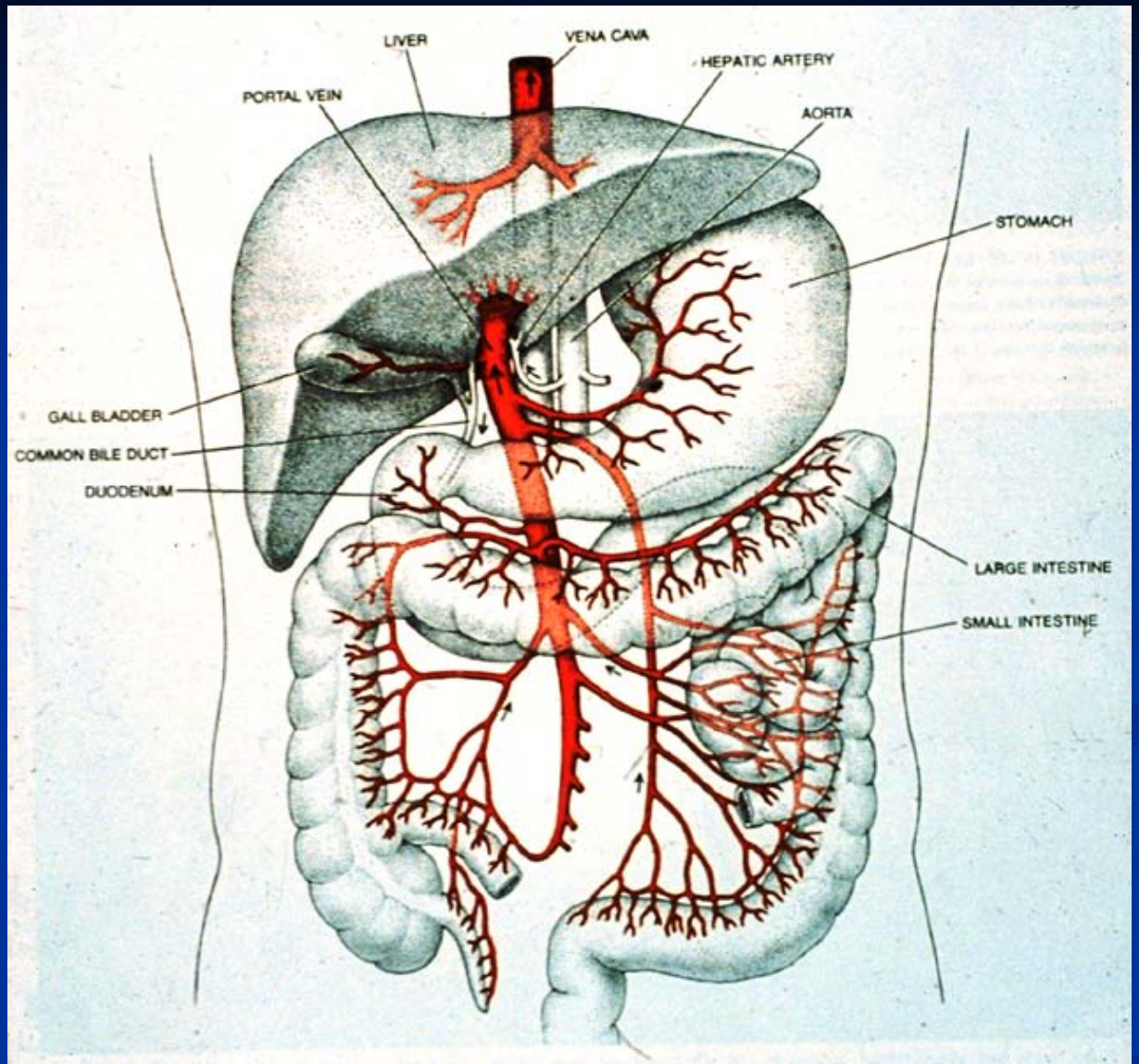
Looking Ten Years Ahead: Potential Therapies for PSC

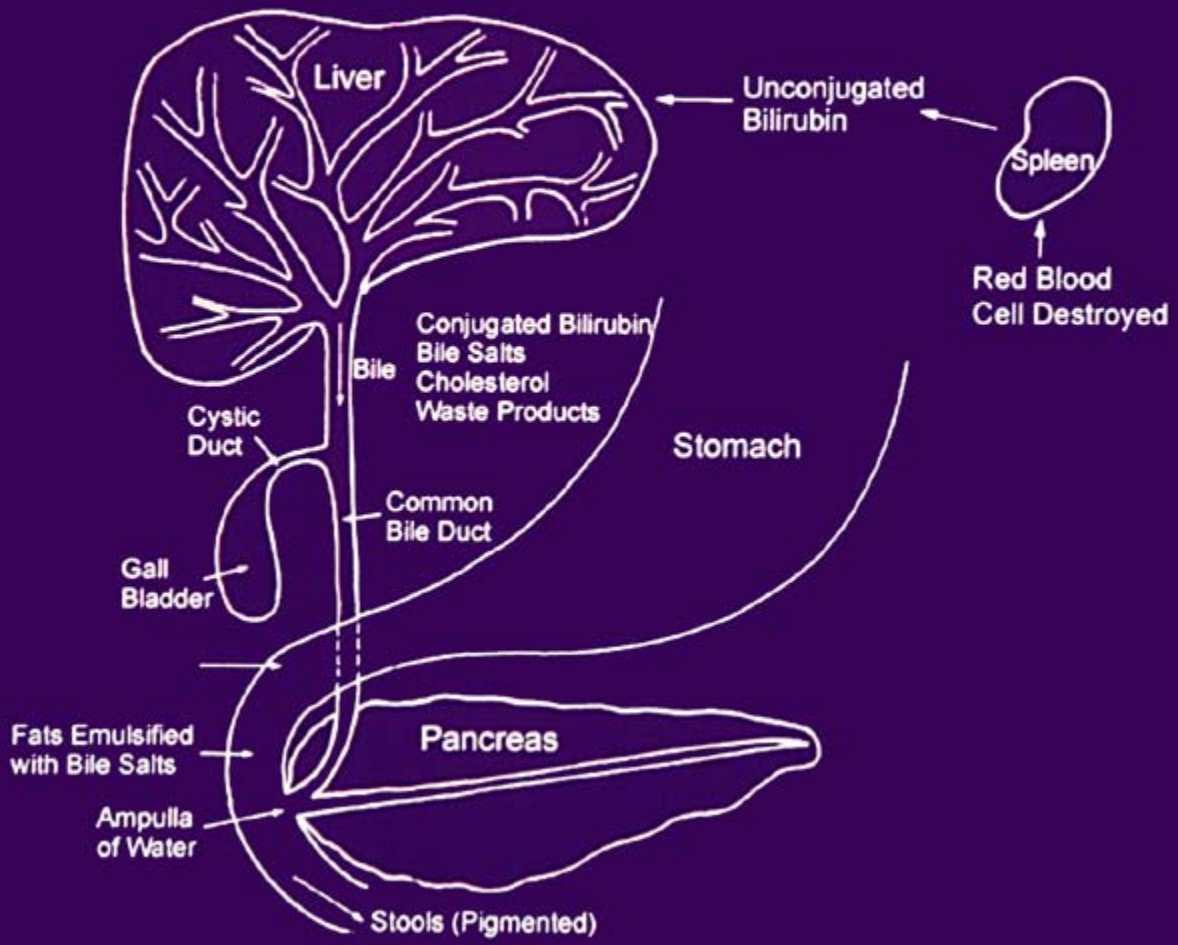
Jenny Heathcote MD
University of Toronto

LIVER CENTRE
Toronto Western Site

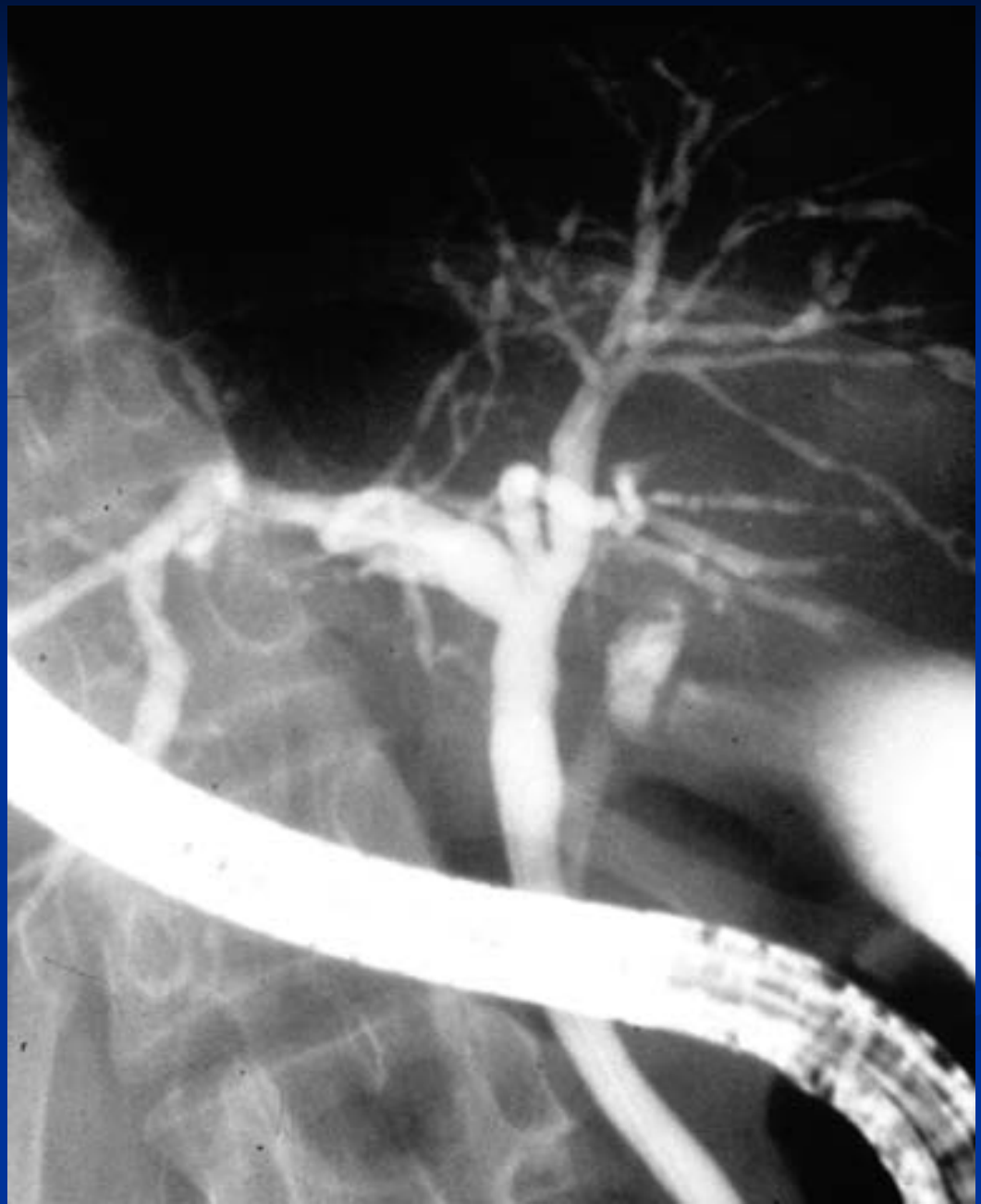


LIVER is a primary site of metabolism of substances entering the body through the alimentary tract. All the fine blood vessels that absorb nutrients and other substances through the wall of the intestines come together and enter the liver through the portal vein. The liver's supply of oxygenated blood from the heart enters through the hepatic artery. After passing through the sinusoids of the liver (*see illustration on page 26*) the blood is collected by the hepatic veins, which feed into the vena cava. The liver secretes bile, which is collected by the bile duct, stored in the gall bladder and emptied into the duodenum, the first segment of the small intestine.

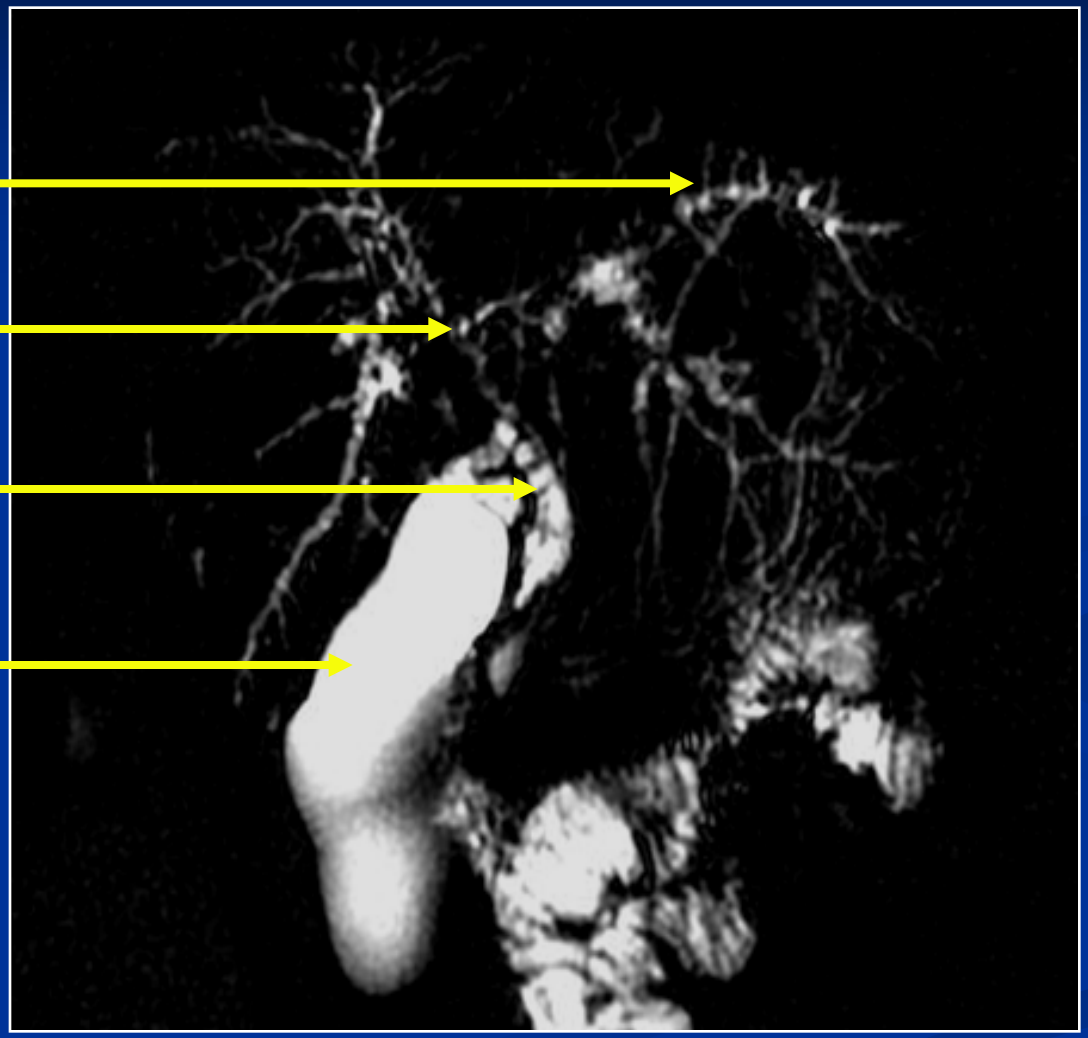
Liver and Biliary System



ERCP



MRC



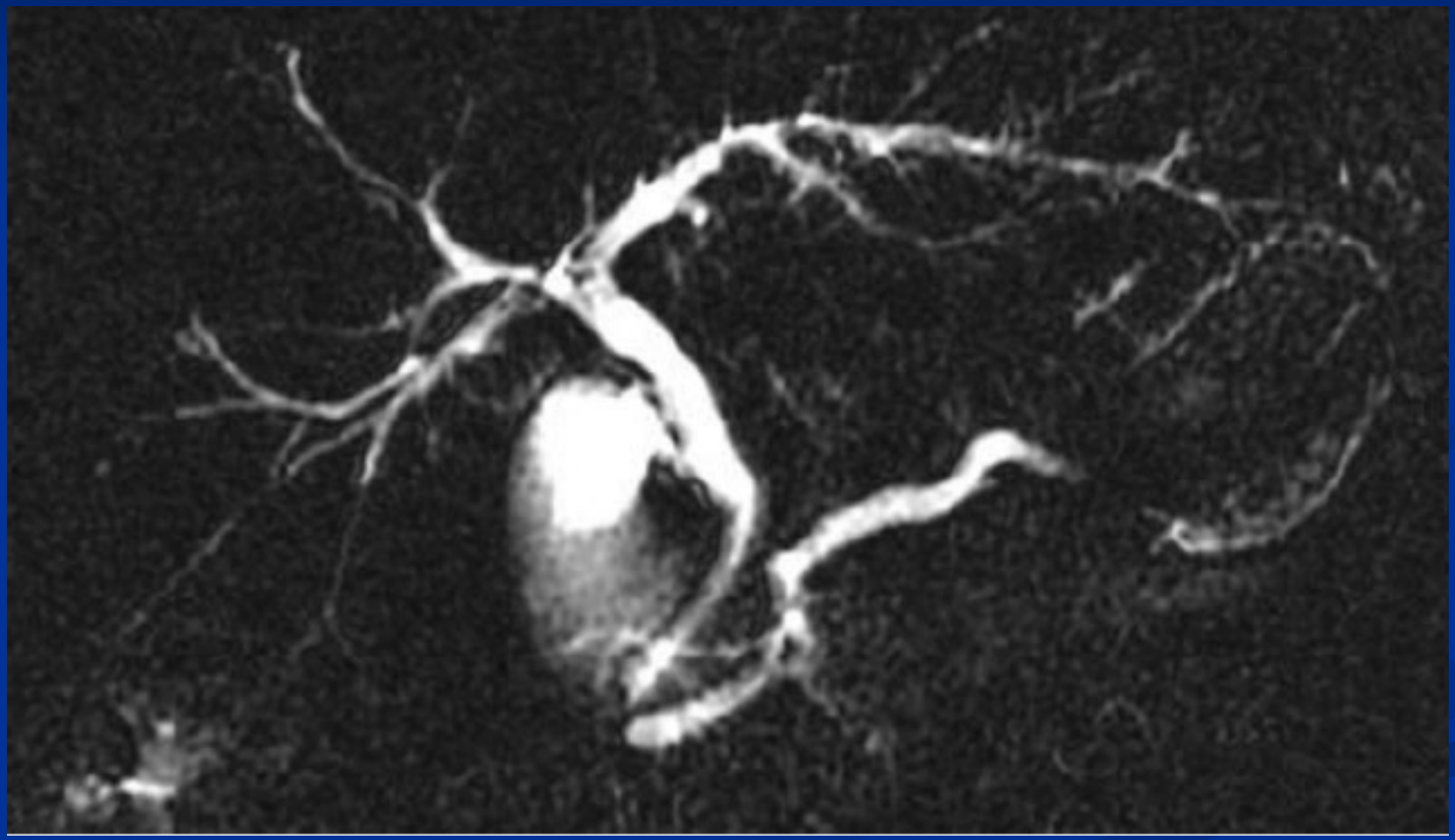
PSC

Potential Causes: Sclerosing Cholangitis

Primary – a ‘complex’ disease likely a genetic predisposition to an untoward response to an external agent(s) ? infection

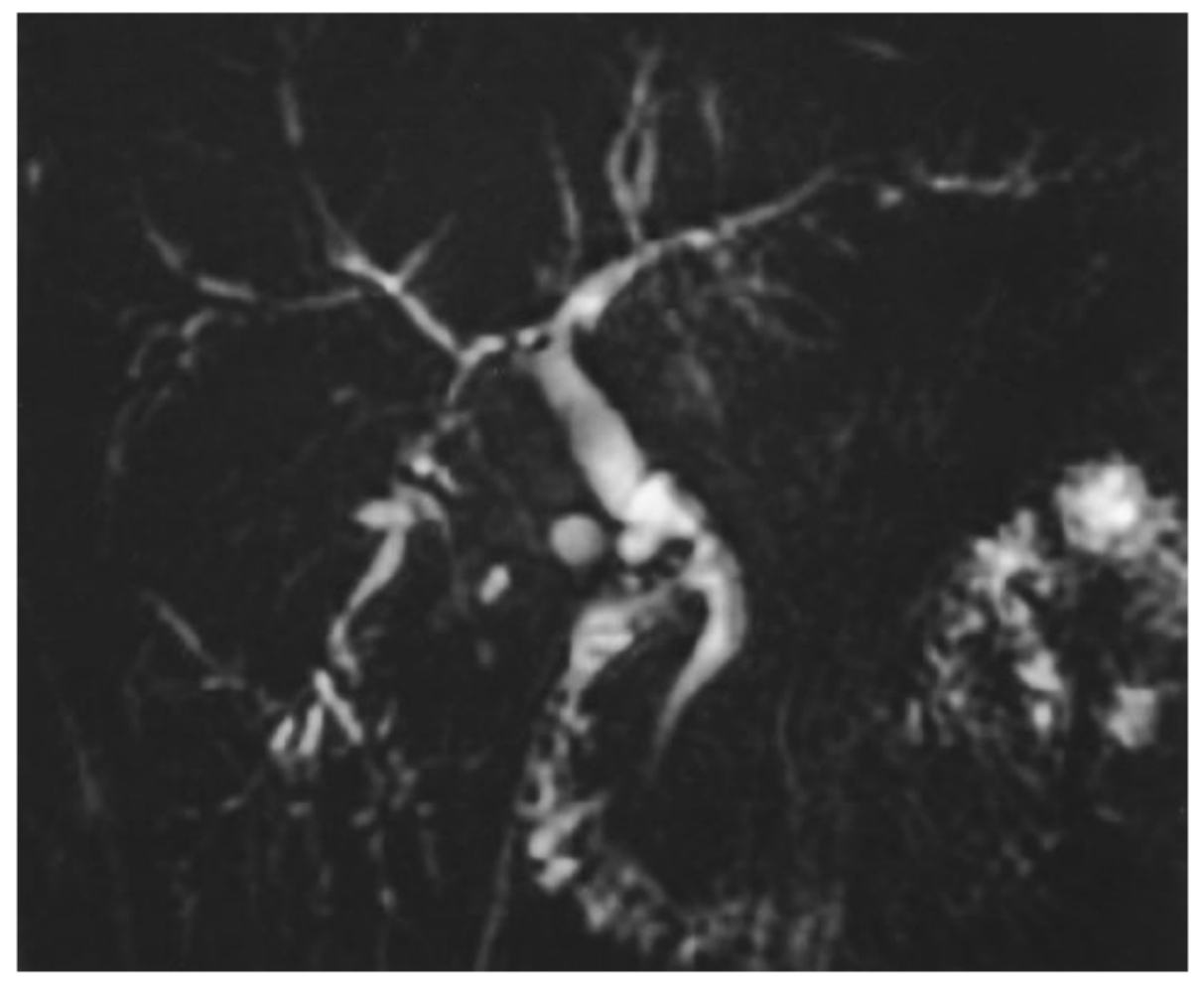
Secondary – many causes, some reversible, others not

AIDS-related cholangiopathy in HIV+ve male with cholestasis



Abdalian et al. Hepatol 2006; 44:1063

Ischemic cholangitis in male who developed jaundice 5 days after liver transplant

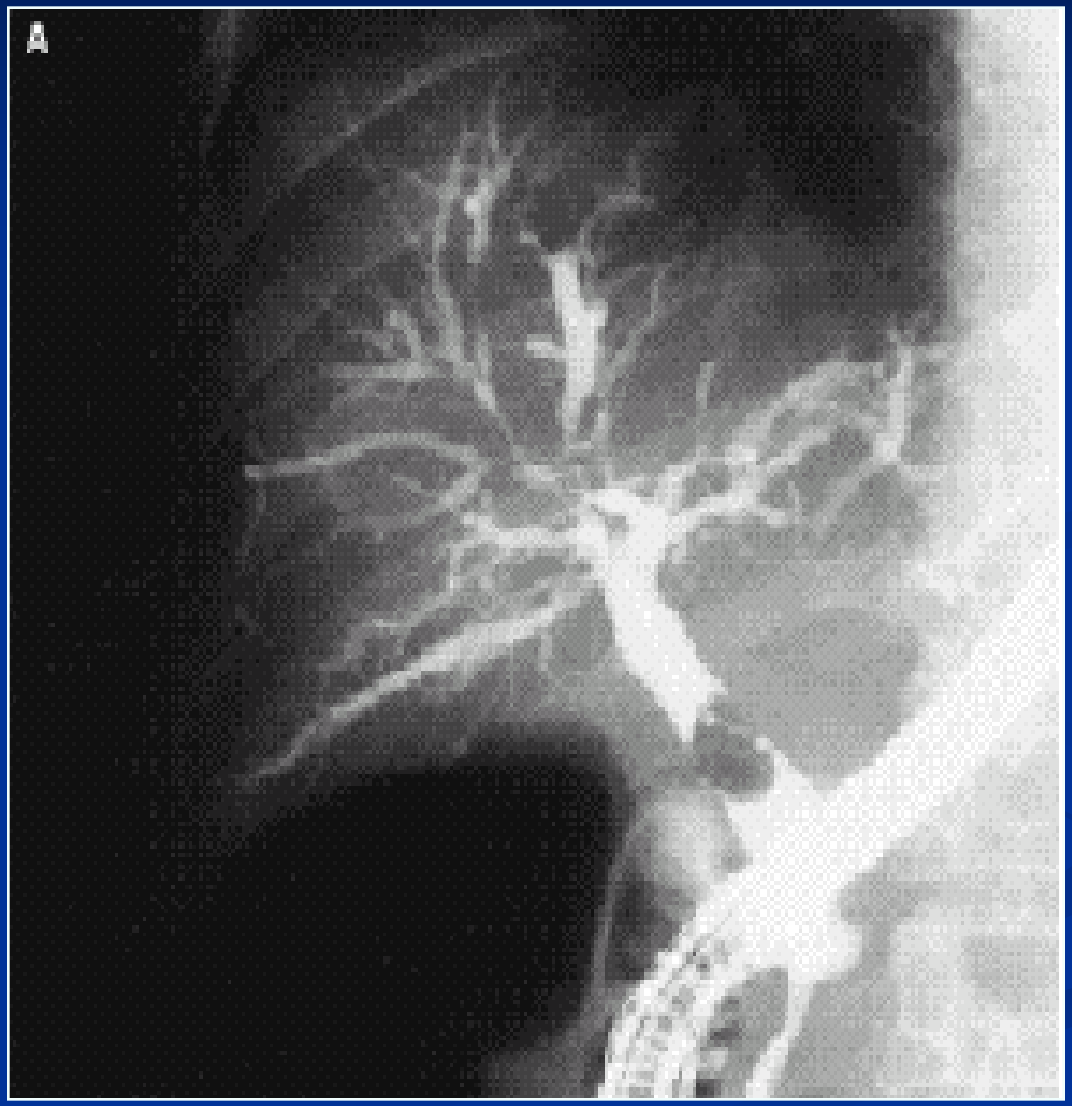


Abdalian et al. Hepatol 2006; 44:1063

Are there differences between primary and secondary SC?

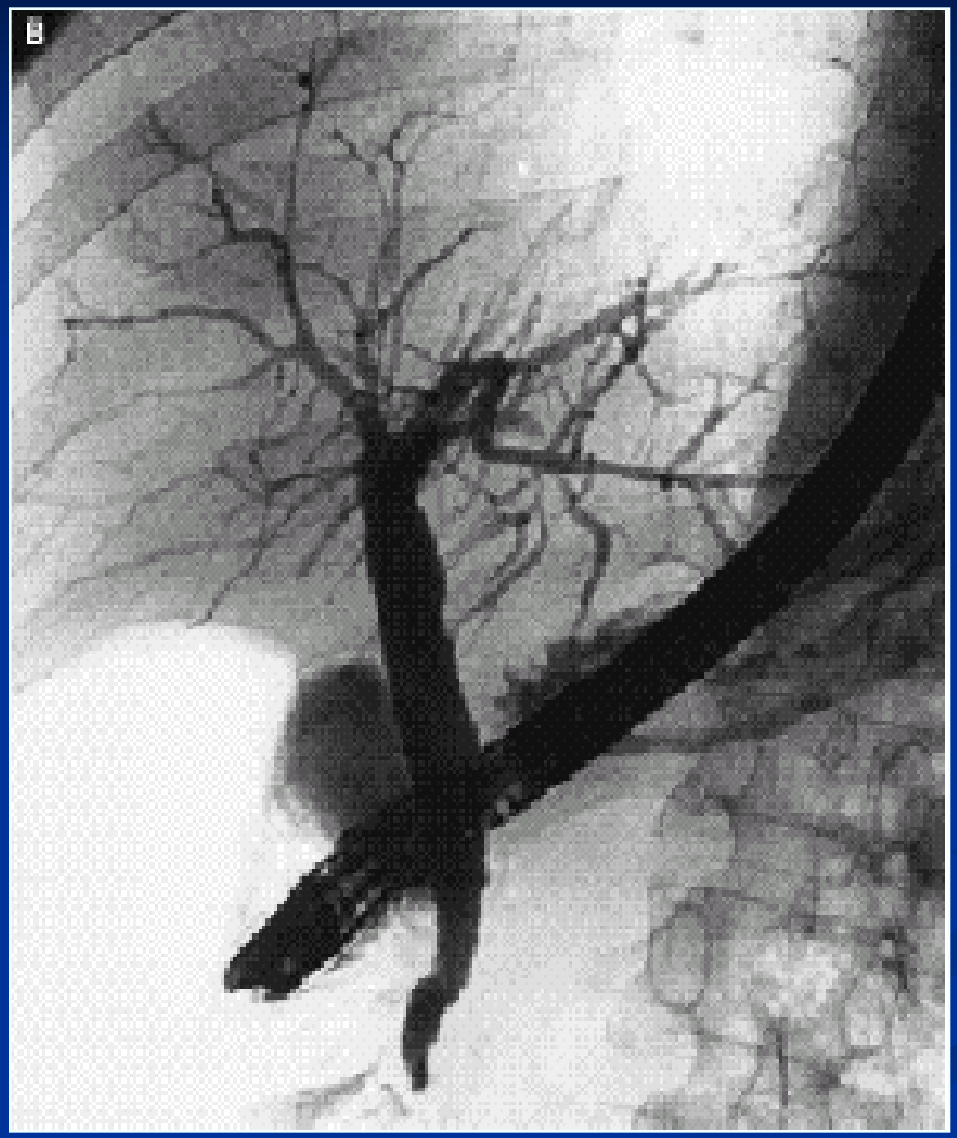
- Cause (pathogenesis)
- Management
- Outcome

AIC with marked narrowing of the lower end of the bile duct (AIP/↑ IgG4)



Erkelens et al. Lancet 1999; 354:43

ERC: 3 Months after steroid therapy



Erkelens et al. Lancet 1999; 354:43

Therapy for PSC

What has been tried?

Specific Therapies evaluated in PSC

Year	Antibiotic	# of patients	Study	Outcome
2004	Metronidazole	80	RCT	↓ liver enzymes
2007	Vancomycin	14	Case series	"
2008	Minocyclin	16	Case series	"
2008	Probiotics	14	Case series	No benefit

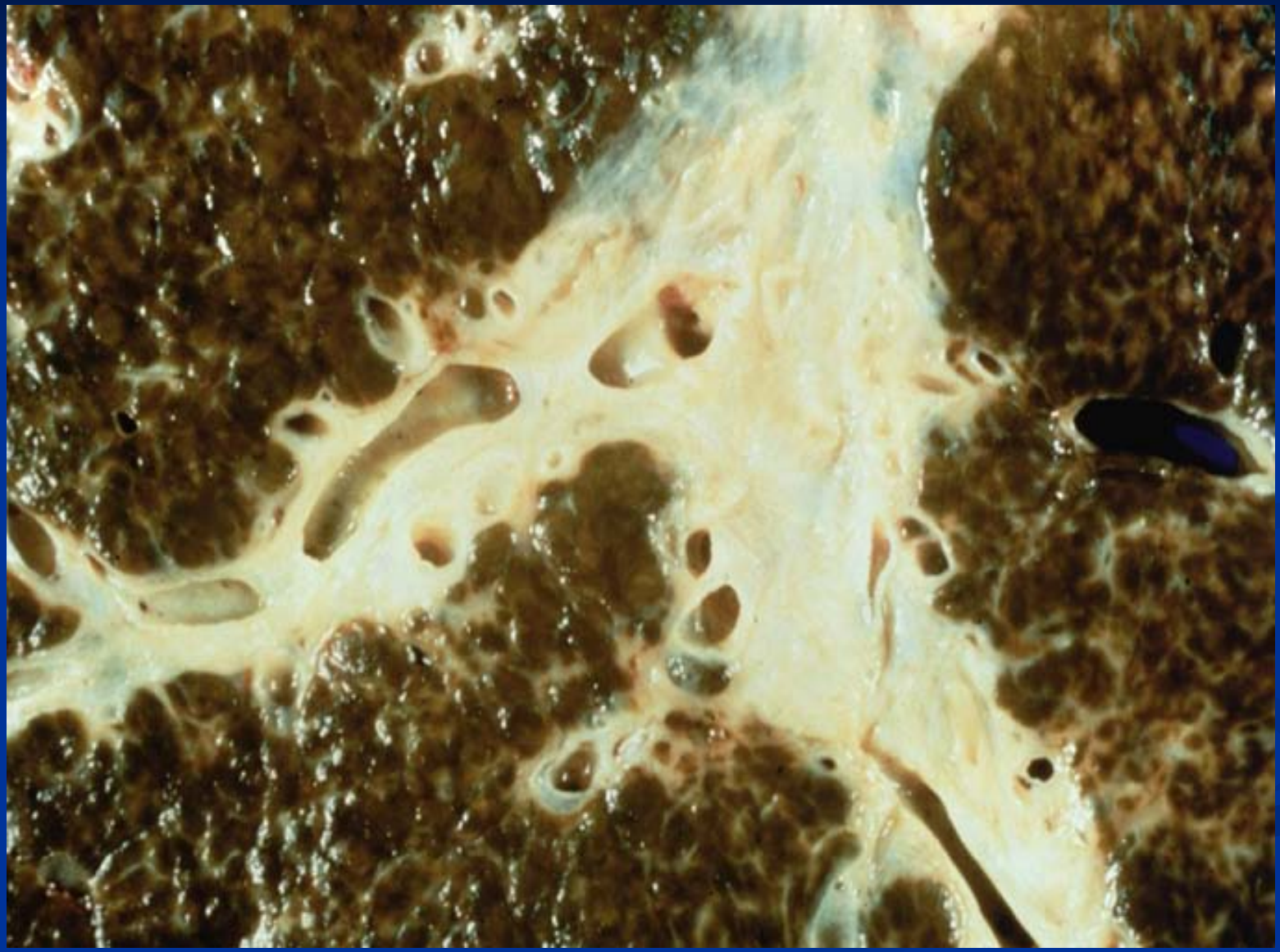
Specific Therapies evaluated in PSC

Year	Immune Modulators	# of patients	Study	Outcome
1999	Prednisone + Azathiopine +UDCA	15	Case series	↓ liver enzymes
2000	Budesonide	21	Case series	Nil
2007	Tacrolimus	16	Case series	↓ liver enzymes
2008	Infliximab	24	RCT	No benefit

Ursodeoxycholic acid for PSC

Year	Author	# of patients	Study	Outcome
1997	Lindor (13-15 mg/kg) 2 yrs	105	RCT	↓ liver enzymes No survival benefit
2005	Olsson (23 mg/kg) 5 yrs	219	RCT	↓ liver enzymes No survival benefit
2008	Cullen (30 mg/kg) 2 yrs	31	RCT	Estimated survival benefit
2008	Lindor (28-30 mg/kg) 6 yrs – stopped early	150	RCT	Survival appears worse

Why medical therapy fails in PSC?



PSC

How do we go FORWARD

only

by going BACK to basics ?

PSC: the link to colitis

PSC: 60 – 80% have colitis

Colitis: 3 – 5 % have PSC - ? true

(Can only diagnose well established PSC)

Colitis

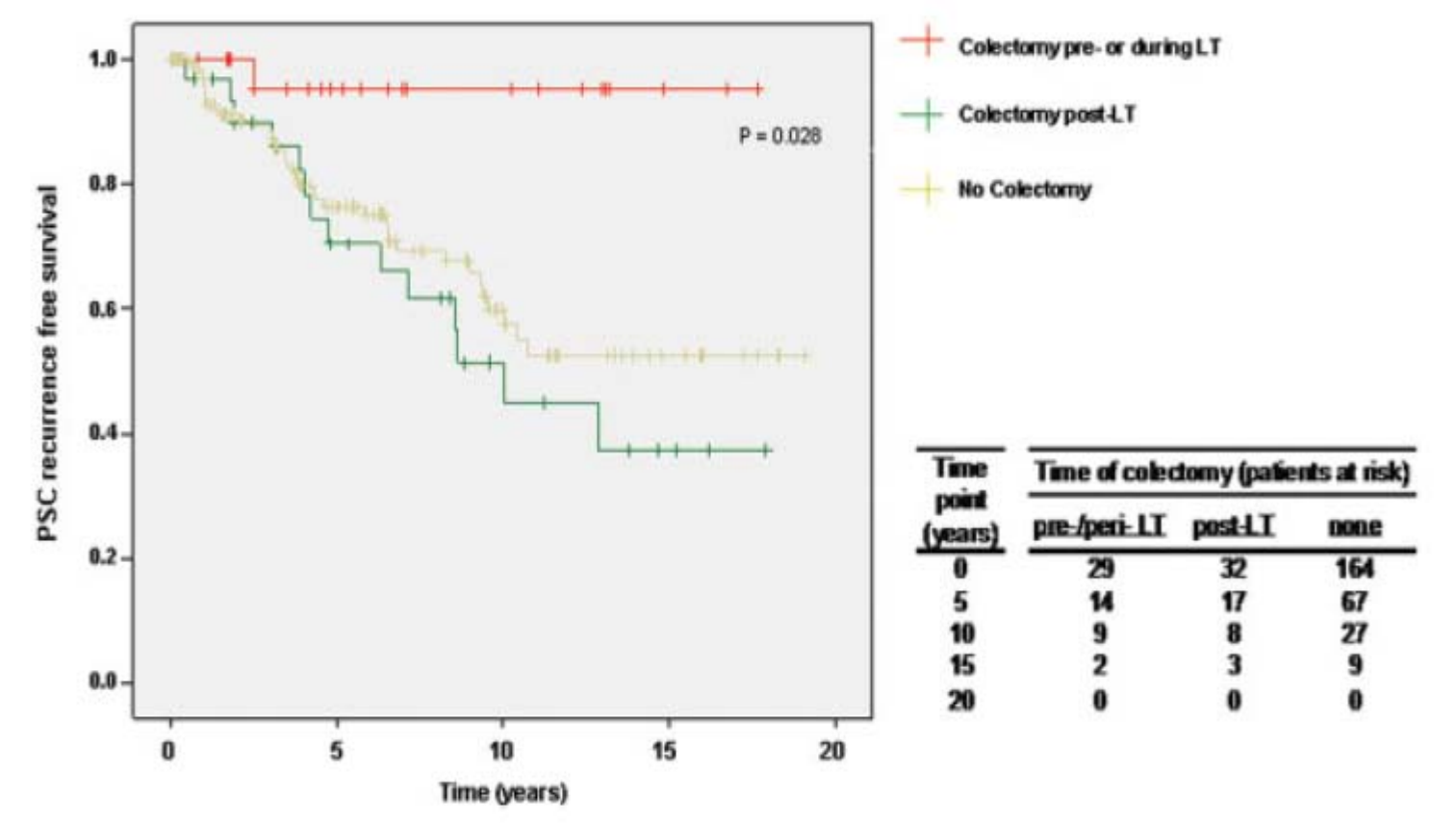
- Destructive inflammation of colon
- Micro abscesses, infiltration with several types of white blood cells (WBC)
- Leaky bowel causes WBC to migrate to the liver (via portal vein)
- Inflammatory “mediators” produced by WBC both in the colon and the liver may promote liver damage e.g. TNFα

Part of the puzzle!

- PSC may precede symptomatic colitis by 20 yrs +
- But PSC often diagnosed only following development of colitis (up to 20 yrs later)
- PSC may recur (rPSC) post liver transplant

So if there is a single mechanism something must be common e.g. genetics, the "memory" WBC

Likelihood of rPSC according to "colectomy" status (230 patients)



Time point (years)	Time of colectomy (patients at risk)		
	pre-/peri-LT	post-LT	none
0	29	32	164
5	14	17	67
10	9	8	27
15	2	3	9
20	0	0	0

Alabraba et al. Liver Transplant. 2009; 15:330

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Theory 1: Consequences of a "Leaky colon" at time of liver transplant

- White blood cells from inflamed gut continue to migrate to new liver
- These 'memory' white blood cells reactivated by steroids
- Reactivated WBC leads to higher concentrations of inflammatory mediators in the liver and the colon

Adams et al. Lancet 2002; 359:150

Predictive Factors: rPSC (post-transplant) [7 of 53 subjects transplanted for PSC]

- Prolonged use of steroids for “rejection”
- > 3 months corticosteroids (for colitis)

Cholangites et al. Liver Transplant. 2008; 14:138

Theory 2: Progenitor (stem) cells in the liver

- Have the potential to transform into both new liver cells and new bile duct cells
- "Body messengers" – cytokines and chemokines determine whether "stem cells" turn into bile duct or liver cells

Could it be that disregulation of the control of stem cells in the liver is present in people with PSC?

Other theories

- Bacterial
- Poor blood supply
- Acute “autoimmune”

Why are studies of genetic associations in PSC important?

- May identify minor changes in genes which alter a specific cell signaling pathway

- Some signaling pathways may be amenable to targeted drug therapy e.g. block a “harmful” pathway

Could an individual’s genetic profile identify those “at risk of PSC”?

(prior to scarring of the bile ducts)

How do we get there?

Large scale genetic studies

(both those with colitis and/or PSC) – please volunteer!

Identify “risk” genes

Develop appropriate “knockout” animal models

Meanwhile
Preventive Strategies: Sclerosing Cholangitis

- Cholangitis/sepsis (marked by fever): reduced by avoiding ERCP, prompt use of antibiotics (emergency prescription)
- Screening for esophageal varices (if required)
- Annual colonoscopy (check for cancer) if colitis co-exists

  (try to avoid stoma if colectomy needed)
- If gallbladder polyps present need a cholecystectomy to avoid gallbladder cancer
- Thin bones: Ca + vit D supplements ± bisphosphonates
- ? Colectomy for colitis prior to liver transplant – difficult decision

  [Screen for cholangiocarcinoma (cancer of bile ducts)]

Liver Transplantation for PSC

Survival (including those with rPSC)

1 year	90	-	97%
5 years	85	-	88%

Problems with rejection, infection, colon cancer and rPSC

Nevertheless
proceed only when you need it!

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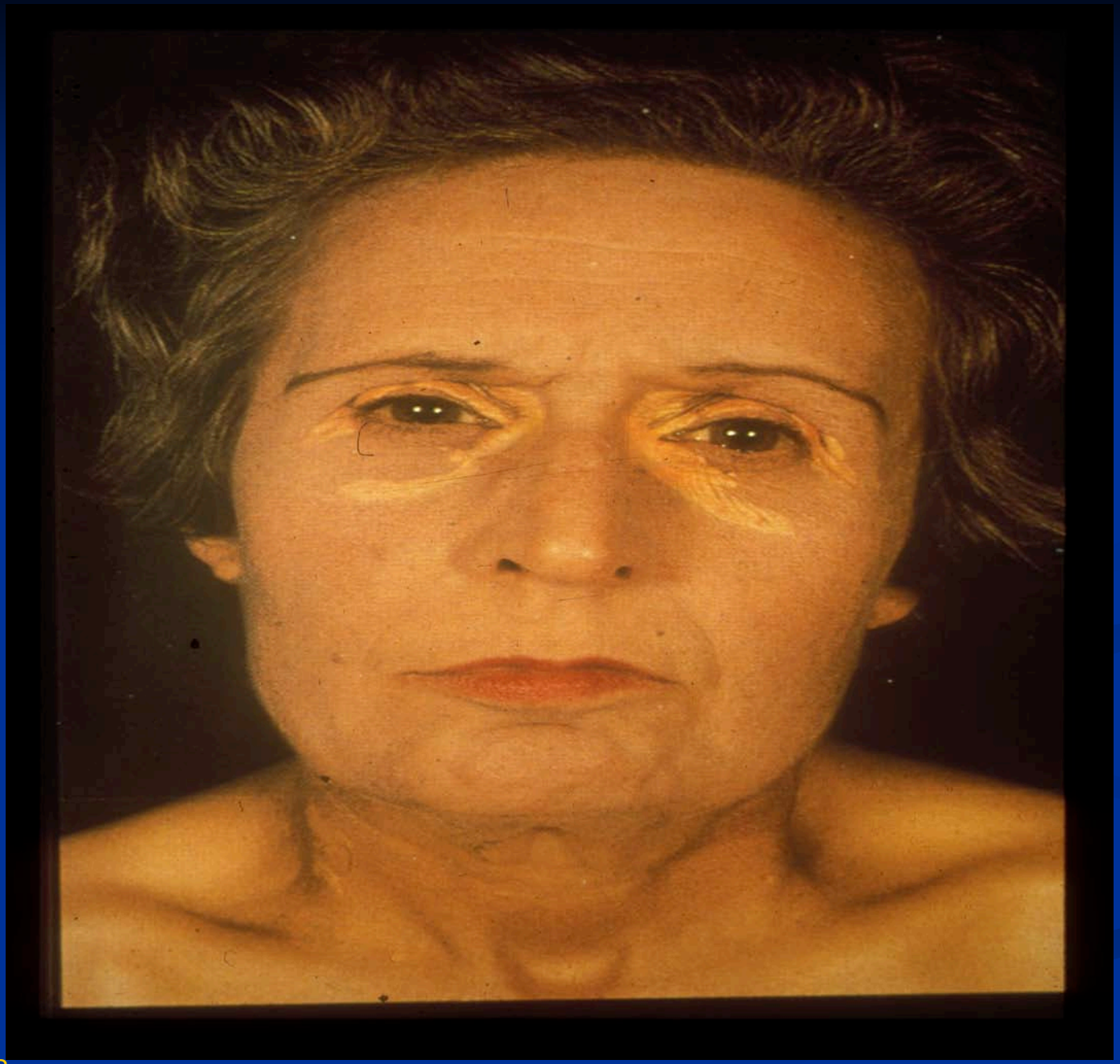
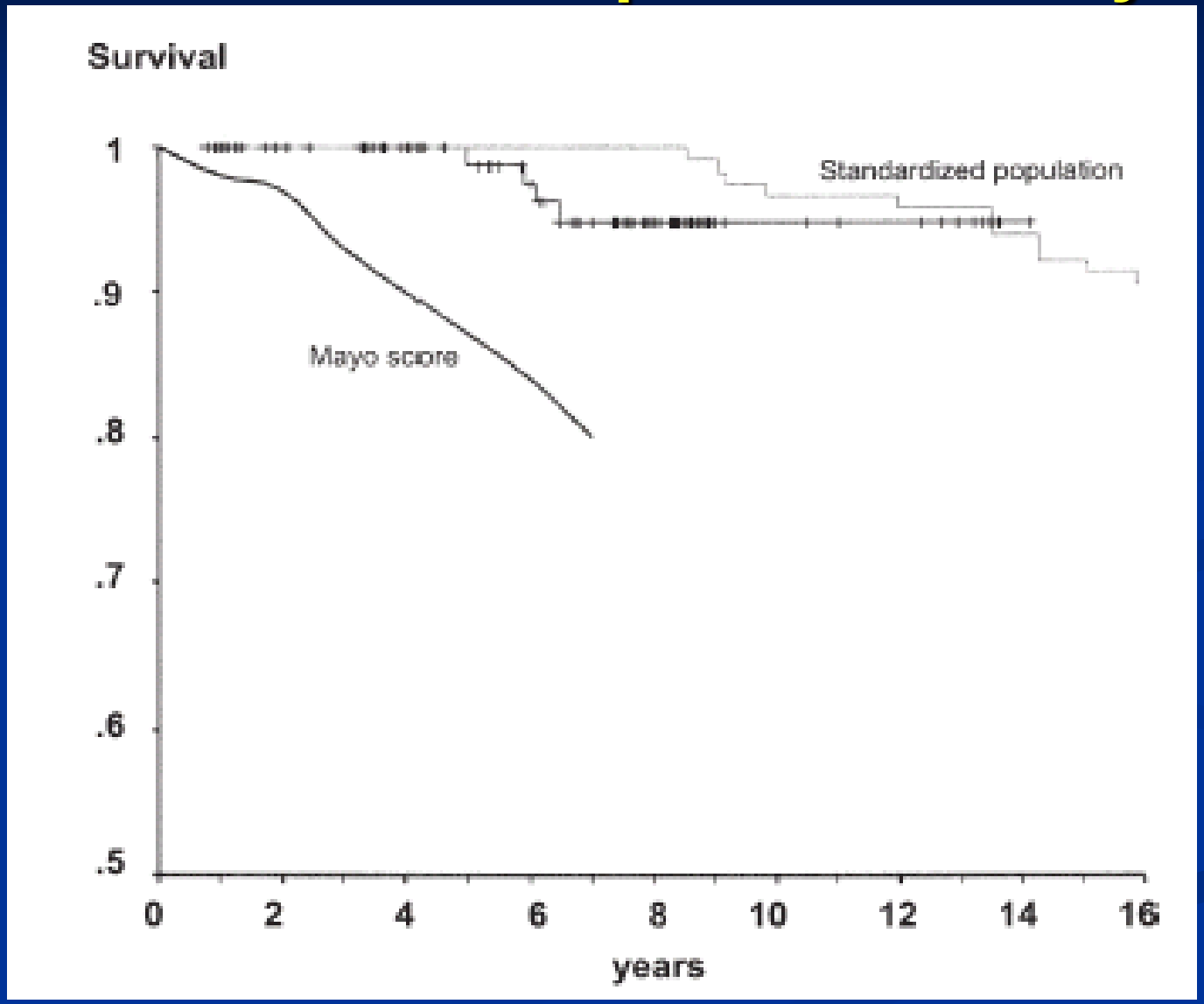
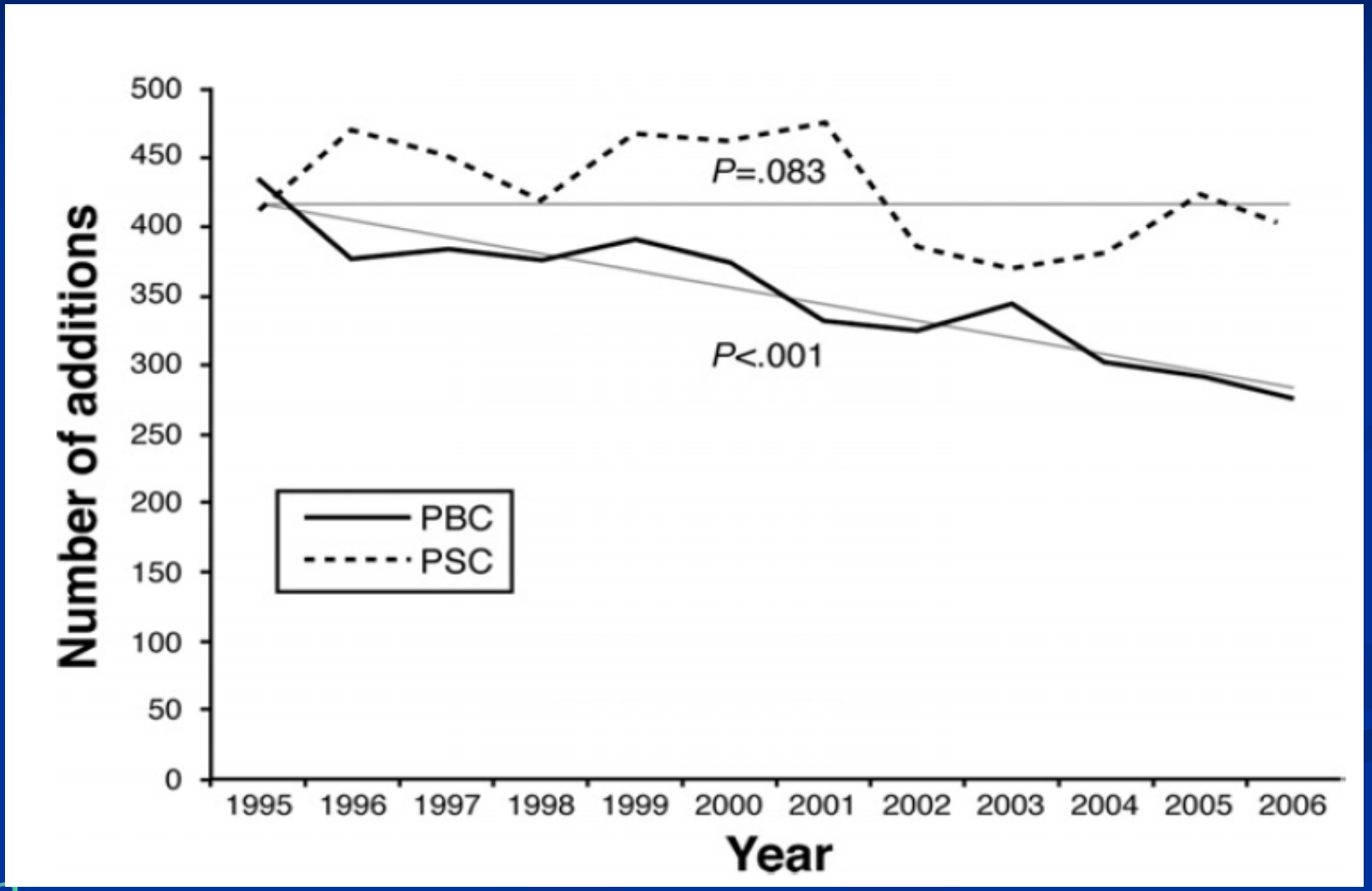


Survival to Death or Liver Tx for early PBC Good Biochemical Response After 1 yr UDCA



Pares et al. Gastroenterology 2006;130:715

Annual Transplant Waitlist PBC/PSC



Lee et al. J Clin Gastroenterol Hepatol 2007; 5:1313

Thank You