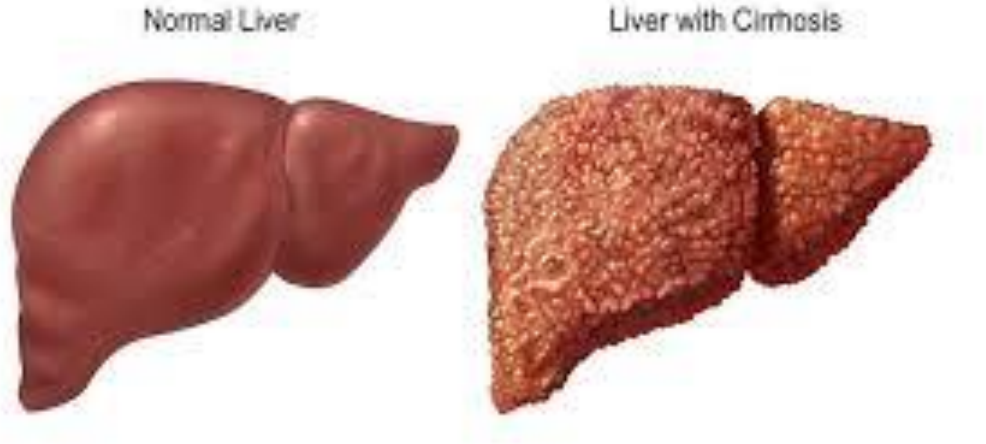
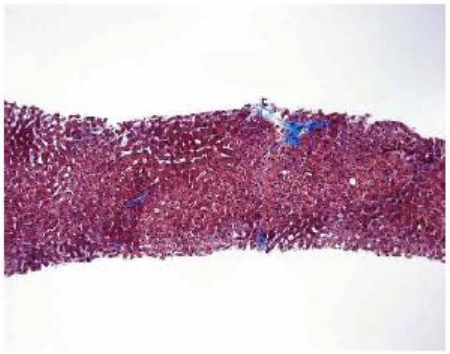
CIRRHOSIS 2018

Joseph Alcorn MD

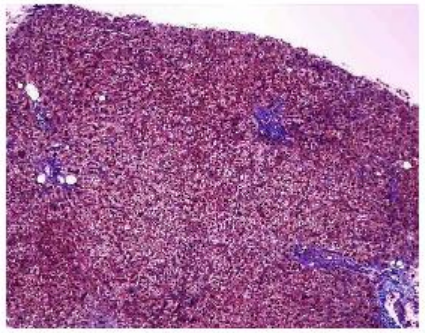
CIRRHOSIS AIN'T WHAT IT USED TO BE



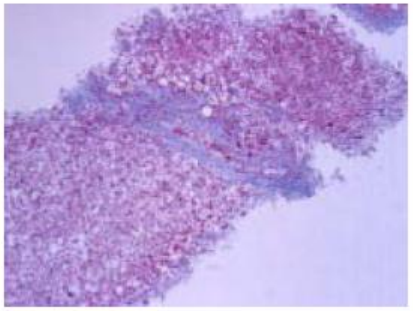
OLD SCHOOL – CIRRHOSIS VS NOT



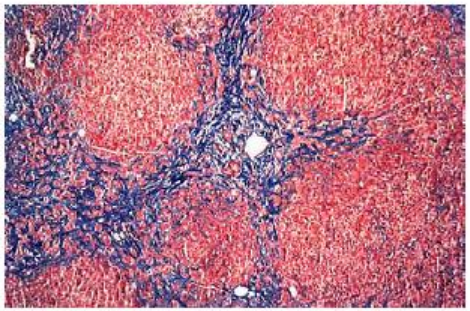
Stage 1



Stage 2



Stage 3



Stage 4

New School: Gradient of scarring

THE CONSEQUENCES ....

Varices

Hepatic Encephalopathy

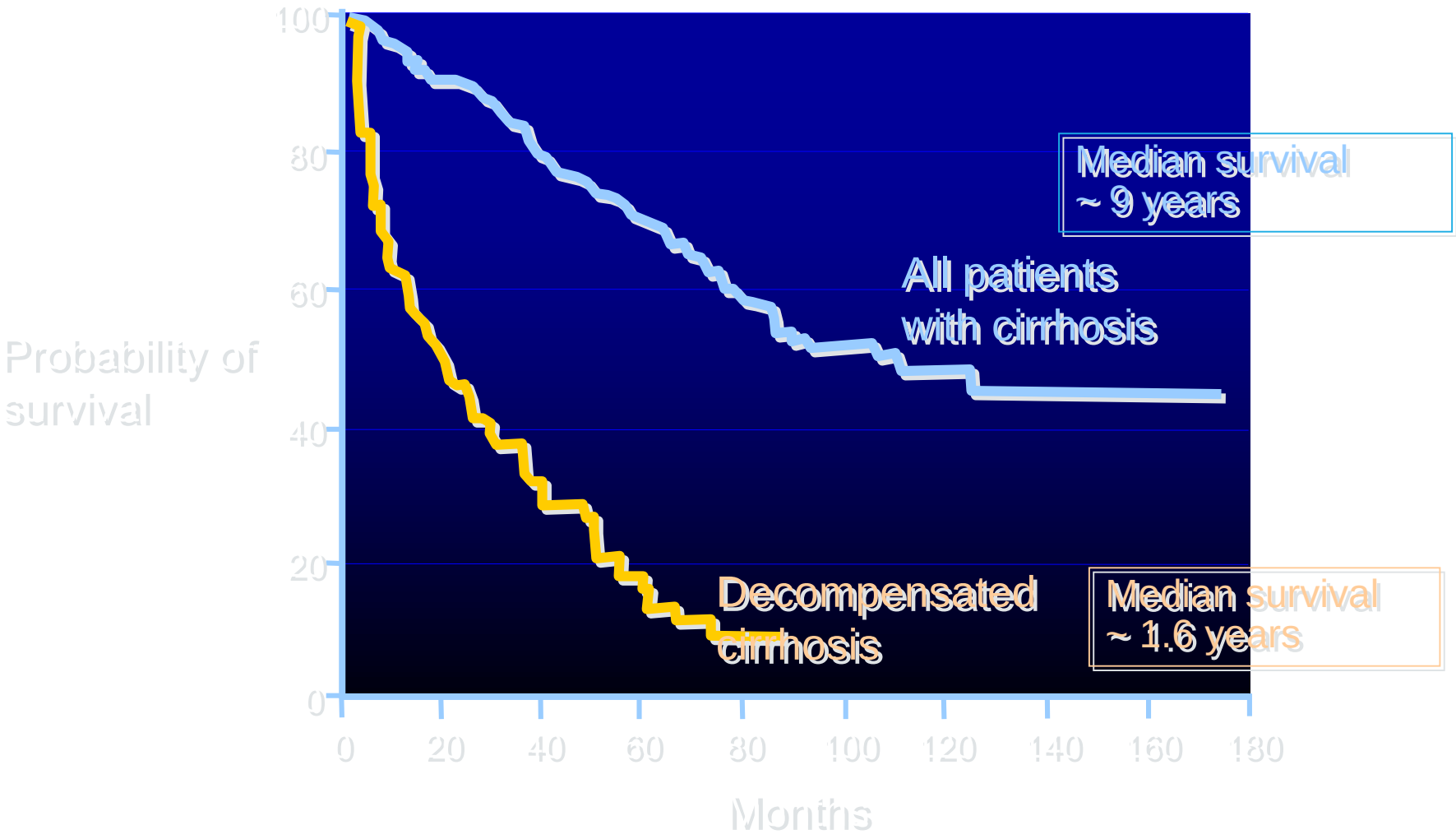
Sarcopenia

Ascites

WE'RE # 1!!

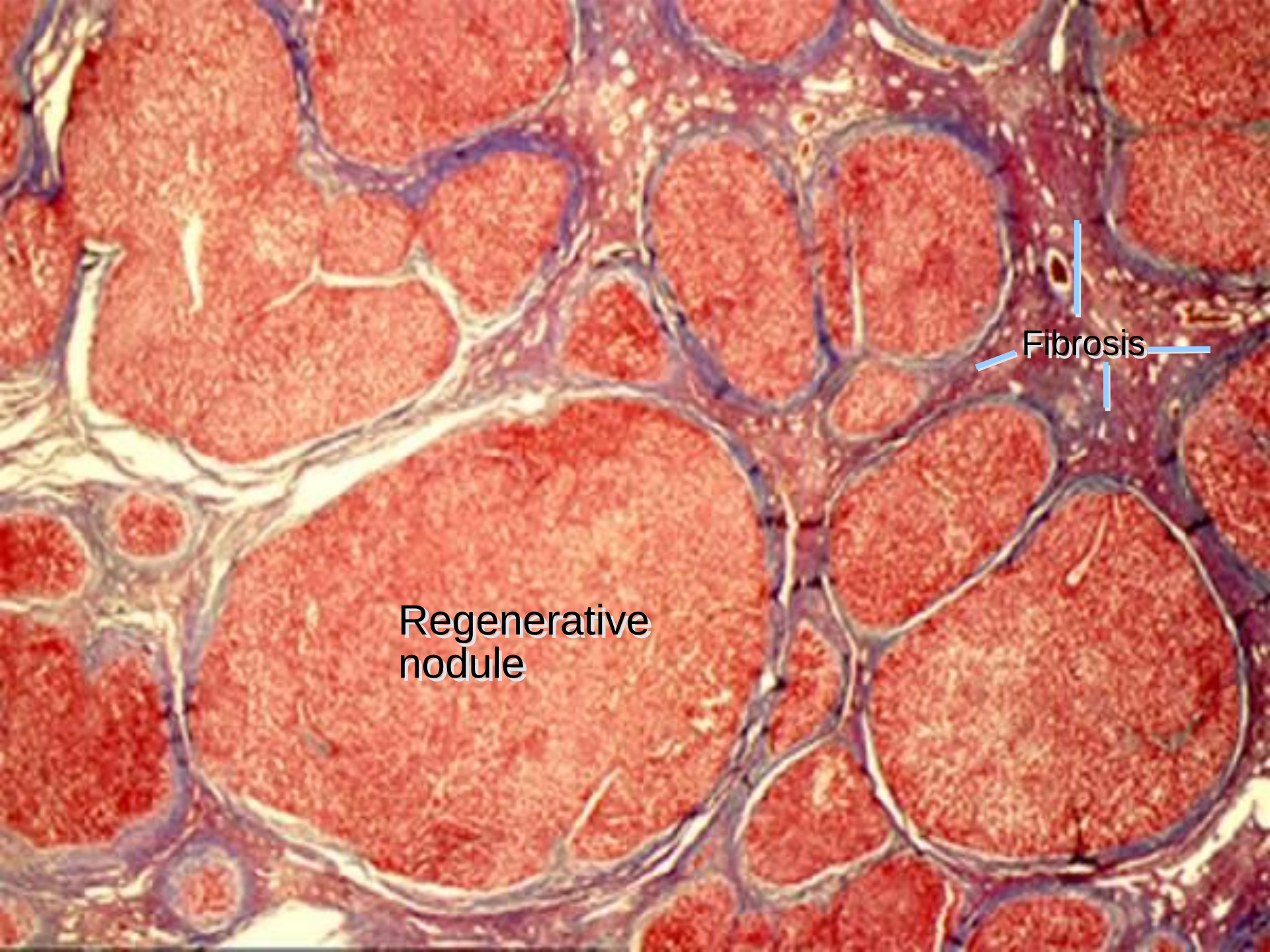
NM Leading Causes of Death, 2016	Deaths	Rate***	State Rank*	U.S. Rate**
1. Heart Disease	3,800	150.6	35th	165.5
2. Cancer	3,560	138.8	46th	155.8
3. Accidents	1,487	69.5	3rd	47.4
4. Chronic Lower Respiratory Disease	1,131	44.4	23rd (tie)	40.6
5. Stroke	885	35.5	32nd	37.3
6. Diabetes	678	27.2	5th	21.0
7. Alzheimer's disease	583	23.5	39th	30.3
8. Chronic Liver Disease/Cirrhosis	572	24.9	1st	10.7
9. Suicide	471	22.5	4th	13.5
10. Flu/Pneumonia	353	14.6	17th	13.5

Decompensation Shortens Survival

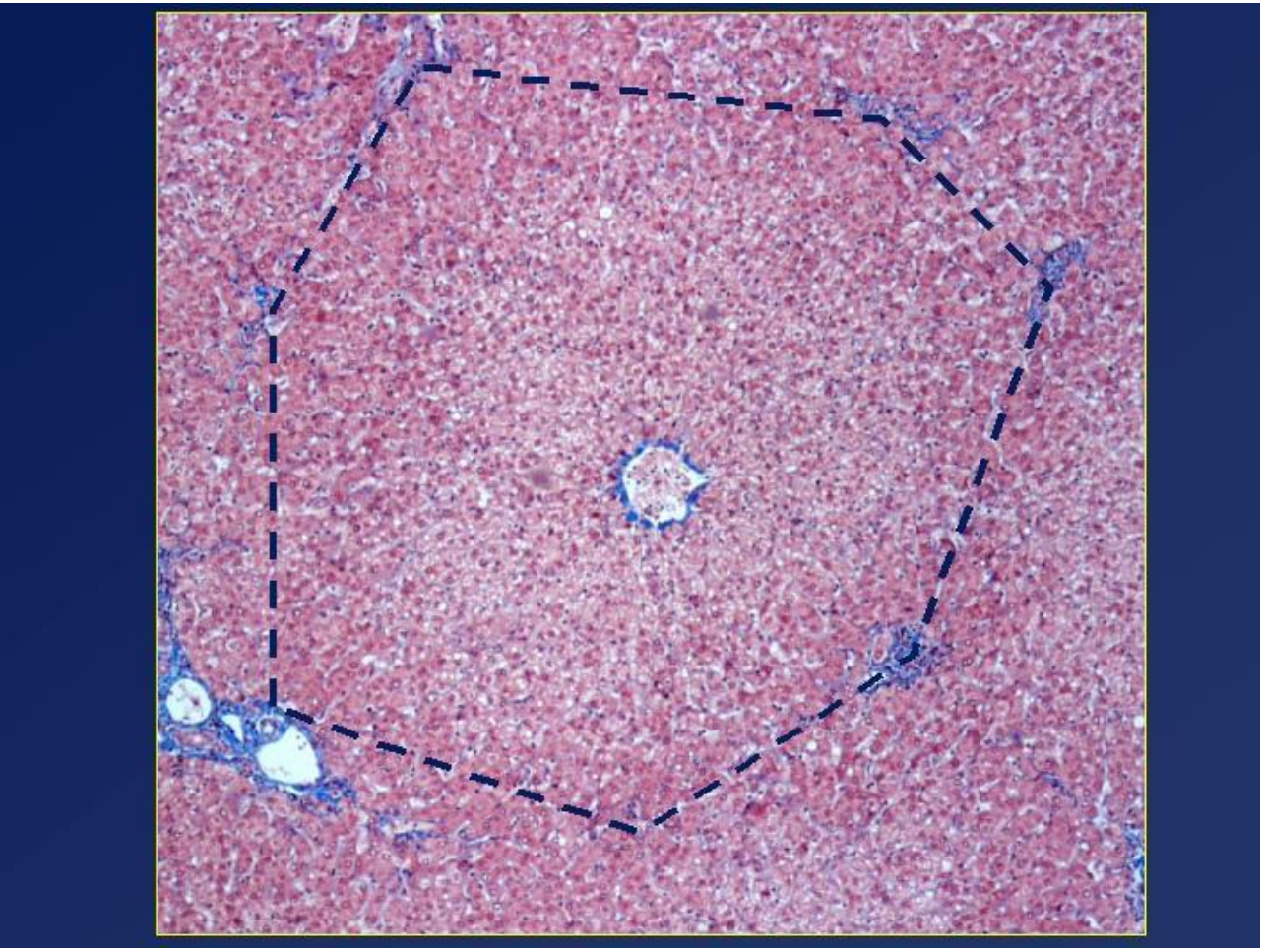


Gines et. al., Hepatology 1987;7:122

NEW SCHOOL: LIVER FIBROSIS IS A GRADIENT


Fibrosis
Regenerative nodule

CLASSIC LOBULE



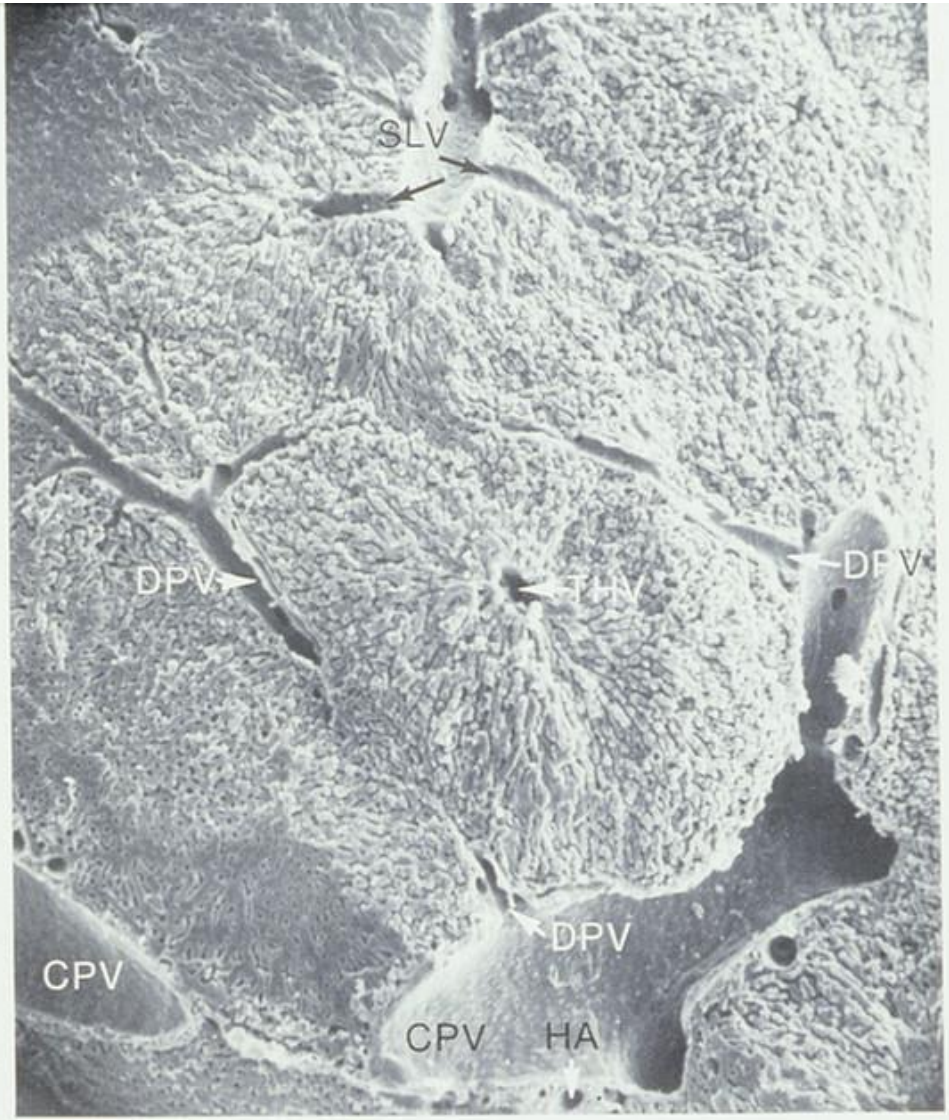


FIG. 7. This scanning electron micrograph (×130) shows the relationship between the terminal branches of the portal vein, distributing portal veins (DPV), and the terminal hepatic venule (THV). Note that they are in different planes. Also shown are conducting portal veins (CPV), hepatic artery branches (HA), and a sublobular hepatic vein (SLV) sectioned to illustrate its continuity (*arrows*) with terminal hepatic veins. (From ref. 168.)

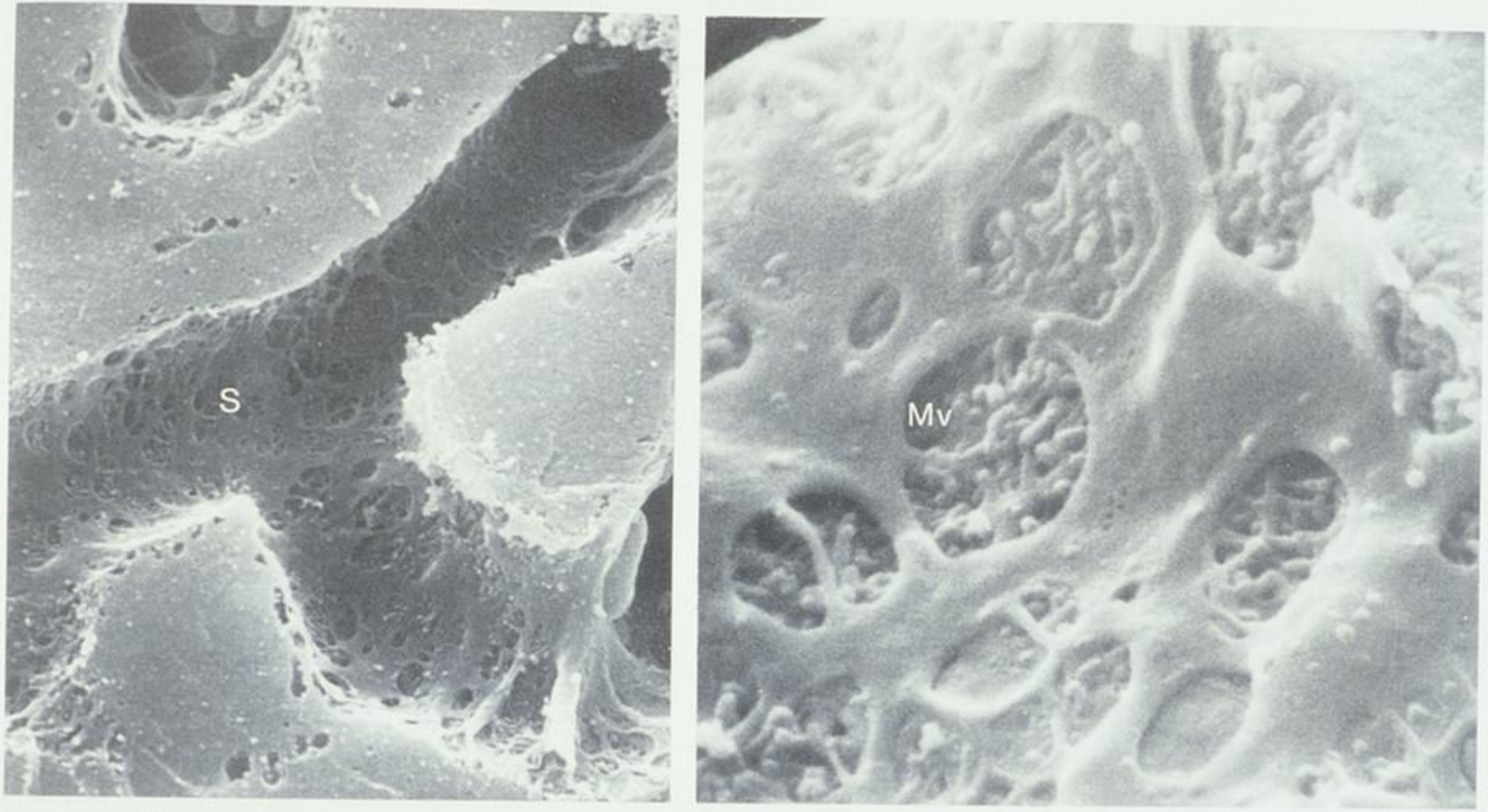
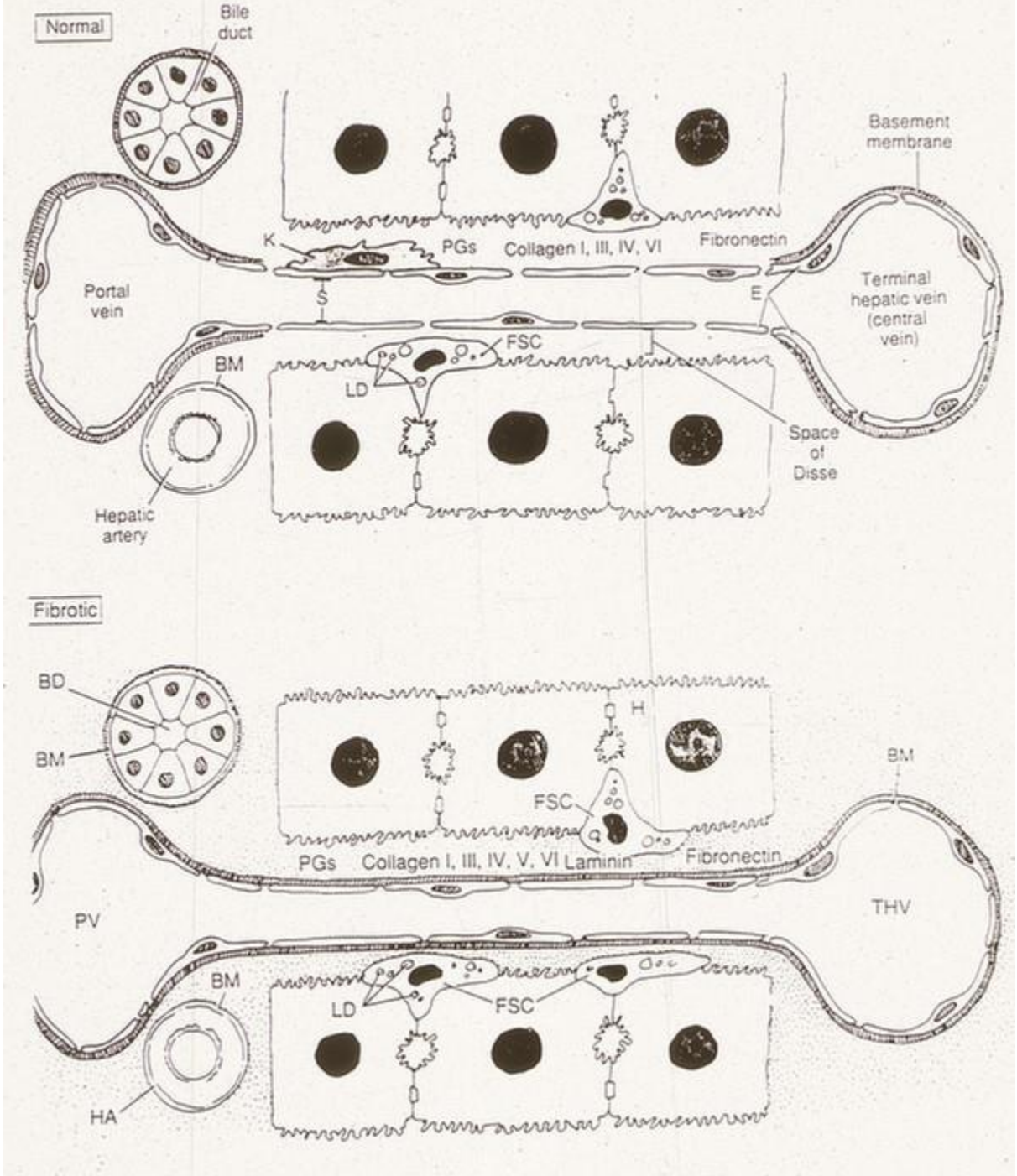
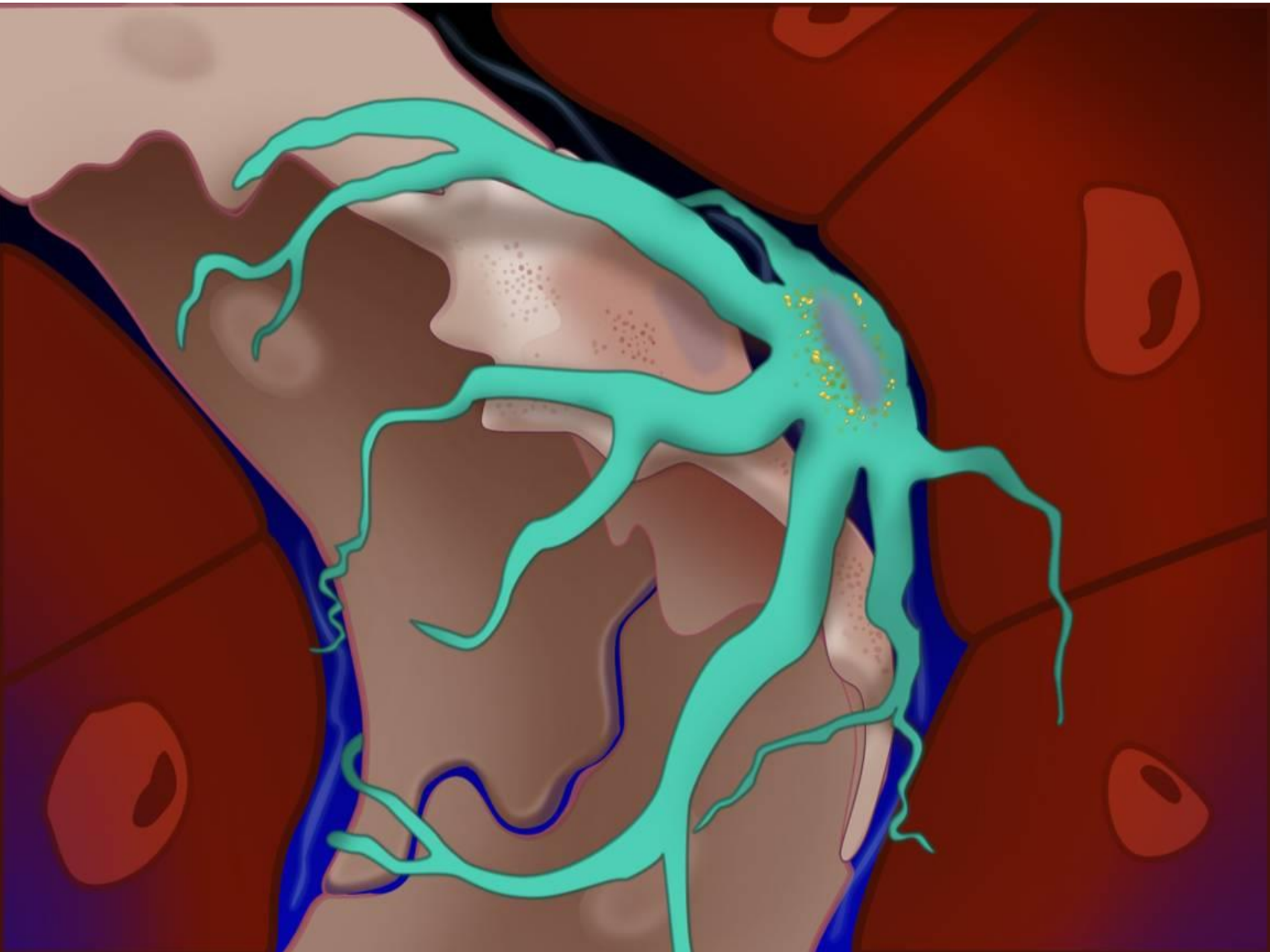
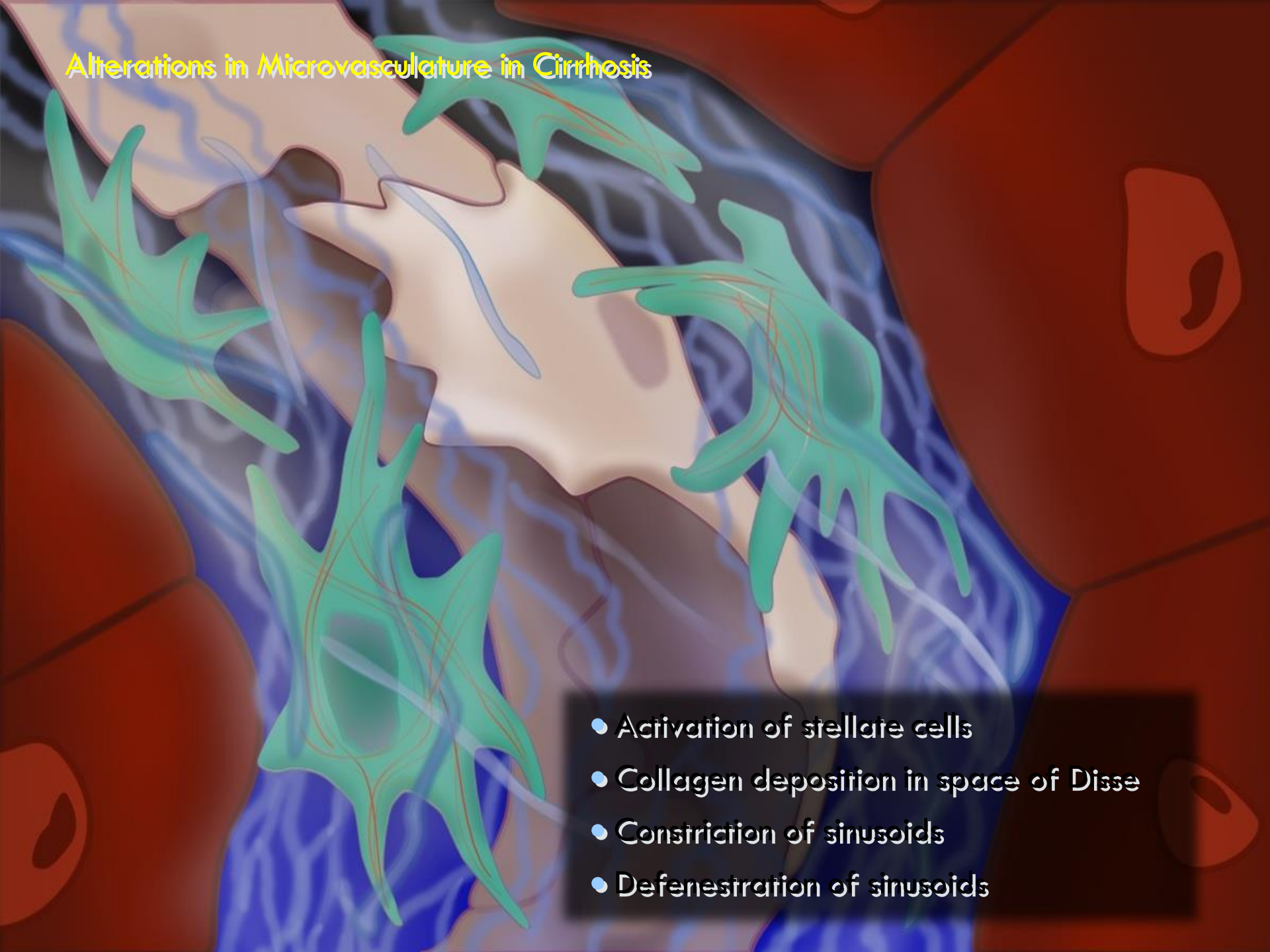


FIG. 6. Hepatic sinusoids. **Left:** These scanning electron micrographs of sinusoids (S) show the multiple and varying-sized fenestrations in the endothelial lining cells (×3,585). **Right:** Further enlargement (×12,725) shows the microvilli (Mv) of underlying hepatocytes readily exposed to the sinusoidal contents. (From ref. 168.)

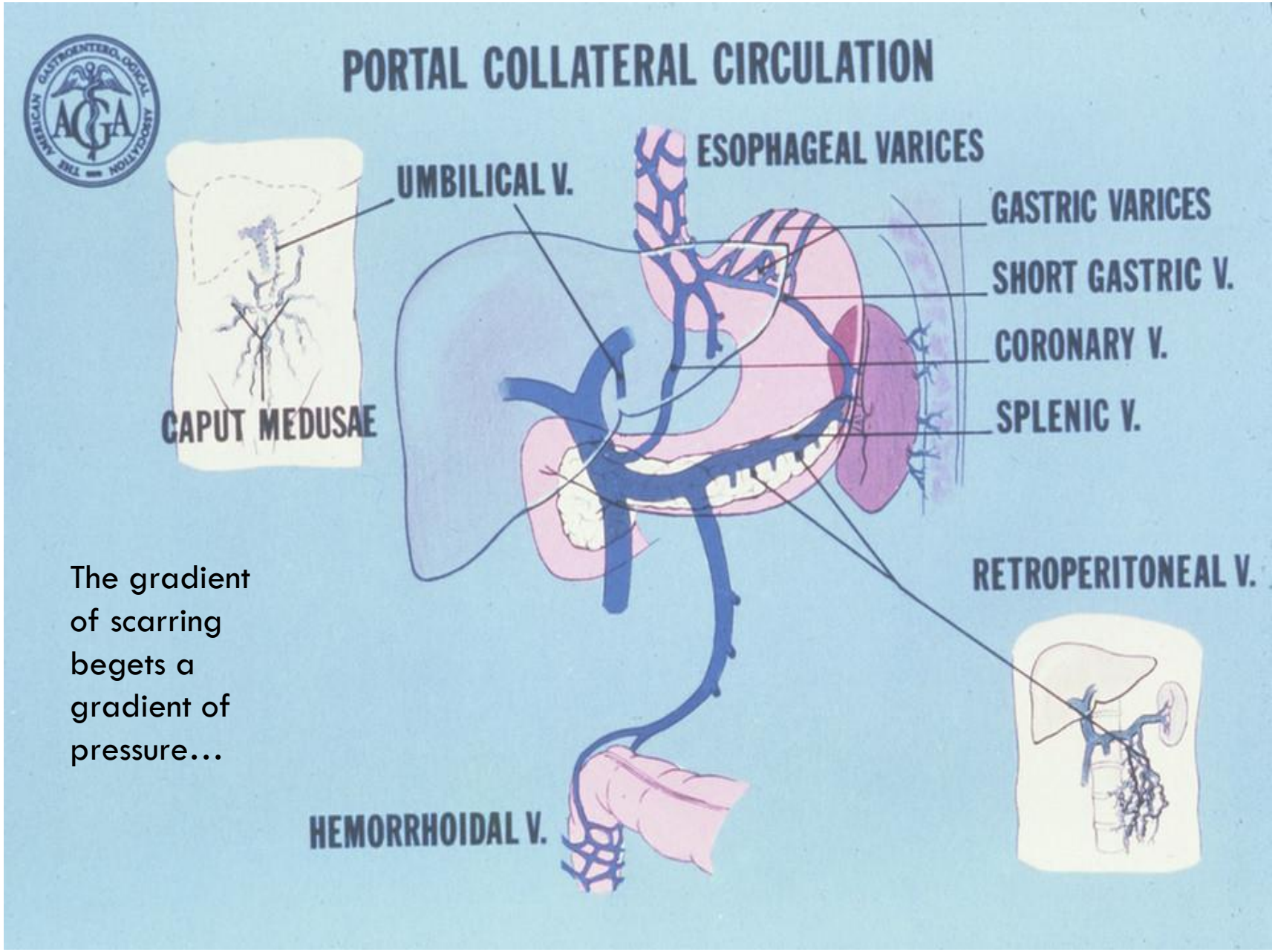

Normal
Bile duct
Basement membrane
K
PGs
Collagen I, III, IV, VI
Fibronectin
Portal vein
S
E
Terminal hepatic vein (central vein)
FSC
BM
LD
Space of Disse
Hepatic artery
Fibrotic
BD
BM
H
BM
FSC
PGs
Collagen I, III, IV, V, VI
Laminin
Fibronectin
PV
THV
BM
LD
FSC
HA



Alterations in Microvasculature in Cirrhosis



- Activation of stellate cells
- Collagen deposition in space of Disse
- Constriction of sinusoids
- Defenestration of sinusoids



The gradient of scarring begets a gradient of pressure…

THE BADNESS IS IN THE PRESSURE

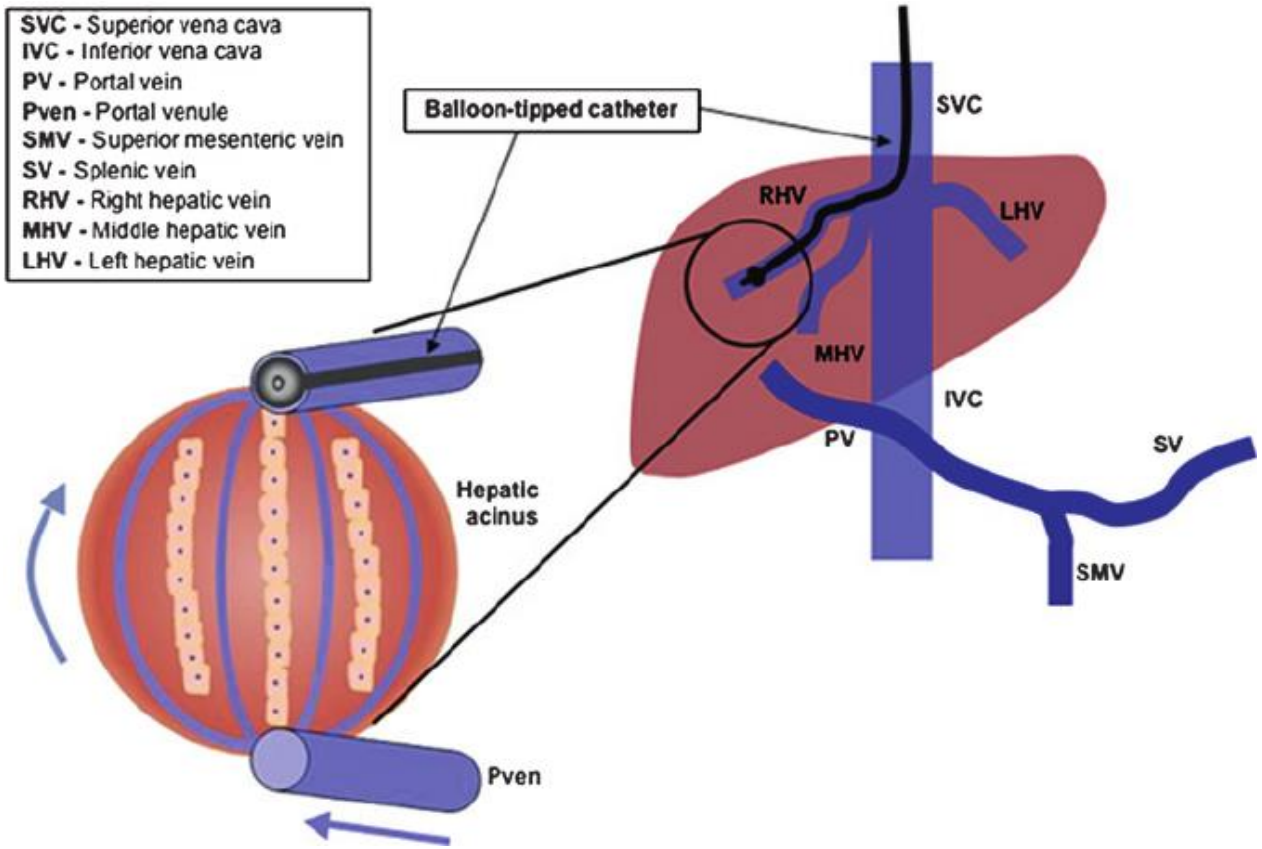
Normal Portal-venous Gradient

- less than 5 mm Hg

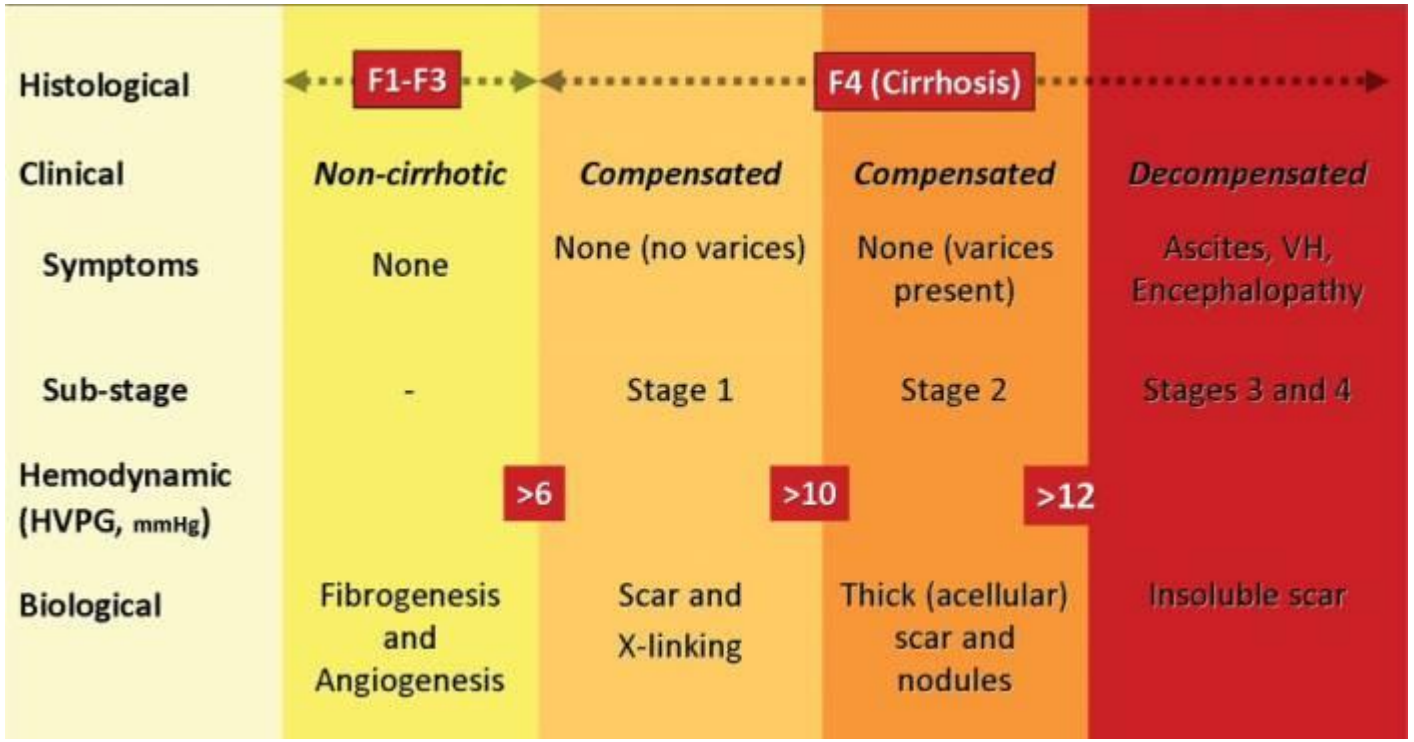
Complications of liver Disease

- being with gradient > 10 mm

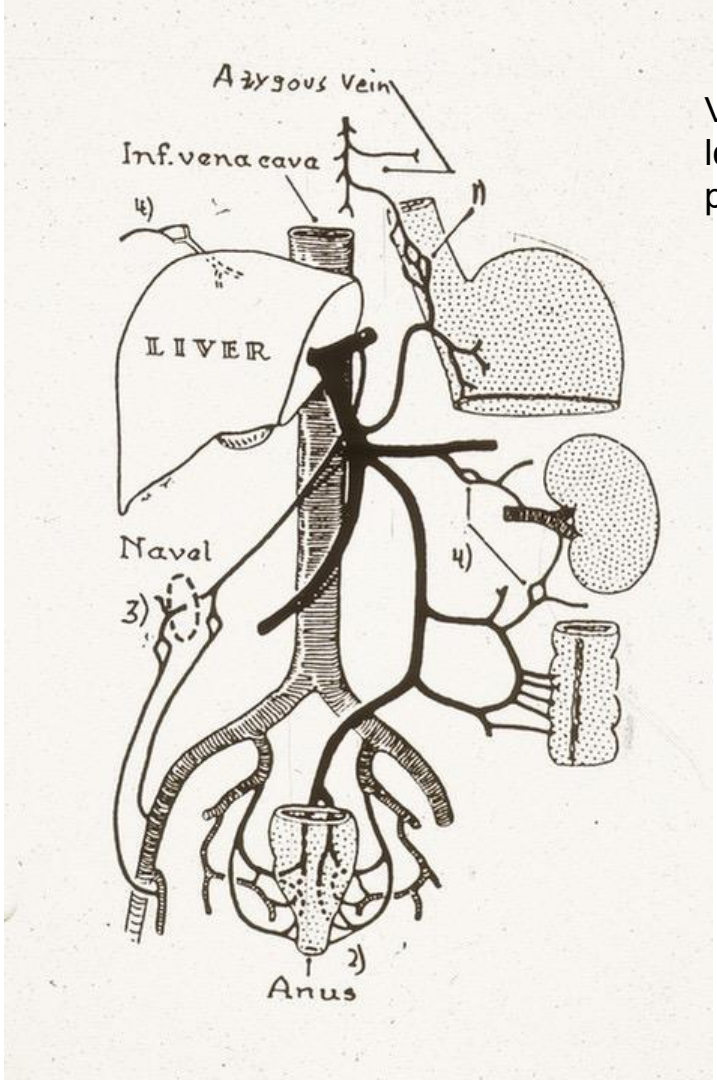
PORTAL VENOUS GRADIENT



THE POWER OF THE GRADIENT



PORTAL HTN



Vascular resistance in the liver leads to backpressure in predictable places…

	COMPENSATED			DECOMPENSATED (CSPH present in all cases)		
STAGE (11)	**Stage 1a**	**Stage 1b**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**
Features	No CSPH No varices	CSPH No varices	CSPH Varices	Variceal bleeding without any other complication	First non-bleeding decompensation (e.g. ascites, HE, SBP)	Any second decompensation (e.g. recurrent variceal Hemorrhage; refractory ascites; HRS; hyponatremia; recurrent HE; Jaundice
1-year Mortality (11)	1.5%		2%	10%	21%	5-year-Mortality: 87%
Progression/ Complications (annual incidence) (11)		7% GEV (Stage 2) 4% Ascites (Stage 4)	4% EV bleeding (Stage 3) 6.6% Ascites (Stage 4)	21% Ascites (Stage 4)	10% further decompensation (Stage 5)	
Aim of therapy (7)	Prevent CSPH Prevent Varices Prevent decompensation			Prevent further decompensation Reduce mortality		Reduce mortality
Major known risk modifiers	Alcohol intake (27) Ongoing liver injury (e.g. HCV, HBV) (27) Obesity (33)		All previous + HVPG response to NSBB (39-41)	Liver and renal function (5) HVPG response to NSBB (39-41) Alcohol intake Sarcopenia (34) Vitamin D deficiency (35)		
Evidence-based therapy	Etiologic Rx (27) Stop alcohol (27) Consider lifestyle changes (45) Consider Statins (47-52)		All previous + NSBB or Carvedilol (7; 27) Consider Statins (47-52)	Acute episode: vasoactive drugs + EVL + antibiotic proph. + avoid overtransfuse (7; 27) Prevention of rebleeding: NSBB+EVL+ Statins (53) Early TIPS in high risk patients (64;65) Nutritional therapy Consider OLT	Ascites (6): standard medical therapy+/-LVP; prophylaxis of SBP in high risk patients; weekly i.v. Albumin+ standard medical therapy: new approach? (59) SBP: Targeted antibiotic therapy; prophylactic antibiotics after a first SBP episode (6;8) HE: Rifaximin (56) Nutritional therapy Consider OLT	Recurrent or refractory ascites (selected patients), recurrent bleeding: TIPS (6; 7; 66) HRS: Terlipressin +Albumin (6) Ascites in Child C: Norfloxacin (62) Nutritional therapy Consider OLT

Primary Care Provider

HCC

HEPATOCELLULAR CARCINOMA

Increased more than 3X in last 20-30 years

- J Clin Gastro 2013 **47**:S2-S6

HCC is cured only in patients identified in early stage disease

- NEJM 2011 **365**: 1118-1127

Without treatment 5 year survival is less than 15%

- Gastroenterology 2008 **134**: 1752-1763

Hence American, European and Asian Guidelines recommend screening for HCC in patients **at risk**….citing the one Chinese RCT….

IF YOU ARE WAITING FOR BETTER DATA…

Fuggedabout it…

Patients no longer allow themselves to be randomized

Poustchi H et al Hepatology 2011;54:1998

Impact on overall HCC survival hard to define when screening rates are only 20-30% HB El-Serag et al J of Hepatology 2006; 44:158; JA Davila et al Hepatology 2010;52:132

1) Small treatable HCCs represent less than 20% without surveillance, > 70% with surveillance AC Chan et al Ann Surg 2008;247:666
2) Survival rates have increased consistently with surveillance, seemingly due to higher proportion of treatable disease GuiuB et al Clin Gastro Hepatol 2010; 8:986; Anderson KL et al Clin Gastroenterol Hepatol 2008; 6:1418;
3) Patients identified as candidates for and provided loco-regional therapy live longer than those who do not. Llovet JM et al Hepatology 2003; 37:429

HOW ARE WE DOING AT HCC SCREENING? –

10,695 VETERANS WITH HCC BETWEEN 2004 AND 2011

Variable	No surveillance n = 475 (53.5%)	Surveillance n = 412 (46.5%)	*p* value
Age (years)			
≤55	90 (18.9%)	82 (19.9%)	<0.01
56-60	140 (29.5%)	150 (36.4%)	
61-65	109 (22.9%)	115 (27.9%)	
66-70	44 (9.3%)	40 (9.7%)	
71+	92 (19.4%)	25 (6.1%)	
Race			
White	274 (57.7%)	262 (63.6%)	0.11
Black	125 (26.3%)	80 (19.4%)	
Hispanic	67 (14.1%)	61 (14.8%)	
Others	9 (1.9%)	9 (2.2%)	
Gender			
Male	474 (99.8%)	412 (100%)	1.00
Non-hepatic Deyo index			<0.01
0	194 (40.8%)	174 (42.2%)	
1	169 (35.6%)	174 (42.2%)	
2+	112 (23.6%)	64 (15.5%)	
Child-Pugh class			
A	161 (33.9%)	168 (40.8%)	0.0334
B	209 (44%)	182 (44.2%)	
C	83 (17.5%)	48 (11.7%)	
Unknown	22 (4.6%)	14 (3.4%)	
MELD score			
<10	135 (28.4%)	156 (37.9%)	<0.01
10-19.9	256 (53.9%)	218 (52.9%)	
20+	38 (8%)	12 (2.9%)	
Unknown	46 (9.7%)	26 (6.3%)	

Variable	No surveillance n = 475 (53.5%)	Surveillance n = 412 (46.5%)	*p* value
HBV	22 (4.6%)	19 (4.6%)	0.99
HCV	333 (70.1%)	358 (86.9%)	<0.01
Alcohol	412 (86.7%)	372 (90.3%)	<0.01
NAFLD	21 (4.4%)	6 (1.5%)	0.01
Annual visit*, yes	298 (62.7%)	283 (68.7%)	0.06
BCLC stage			
0/A	55 (11.6%)	112 (27.2%)	<0.01
B	105 (22.1%)	94 (22.8%)	
C	168 (35.4%)	109 (26.5%)	
D	115 (24.2%)	62 (15%)	
M	32 (6.7%)	35 (8.5%)	
Mode of HCC diagnosis			
Diagnostic	425 (89.5%)	43 (10.4%)	<0.01
Incidental	50 (10.5%)	7 (1.7%)	
Surveillance	-	362 (87.9%)	
HCC treatment			<0.01
Transplantation	18 (3.8%)	15 (3.6%)	
Resection	14 (2.9%)	29 (7.0%)	
Ablation	21 (4.4%)	42 (10.2%)	
Palliative	216 (45.5%)	244 (59.2%)	
None	206 (43.4%)	82 (19.9%)	
Method of surveillance			
Imaging +AFP	-	320 (77.7%)	
Imaging only	-	92 (22.3%)	

US: less than 20% of HCC found by screening

Hepatology 2010 52:132

J of Hepatology 2016 **65**:1148

HCC AND RISK FACTORS – OTHER CAUSES

HCC incidence

Stage IV PBC	3-5%/yr
Cirrhotic Hemochromatosis	1.5%
Alpha1AT cirrhosis	1.5%
Cryptogenic cirrhosis	1.5%
Alcoholic Cirrhosis	? 2%
NASH Cirrhosis	? 2%
Wilson's Dz Cirrhosis	?

Multipliers

Family History

Alcohol

There are reasons other than HCC to drive an interest in the dx of cirrhosis – risks of hemorrhage and HE and unappreciated surgical risks….

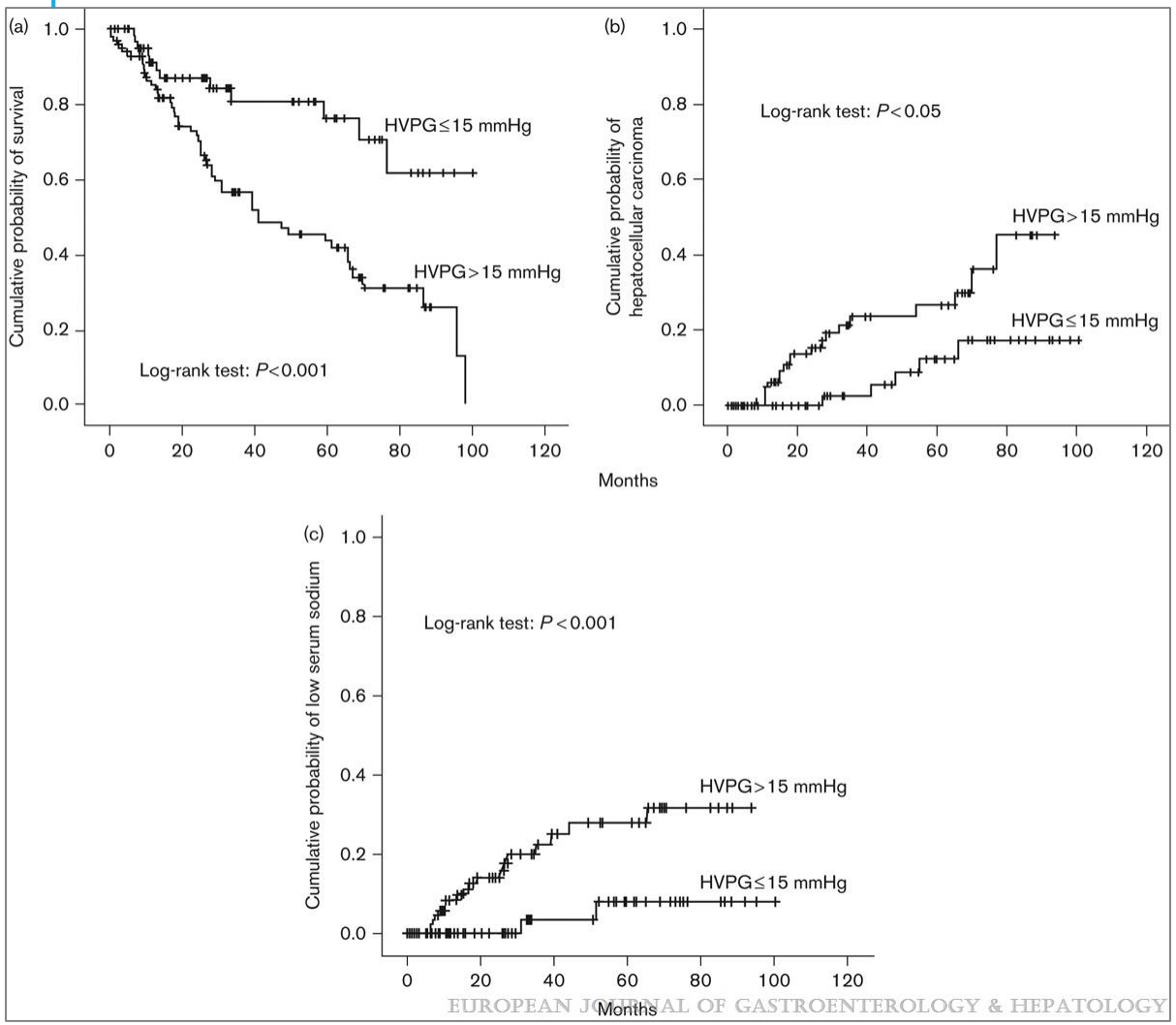
FIG. 2

Hepatic venous pressure gradient can predict the development of hepatocellular carcinoma and hyponatremia in decompensated alcoholic cirrhosis

Kim, Moon Young; Baik, Soon Koo; Yea, Chang Jin; Lee, Il Young; Kim, Hye Jung; Park, Kyong Won; Kim, Hearn Kook; Suk, Ki Tae; Kim, Jae Woo; Kim, Hyun Soo; Kwon, Sang Ok; Cha, Seung Hwan; Kim, Young Ju; Koh, Sang Baek; Chang, Sei Jin

European Journal of Gastroenterology & Hepatology21(11):1241-1246, November 2009.

doi: 10.1097/MEG.0b013e32832a21c1



Kaplan–Meier curves of (a) survival; (b) the development of hepatocellular carcinoma; (c) the development of low serum sodium (<130 mEq/l) according to hepatic venous pressure gradient (HVPG) above or below 15 mmHg.

GUIDELINES

American and **European Association for the Study of Liver Disease Guidelines** are readily available re evaluation and treatment of Ascites, SBP, Liver Failure, Hep B, Hep C, Wilson's Disease, Hemachromatosis, Autoimmune Hepatitis, Alcoholic Hepatitis, Variceal Bleeding, Vascular Disease of the Liver, Liver Transplantation, HCC among others……(and advocate HCC screening)

- www.aasld.org www.easl.eu

……but none on identifying Cirrhosis….

SO IF FOLLOWING GUIDELINES HAS MERIT…

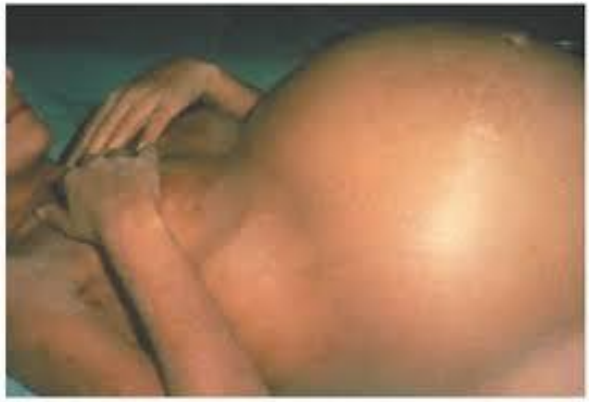
We need to be better at recognizing the patient at risk…..

Dr Robert Saundby M.D. Edin in BMJ 6/26/1886:

- Alcoholic
- Cardiac
- Biliary
- Syphilitic
- Tubercular
- Malarial
- Scarlatinal

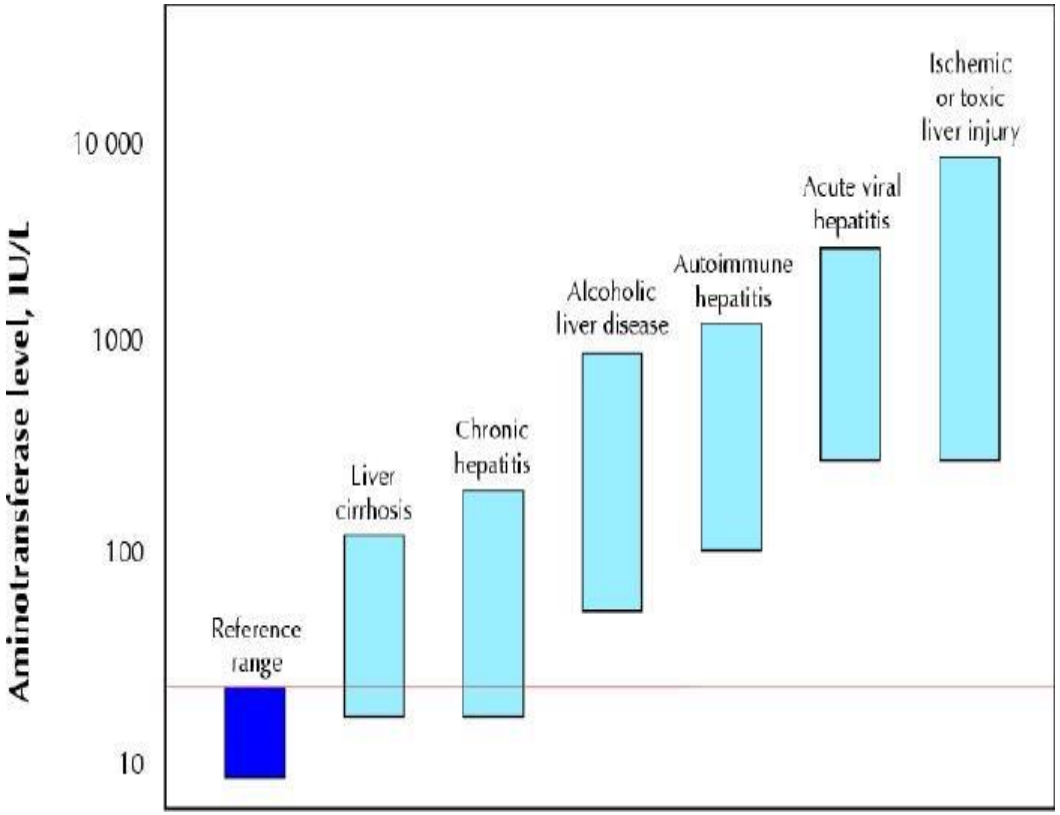
Diagnosis by Autopsy

ADVANCED CIRRHOSIS IS EASY



How do we find the EARLY cases….

BROADLY SPEAKING



CIRRHOSIS SUGGESTED BY

Abnormalities of INR, Bilirubin & Albumin

Physical/Imaging findings of Portal Htn

Risk factors for known liver diseases

- Metabolic - ? Family history
- Viral – exposure?
- NAFLD - habitus

Child-Turcotte-Pugh (CTP) Score

	Points 1	2	3
Encephalopathy	None	Grade 1-2 (precipitant)	Grade 3-4 (chronic)
Ascites	None	Mild	Moderate
Bilirub	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
PT (seconds prolonged)	<4	4-6	>6
or INR	<1.7	1.7-2.3	>2.3

Child A: 5-6 pts Child B: 7-9 pts Child C: 10-15 pts

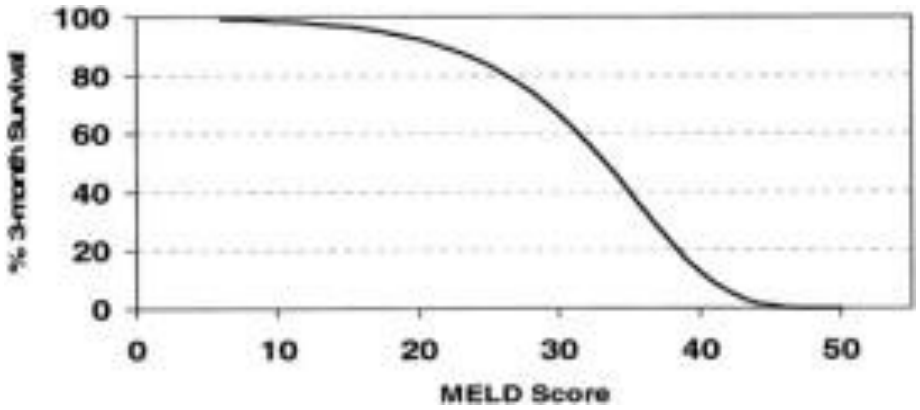
Survival by Child's Class

Child's Class	Points	1 Yr survival	2 Yr Survival
A	*5-6*	*100*	*85*
B	*7-9*	*80*	*60*
C	*10-15*	*45*	*35*

The LFTs with *prognostic power* are Bilirubin, Albumin and INR

SURVIVAL AND MELD SCORE

INR BILI (Creat
Na+)



3 Month Mortality :

MELD score > 40 : 71.3% mortality
MELD score 30–39 : 52.6% mortality
MELD score 20–29 : 19.6% mortality
MELD score 10–19 : 6.0% mortality
MELD score < 9 : 1.9% mortality

HOW DO YOU FIND EARLY CIRRHOSIS?

Lab?

Elevated transaminases - 7.9%

- Of these, 10-15% cirrhotic Am J Gas 2003 **98**:960

(Elevated liver enzymes, approached by lab tests alone roughly 500$ for 50% yield) J of Hepatology 2017 **66**:313

SINGLE MOST USEFUL LAB TEST – PLATELETS < 160 (LR 6.3) ; Albumin <3.5; elevated INR (LR 4-5)

Signs

Likelihood Ratio >4 for distended abd veins, encephalopathy, ascites and spider nevi JAMA 2012 **307**:832

WHAT ELSE CHANGES PRE-TEST PROBABILITIES?

Risk factors for chronic liver disease

DM – LR 2.8

History of obesity

Family history of liver disease

1945-1965 cohort

Sex Drugs & Rock and Roll

THE LURKING CIRRHOTIC….

Right Birth Cohort – but Hep C Neg…

Obese

Used to drink

Ambiguous family history

A liver test abnormality now and then over the years…..

Platelets between 140 and 160…..

- MUST image that patient.

IMAGING EVIDENCE OF CIRRHOSIS

ABDOMINAL US

- Liver morphology
- Liver Density
- Para-umbilical veins
- Portal vein dilation
- Ascites
- Splenomegaly

Cross-sectional imaging – same as US plus

- Collaterals/varices
- Portal thrombosis

SUSPICION/LAB/IMAGING – BINGO!

Diagnosis!

Transplant Potential

HCC Screening

Variceal Screening

Treatable liver disease:

- Nash
- Ash
- Hep B
- Hep C
- Hemochromatosis & Wilson's Disease
- PBC and PSC
- Family implications…

Address comorbidities

Potential Cure

(Depending on gradient…)

Recognizing Cirrhosis NEJM 8/25/2016

High index of awareness of the possibility of cirrhosis
- History: risk factors
- Physical examination: firm liver, ascites, stigmata of cirrhosis
- Abnormal liver tests
- Platelet count <160,000/mm^3

↓

Suspicion of cirrhosis

↓

Abdominal imaging suggestive of or confirming cirrhosis

↓

Refer to gastroenterologist or hepatologist (if available)

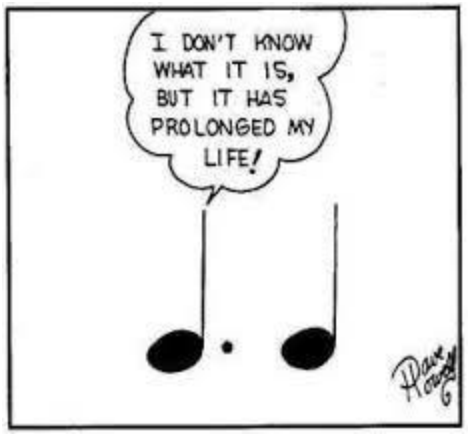
- Screen for reversible causes of cirrhosis and treat if treatable
- Care coordination

↓

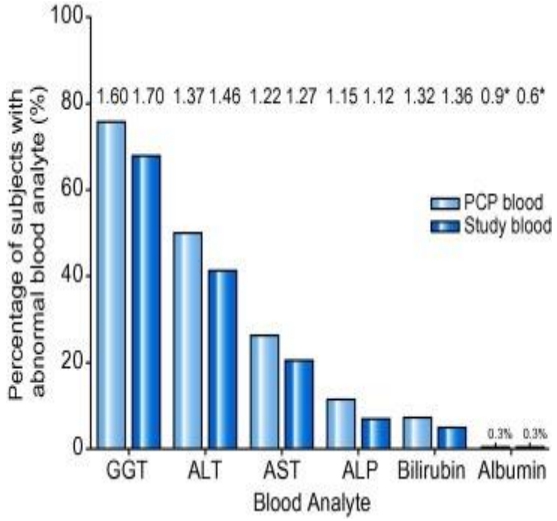
Management of cirrhosis and prevention of complications
- Education
- Lifestyle modification
- Protect liver from harm

↓

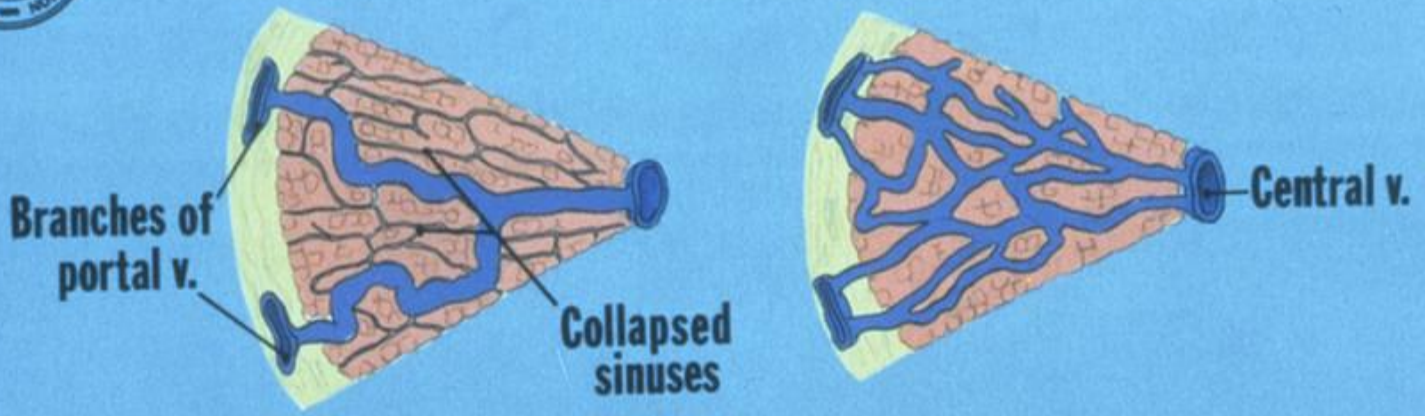
- Discontinue harmful medications
- Monitor blood pressure and discontinue anti-hypertensive agents when mean arterial pressure ≤82 mm Hg
- Avoid alcohol, NSAIDs, herbal supplements, raw shellfish
- Initiate evaluation for liver transplantation if appropriate
- Maintain vigilance for complications of cirrhosis
- Screen for hepato-cellular carcinoma every 6 mo
- Weigh risks and benefits of invasive procedures, especially abdominal surgery
- Screen for esophageal varices

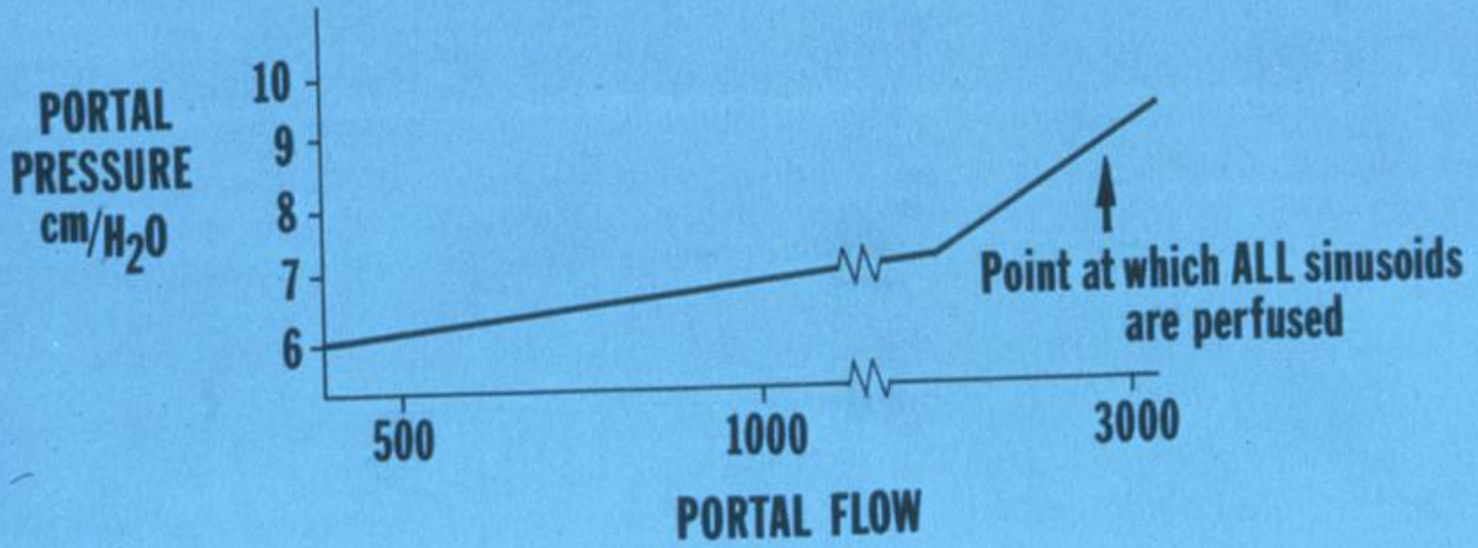

I DON'T KNOW WHAT IT IS, BUT IT HAS PROLONGED MY LIFE!

ABNORMAL “LFT”S IN FATTY LIVER



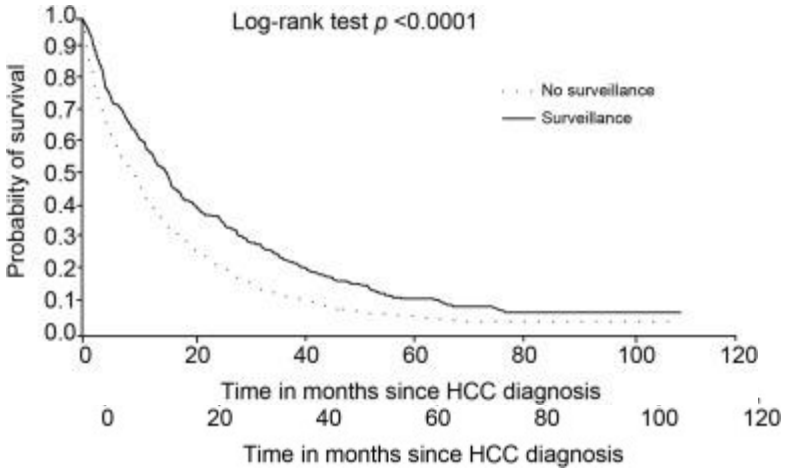
INCREASED PORTAL FLOW USES MORE SINUSOIDS





THE IMPACT OF SCREENING-DERIVED HCC IDENTIFICATION

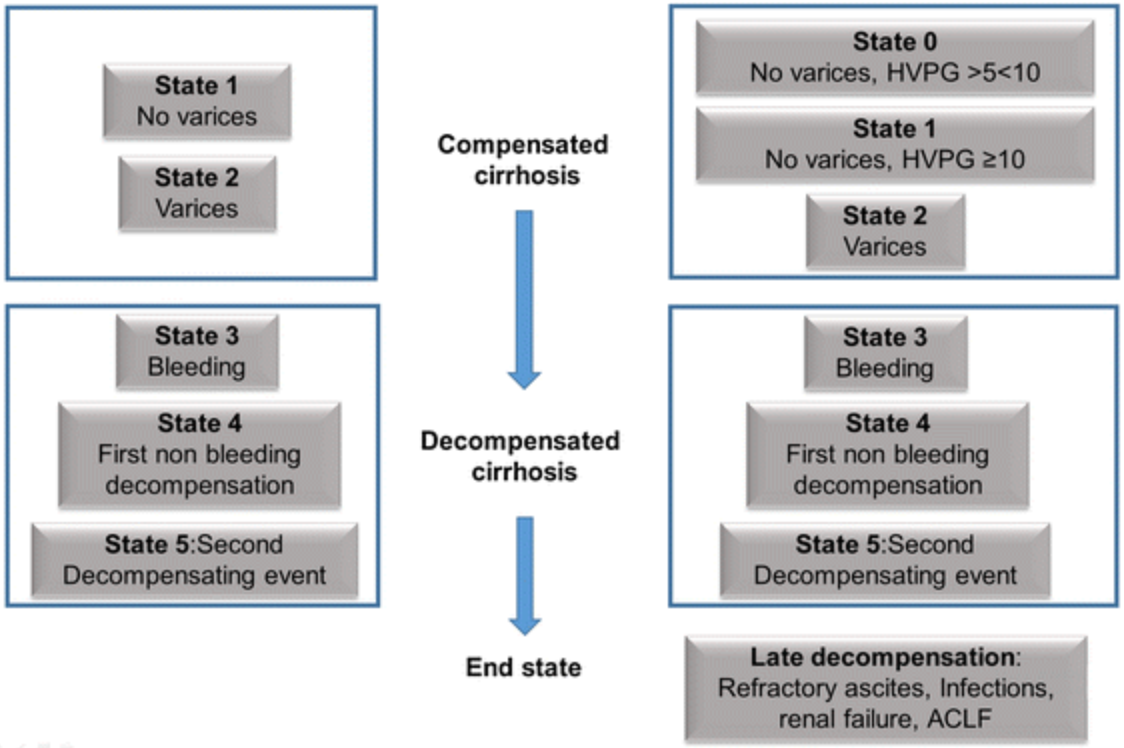
Surveillance meant stat. sig. increase in likelihood of early stage diagnosis and access to potentially curative Rx with overall 1/3 reduction in Mortality Risk



Benefit mediated by stage migration and Rx persisted after adjustment for lead-time and length-time bias…

Fig. 3

Representation of proposed multistate models for the clinical course of cirrhosis. *Left side* Multistate model proposed by a prospective cohort study. *Right side* More comprehensive model including earlier and later disease states



HCC AND HEP C

Incidence in Hep C cirrhosis 3-5%/yr Gastro 2004 127:S35

Infection to HCC – 17 to 34 years Hepatology 2002 36:S74

Interferon Rx did not affect HCC rate with advanced fibrosis NEJM 2008 359:2429; Gastro 2011 140:1990

Recent meta-analysis of 25,000+ patients suggests HCC rate 1.5% with SVR, 6.2% without - but **using IF Rx** Ann Int Med 2013 158:329

Bottom line: We are pretty good at finding and treating Hep C – but the HCC risk remains…and the impact of DAAs on this risk may not be the same as the impact of Interferon…

El-Serag, H.B. and Mason, A.C. (1999) Rising incidence of hepatocellular carcinoma in the United States. NEJM, 340:745