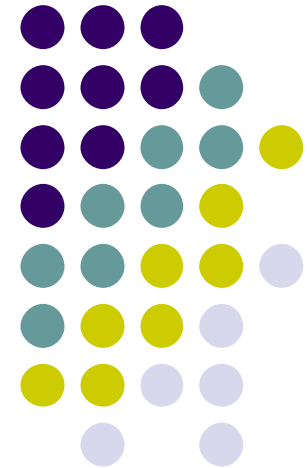


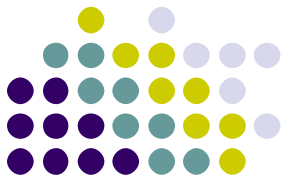


# Nottingham 2006

## Patterns of liver fibrosis and their clinical significance

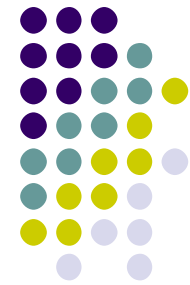
Alastair D Burt  
Professor of Pathology and Dean of Clinical Medicine  
University of Newcastle upon Tyne







Collapse of reticulin framework or  
dynamic process ? Popper 1960s



# Hepatic fibrosis

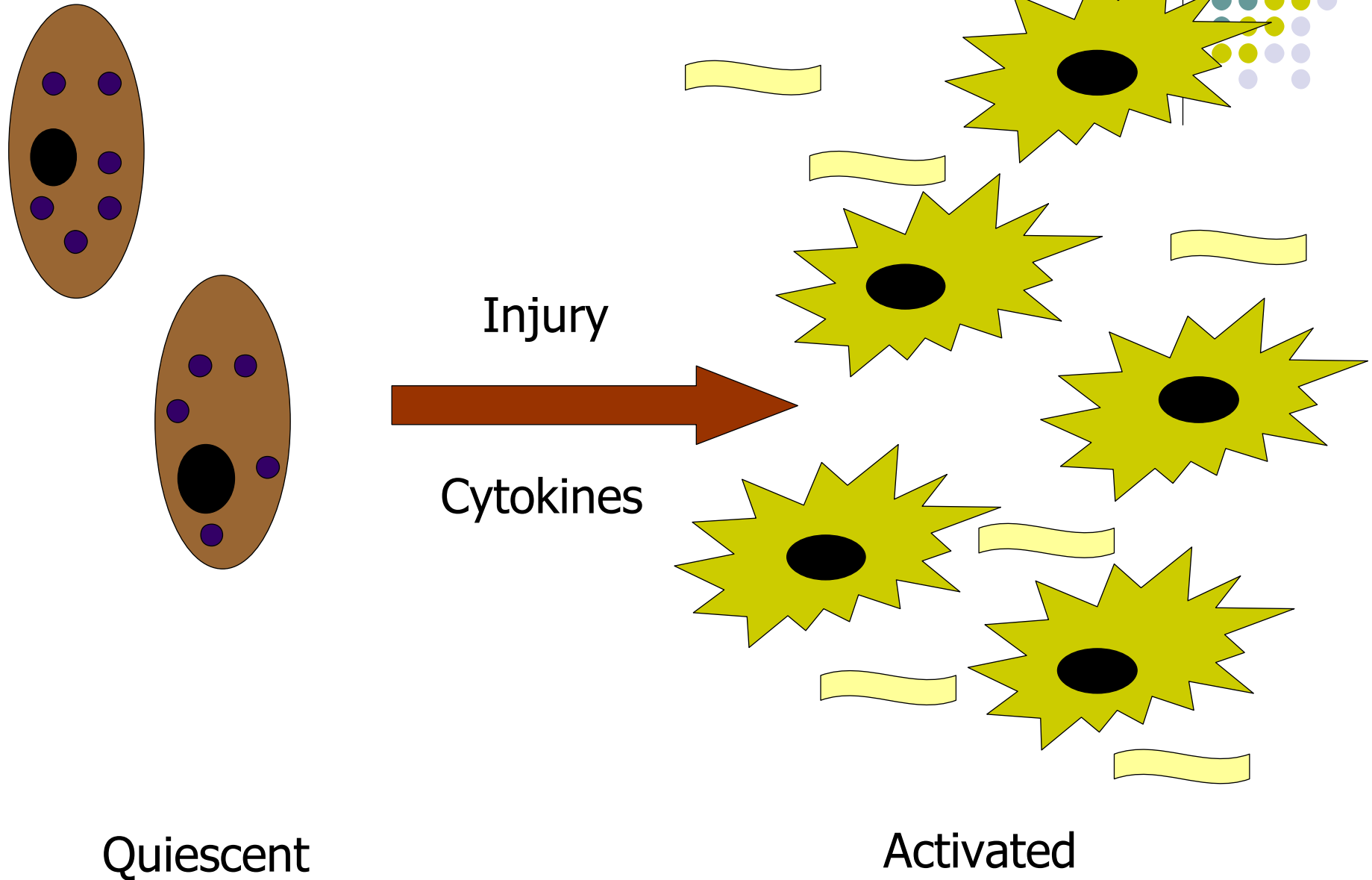
- Consequence of repair process following chronic liver injury with resultant net accumulation of extracellular matrix proteins with abnormal distribution: dynamic process involves increased production and decreased turnover of matrix
- Effects not only space occupying but influence gene transcription, cellular proliferation etc: via integrins and non-integrin ECM receptors

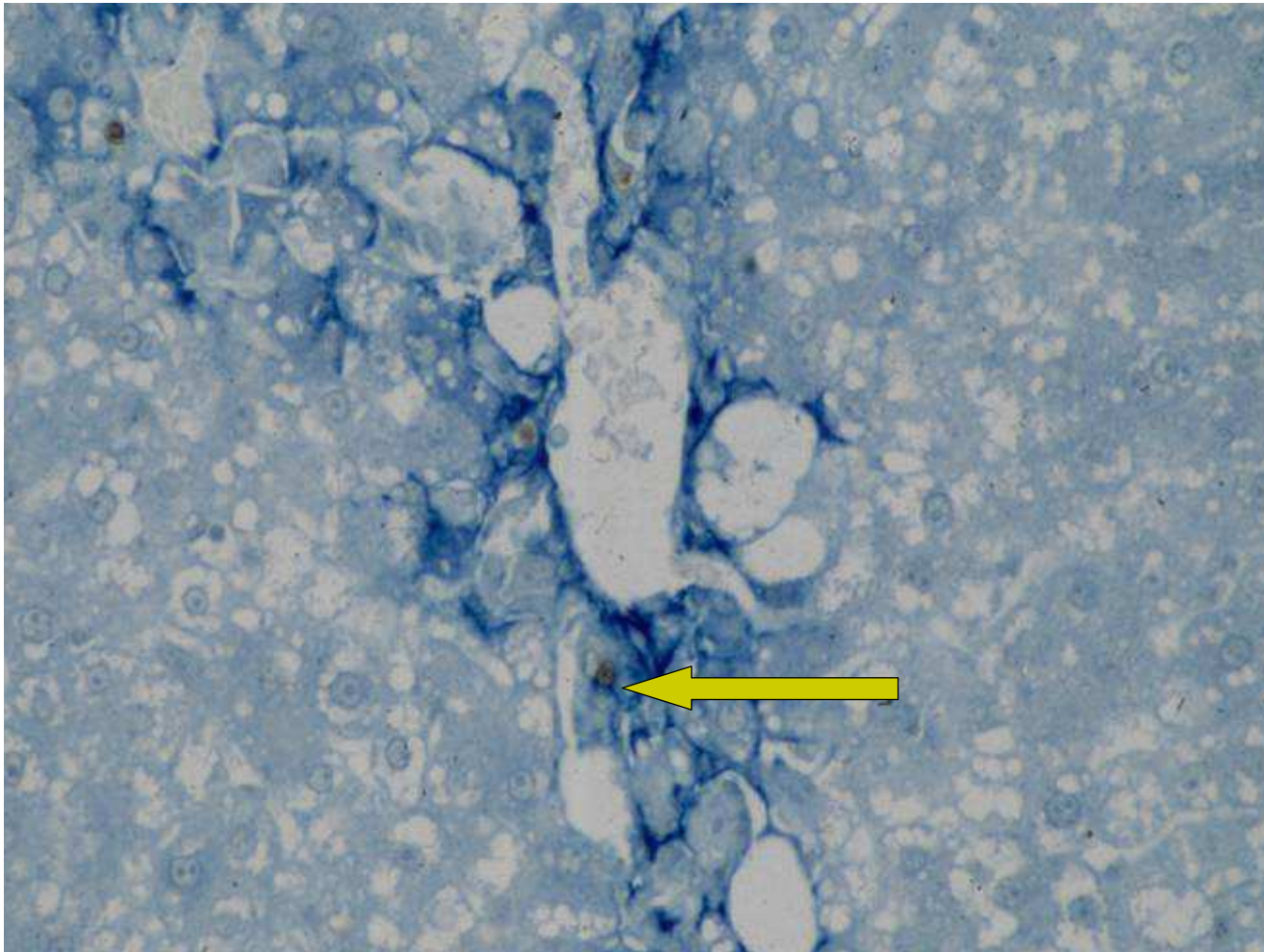
# Hepatic stellate cells: principal effectors in liver fibrogenesis



- Found within the space of Disse
- Pericyte-like with long cytoplasmic processes:  
?contractile
- Principal site of storage of vitamin A (fat-storing cells)
- ? Origin
  - Mesenchymal
  - Neural crest
  - Bone marrow
  - (Epithelial-mesenchymal transition)

# HSC response to injury





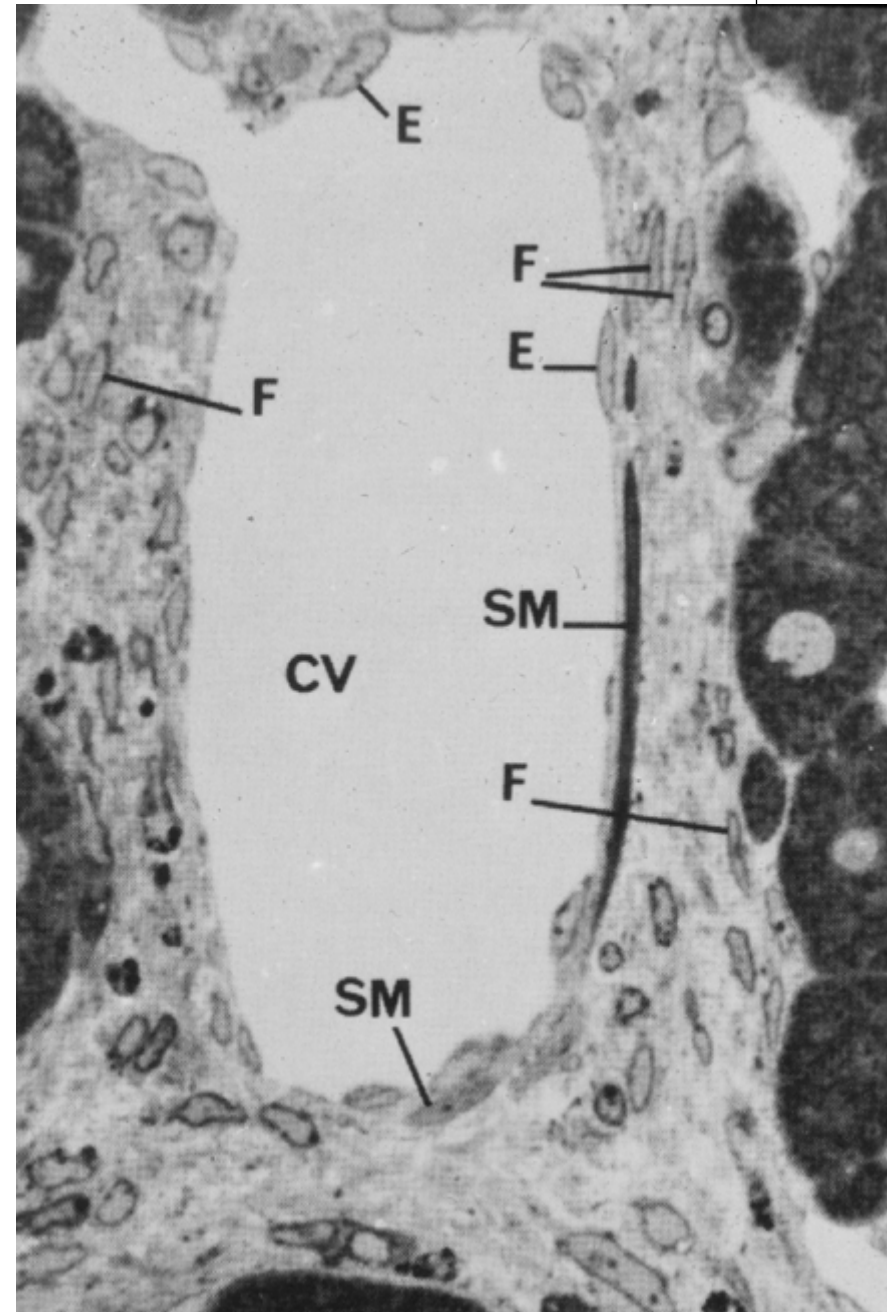
HSC apoptosis  
in CCL4 injury

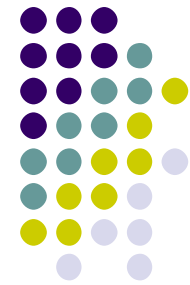
- **Fibrosis may be reversible: animal models and anti-viral trials**
- **HSC apoptosis important as is changing profile of MMPs/TIMPs**

# Second layer cells and myofibroblasts

*Other possible effectors:*

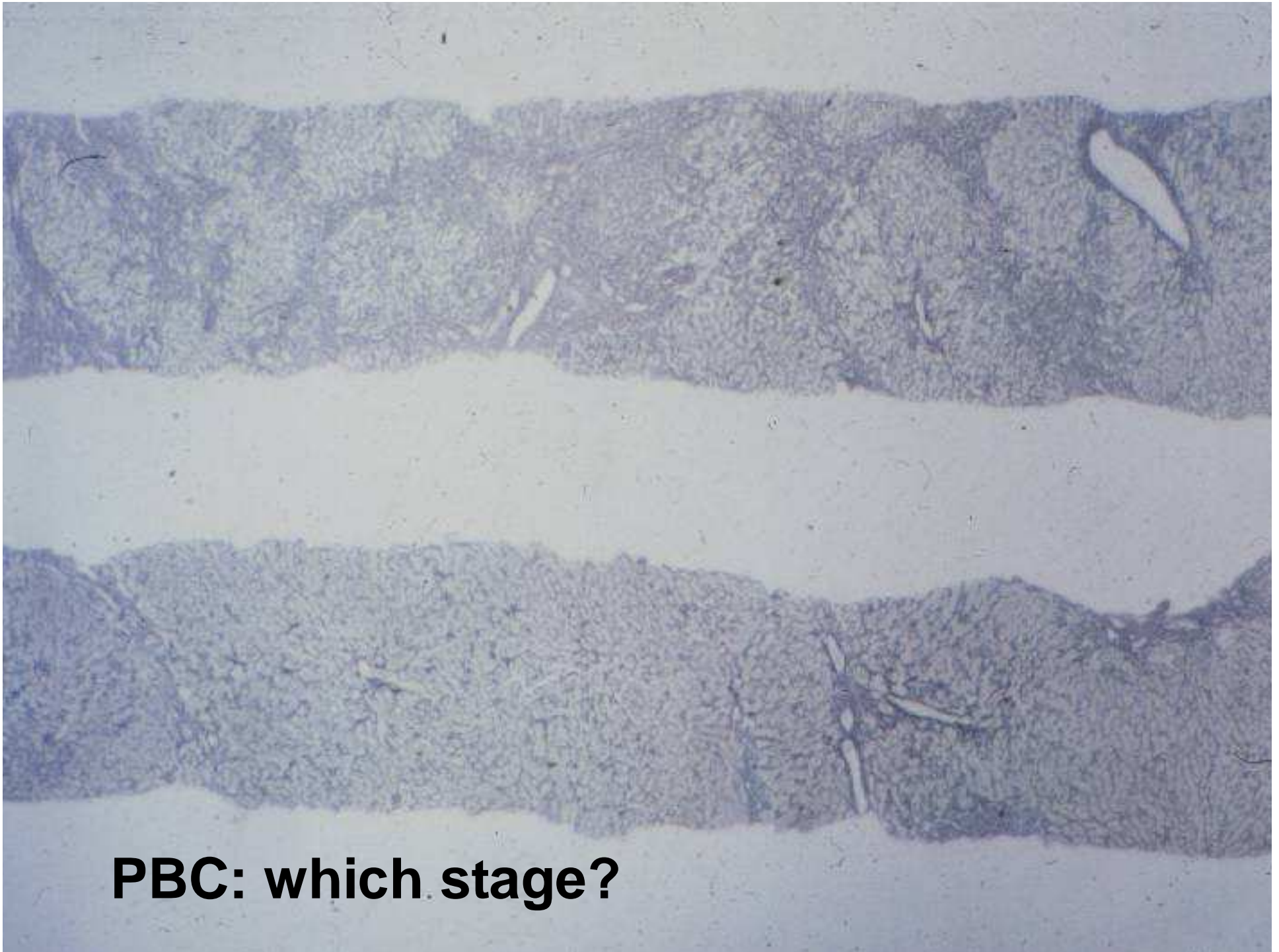
- *Bile duct epithelium*
- *Hepatocytes*
- *EMT*
- *Endothelium*
- *'Fibrocytes'*
- *Other portal tract fibroblasts*



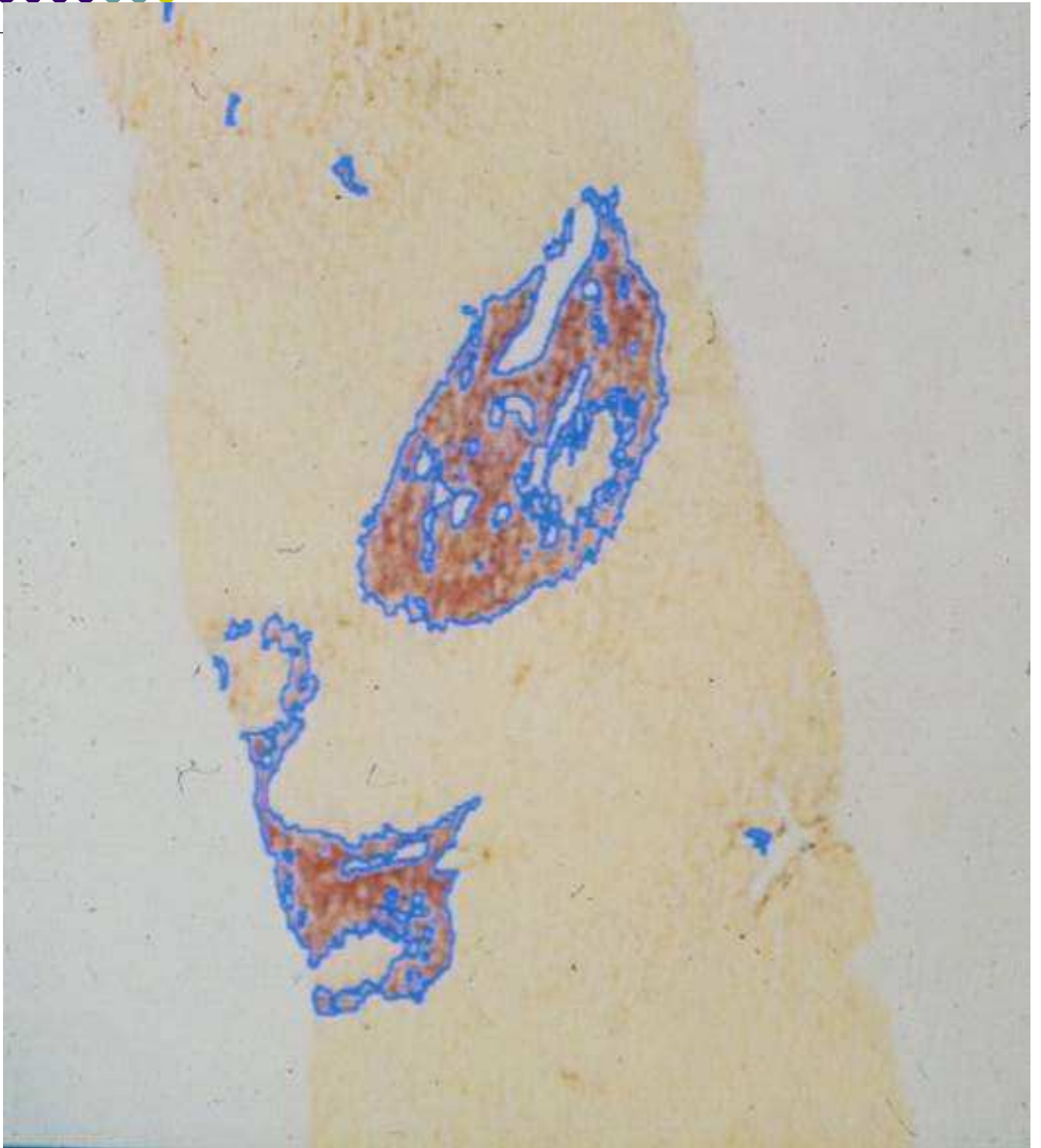
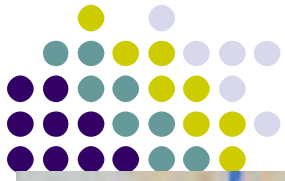


# Assessment of fibrosis

- Histochemistry
  - Silver impregnation: type III/fibronectin and type I
  - Trichrome stains/Van Gieson
  - Picro Sirius Red
  - Orcein/Victoria Blue
- Immunohistochemistry
  - Collagen subtypes
  - Elastin
  - Activated HSCs ( $\alpha$  SMA)
- Quantitative
  - Semi-quantitative scoring
  - Elution of Picro Sirius Red
  - Image analysis

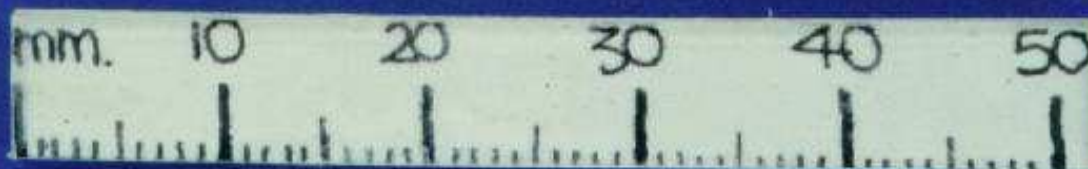


**PBC: which stage?**





*Oh yes it does!!*



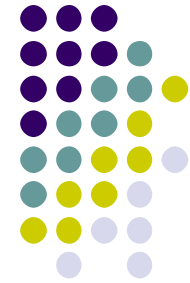
# Sampling variability of liver fibrosis in chronic hepatitis C



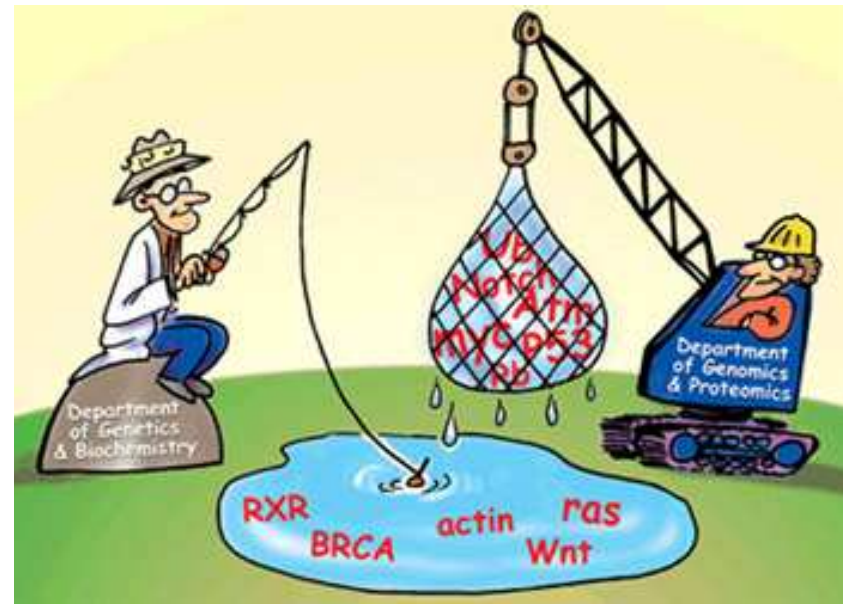
- Surgical specimens of livers from patients with HCV
- Image analysis and METAVIR: overall reference value
- Virtual biopsies of increasing length
- 15mm biopsies categorised correctly in 55%; increased to 65% with 25mm
- Concluded that at least 25mm required for accurate semi-quantitative assessment of fibrosis

*Bedossa et al, 2003*

# Surrogate markers of hepatic fibrosis



- Forns score: based on age, GGT, platelets, cholesterol
- FIBROTEST: apoA1, haptoglobin,  $\alpha$ 2-MG, GGT, bilirubin
- Effective at identifying patients with mild fibrosis
- Large percentage within indeterminate range
- ? Enhanced by incorporating ECM markers



# Patterns of hepatic fibrosis



- **Localised**

- Abscess
- Inflammatory pseudotumour
- Intra and peritumoral
- Trauma

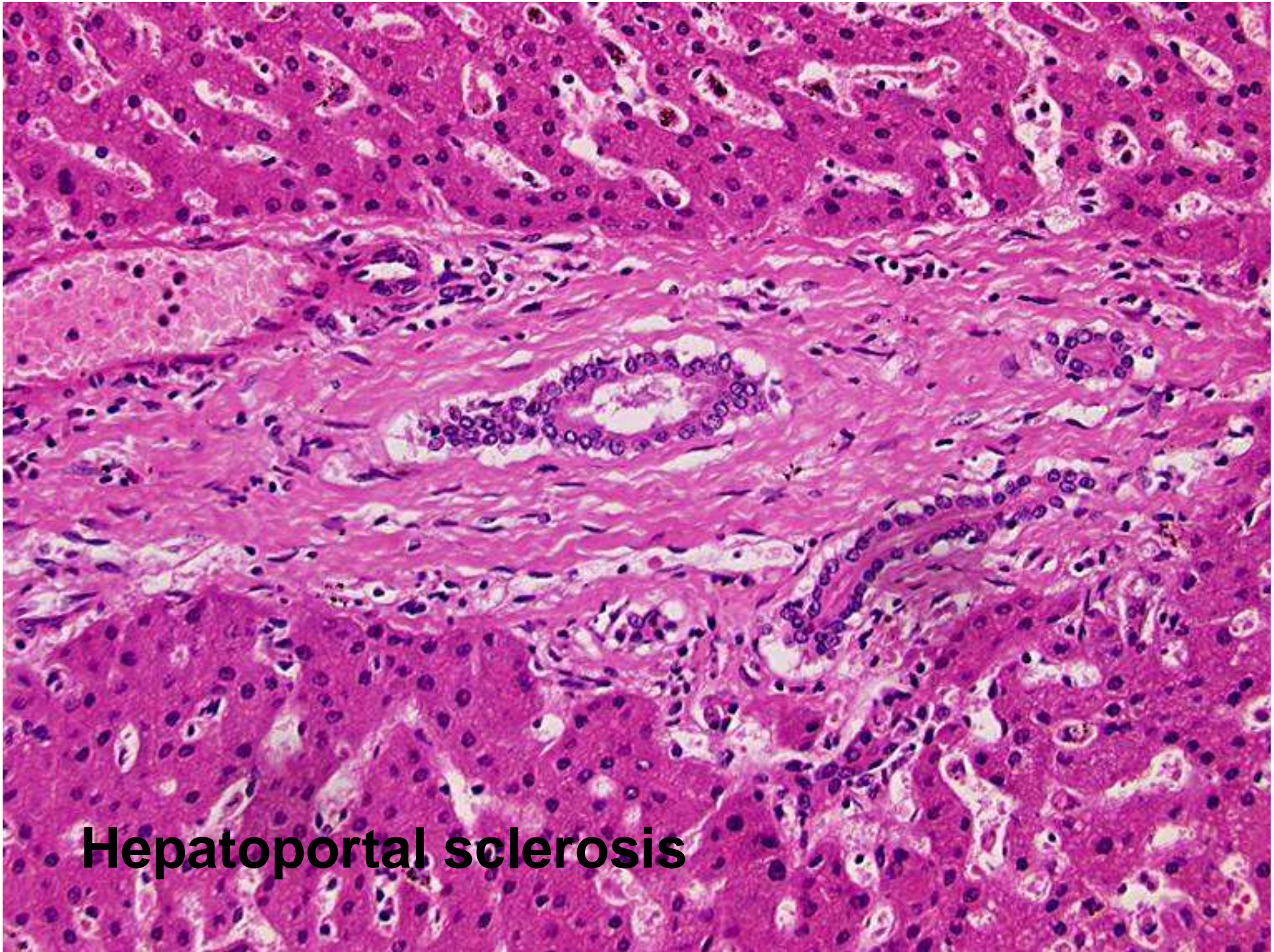
- **Generalised**

- Portal tracts/zone 1
- Hepatic veins/zone 3
- Perisinusoidal
- Septal
- Others.....

# Portal tracts/zone 1 and fibrosis

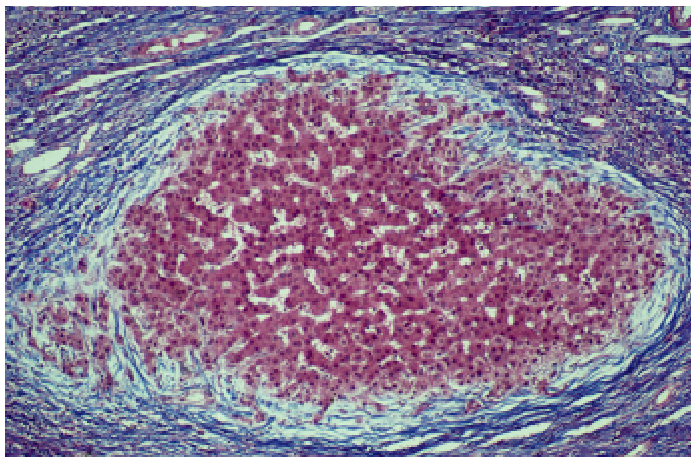
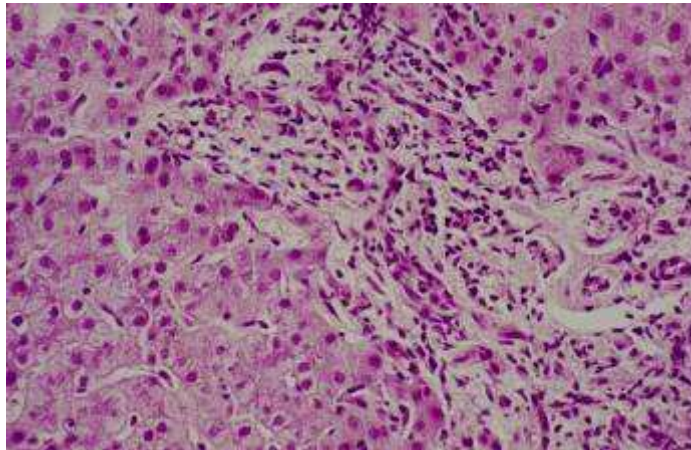
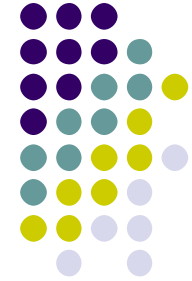


- **Portal tract fibrosis**
  - Increased density and fibrous enlargement of PTs
  - *Biliary diseases; chronic hepatitides; NASH; ?? ALD*
- **Pipe stem fibrosis**
  - *Schistosomiasis*
- **Hepatoportal fibrosis**
  - *Idiopathic non-cirrhotic hypertension*
- **Periportal fibrosis**
  - Fibrous spurs extending from PTs
  - May be associated with interface hepatitis
- **Periductal fibrosis**
  - *Sclerosing cholangitis (primary or secondary)*
- **Periductular fibrosis**
  - Accompanies ductular reaction: *cholestatic diseases and chronic hepatitides*

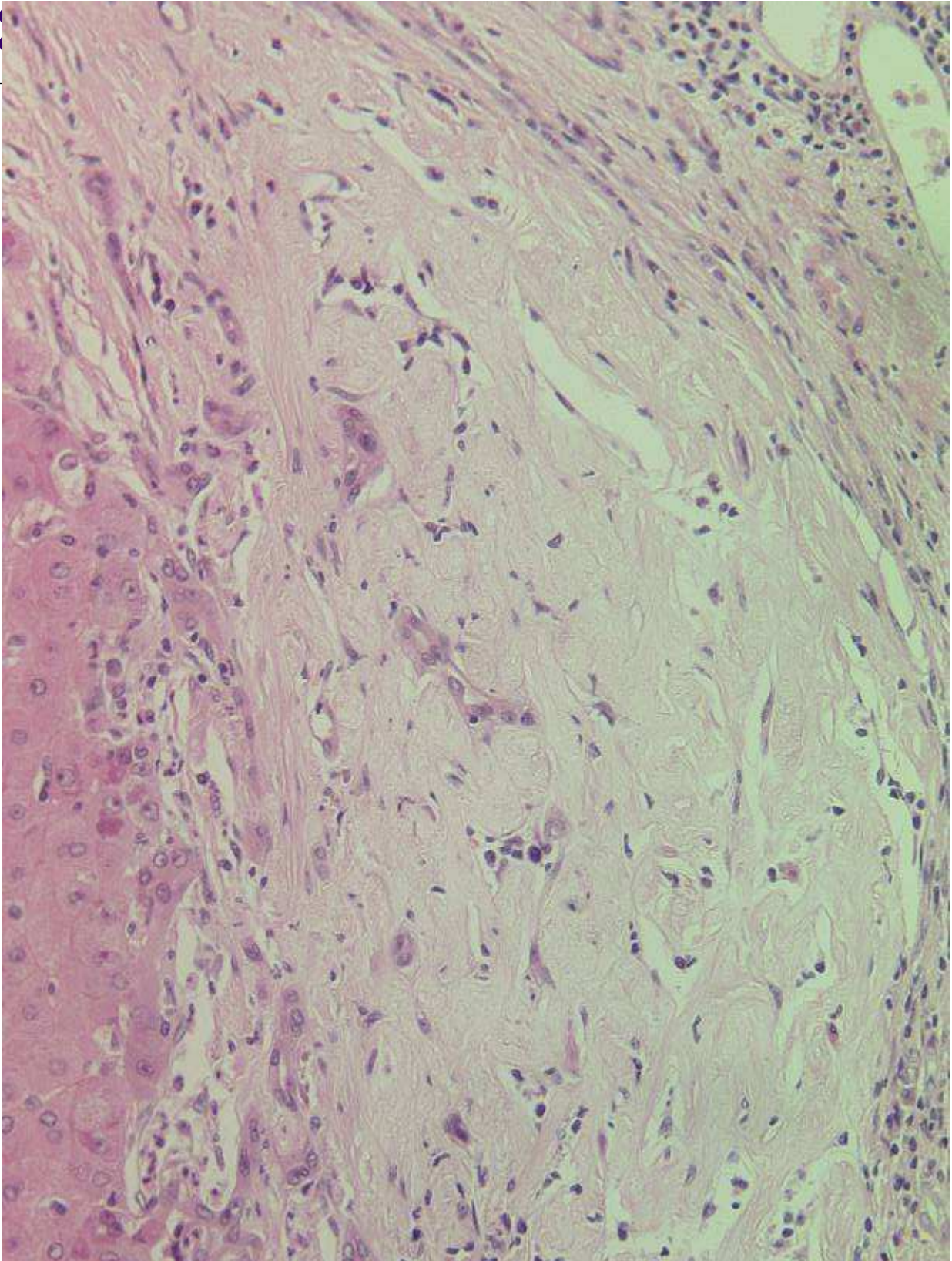
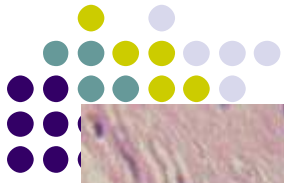


**Hepatoportal sclerosis**

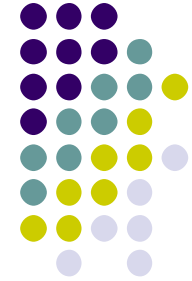
# Progressive fibrosis in autoimmune biliary disease



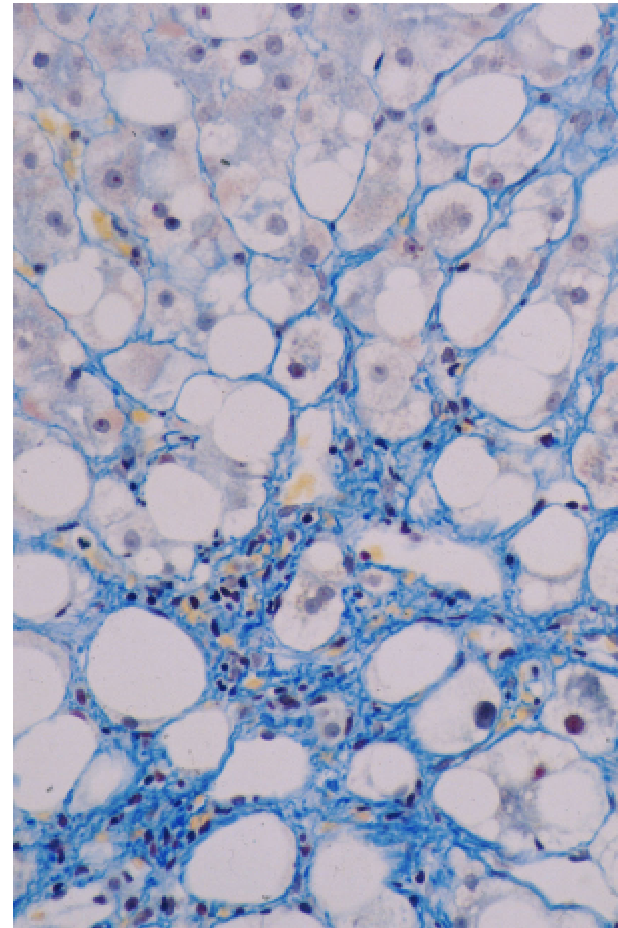
- Progressive periportal fibrosis is associated with and may be driven by the so-called ductular reaction
- Portal-portal fibrous linkage ensues leading to a monolobular form of cirrhosis



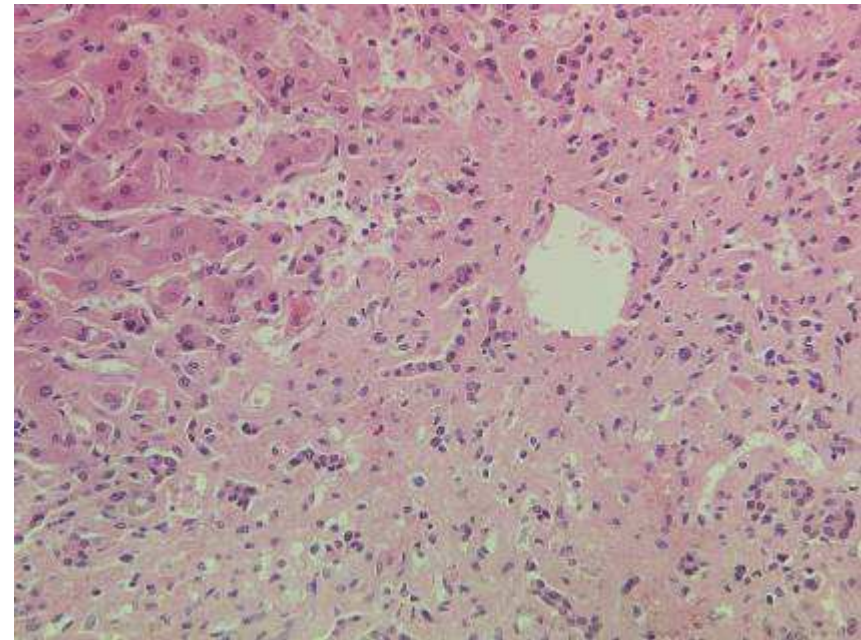
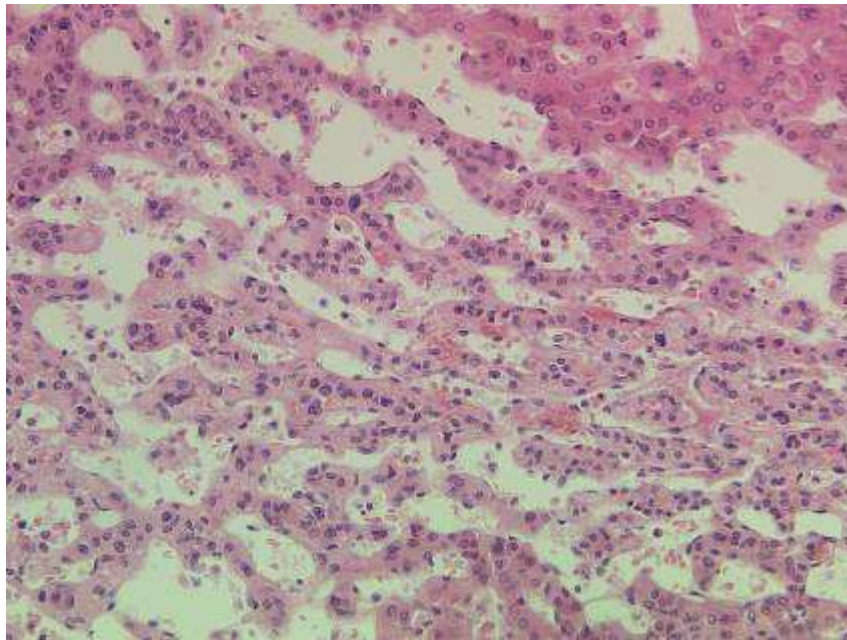
# Hepatic veins/zone 3 and fibrosis



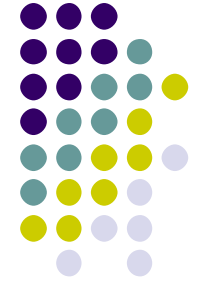
- Perivenular fibrosis
  - *Alcoholic liver disease*
  - *NASH*
  - *Veno-occlusive disease*
- Centrilobular fibrosis (? distinct)
  - *Alcoholic liver disease* ('central sclerosing hyaline necrosis')
  - *NASH*
  - *Ischaemic injury (chronic venous outflow obstruction)*



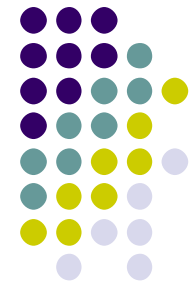
# Ischaemic fibrosis



# Pericellular/perisinusoidal fibrosis

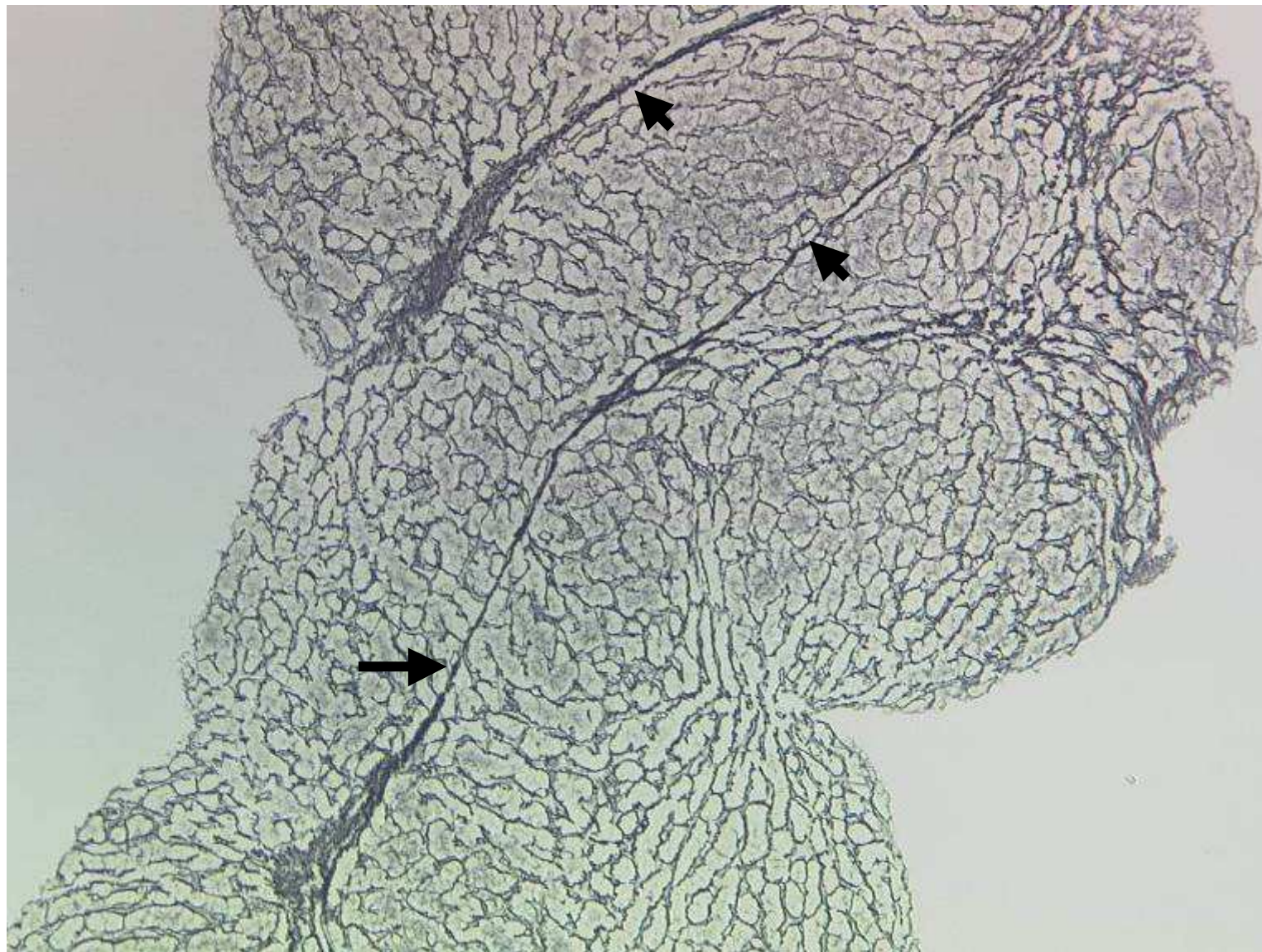


- Zone 3 predominance
  - Chicken wire appearance: *alcoholic liver disease/NASH*
- Diffuse
  - *Diabetes type 1*
  - Similar appearance with *amyloidosis* and *light chain disease*
  - *Congenital syphilis*

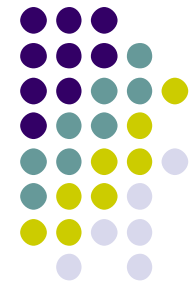


# Septal fibrosis

- Portal-portal septa
  - Link adjacent portal tracts
  - *Chronic cholestatic diseases* ('biliary fibrosis'); *chronic hepatitis*
- Central-central septa
  - Scarring stage of confluent necrosis/central-central bridging necrosis
- Portal-central septa
  - Scarring of portal-central bridging necrosis
- Active septa
  - Prominent inflammatory infiltrate and ongoing necrosis
- Passive septa
  - Post-necrotic collapse

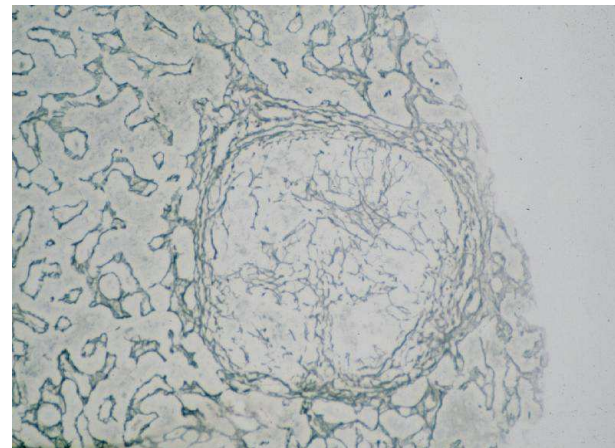


**NEWCASTLE A: POST TREATMENT BIOPSY**



# Other fibrosis

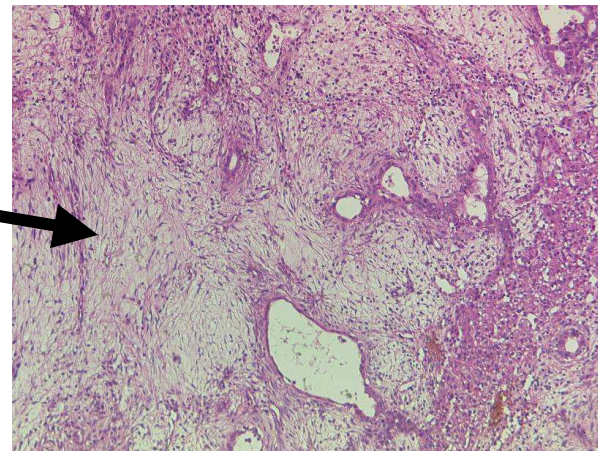
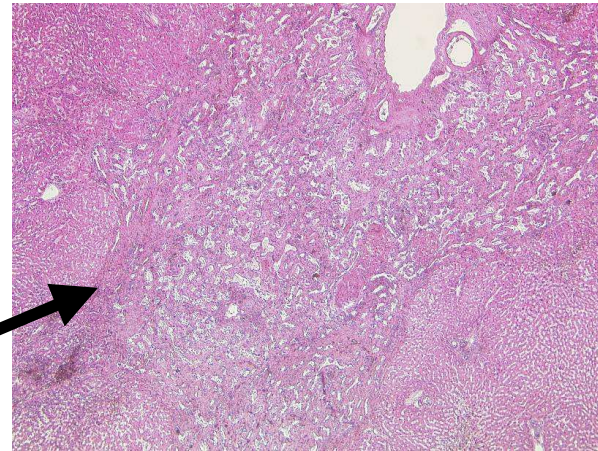
- Glisson's capsule fibrosis
- Granulomas
  - *Sarcoidosis*
  - *Mineral oil granulomas*

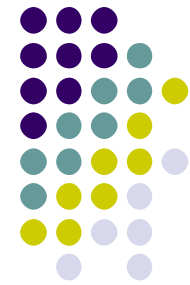


# Other fibrosis



- Developmental abnormalities
  - *Congenital hepatic fibrosis*
  - *Mesenchymal hamartoma*





# Patterns of cirrhosis

- Micronodular
  - Macronodular
  - Mixed
  - Incomplete septal
- 
- *Should we stage cirrhosis?*
    - *Laennec scoring: 4A, B and C*

