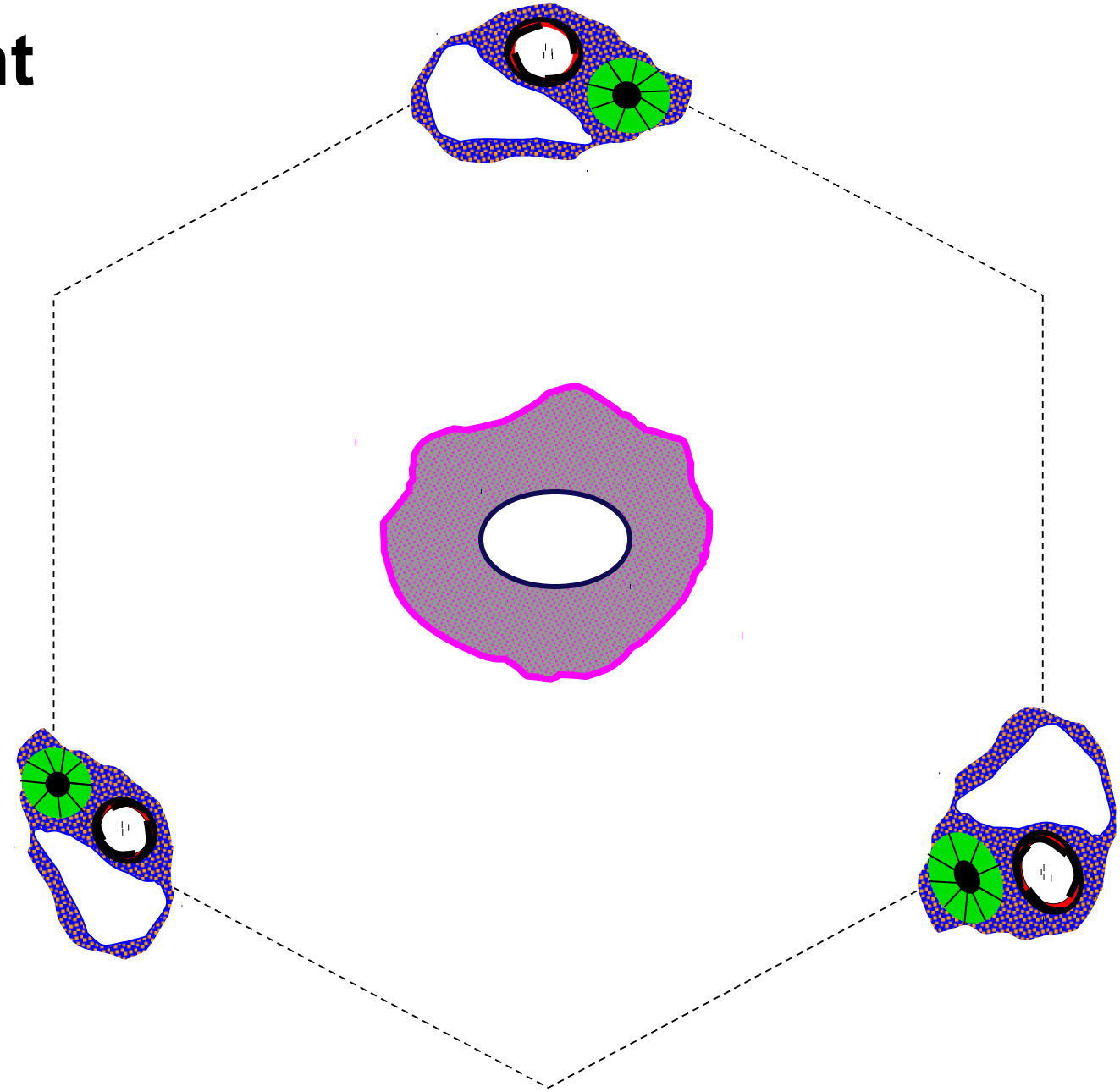
GRADING Of Activity

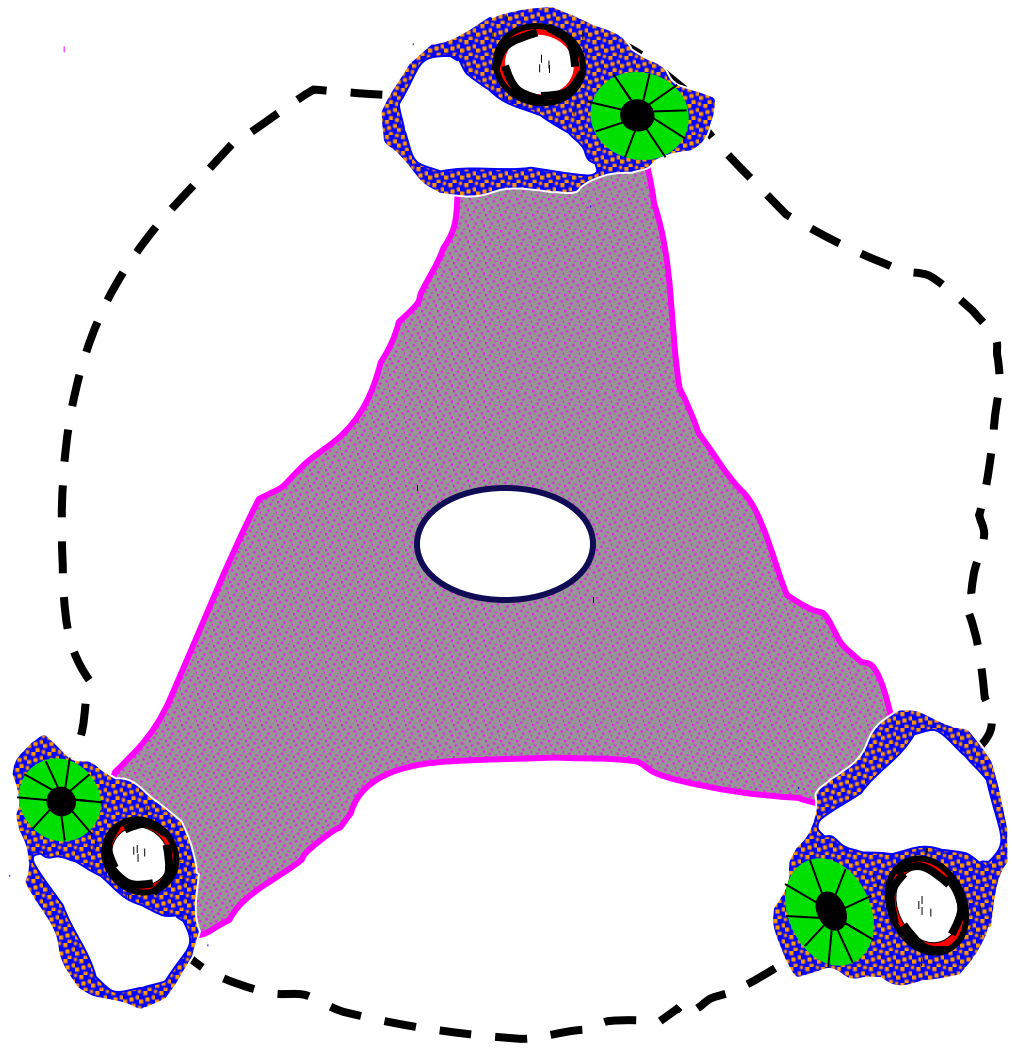


- Portal inflammation
- Interface hepatitis
- Lobular hepatitis
- Confluent necrosis

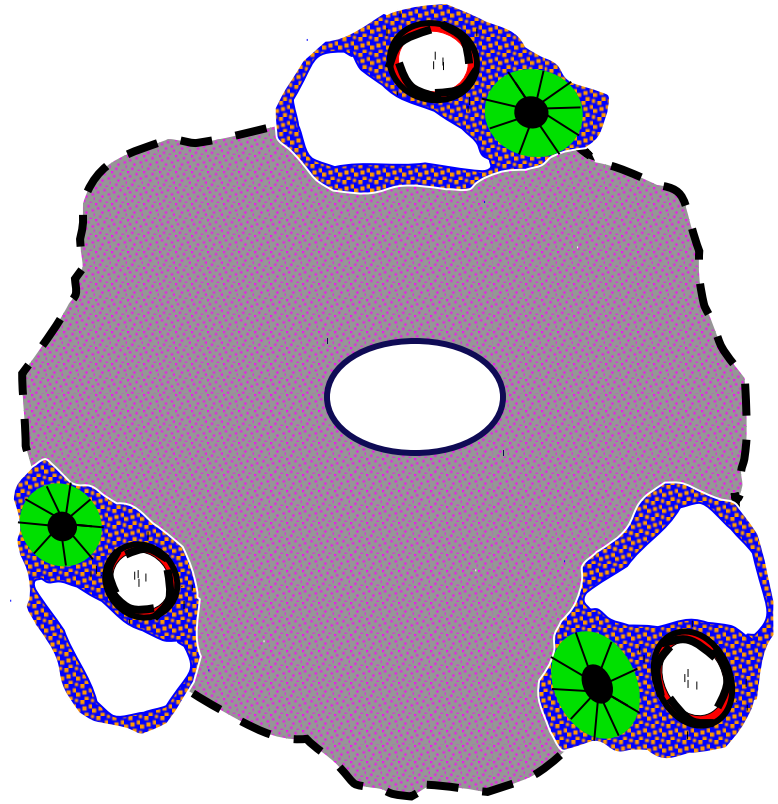
Confluent Necrosis

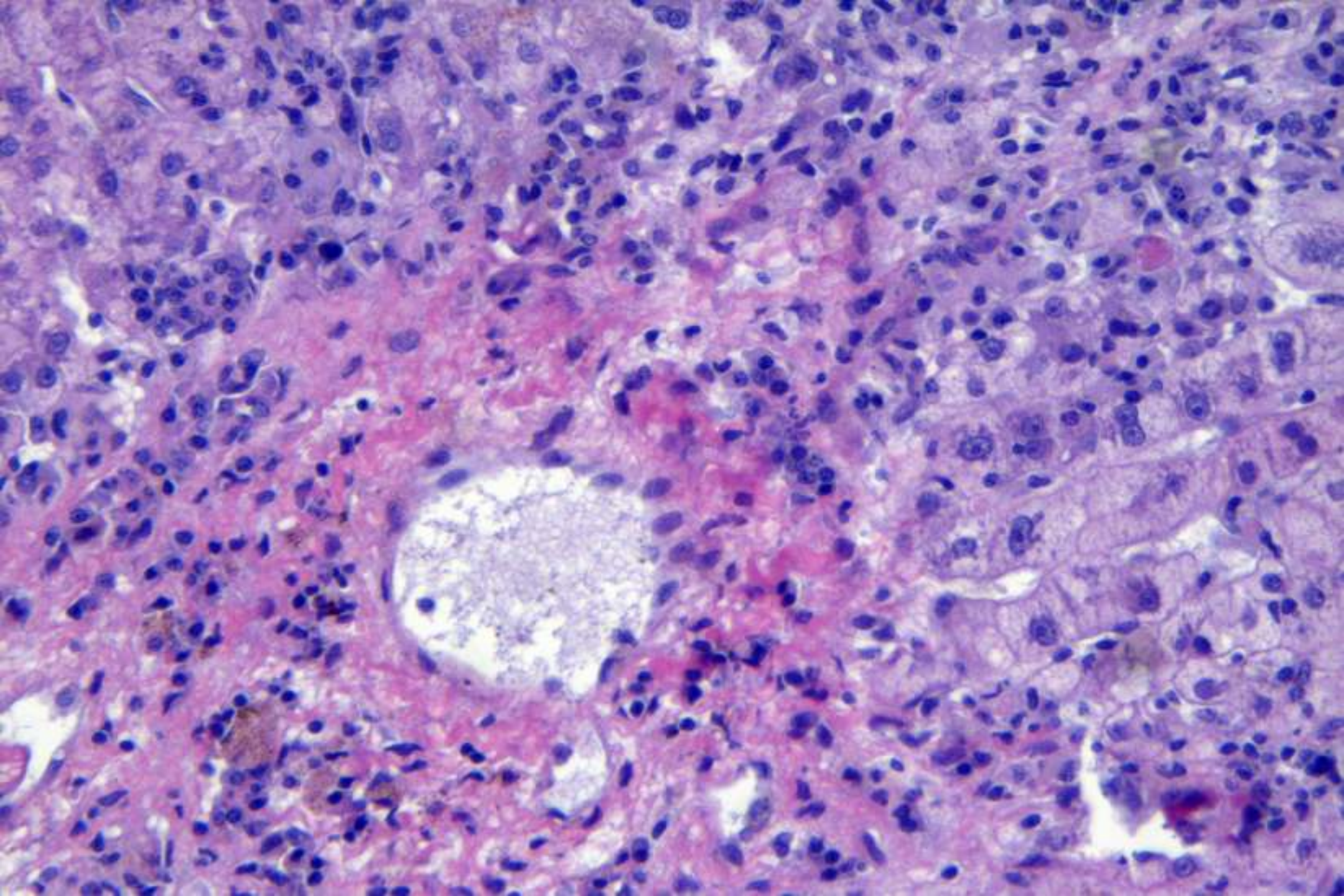


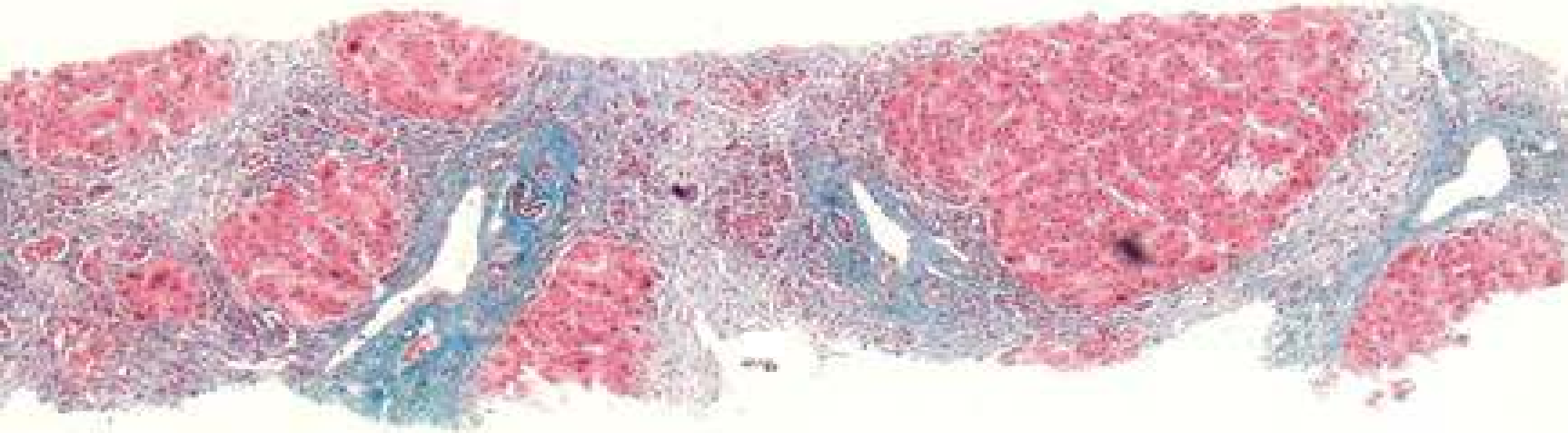
Confluent Necrosis



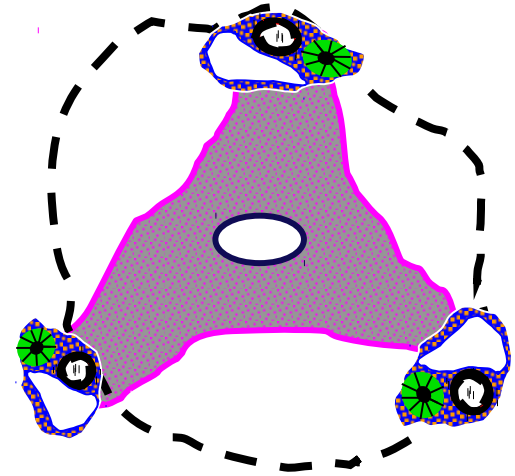
Confluent Necrosis





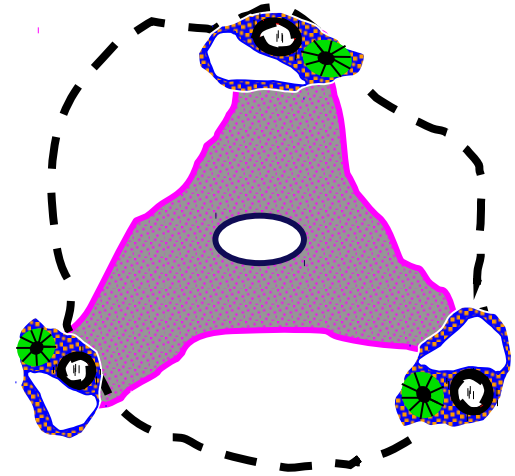


Bridging confluent necrosis



Confluent necrosis in HBV, think about:

- HBeAg to Ab conversion
- **HDV super-infection on HBV**
- **HIV co-infection**
- **Autoimmune hepatitis**
- **Drug/toxin induced injury, as always**



Confluent necrosis in HCV, think about:

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For Peer Review

Special Article

Am J Clin Patho 2012; 137: 5-9

Beyond "Cirrhosis"

A Proposal From the International Liver Pathology Study Group

Prodromos Hytiroglou, MD,[1] Dale C. Snover, MD,[2] Venancio Alves, MD,[3] Charles Balabaud, MD,[4] Prithi S. Bhathal, MD,[5] Paulette Bioulac-Sage, MD,[6] James M. Crawford, MD,[7] Amar P. Dhillon, MD,[8] Linda Ferrell, MD,[9] Maria Guido, MD,[10] Yasuni Nakanuma, MD,[11] Valerie Paradis, MD,[12] Alberto Quaglia, MD,[13] Neil D. Theise, MD,[14] Swan N. Thung, MD,[15] Wilson M.S. Tsui, MD,[16] and Dirk J. van Leeuwen, MD[17]

Histopathology

Histopathology 2016, **68**, 953–967. DOI: 10.1111/his.12957

REVIEW

Role of aetiology in the progression, regression, and parenchymal remodelling of liver disease: implications for liver biopsy interpretation

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