Congenital Hepatic Fibrosis:

The Liver Disease of ARPKD

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(Medical Illustrations on slides 4, 5, 6 are by Frank H. Netter)

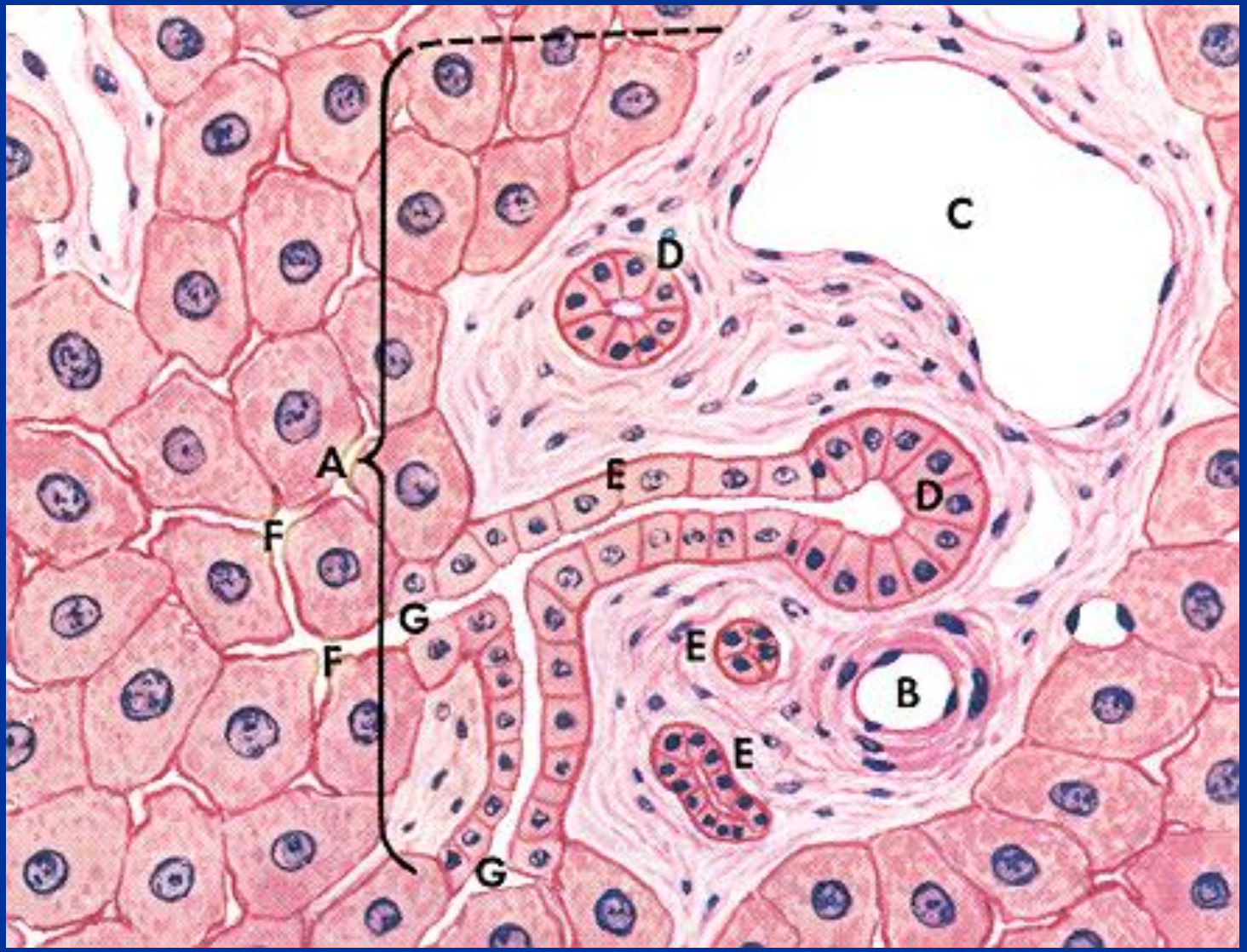
Congenital Hepatic Fibrosis

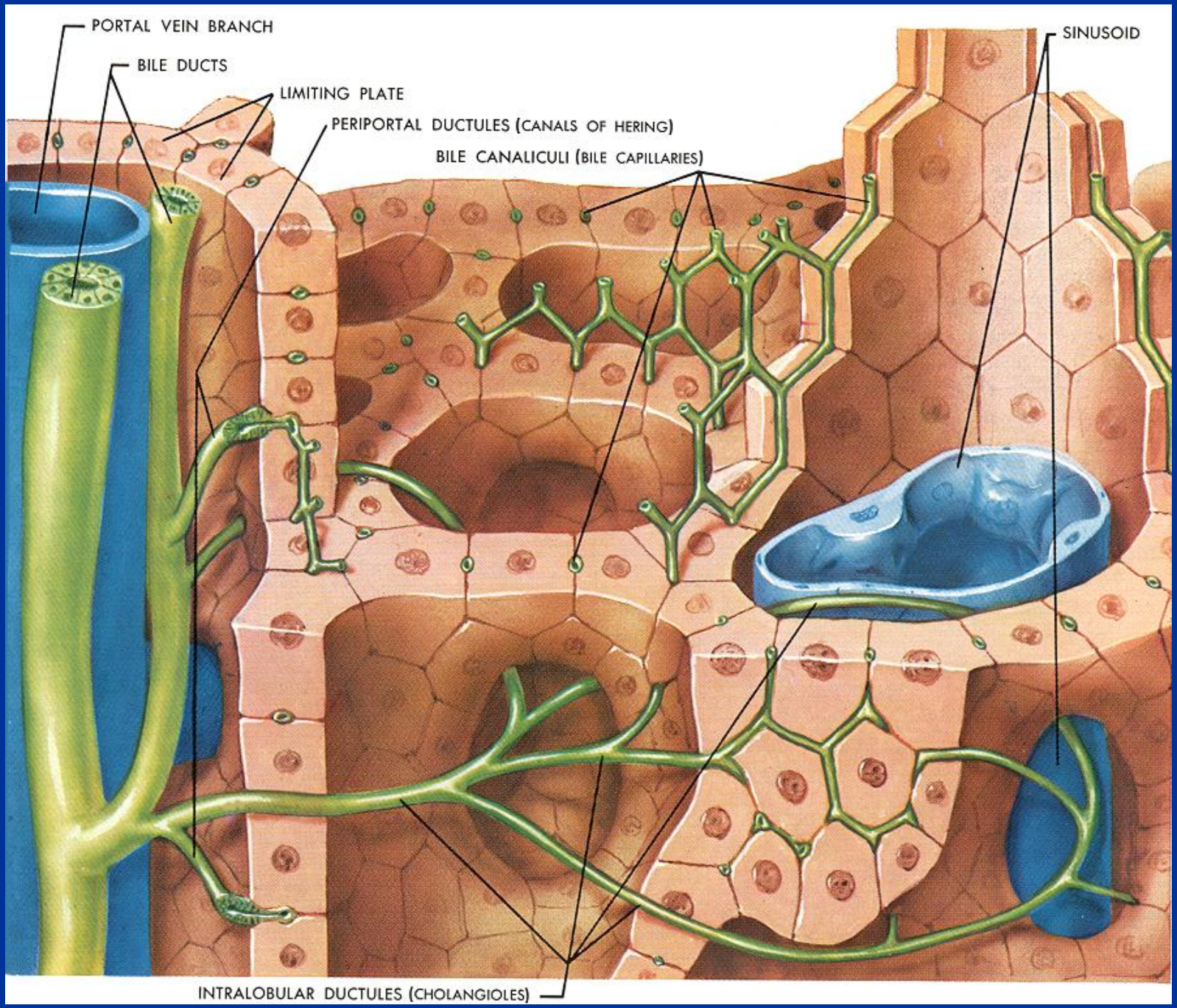
- Congenital - inherited, predetermined, or present at birth
- Hepatic - of the liver, - the disease is defined by the hepatologists rather than the nephrologists
- Fibrosis - scarring of the liver in the portal tracts - which carry blood to the liver and bile away from the liver
- For many - this term is the same as the lesion in CHF, which is the ductal plate malformation

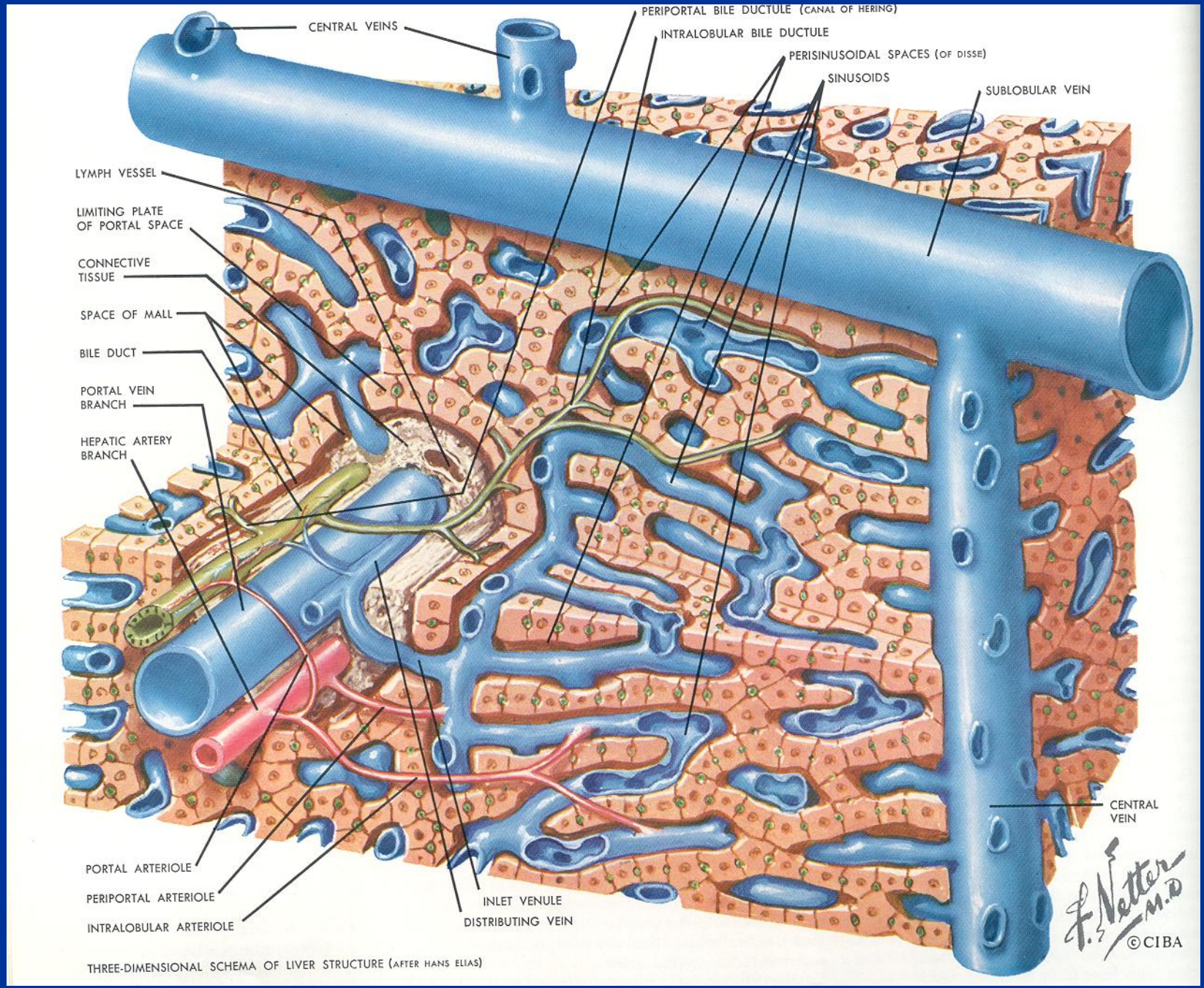
Definitions

- ARPKD: The genetic disease name, and the renal disease
- PKHD1: The gene that is mutated in ARPKD
- Fibrocystin: The protein coded by the PKHD1 gene
- CHF: The liver disease name for the pathology picture of DPM. It is due to ARPKD and many other kidney diseases
- DPM: Ductal Plate Malformation - Histology (pathology) of abnormal development of the portal tract in the liver and the bile ducts, with large amounts of fibrosis and abnormally structured bile ducts
- HTN: elevated systemic (arm) arterial blood pressure, commonly due to kidney disease
- PHTN: portal hypertension, elevated venous portal (liver, spleen) blood pressure, due to (in CHF) fibrosis and abnormal blood flow through the liver.

Diagram of Normal Portal Tract (Triad)

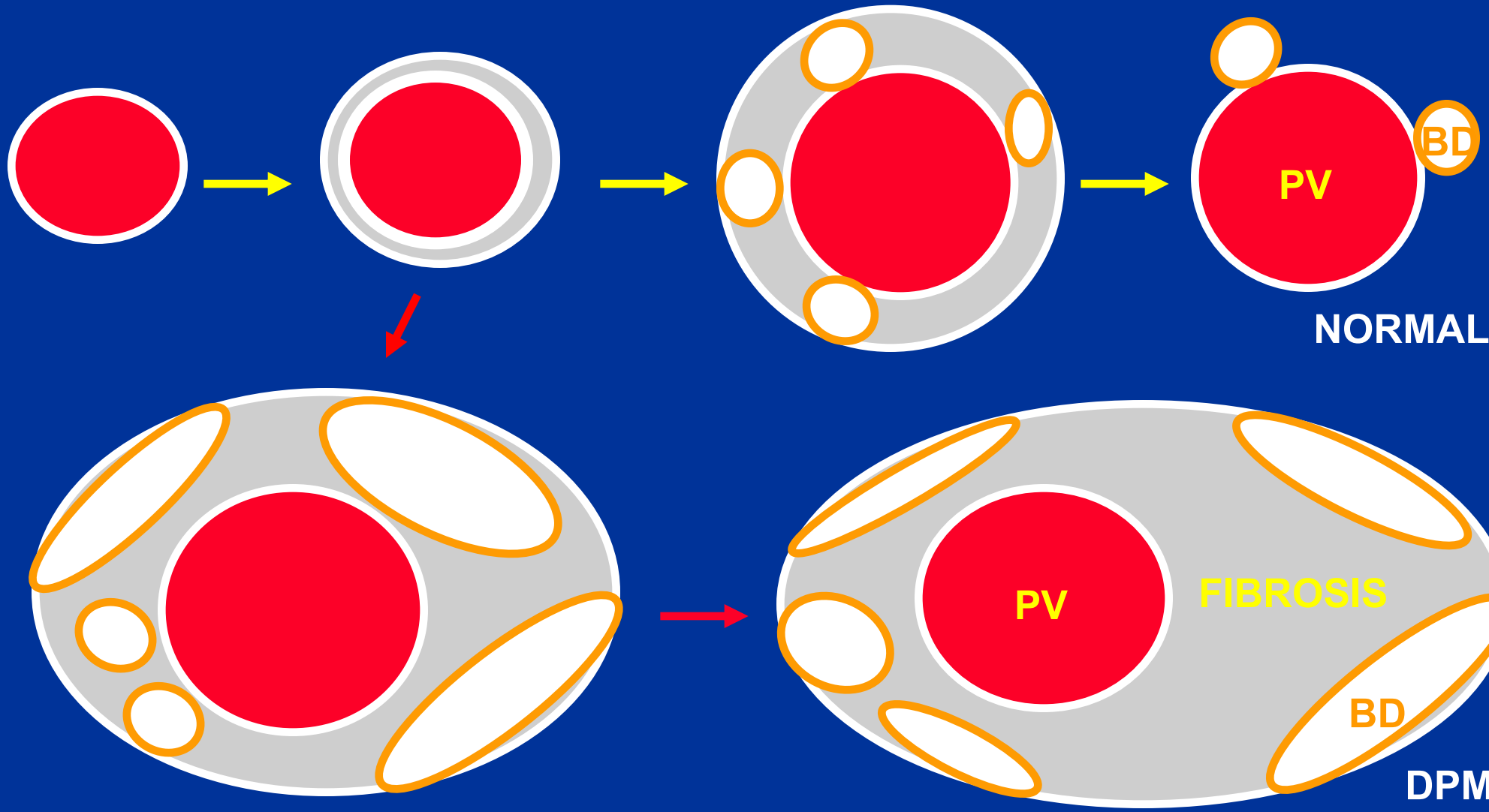



PORTAL VEIN BRANCH
BILE DUCTS
LIMITING PLATE
PERIPORTAL DUCTULES (CANALS OF HERING)
BILE CANALICULI (BILE CAPILLARIES)
SINUSOID
INTRALOBULAR DUCTULES (CHOLANGIOLES)

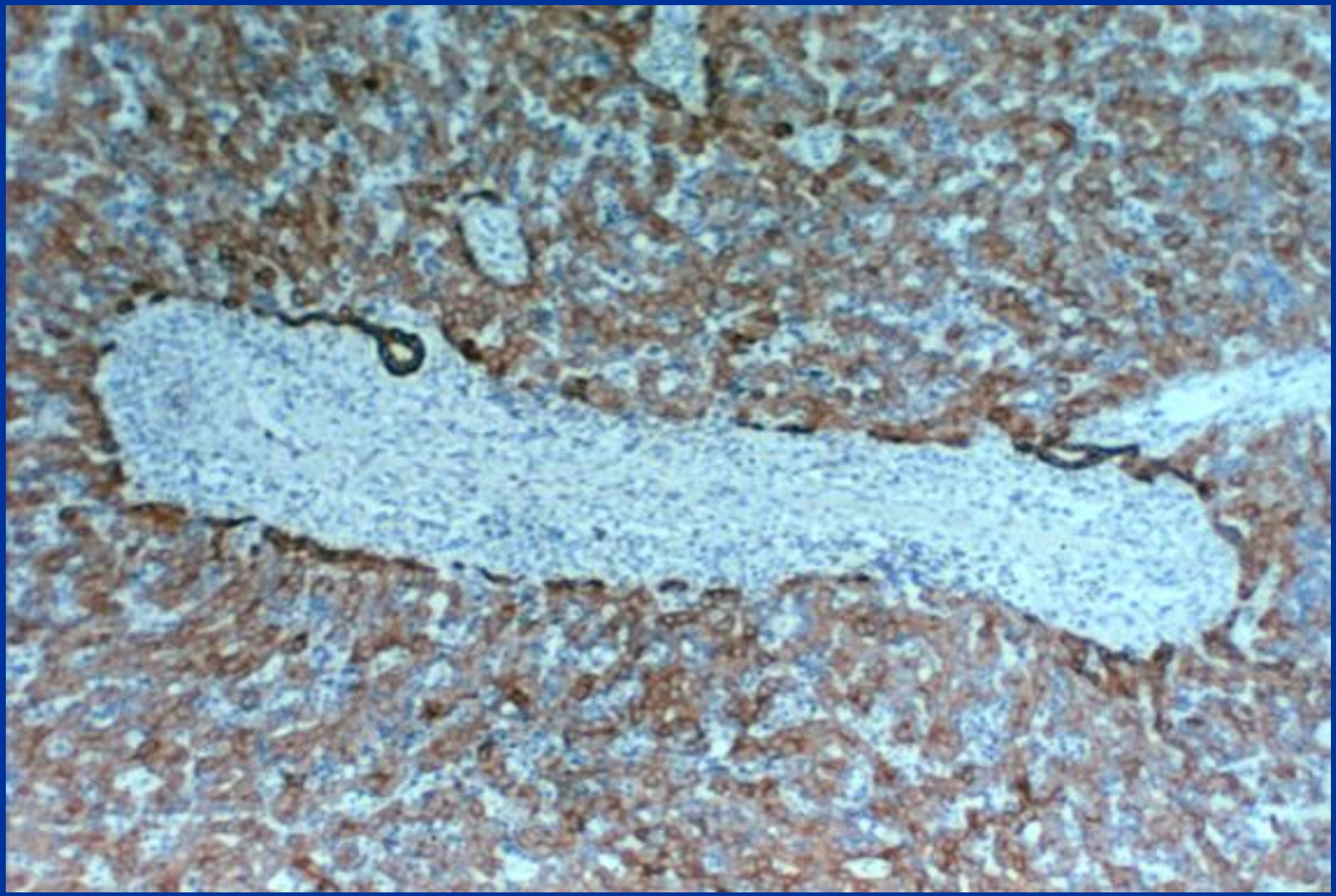


THREE-DIMENSIONAL SCHEMA OF LIVER STRUCTURE (AFTER HANS ELIAS)

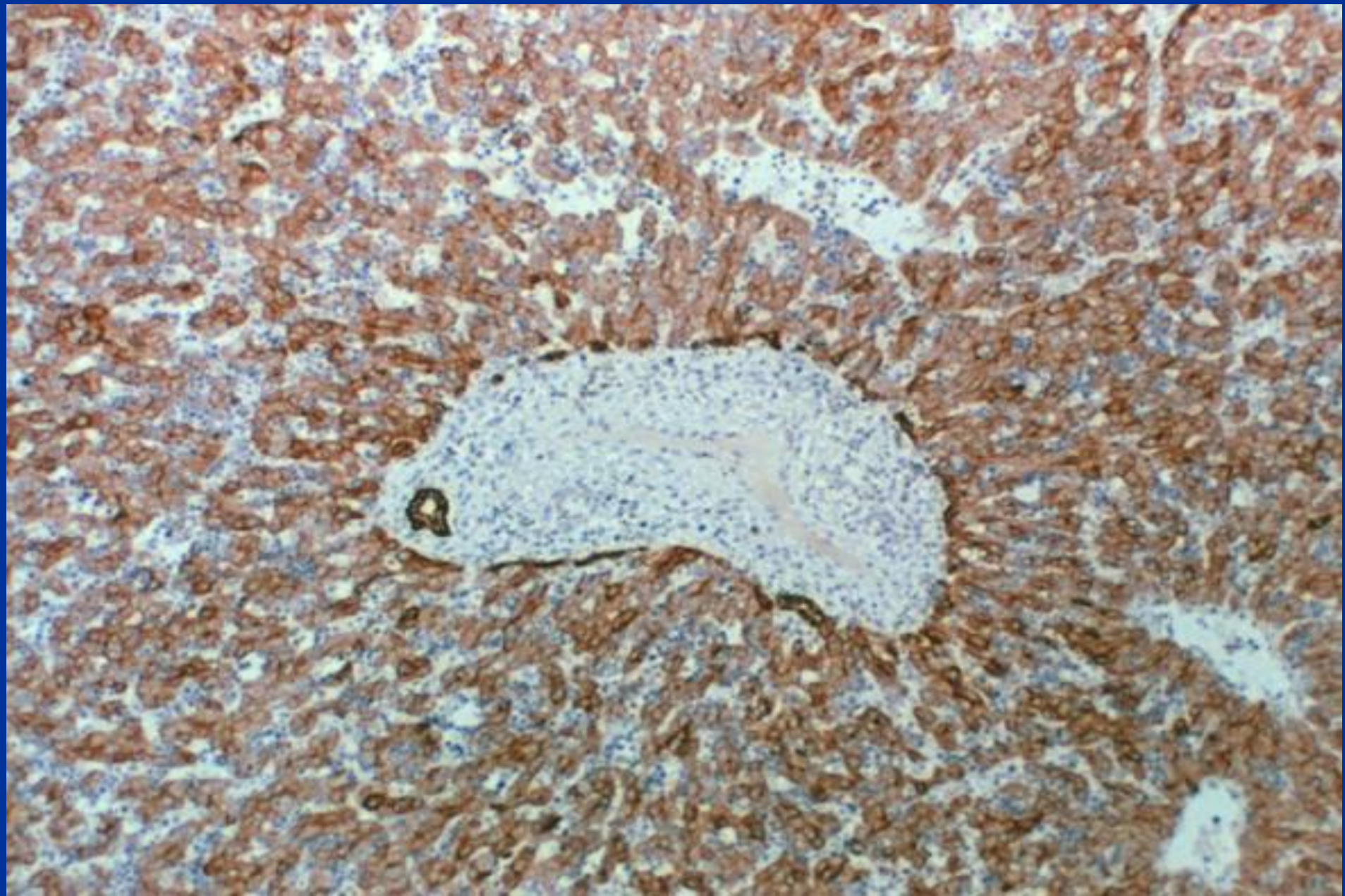
Development Of The Fetal Bile Ducts



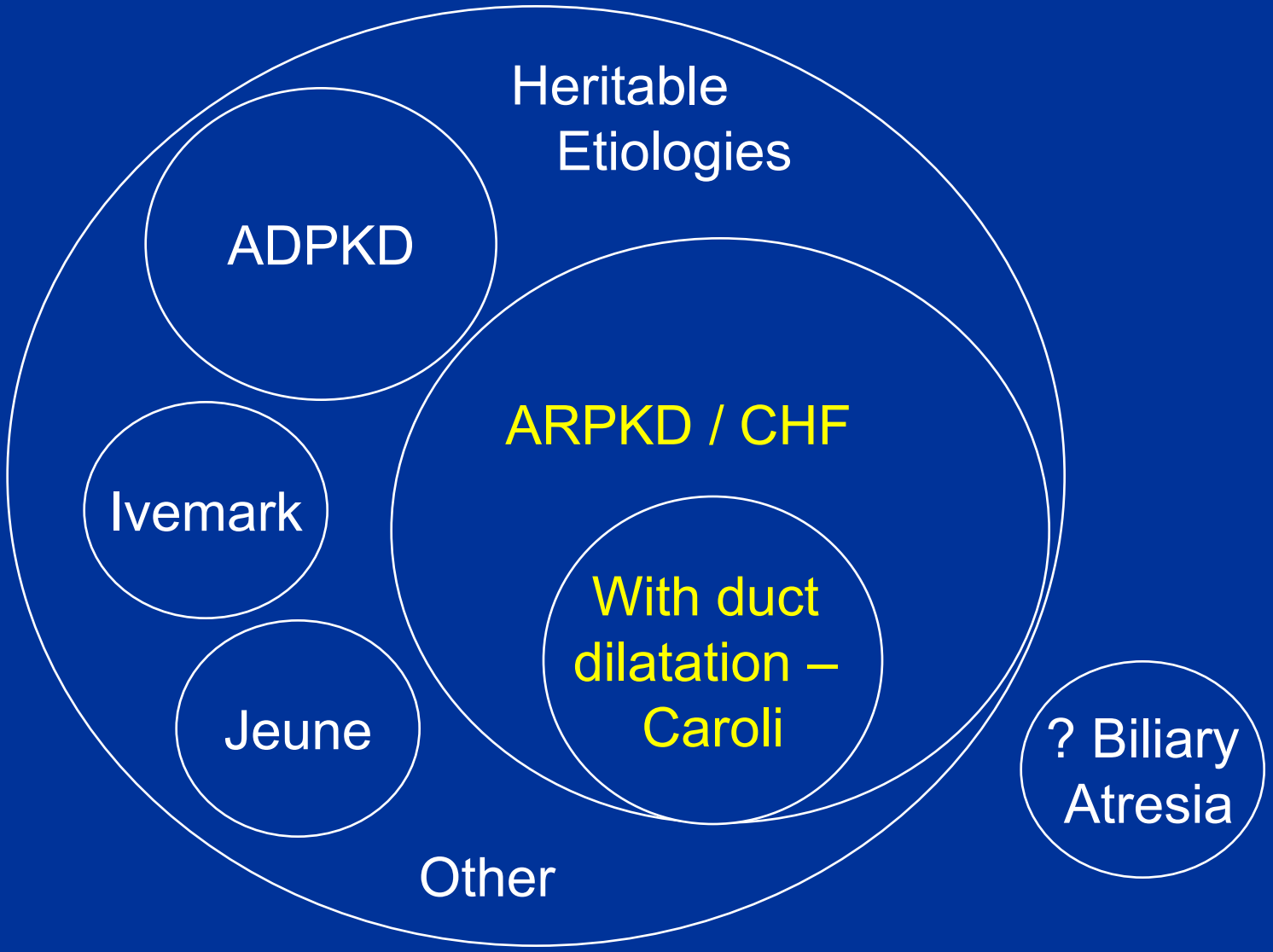
Normal Human Ductal Plate



Normal Human Ductal Plate



Ductal Plate Malformation Associations (Diseases)



Ductal Plate Malformation Associated Syndromes

- Infantile polycystic disease / ARPKD (Congenital hepatic fibrosis)
- Adult polycystic disease / ADPKD
- Tuberous sclerosis
- Meckel-Gruber syndrome
- Ivemark syndrome (renal-hepatic-pancreatic dysplasia)
- Bardet-Biedl syndrome
- Joubert syndrome
- COACH syndrome
- Beemer-Langer syndrome
- Jeune syndrome
- Ellis-Van Creveld syndrome
- Saldino-Noonan syndrome
- Vaginal atresia syndrome
- CDG type Ib (mannosephosphate isomerase deficiency)
- With chromosomal abnormalities (trisomy 9)

Ductal Plate – Scientifically Speaking

- From the 12th week of gestation a progressive remodeling of the ductal plates occurs

- Longitudinal tubular dilatations appear along the double biliary epithelial sleeves surrounding the future portal tracts

- Ingrowth of the mesenchyme results in a tubular channel (bile duct) within the periportal mesenchyme (future portal tract) with preserved epithelial channels between the lumen of the incorporated tubule and the lumen of the ductal plate (future ductules)

Ductal Plate – Scientifically Speaking

- Protostructure of the intrahepatic biliary system begins to develop at around 8 weeks of gestation

- Consists of of a double-layered cylinder of biliary-type cells with a slit-like lumen forming around the portal vein and its surrounding mesenchyme

- In the following weeks ductal plates appear around smaller portal veins as they develop distally from the hilum of the liver

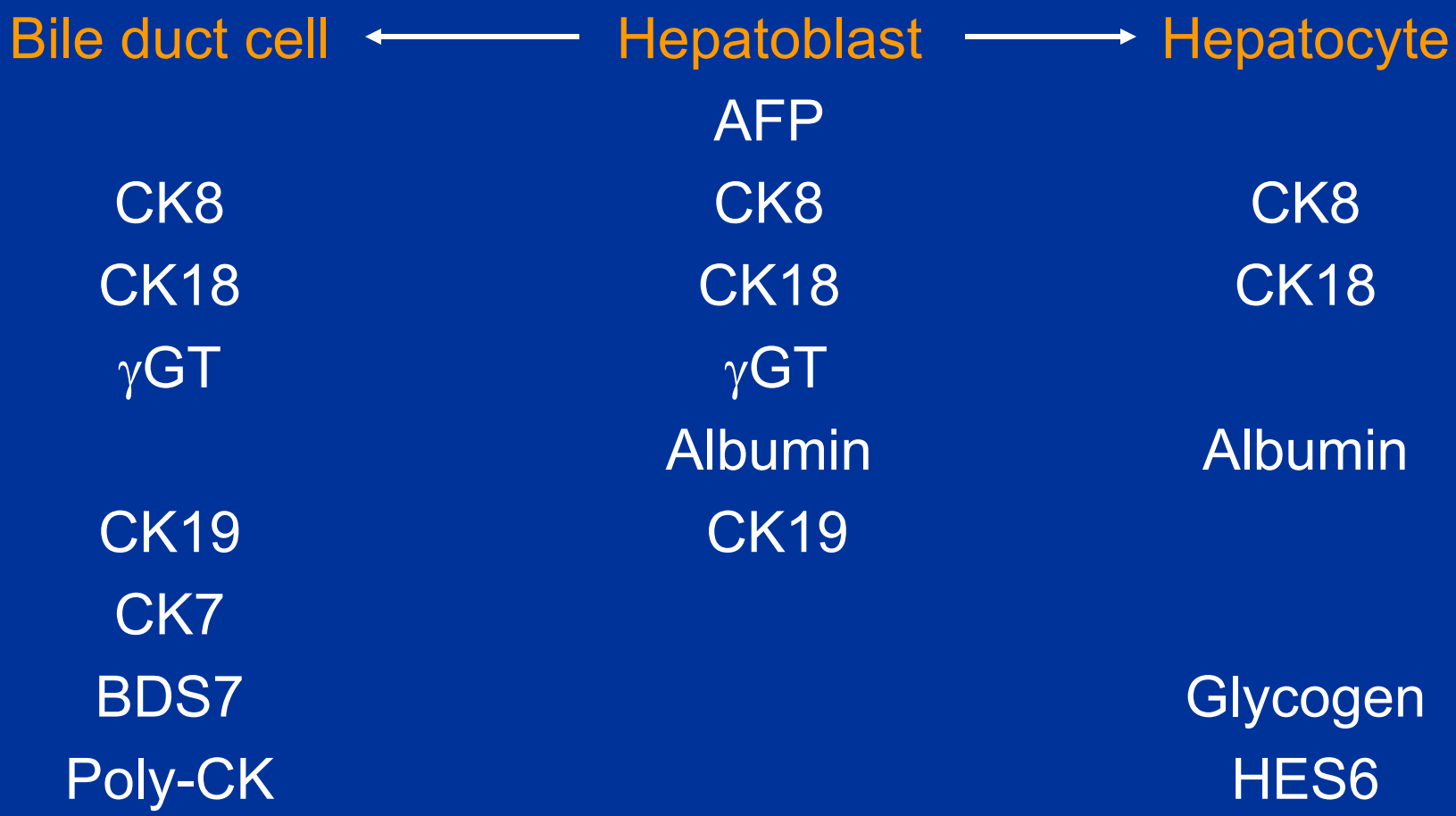
- Hepatoblasts not involved in ductal plate formation differentiate into parenchymal liver cells

Ductal Plate – Scientifically Speaking

- Remodeling process also follows the branching growth of the portal vein from the hilum to the periphery of the liver with continuous development throughout fetal life (with more mature ducts being present in the hilar region)

- The mechanisms involved in this remodeling remain largely unknown but evidence supports an important role for epithelial proliferation and apoptosis.

Development Of The Fetal Liver



Ductal Plate Formation and Differentiation Genes

Liver:	
Gene	Locus
Foxa (Hnf3)	14q12
Smad2, Smad3	18q21, 15q21
FGF signaling	(multiple loci)
Hex	1q42
Prox1	1q32
BMP4	14q22
Hlx	1q41
Hgf	7q21
Hnf4	20q12
Hnf1α	12q24
Tgf-β	19q13
c-Met (hgf rec)	?

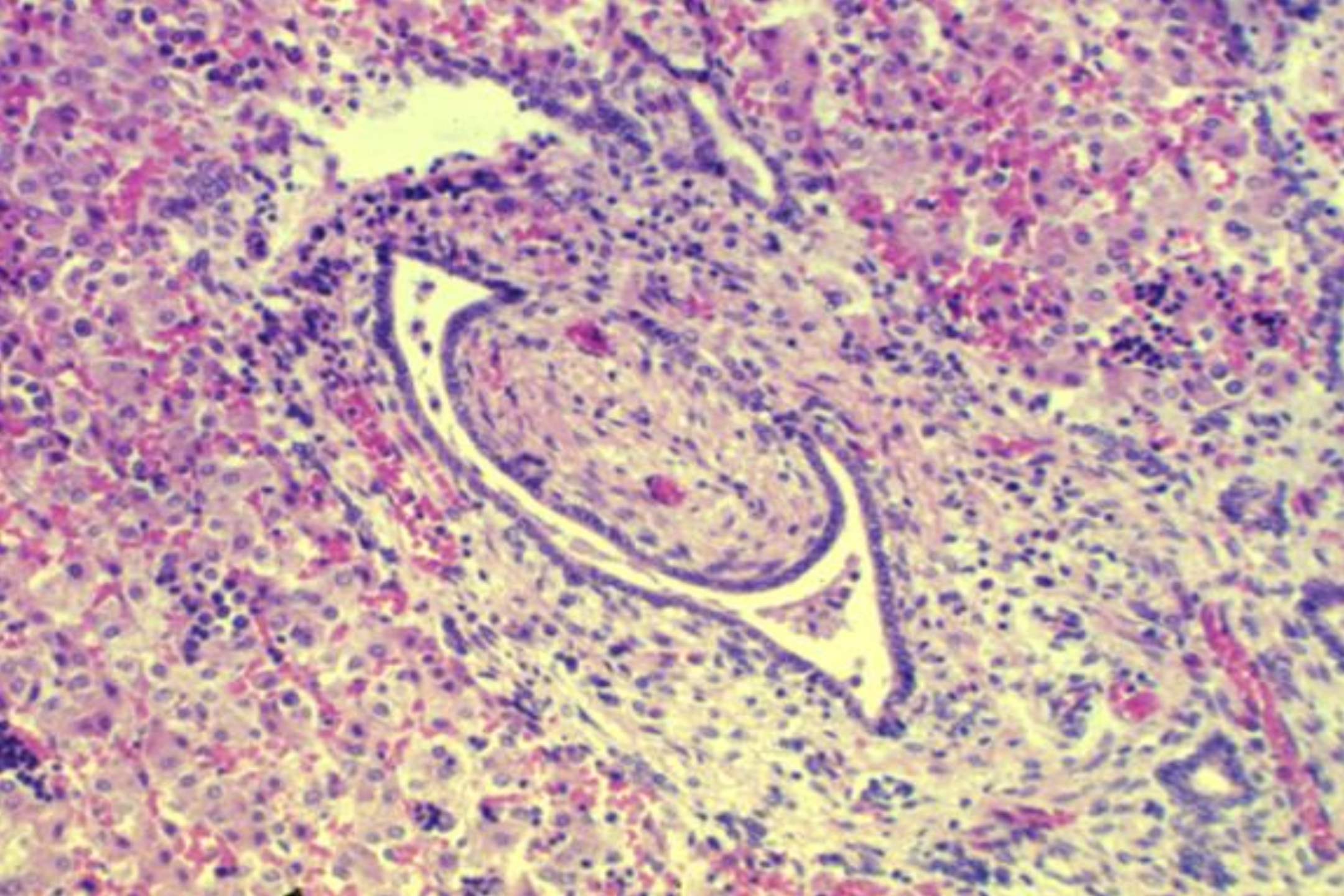
Ducts:	
Gene	Locus
Hnf6	15q21
Hnf1β	?
Foxf1	16q24
ARPKD	6p21

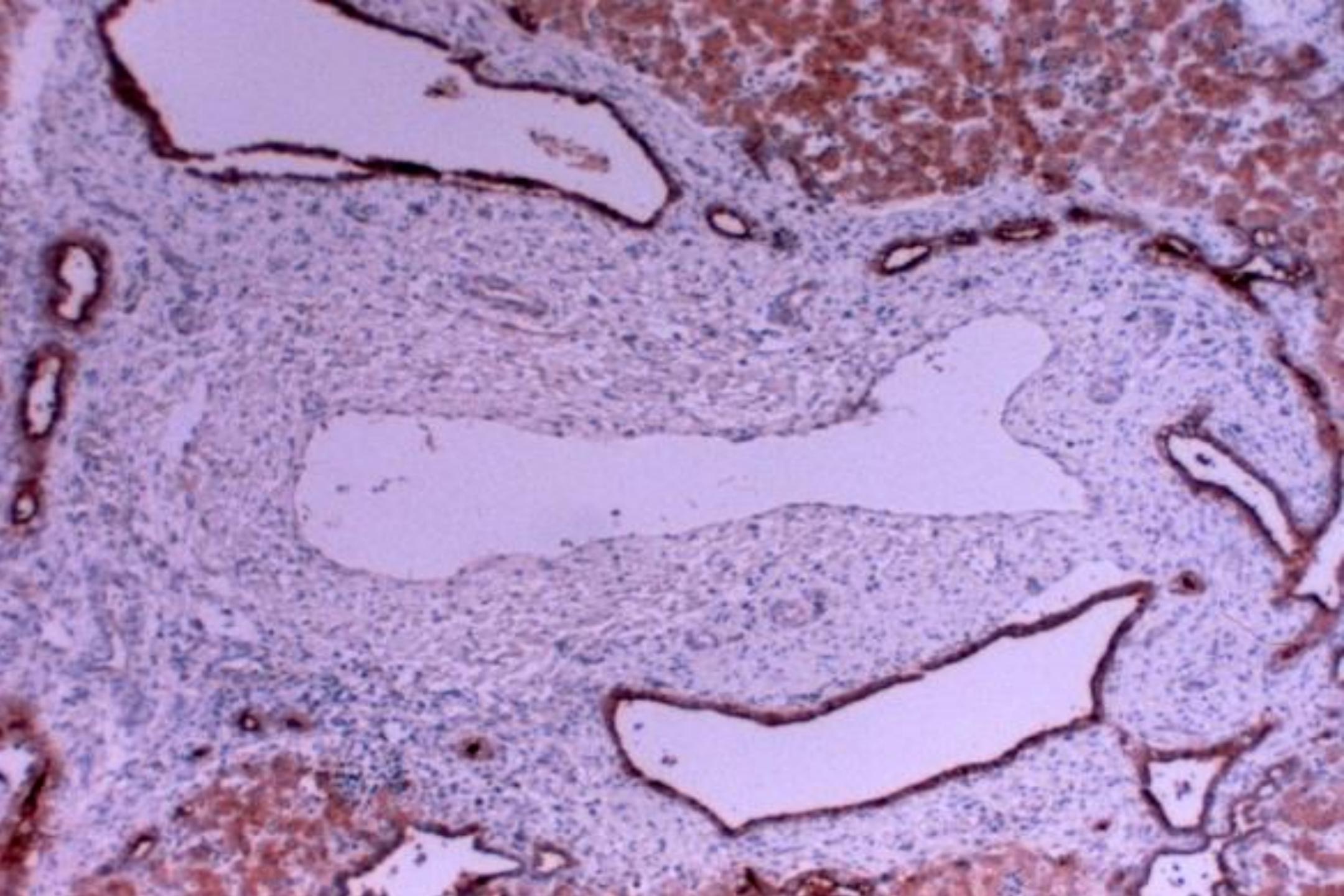
Ductal Plate Malformation (DPM)

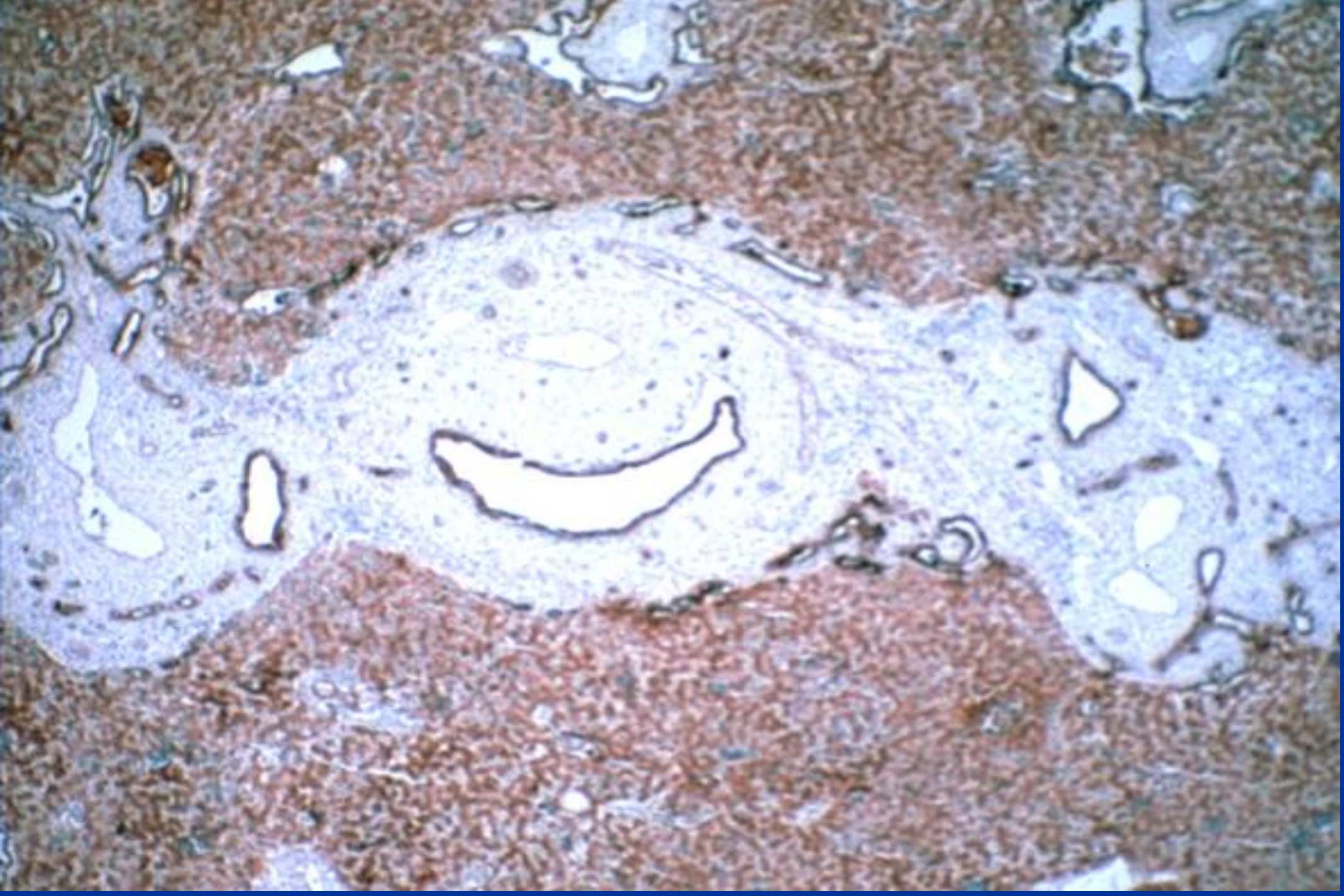
- Perturbation of these epithelial-mesenchymal interactions leads to a lack of, or incomplete, remodeling of the ductal plates leading to a persistence of excess embryonic bile duct structures in ductal plate configuration

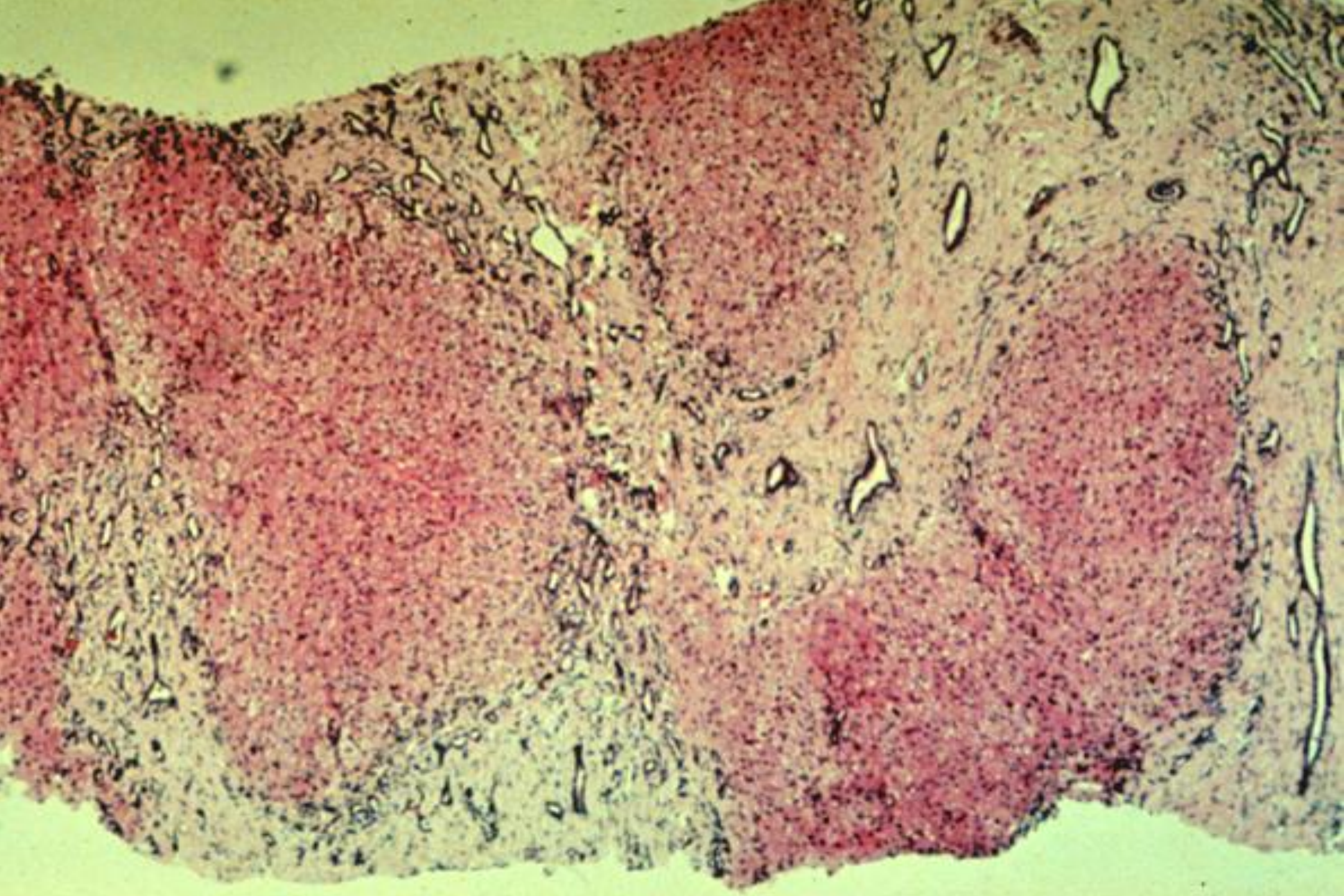
- Histologically appear as a circular lumen containing a fibrovascular axis in the center (complete lack of remodeling), or rings of interrupted curved lumina around a central fibrovascular axis or a grossly dilated duct containing a polypoid projection (incomplete remodeling)

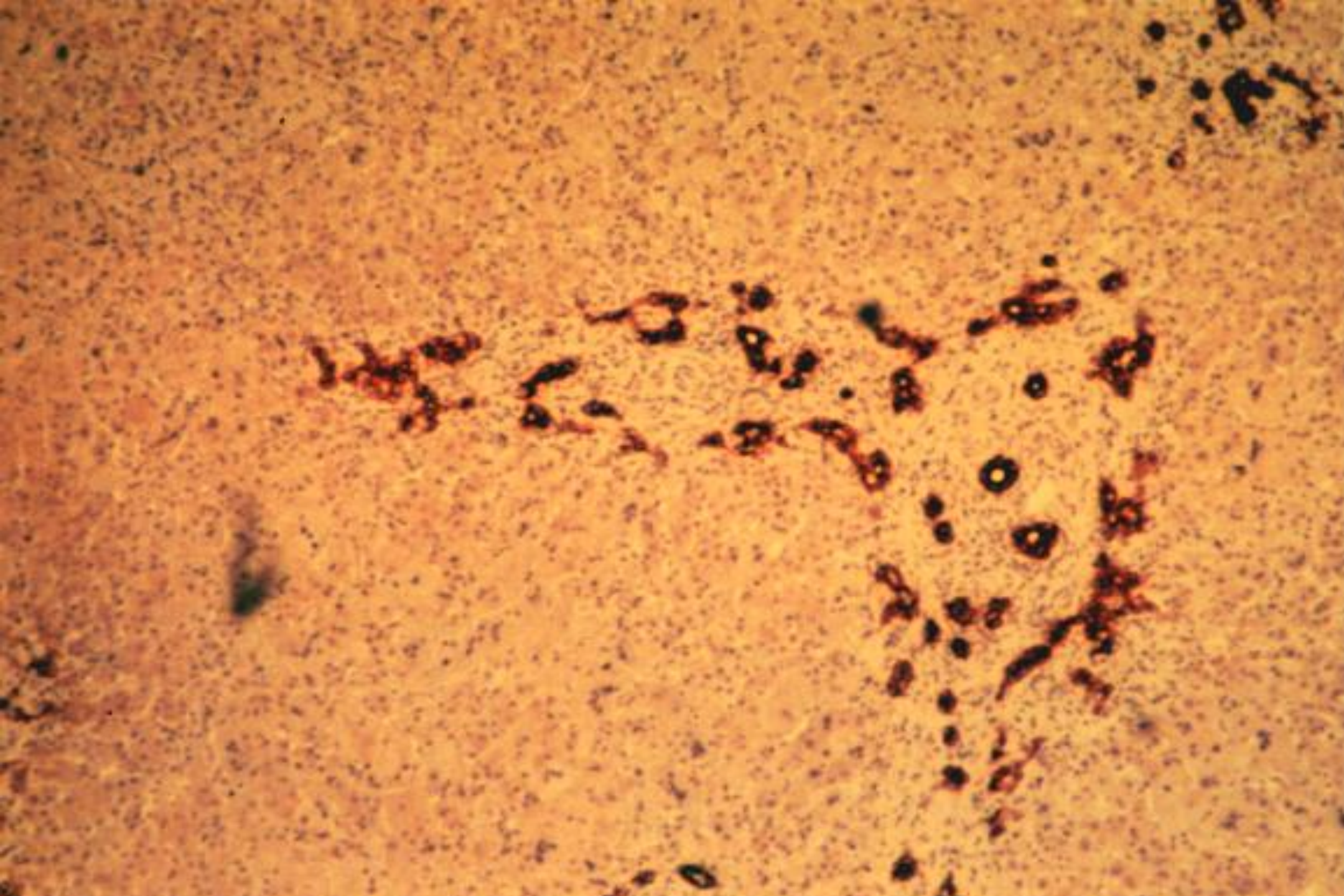
- DPM is often associated with abnormalities in the ramification pattern of the portal vein (“pollard willow” pattern)











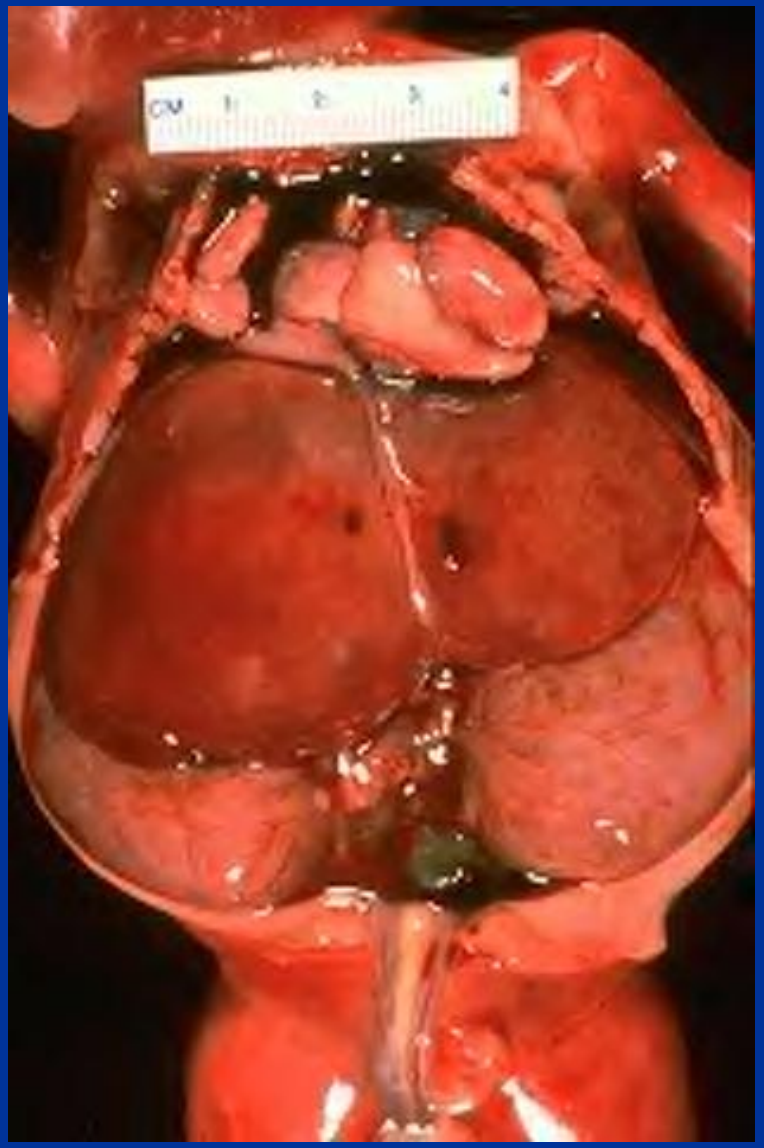
ARPKD (CHF)

- AR
- Potter facies (oligohydramnios)
- Lung hypoplasia
- Periportal fibrosis, portal hypertension, hepatomegaly, cysts, pancreatic cysts
- Enlarged, cystic kidneys, fibrosis, renal failure

Locus: 6p21

Gene: fibrocystin (? receptor protein involved in collecting-duct and biliary differentiation)

ARPKD – Infantile Polycystic Disease

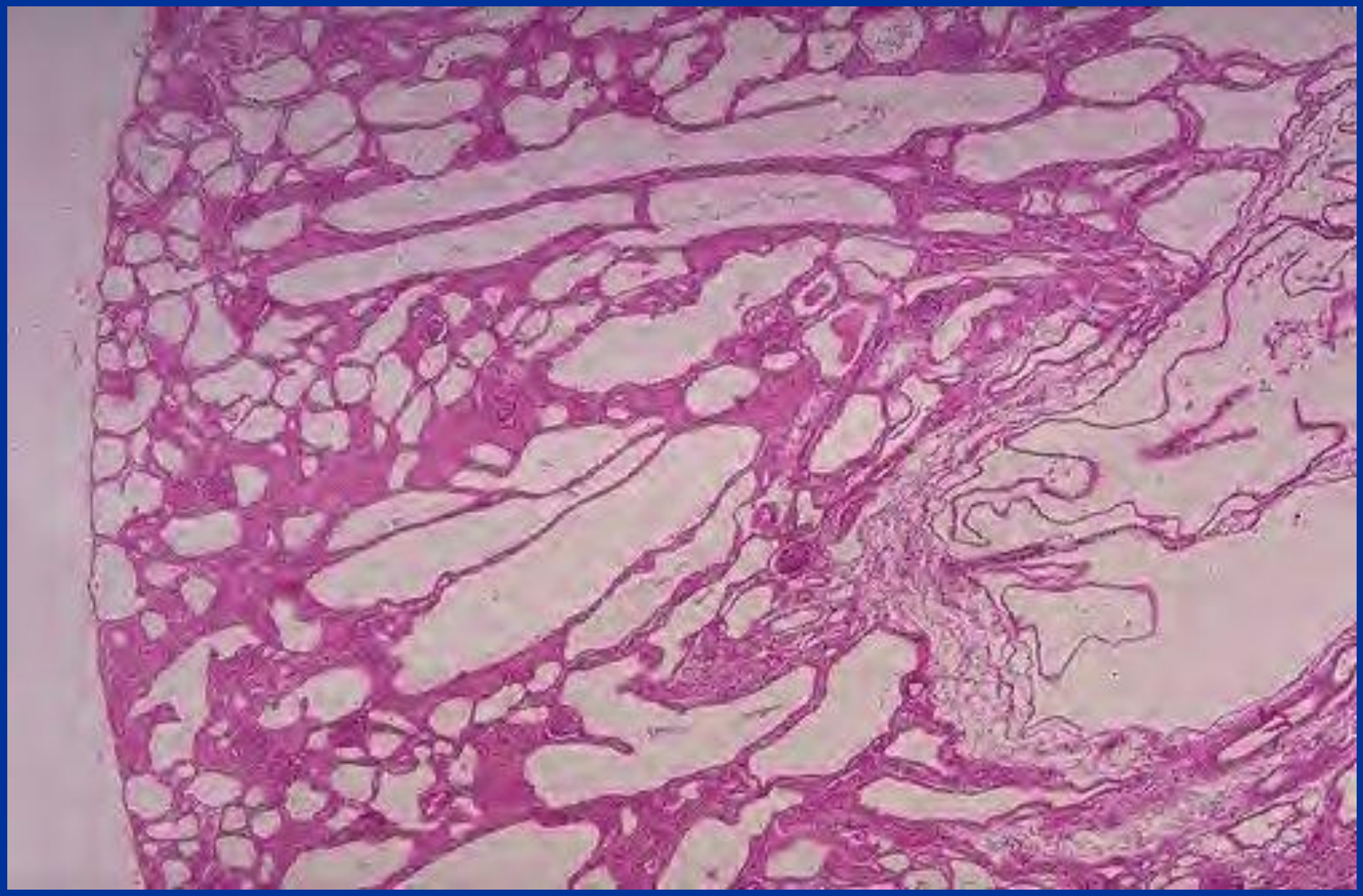


- Oligohydramnios
- Pulmonary hypoplasia
- Nephromegaly

ARPKD Kidney

Small, uniformly distributed cysts

ARPKD cysts



fill most of parenchyma, radially arranged

Congenital Hepatic Fibrosis

- Coined by Kerr, Sherlock and Walker in 1961
- Recognized a unique subset of pediatric patients with profound fibrosis rather than cirrhosis
- Early (congenital) rather than acquired fibrosis, as is seen in most metabolic and inflammatory hepatic diseases in childhood
- Associated renal disease
- Not a disease entity, but a useful clinical pattern

Features Of Congenital Hepatic Fibrosis

Variable clinical features and age at presentation

- Hepatomegaly
- Portal hypertension with splenomegaly
- Variceal hemorrhage
- Cholangitis (acute or chronic)
- Cholestasis
- Communicating biliary cysts
- Chronic liver failure
- Latent form

Congenital Hepatic Fibrosis Features

- DPM - dilated, bizarre, peripheral bile ducts with occasional ectasia and stasis
- Extensive portal fibrosis
- Minimal portal inflammation
- Normal lobular architecture, without necrosis or inflammation
- Microscopic and macroscopic communicating biliary cysts are common
- Biliary stasis occurs, but is not common
- Portal vein abnormalities may be present
- Synthetic function is generally normal

Clinical Picture Consistent With CHF

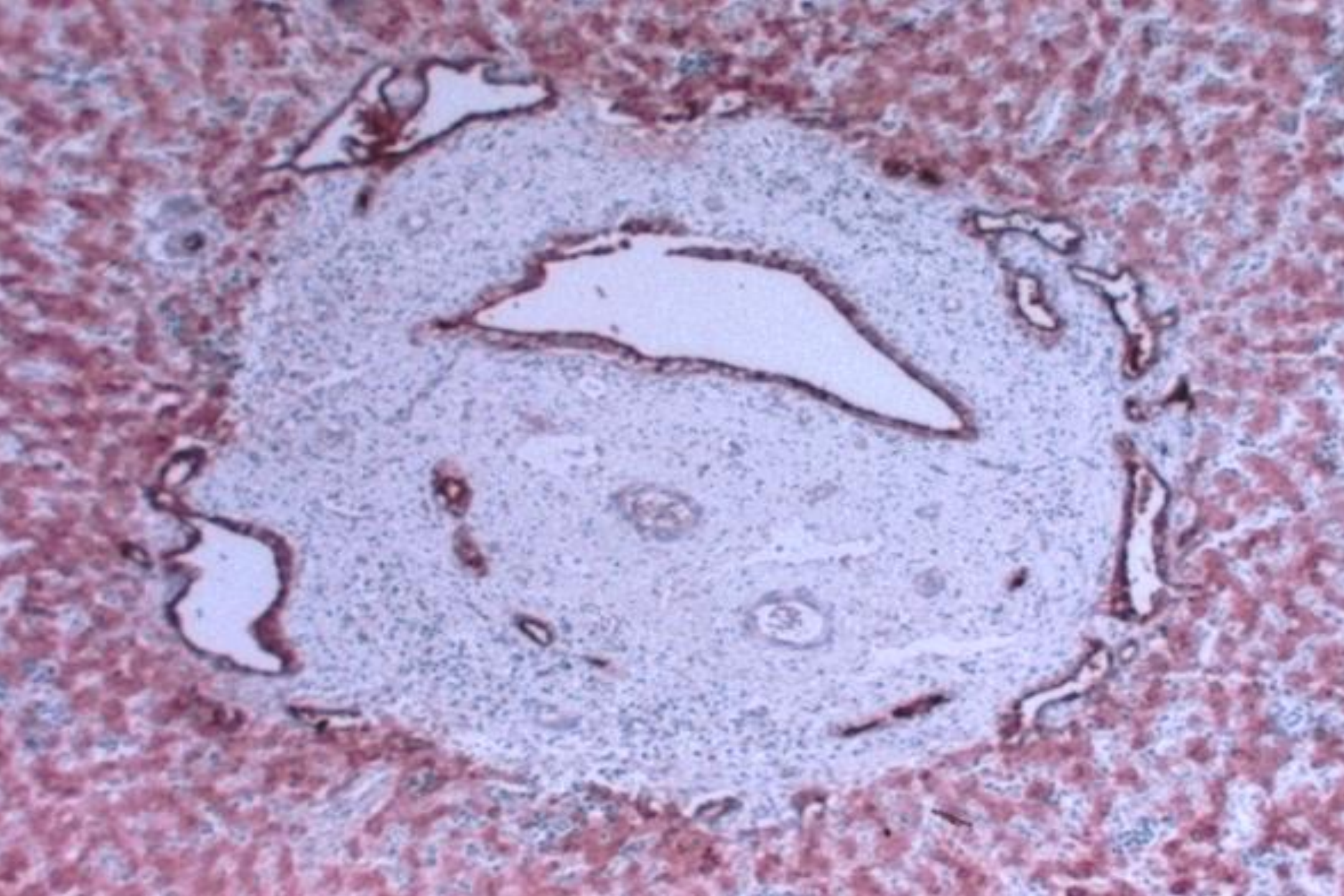
- Highly variable clinical course
- Some correlation with age at discovery
- Many patients are (and remain) symptom and disease free
- Not the same as cirrhosis
- Liver failure and transplantation are not common

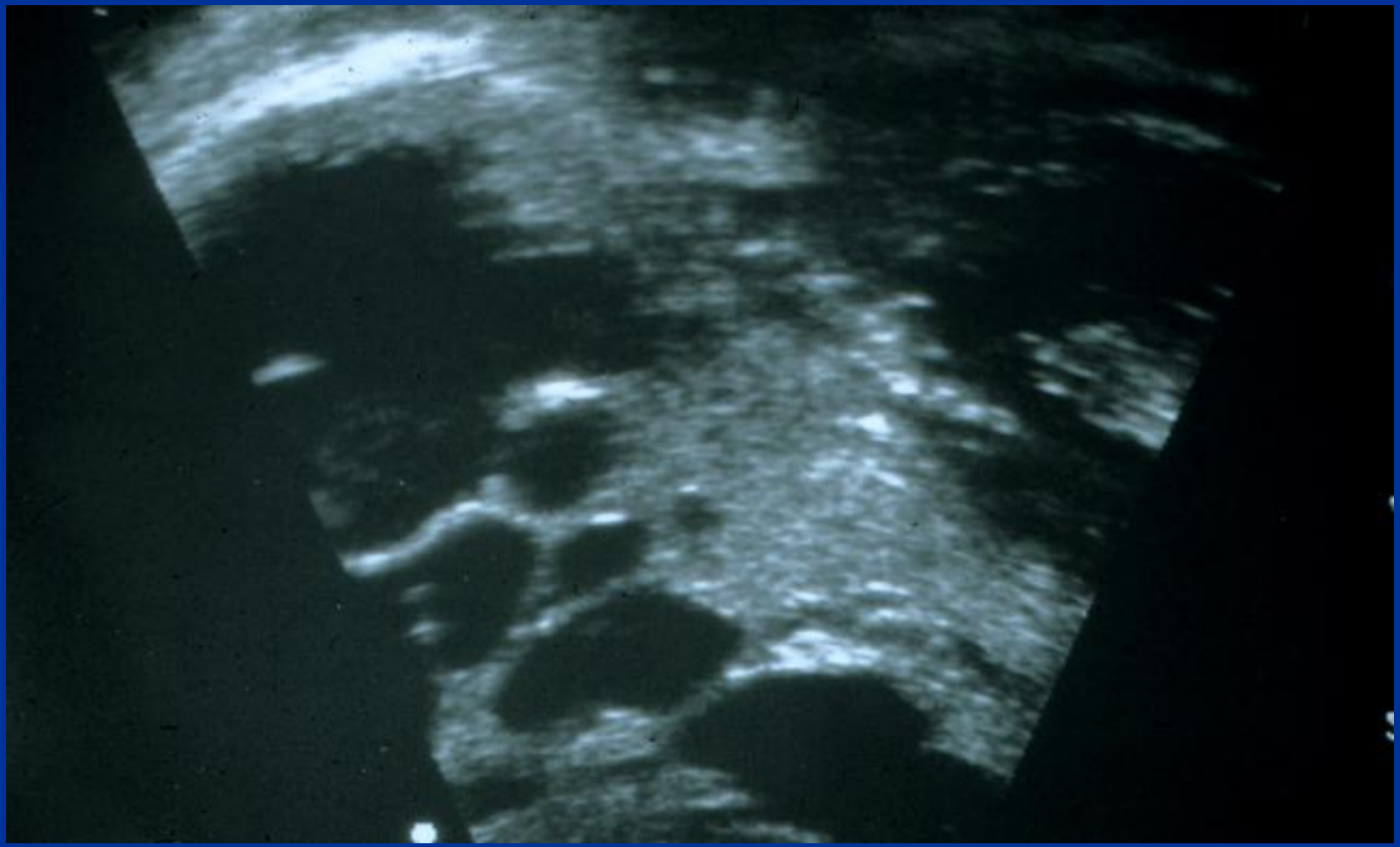
CHF - Clinical Manifestations

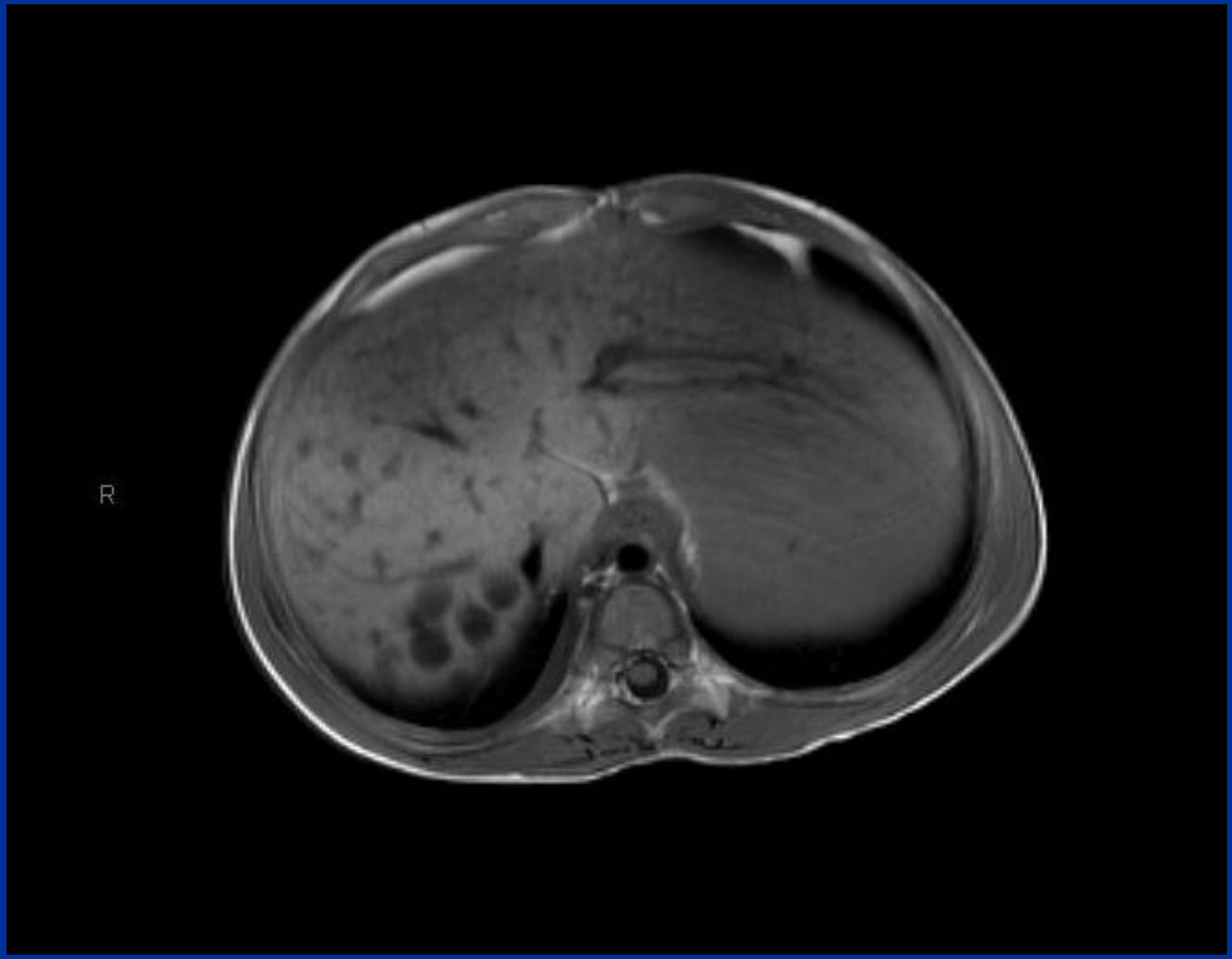
- Hepatomegaly - large liver
- Splenomegaly - large spleen due to pressure
- Portal hypertension - increased pressure in the portal vein
- Portal hypertensive gastropathy – stomach portal pressure
- Esophageal varices, with or without bleeding, due to PHTN
- Bile duct dilatation - because of the abnormal ducts
- Cholangitis - infection of bile and ducts, due to stasis
- Hepatic vascular anomalies - part of the development
- Renal disease, asymptomatic, or
- Renal disease, significant

Caroli Syndrome and Caroli Disease

- Caroli described two forms of congenital, macroscopic, inherited bile duct dilatation
  - typical DPM with portal fibrosis - Caroli syndrome
  - isolated entity - Caroli disease
- Both are associated with renal disease
- May be associated with choledochal cyst
- The term Caroli disease is now commonly used to describe any form of communicating ductular dilatation



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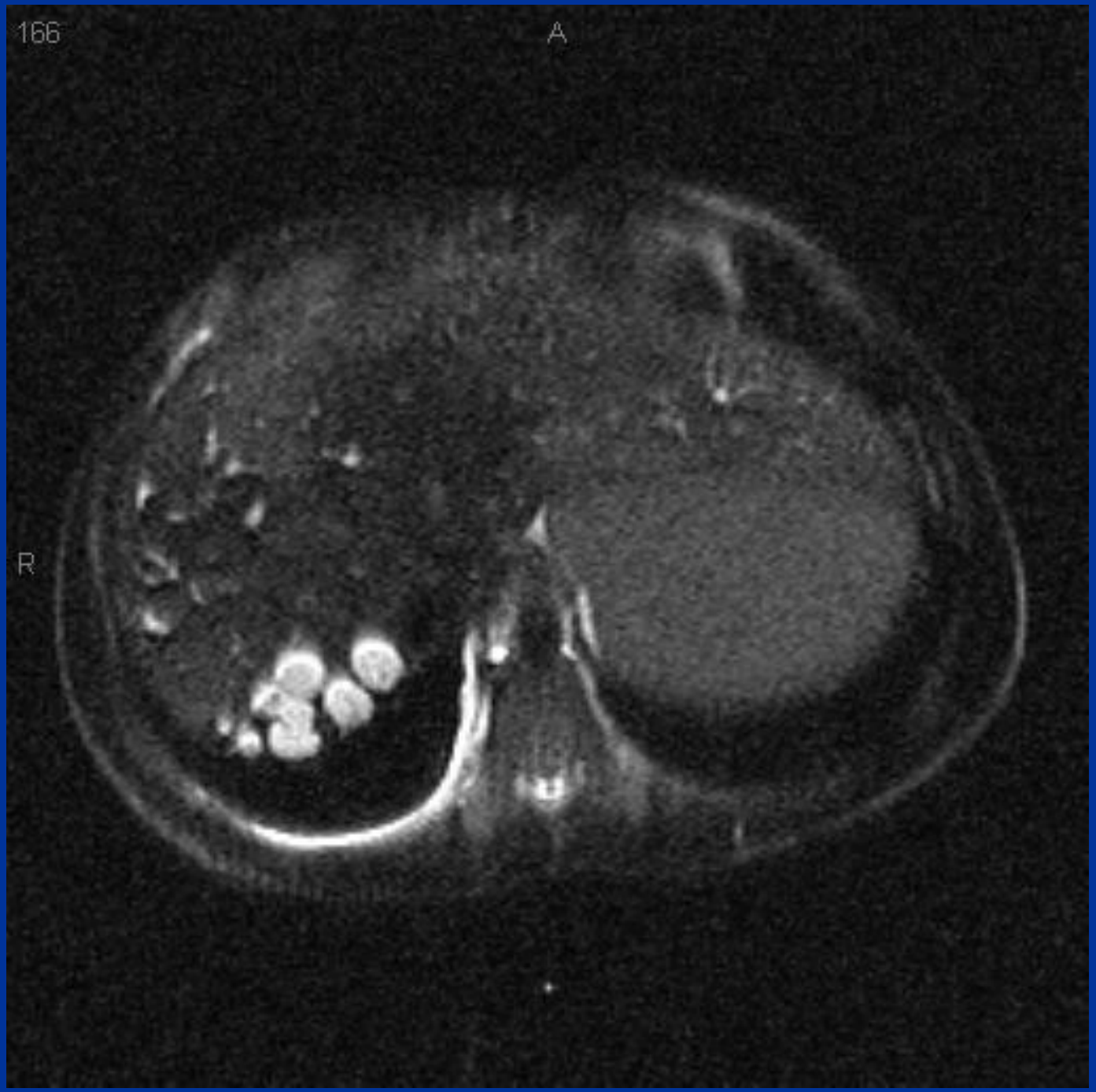
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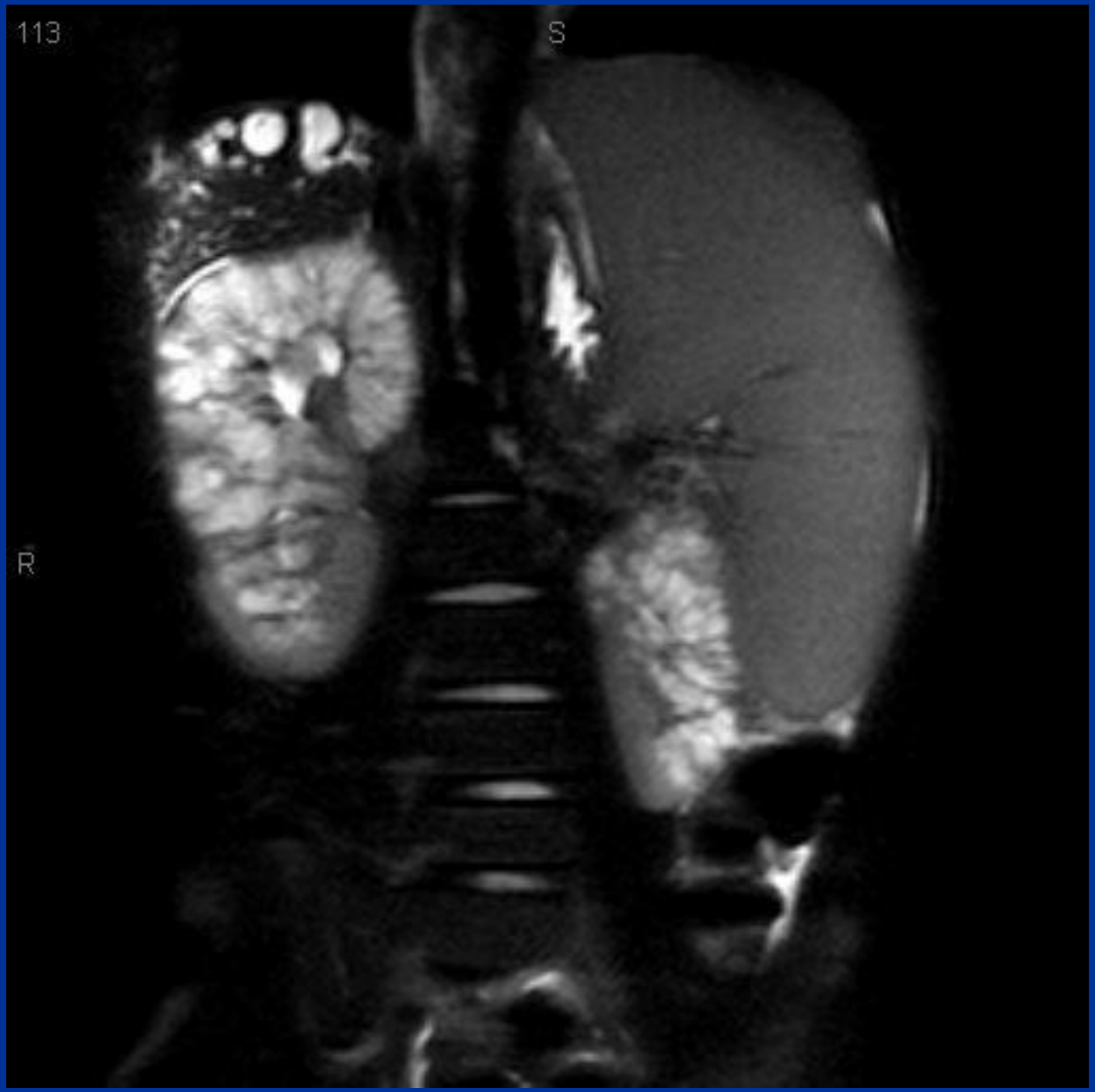
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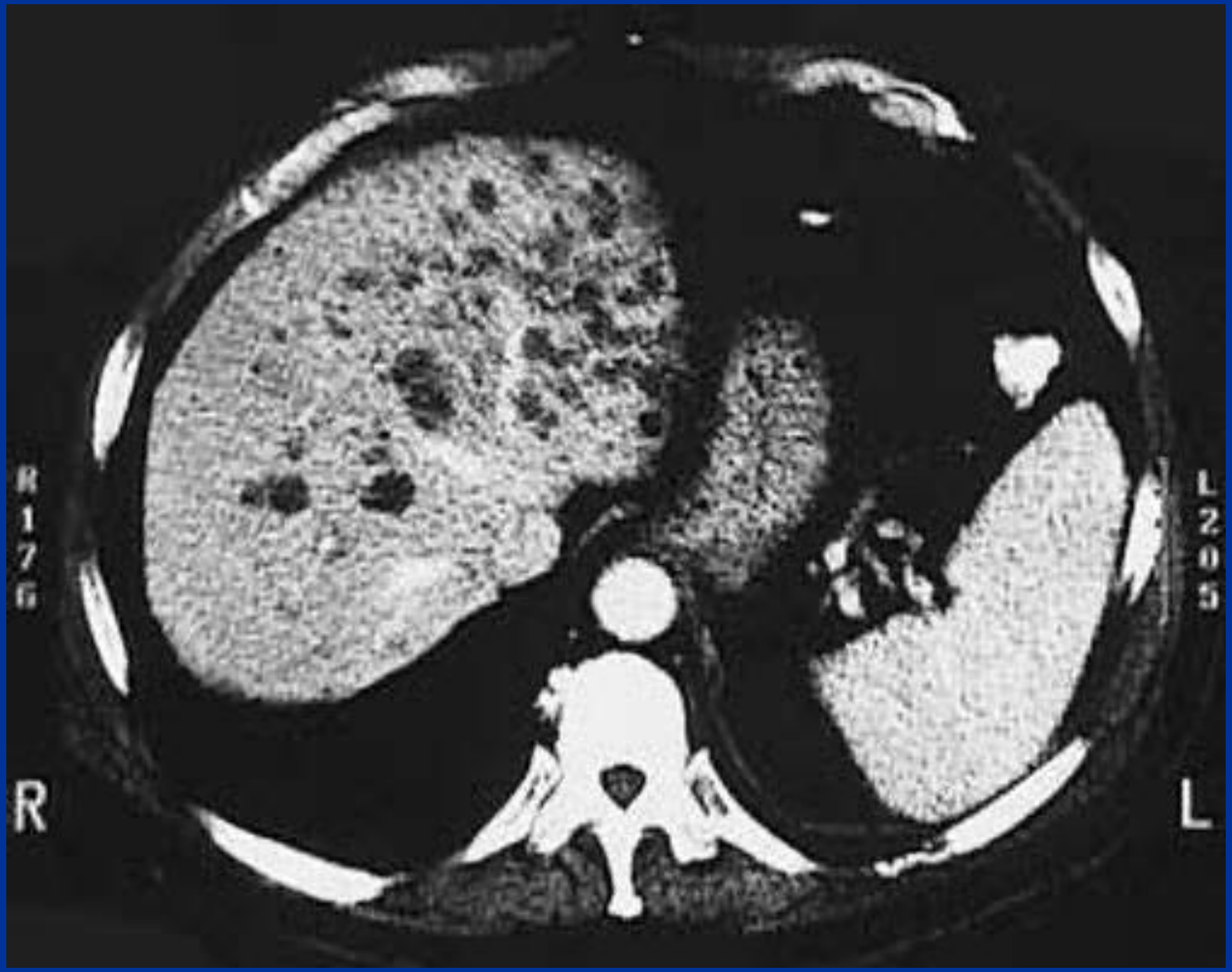
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Congenital Hepatic Fibrosis Therapy

- Therapy for portal hypertension
  - Medical prophylactic and urgent
  - Endoscopic prophylactic and urgent
  - Radiologic shunts
  - Surgical shunts
- Cholangitis therapy prophylactic and therapeutic
- Choleretic therapy
- Liver and/or renal transplantation
- Other – growth hormone, vitamins
- Experimental – antifibrotic therapy

Cholangitis

- Refractory to intravenous therapy because of focal duct dilatation and stasis
- Commonly gram negative rod pathogens
- Contributes significantly to progressive hepatic damage and leads ultimately to transplantation
- Therapy is optimized by direct culture via hepatic biopsy or needle aspiration
- Percutaneous drainage
- Prophylactic antibiotic use is common but not proven

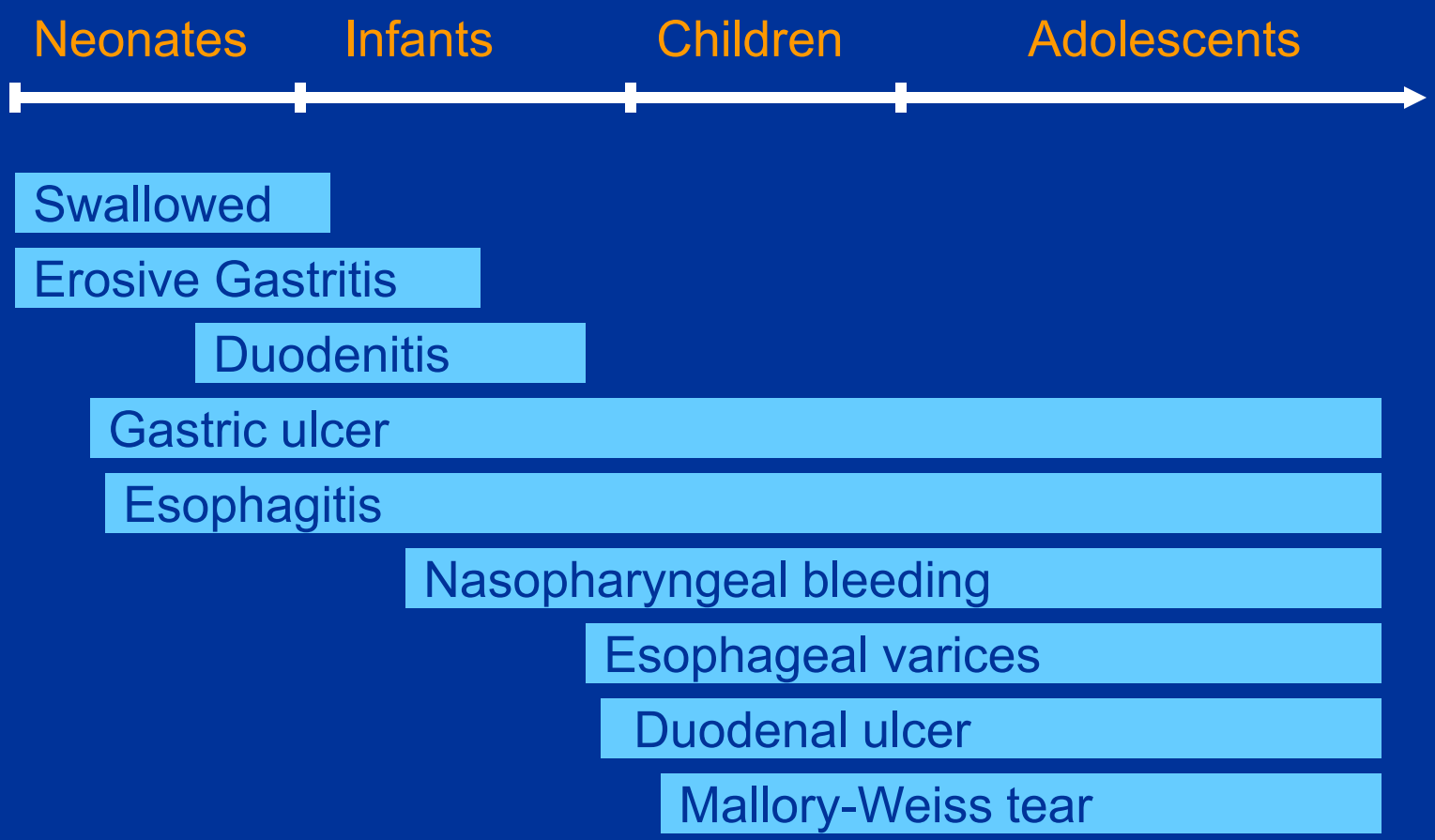
Portal Hypertension

- The hepatic fibrosis slows normal flow through the liver
- The “portal” vein carries this blood into the liver
- When flow is obstructed, portal pressure increases, and blood flow “backs up” in the vessels that feed the portal vein
- The spleen and the vein from the stomach and intestine feed the portal vein
- The stomach has portal hypertensive gastropathy, and may ulcerate or bleed
- When the pressure increase is severe the vessels in the esophagus increase in pressure and dilate, because they have thin walls
- The esophageal varices, under pressure, may rupture and cause very severe bleeding

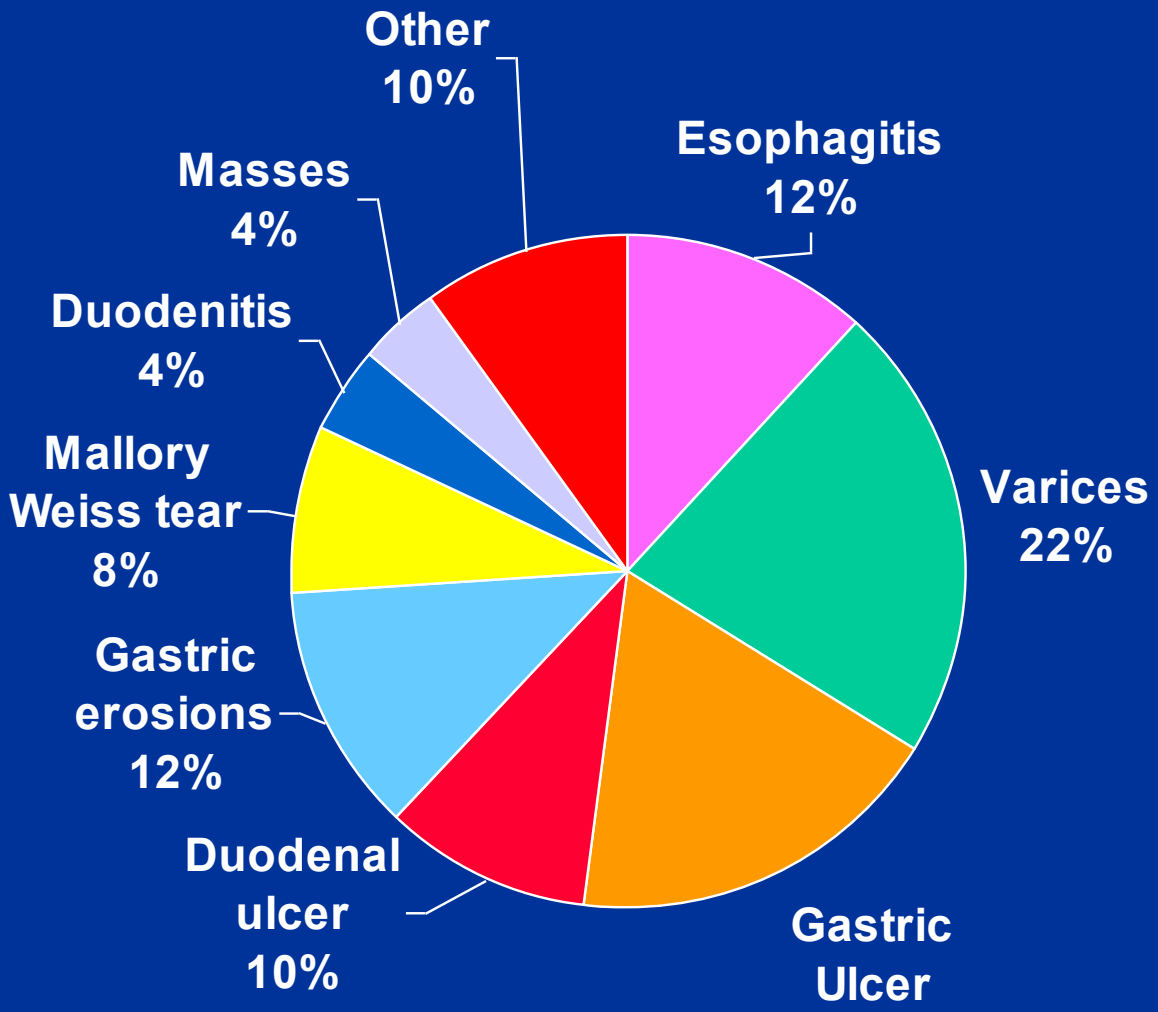
Therapy For Portal Hypertension

- Medical therapy - designed to decrease the pressure and volume in the portal system
- Sclerotherapy - injection of the esophageal varices to clot them or thicken the wall - so that flow will go in a different direction
- Surgical shunts - taking the high pressure portal or splenic blood flow and plugging it into low pressure vessels
- Radiologic shunts - TIPS - making a connection between the high pressure portal vein and the low pressure hepatic vein
- Liver transplantation

Upper GI Bleeding in Pediatrics



Upper GI Bleeding in Pediatrics



MASSIVE GI BLEEDING

Initial Stabilization – Local Emergency Room!!

- ABC's (airway, breathing, circulation)
- Adequate intravenous access
- Fluid resuscitation
  - Initially with normal saline
  - Packed red blood cell transfusion
  - Clotting factors and platelets as needed
- Vitamin K IV
- Acid blockade IV
  - Ranitidine, pantoprazole, lansoprazole

- Nasogastric (NG) tube is essential

NG Tube Placement And Lavage

- Identify location of bleeding
  - Verify bleeding with Gastroccult
- Monitor amount of ongoing losses
- Does not by itself stop bleeding
- No role for iced-saline lavage
- Balance the gastric infusion/suction (I/O) to avoid fluid overload
  - Ball-valve effect - easier to push in than aspirate

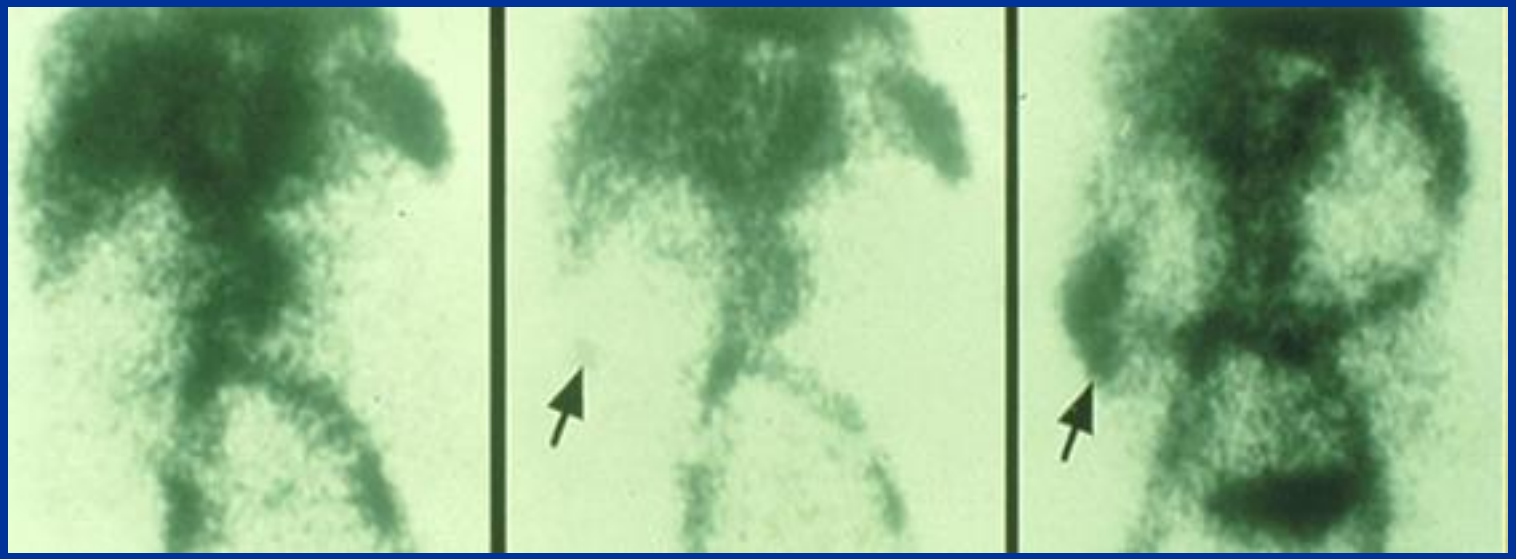
Role of Upper Endoscopy in UGI Bleeding

- Diagnostic
  - Identifies the location and type of bleeding in up to 90%
- Therapeutic
  - Sclerotherapy
  - Variceal band ligation
  - Bipolar coagulation
  - Other techniques

Other Diagnostic Studies in GI Bleeding

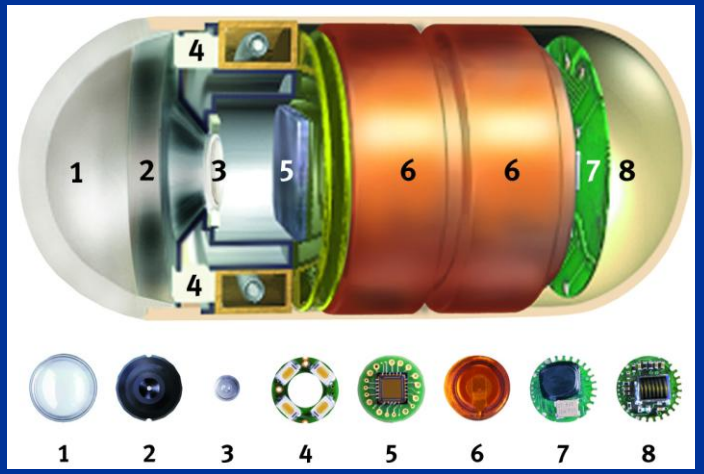
- Bleeding Scans – Scintiscans
  - Tagged RBC
  - Blood pool scan
  - Technetium Meckel scan
- Wireless capsule endoscopy
- Radiologic studies – CT scan, UGI/SBFT, enteroclysis
- Colonoscopy
- Angiography
  - Also therapeutic embolization
- Exploratory laparotomy

Labeled Red Blood Cell Scintigraphy

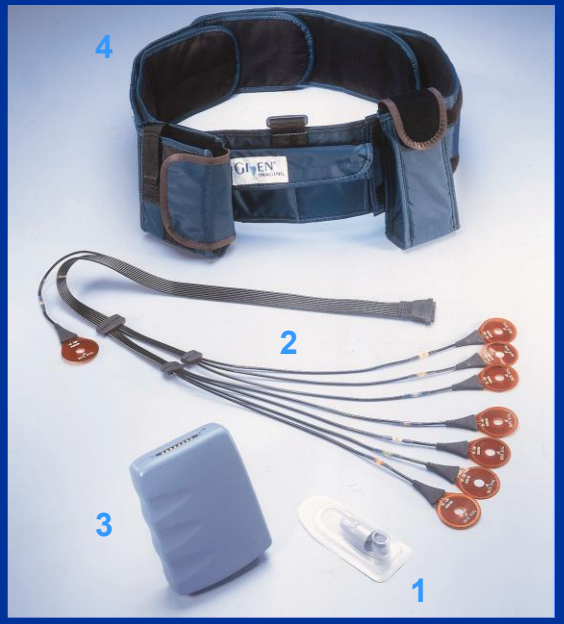


15 min 55 min 65 min

Video Capsule

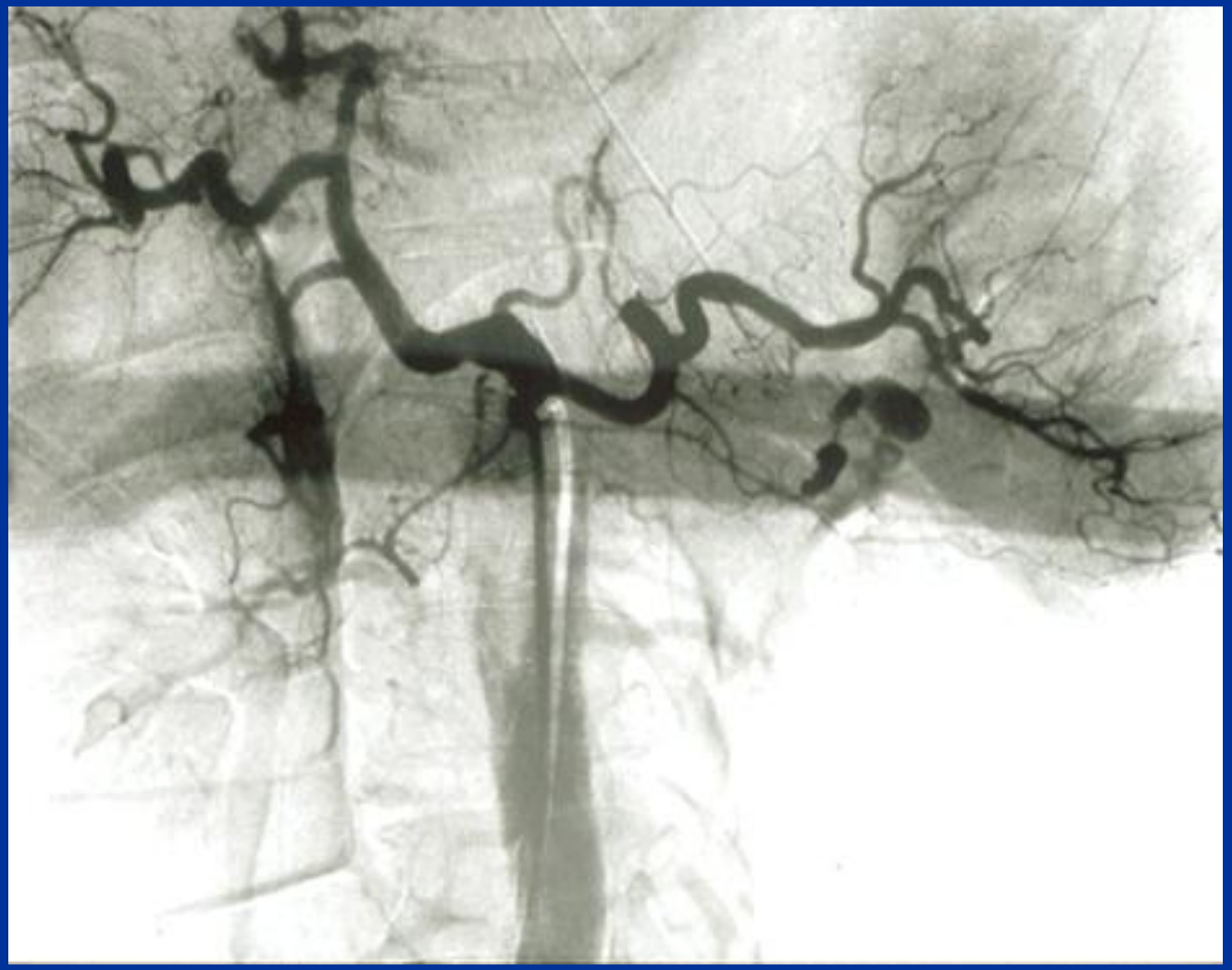


1,2,3 Dome and lens
4 LED
5 CMOS image
6 Battery
7 Transmitter
8 Antenna
Size – 11 x 26 mm



1 Capsule
2 Sensor array
3 Data Recorder
4 Recorder belt

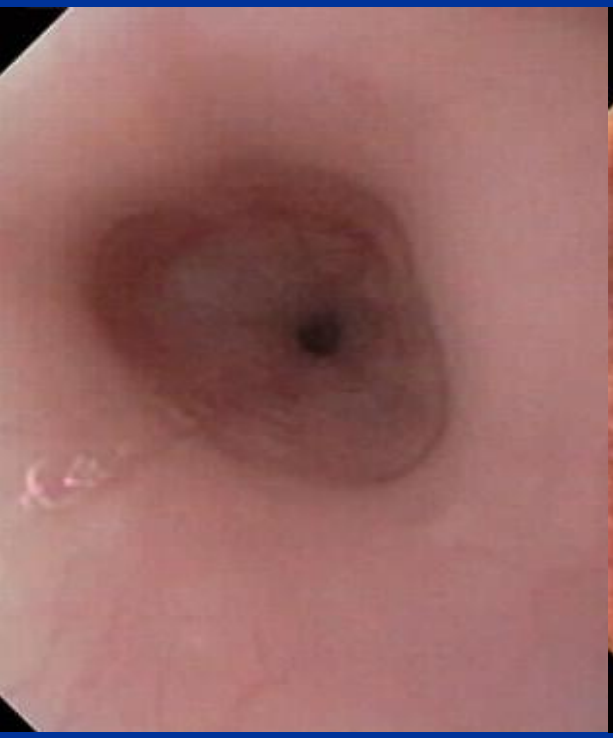
Angiography

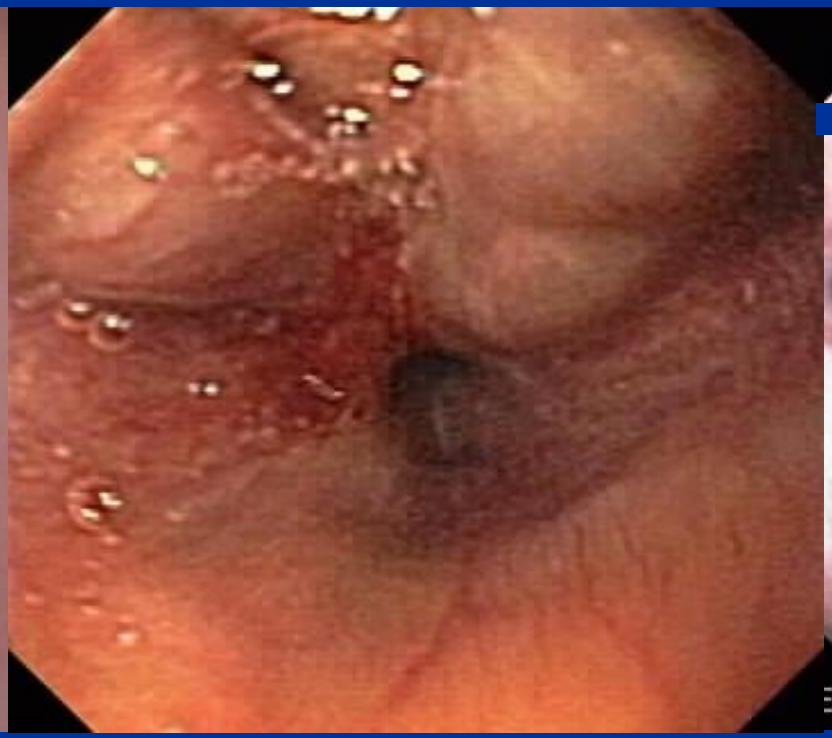


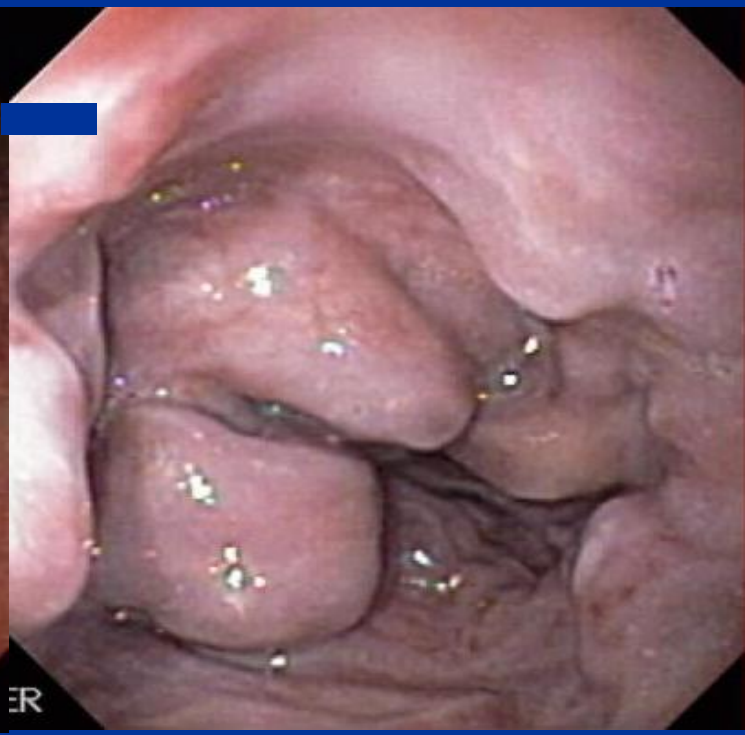
Esophageal Varices

Normal

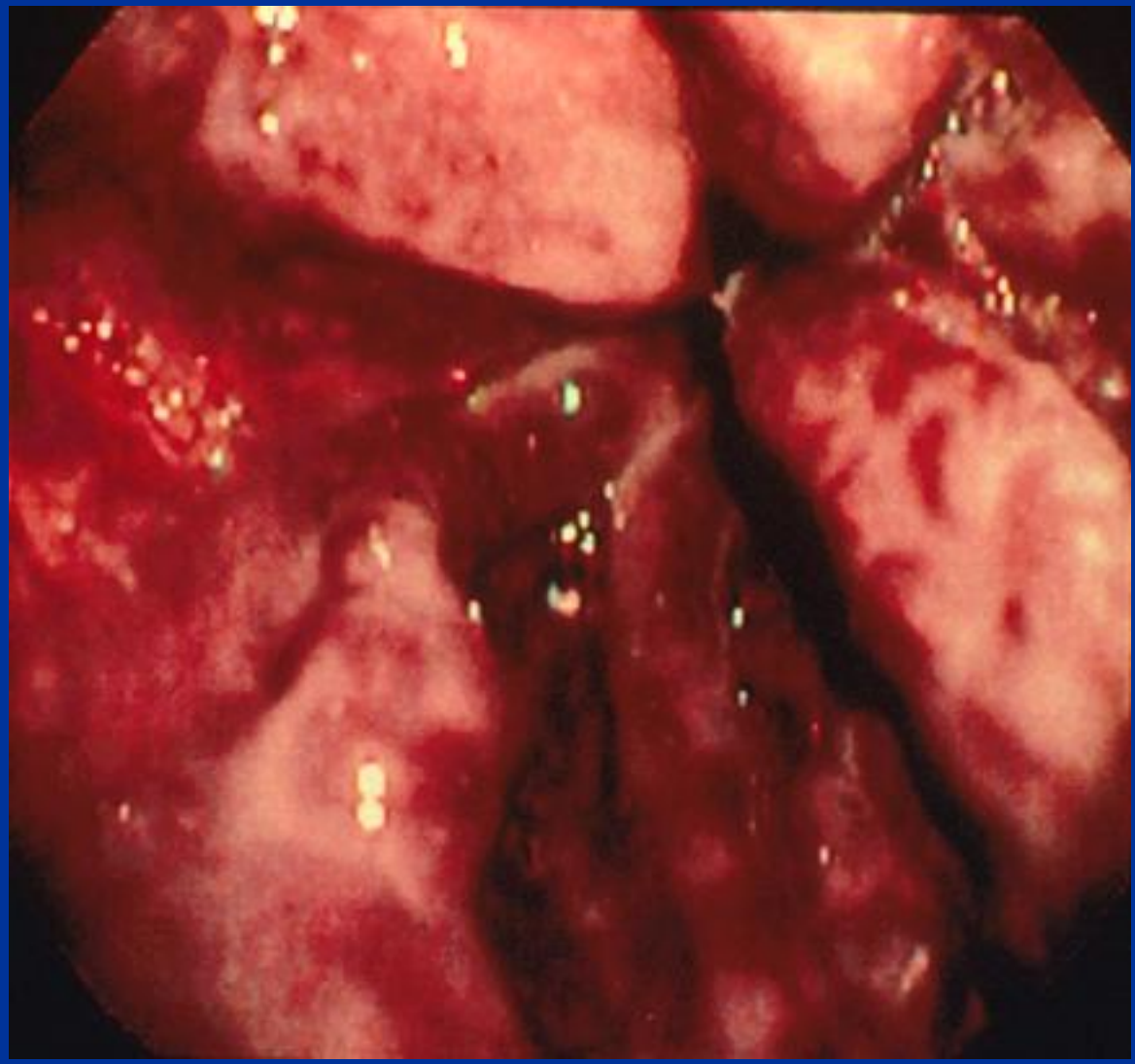
Varices







Bleeding Esophageal Varices



Medical Management of Variceal Upper GI Bleed

- GI / PICU consults
- Acid blockade with IV H2 blockers, PPIs
- Octreotide (1 mcg/kg bolus, then 1 mcg/kg/hour)
  - Follow blood sugars
- Vasopressin less commonly used
  - Side effects include SIADH, seizures, peripheral ischemia
- Packed red blood cell, plasma and platelet transfusions
  - May need 60-100 cc/kg – massive amounts
- Avoid sodium overload

Sengstaken-Blakemore Tube

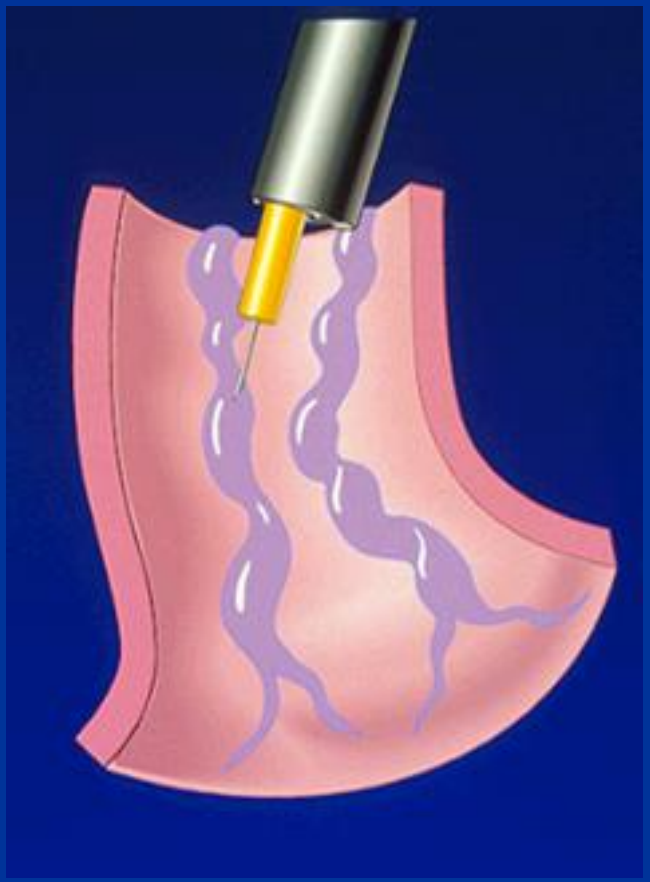
- Purpose - to occlude venous flow
- 3 and 4 lumen pediatric tubes
  - gastric port
  - gastric balloon
  - esophageal balloon
  - (esophageal port)
- 3 lumen tubes require esophageal drainage with a second tube
- Endotracheal intubation
- Requires fixation with weights or a football helmet

Sclerotherapy

- Injection of varices with a sclerosing agent
- Indications and uses
  - Active variceal bleeding
  - Therapy following a bleed
  - Prophylactic therapy
- Role in pretransplant therapy

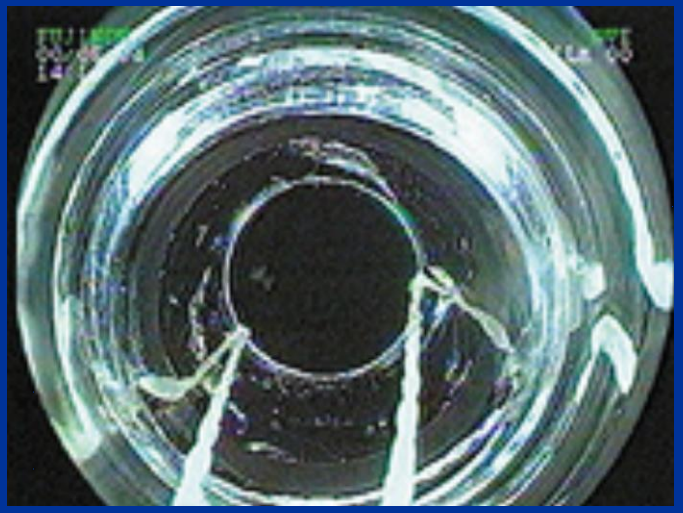
Sclerotherapy

- Bleeding controlled in 80-95%
- Effect on rebleeding rate uncertain
- No effect on survival in adults
- Major complications in 10-20%
- Death in 1-3% in adults
- No large scale studies in children



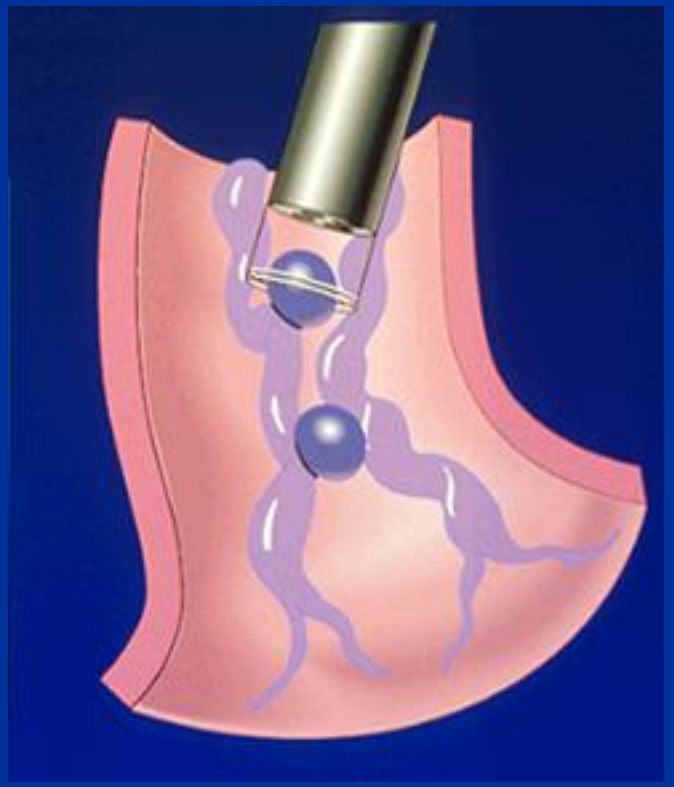
Variceal Band Ligation

- Acute or chronic care of esophageal varices
- Spring loaded multiple rubber bands
- Technique
  - Upper endoscopy
  - Suction to pull varix into chamber
  - Firing a band over the neck of the varix
- Band occludes varix
- Necroses (dies) and falls off after several days
- Minimizes many of the risks of sclerotherapy
- No large scale studies in children
- Chamber cannot fit into the esophagus of infants

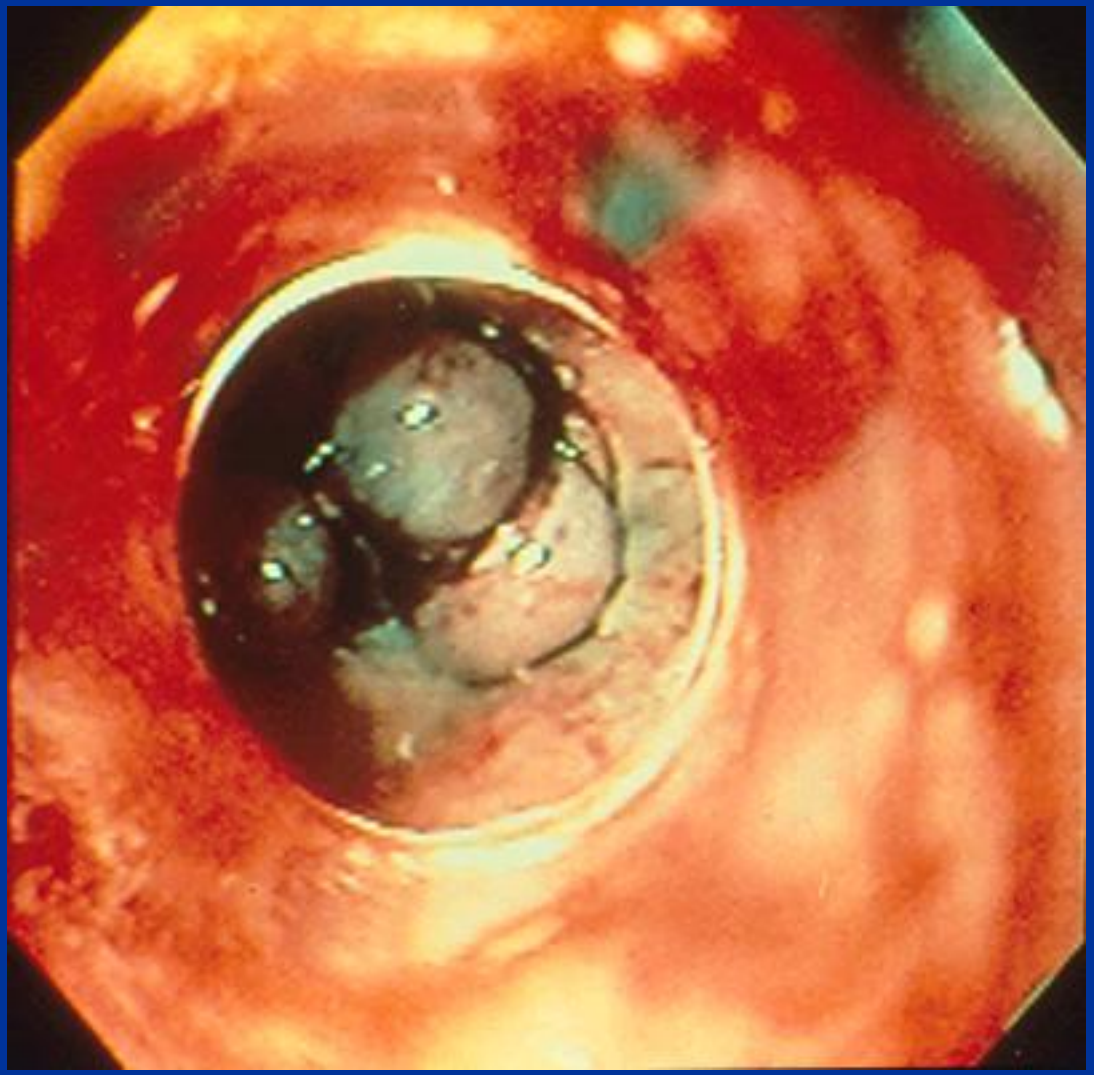


Variceal Ligation - Banding

- Bleeding controlled in 90%
- Rebleeding rate reduced to 30%
- Compared with sclerotherapy
  - Less rebleeding
  - Lower mortality
  - Less complications
  - Fewer treatment sessions

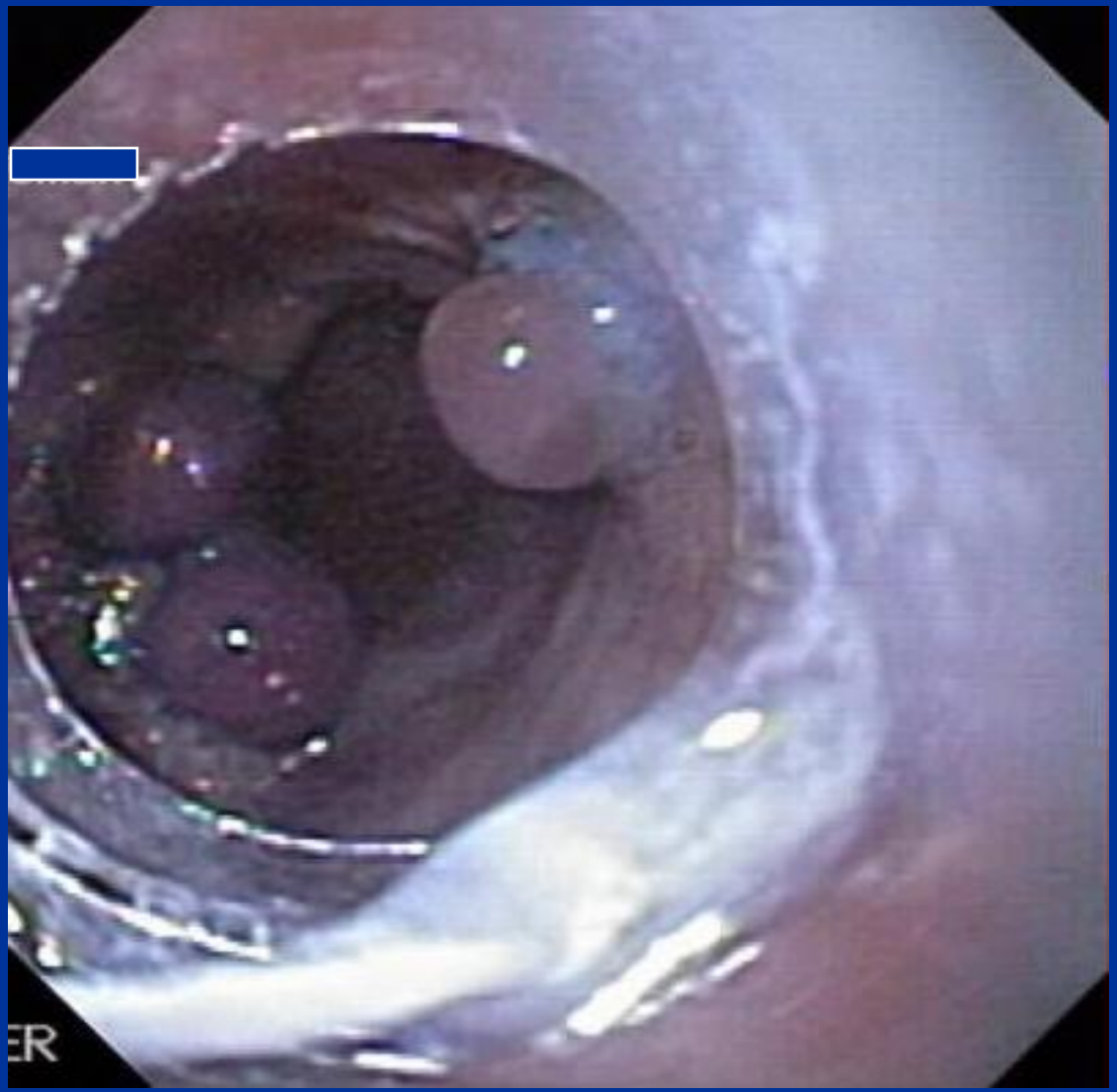


Variceal Bleeding with Band Ligation



Variceal Bleeding

Post Band Ligation



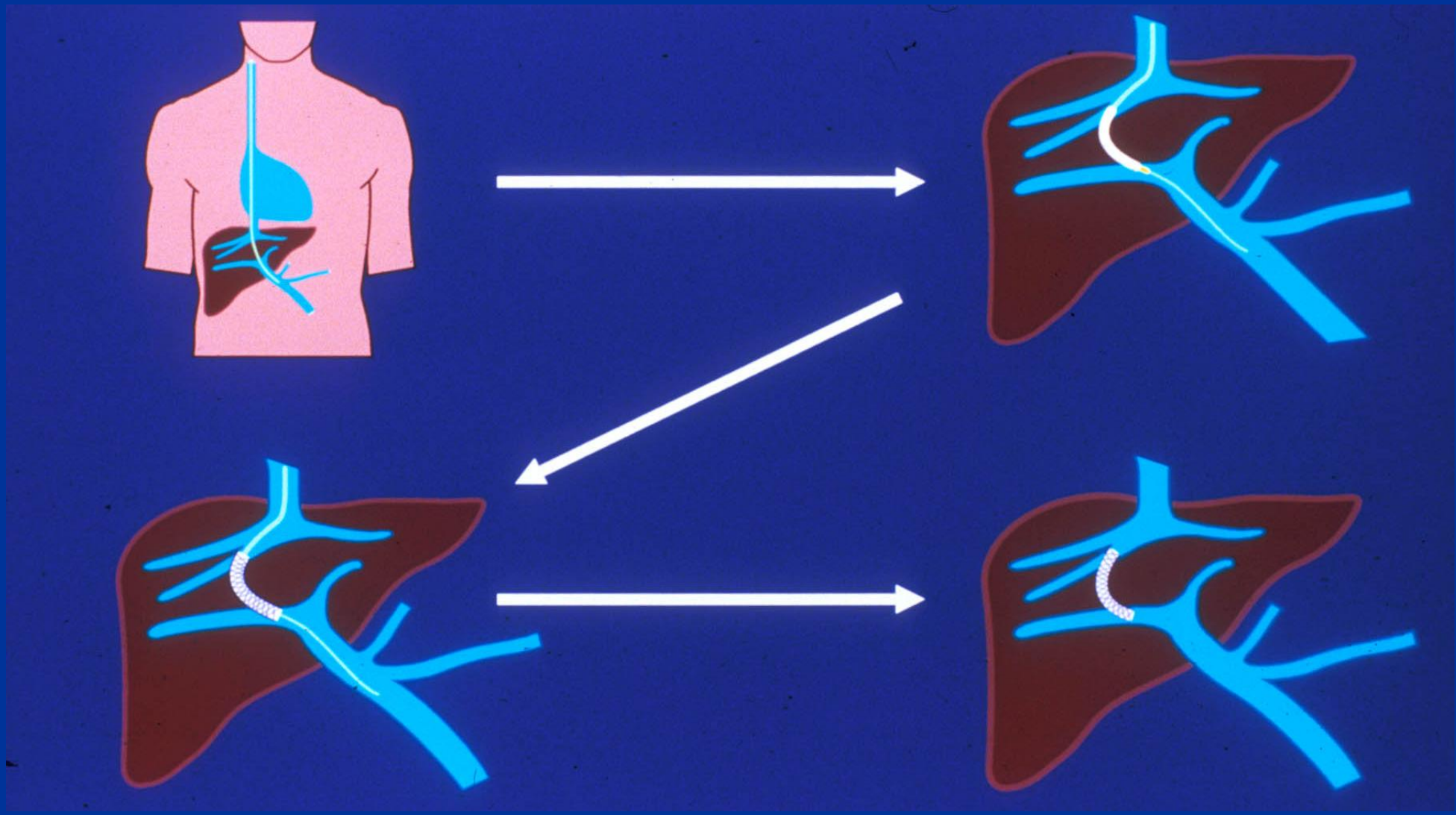
Portosystemic Surgical Shunts

- Techniques
  - Portocaval shunt
  - H-type mesocaval shunt
  - Distal or proximal splenorenal shunt
- Disadvantages
  - Major surgery
  - Rearranges prehepatic vessels pre-transplant
  - May clot with time
  - Difficult or impossible in small infants
  - Post-shunt encephalopathy may occur

Emergency TIPS

- Transvenous (jugular) intrahepatic portosystemic shunt performed by interventional radiologists
- Technique
  - Access the hepatic veins
  - Perforate through to the portal veins
  - Dilate the channel
  - Place a stent and then dilate the stent
- Advantages
  - Can be performed emergently without surgery
  - Does not require surgery of prehepatic vessels
- Disadvantage - commonly re-stenoses

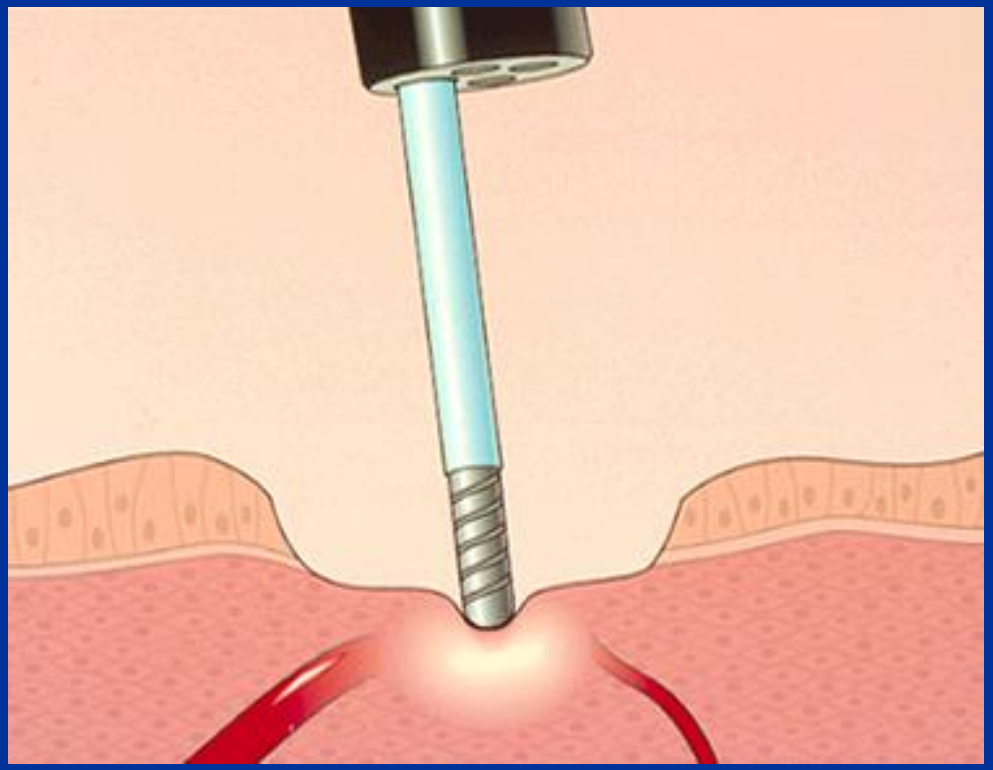
Transjugular Intrahepatic Portosystemic Shunt

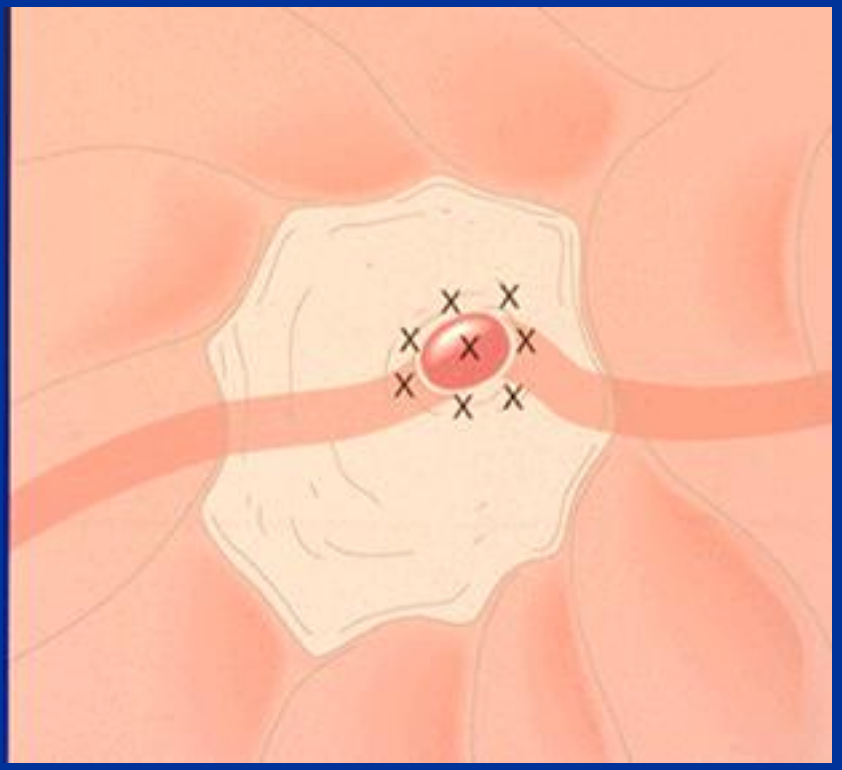


Endoscopic Therapeutic Options

- Injection
- Coagulate
  - Heater probe
  - Bipolar probe
  - Laser coagulator
- Mechanical
  - Hemoclips
  - Banding

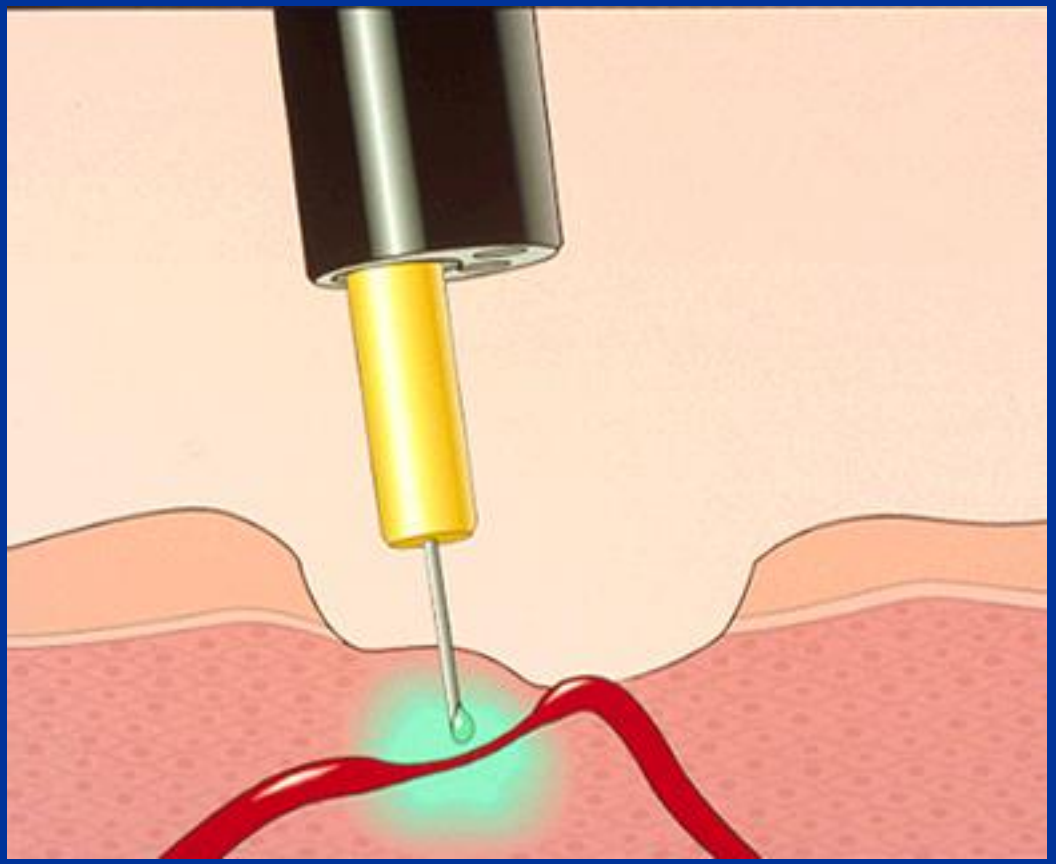
Bipolar Coagulation Strategy





Injection Therapy

- Epinephrine
- Thrombin
- Sodium tetradecyl sulfate
- Morrhuate



Options For Variceal Bleeding

Acute management

- Medications: vasopressin, octreotide, transfusion
- Direct tamponade with Blakemore tube

Chronic management

- Variceal sclerotherapy or ligation
- Radiological intrahepatic portosystemic shunts

Definitive management

- Surgical portosystemic shunts
- Transplantation

Prophylactic management

- Medications: β-blockers

Summary

- Ductal plate malformations are a poorly understood histologic finding that are present in many syndromic entities

- Several genes have been identified that are critical for the normal development of the ductal plate

- Awareness of the genes and pathways involved in ductal plate development may identify candidate genes for these disorders

- Conversely the identification of disease genes for syndromic ductal plate disorders will shed light on the molecular controls of intrahepatic bile duct development

Unanswered Questions – Nearly All of Them!

- Which patients will bleed?
- Can we prevent the bleeding before it occurs?
- What percentage of patients bleed?
- When they bleed, what is the best therapy?
- If they bleed, must they be transplanted?
- Why do some patients develop liver failure?
- What can be done for the portal hypertension?
- Can we reverse the fibrosis?
- Do some patients mature and get better with age?
- If we reverse the fibrosis, will the portal hypertension improve?
- If we transplant, liver first, kidney first, both, living related??
- And so on.
- Many questions – almost no useful studies.

Fred and Suzanne Biesecker Liver Center Faculty at CHOP

Mission: To Provide Care, Education and Research on Pediatric Liver Diseases

Liver and Bile Duct Development
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