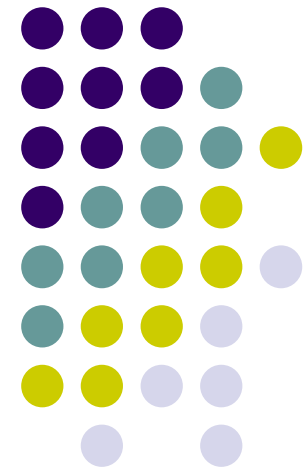
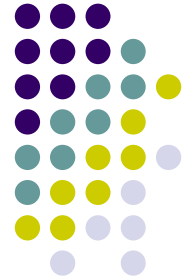




# Update from the Gnomes: liver fibrosis

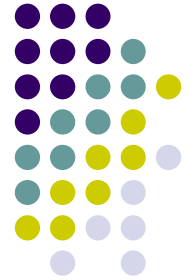


*Alastair D Burt*



# Liver fibrosis

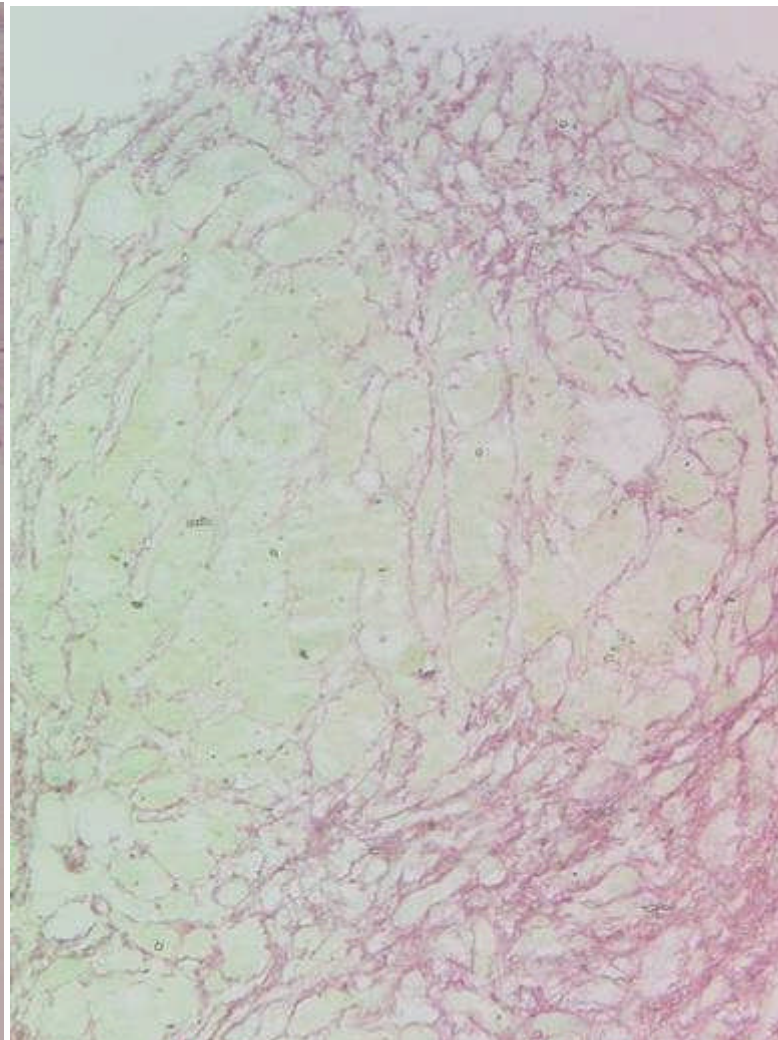
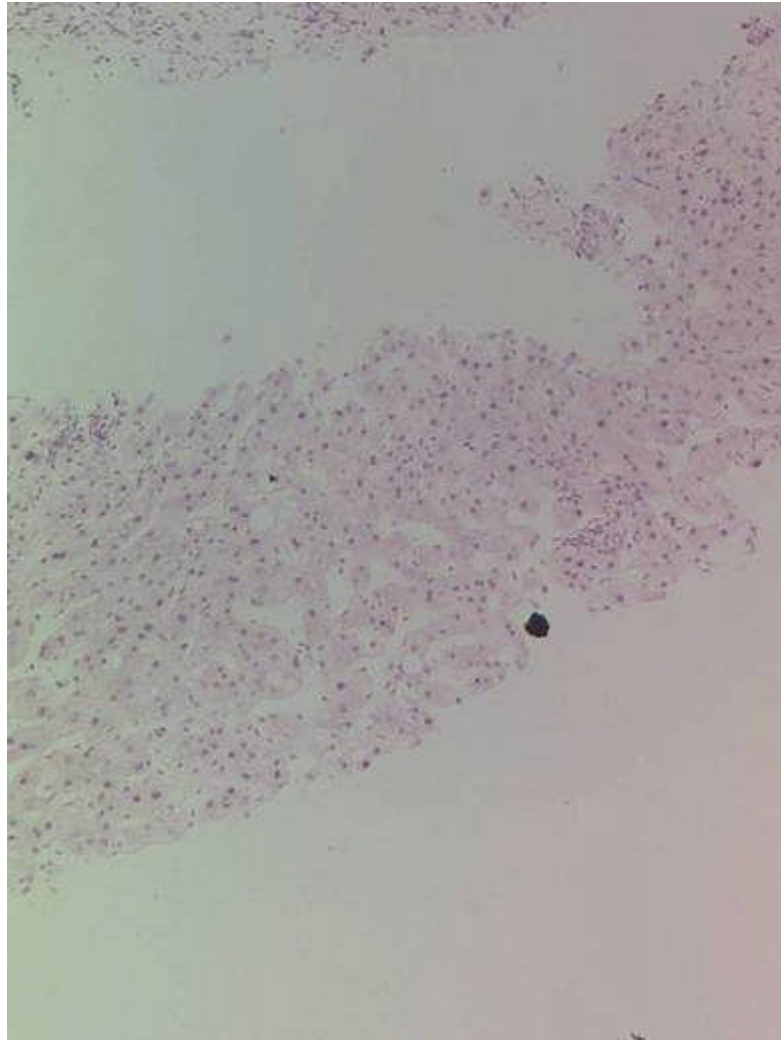
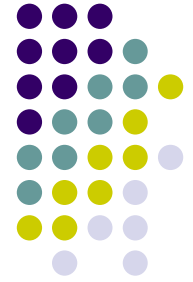
- Changing patterns over time
- Importance of the ductular reaction
- Multiple hits in fibrosis
- Summary of morphological patterns of fibrosis

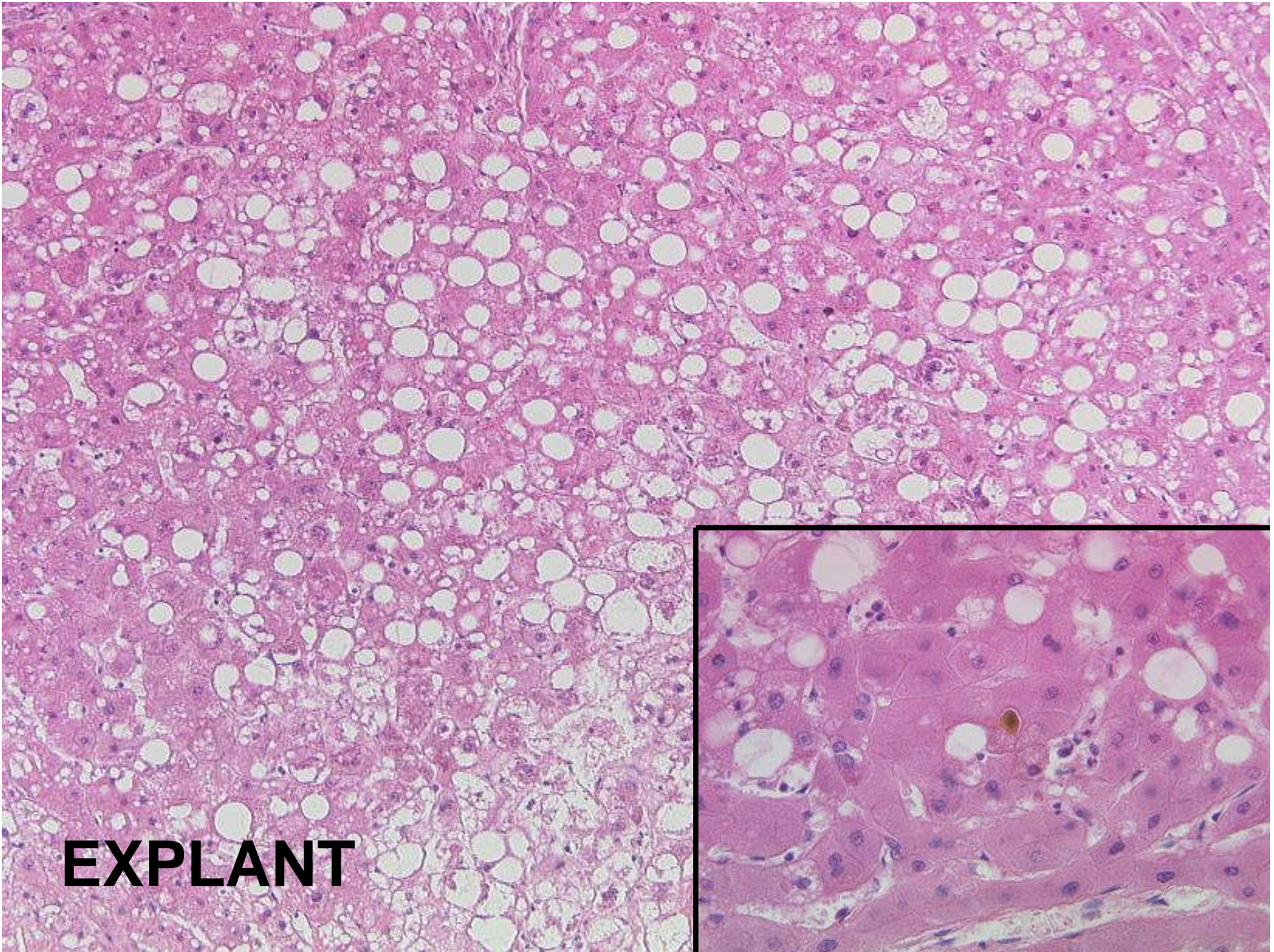


# Newcastle B

- Middle aged male
- > 90kg and type 2 DM: on metformin
- Hypertensive: 204/110
- Alcohol excess ? Duration and amount
- Said to be abstinent for at least 6 months pre Tx
- OLT

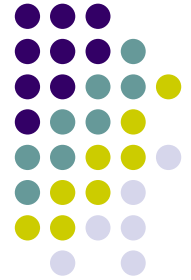
# Transplant assessment biopsy





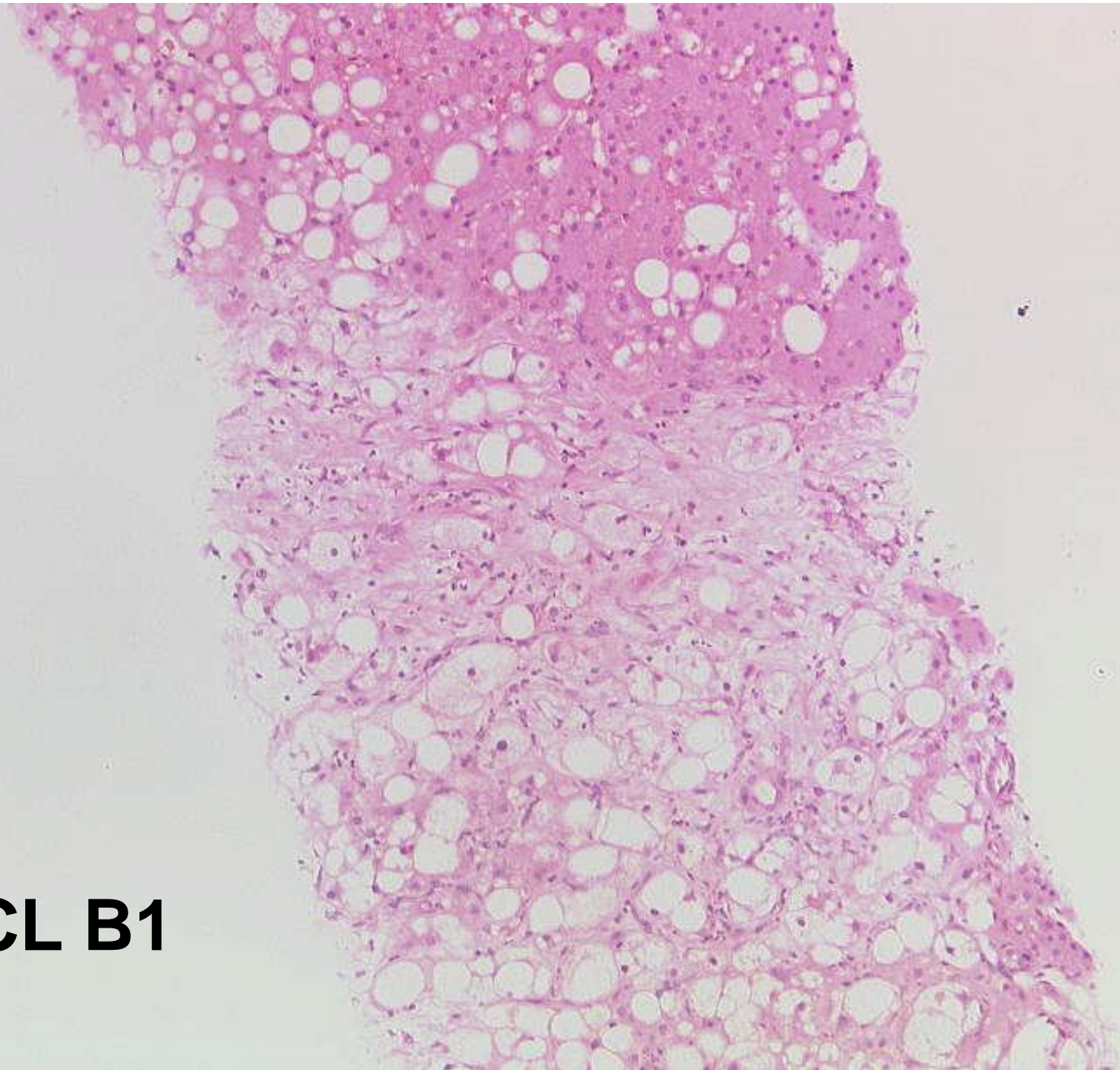
**EXPLANT**

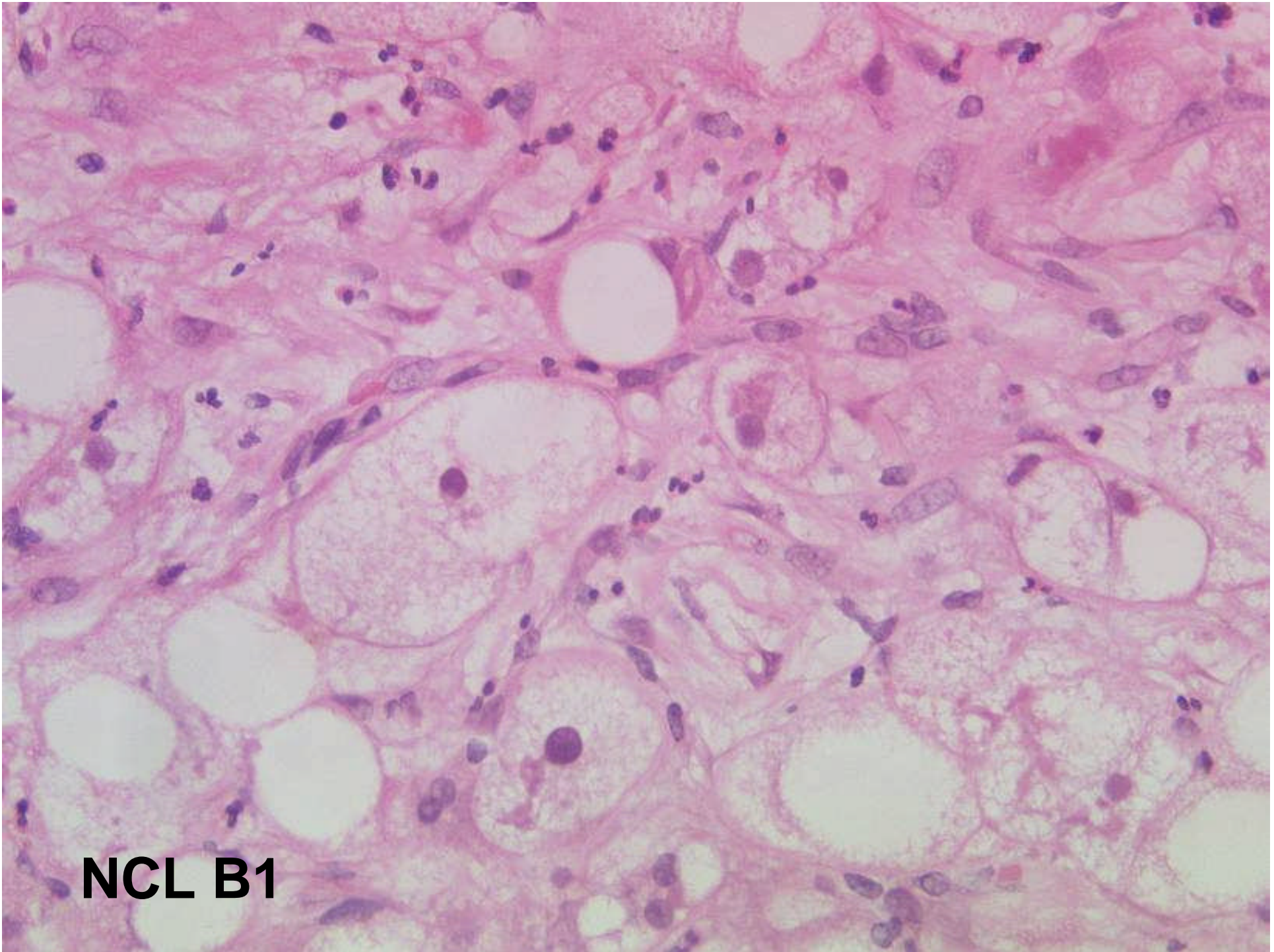
# Newcastle B



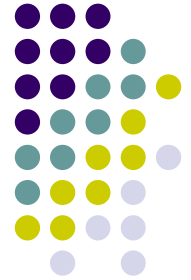
- Time zero biopsy showed minimal post perfusion injury only
- Initial post OLT course unremarkable apart from moderate rejection at day 7
- Increasing BMI: weight gain of 23kg
- Random blood alcohol negative
- Developed abnormal LFTs (10 months post OLT):  
ALT 116/ALP 293

**NCL B1**





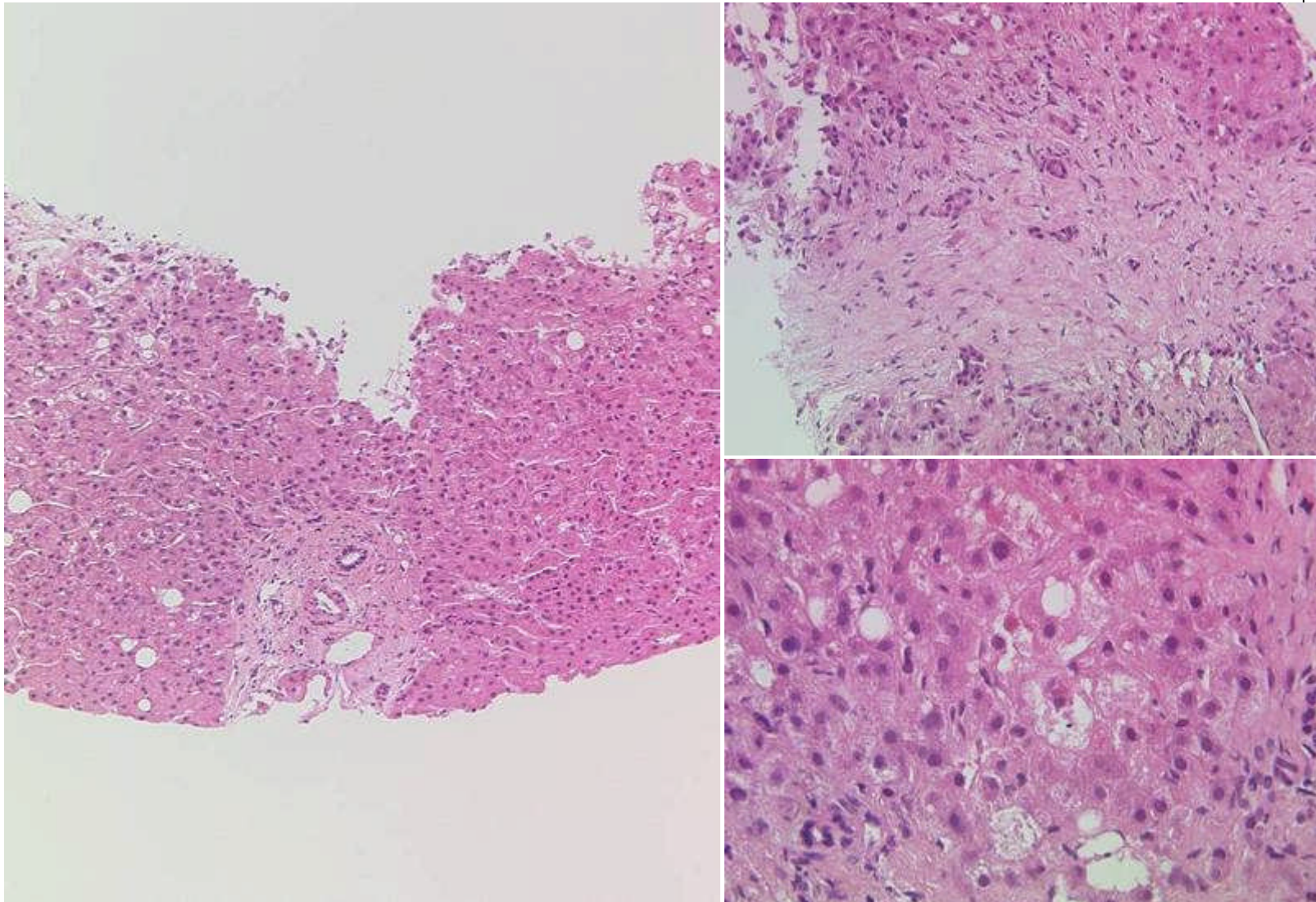
**NCL B1**



## Newcastle B

- Period of weight loss; stabilised at 104kg; associated with improvement of LFTs
- Then further weight gain: only partially explained by oedema BMI = 43
- Enjoyed ‘very occasional glass of wine’ and ‘one light meal a day’
- Evidence of low grade encephalopathy: re-biopsied

# Follow up biopsy



# (Central) sclerosing hyaline necrosis



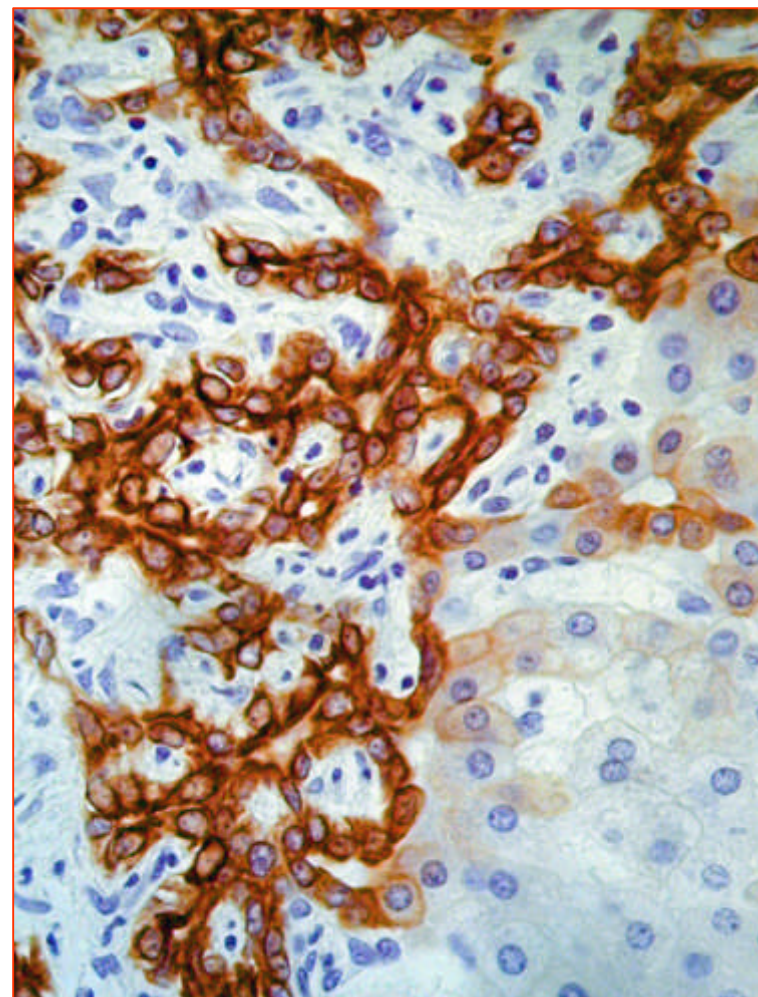
- Coined by *Edmondson et al* (1963)
- Part of spectrum of ASH
- May be associated with portal hypertension in pre-cirrhotic stage
- Large, tender livers (*Karasawa & Chedid, 1976*)
- Not a typical feature of NASH
- Described in Bloom syndrome; DDI-induced injury



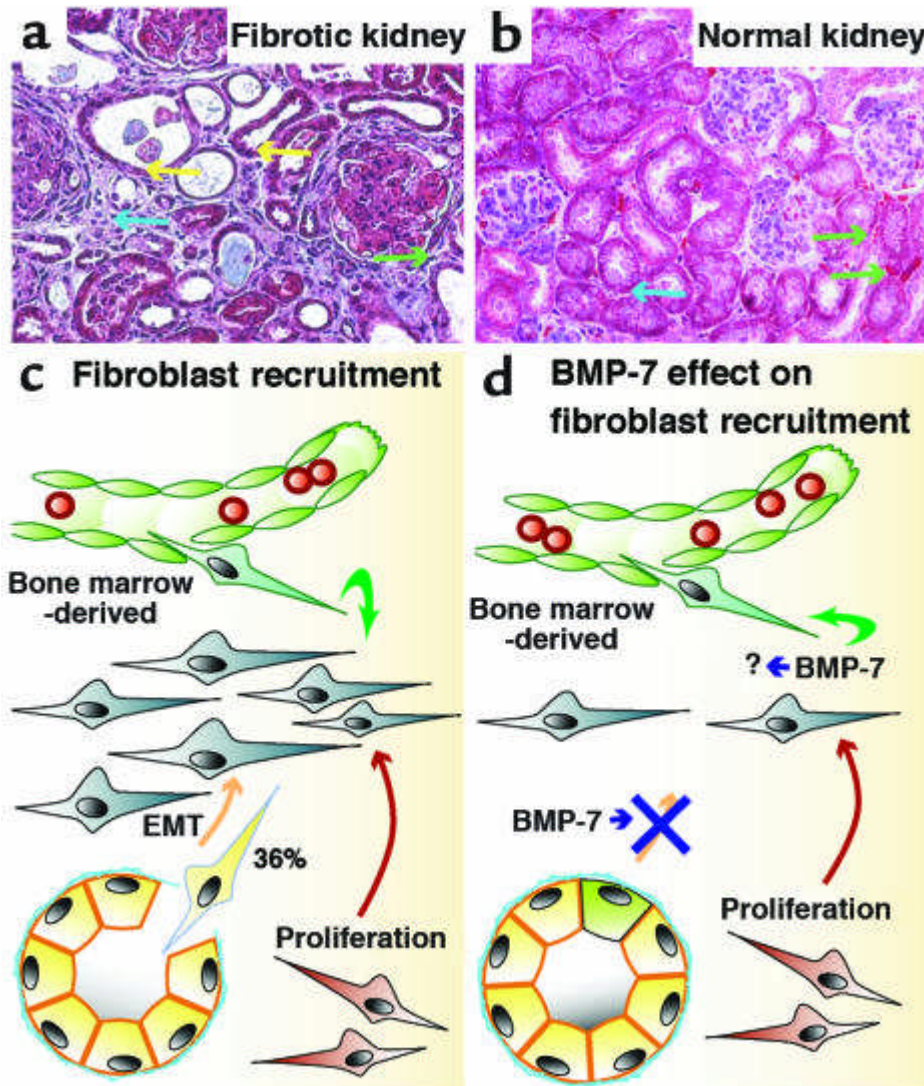
# Ductular reaction

- New ductular structures at interface
- Attempt to bypass obstruction to bile flow
- May resemble ductal plate
- Generally accompanied by inflammation
- Role of metaplasia; proliferation; recruitment
- Driver for portal fibrosis

*Importance of epithelial-mesenchymal transition (EMT)?*

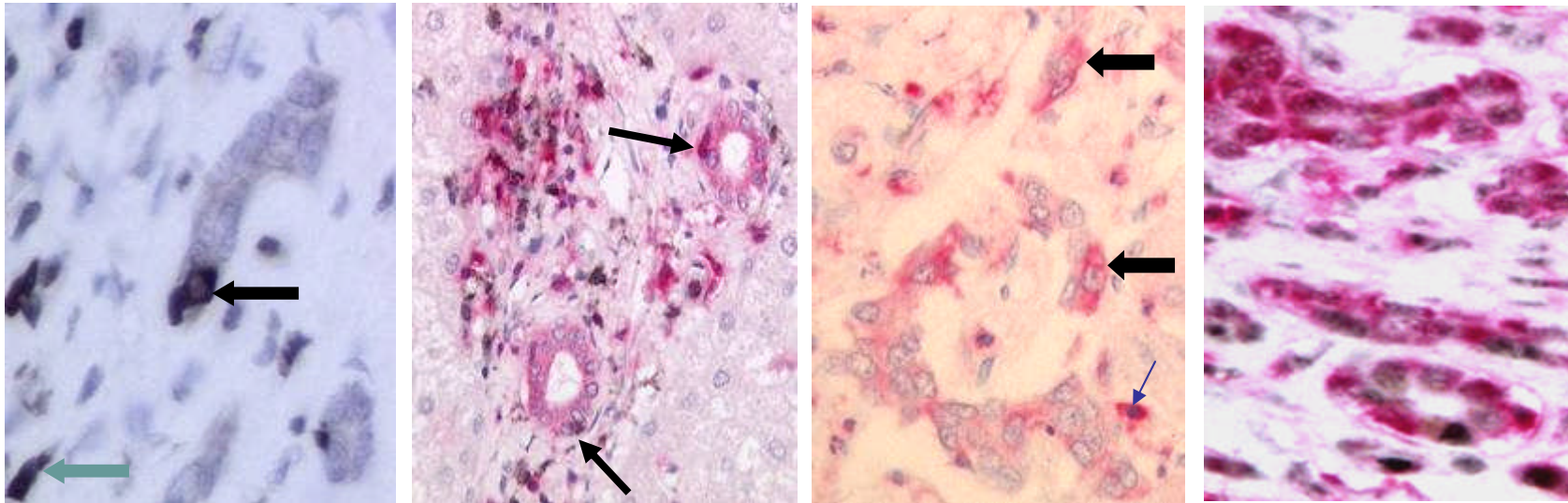


# EMT occurs in experimental renal fibrosis and can be inhibited by BMP-7



*Kalluri & Neilson (2003)*

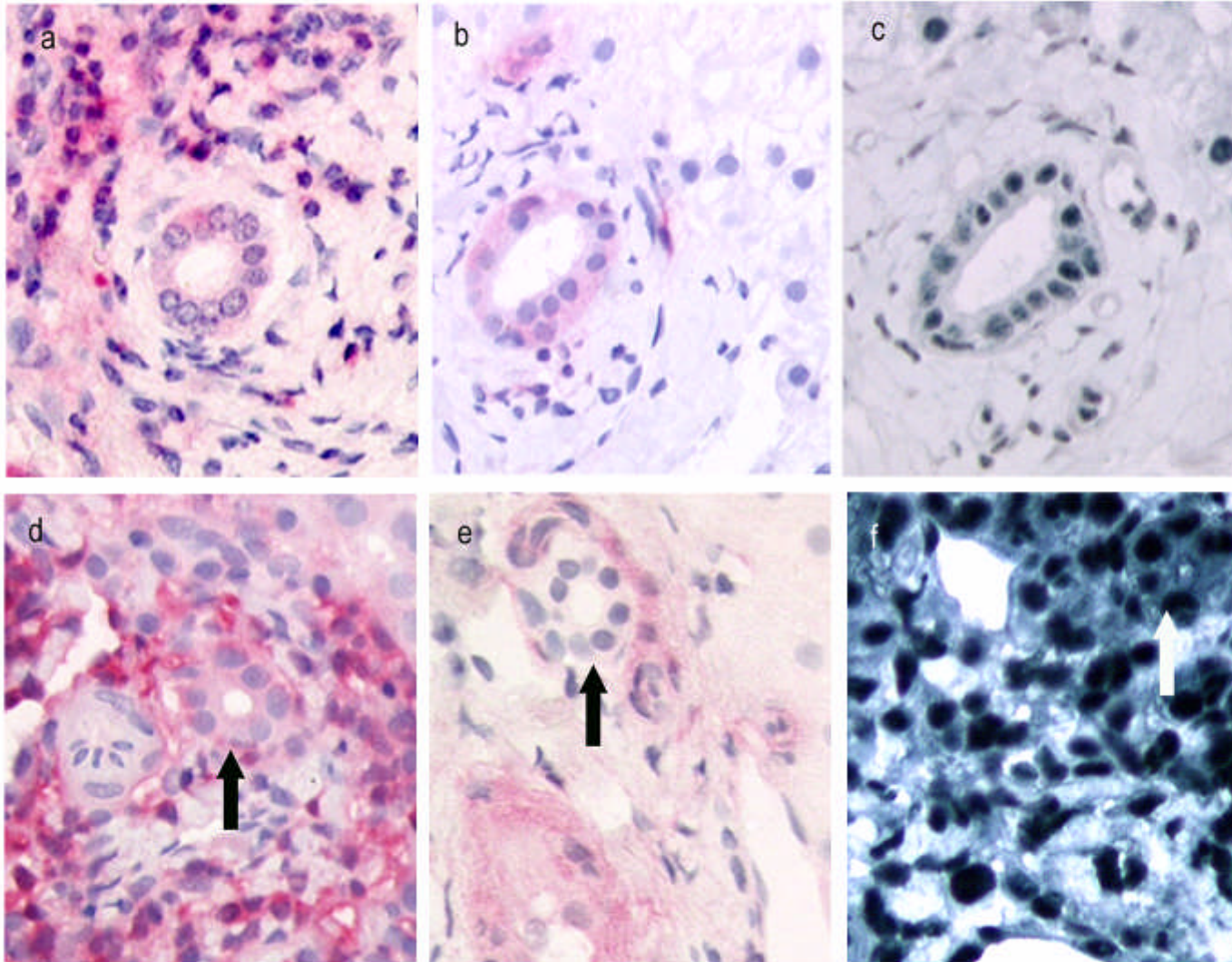
# Evidence for EMT in chronic inflammatory liver diseases



- **S100A4 is expressed by individual epithelial cells within ductules**
- **S100A4 is expressed in biliary epithelium in the presence of CD8+ T cells**
- **Expression of S100A4 in epithelial cells associated with nuclear pSmad2/3**

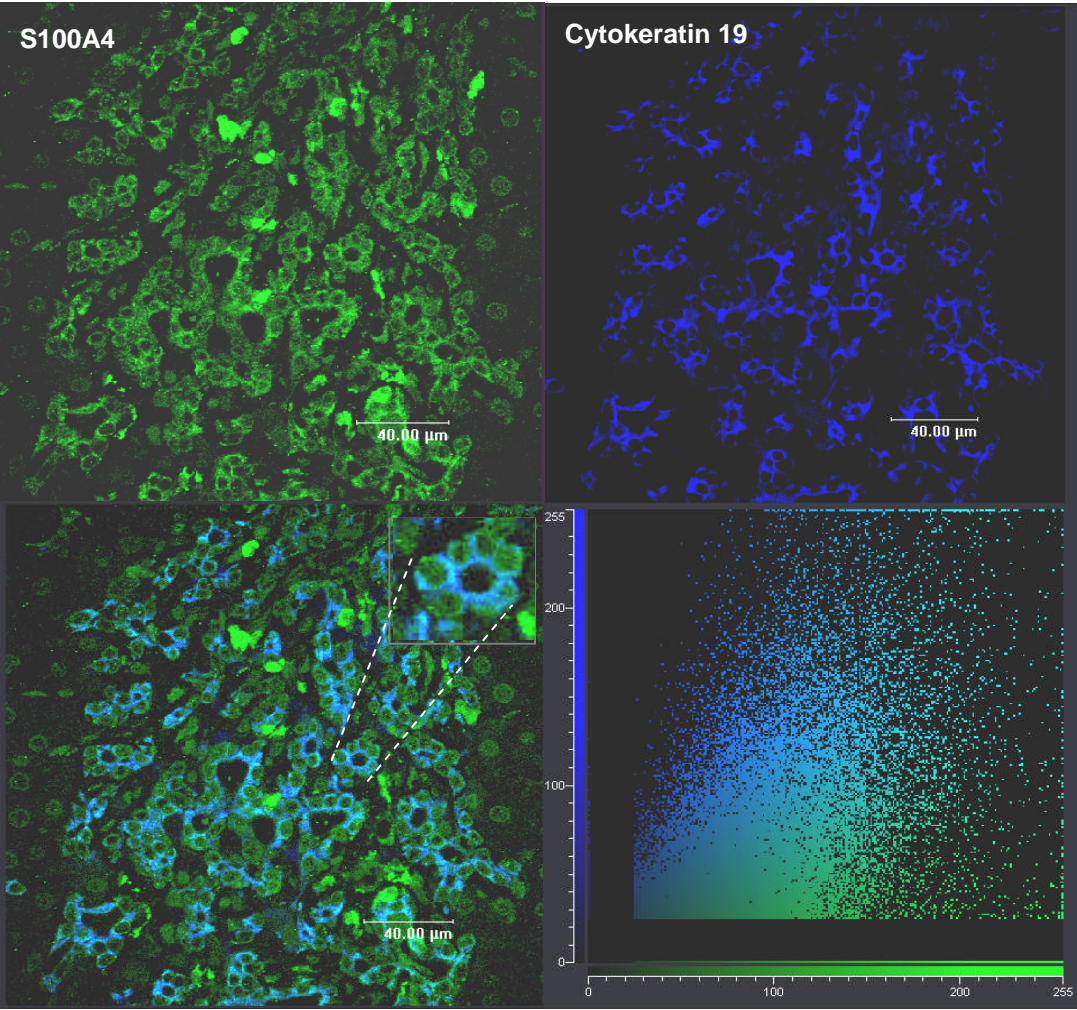
***Robertson et al, Hepatology 2007; Lab Invest 2008 (in press)***

# Biliary EMT in post-transplant recurrence of primary biliary cirrhosis



*Robertson et al, Hepatology, 2007*

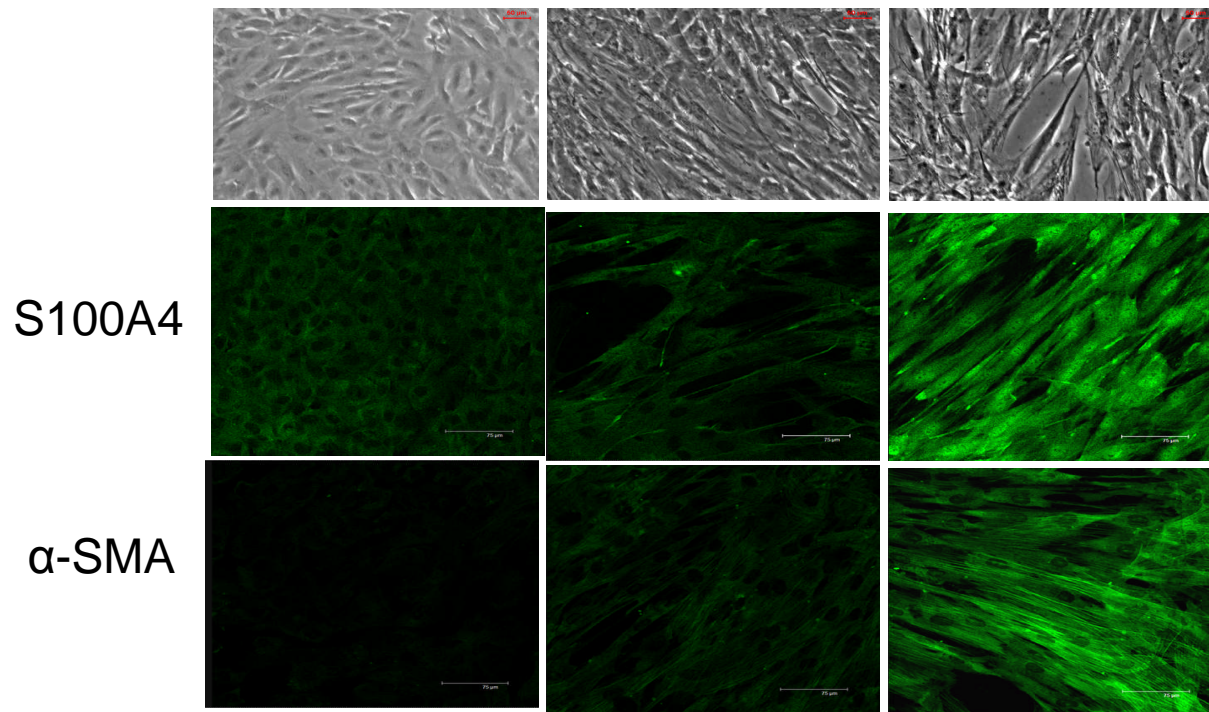
# S100A4 and CK-19 in epithelium in the ductular reaction



# Human intrahepatic biliary epithelial cells: EMT induced by TGF $\beta$



control      1ng/ml TGF- $\beta$       10ng/ml TGF- $\beta$



- Accompanied by nuclear pSmad 2/3
- Partial inhibition by BMP-7 and HGF

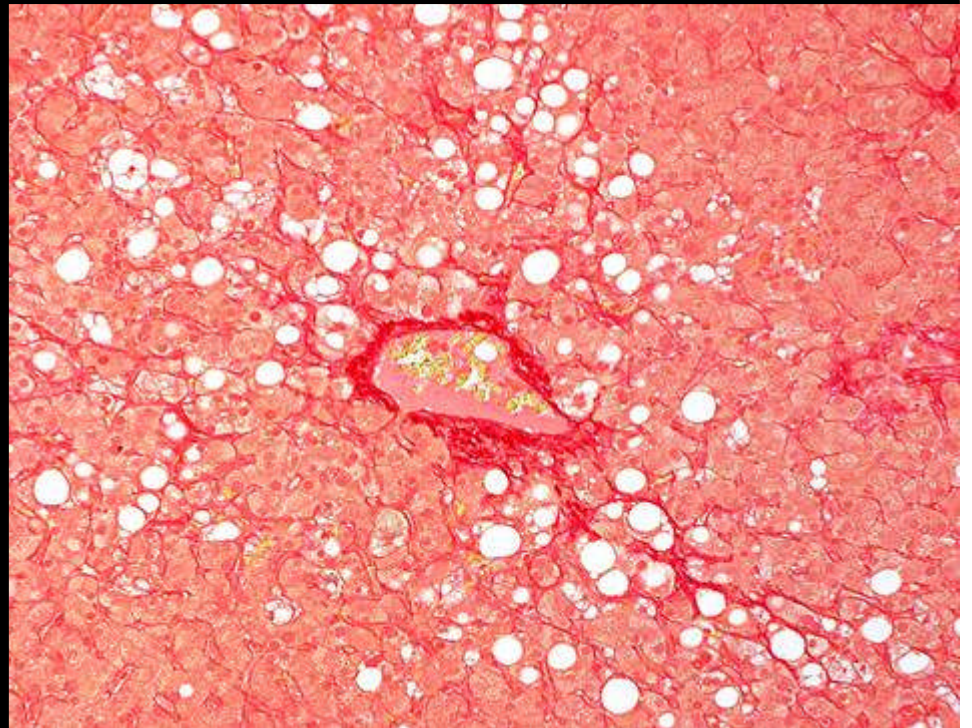
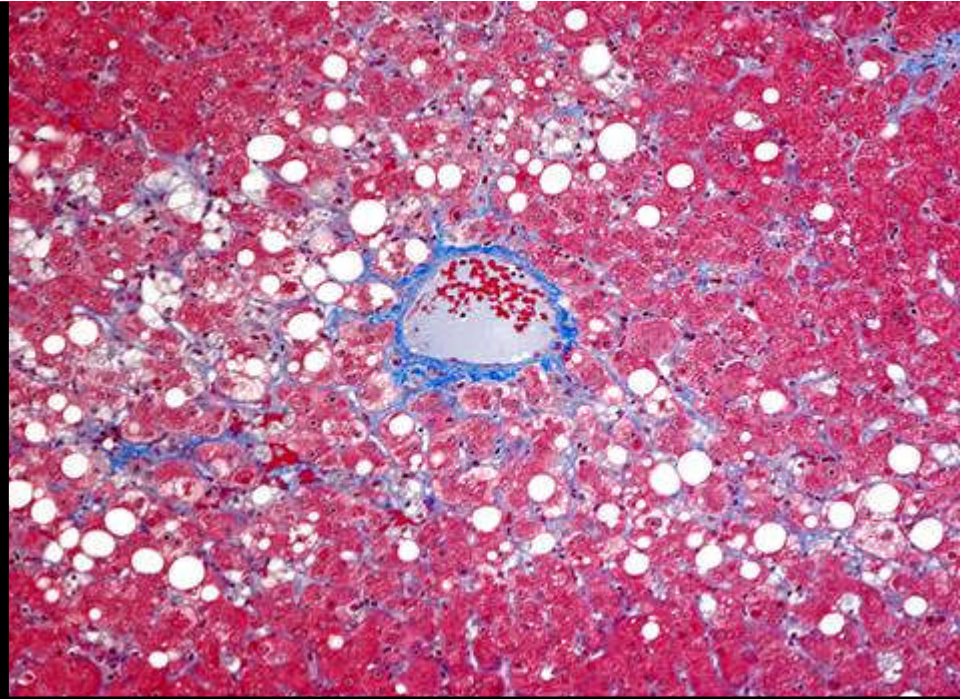
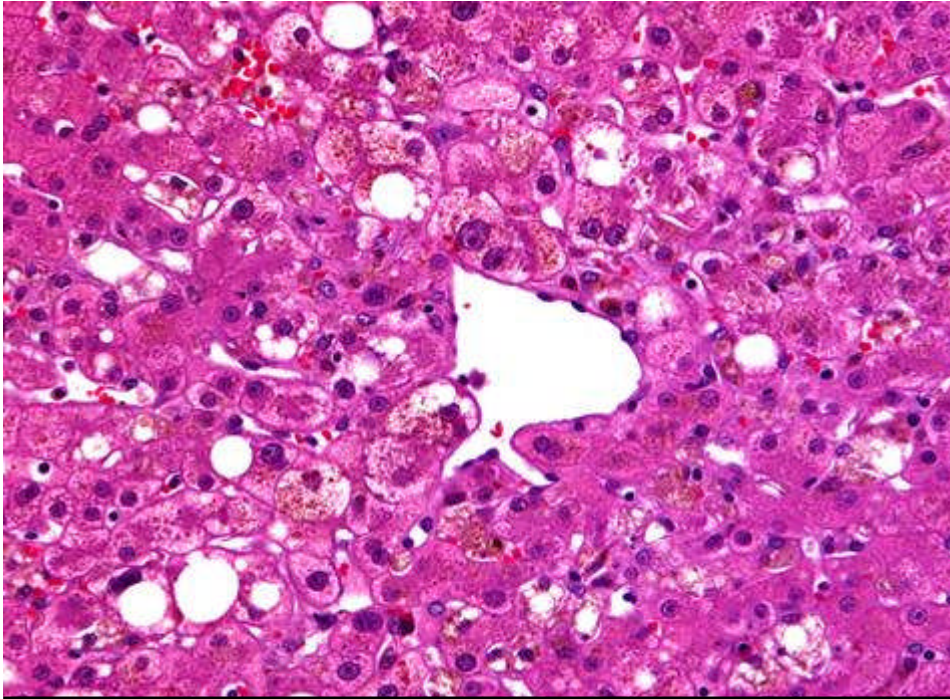
*Robertson et al, Lab Invest, 2008 (in press)*

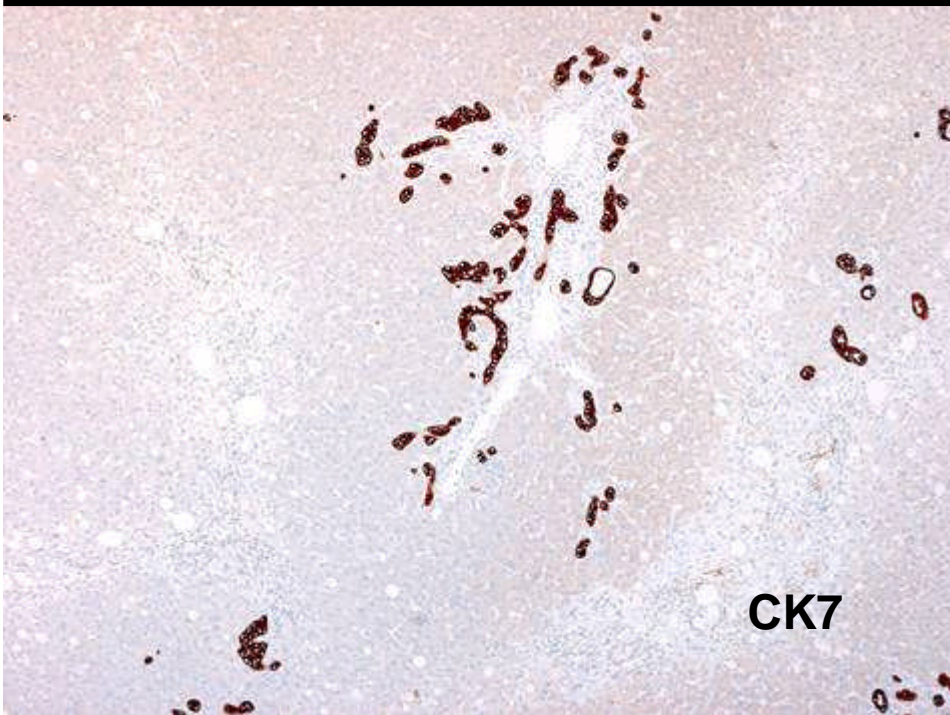
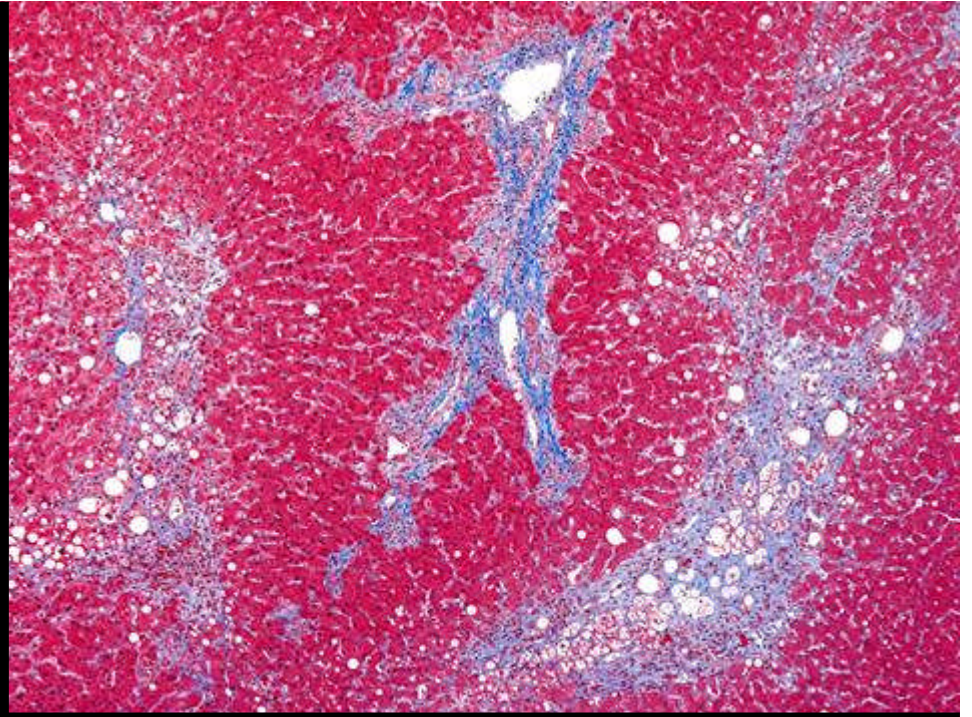
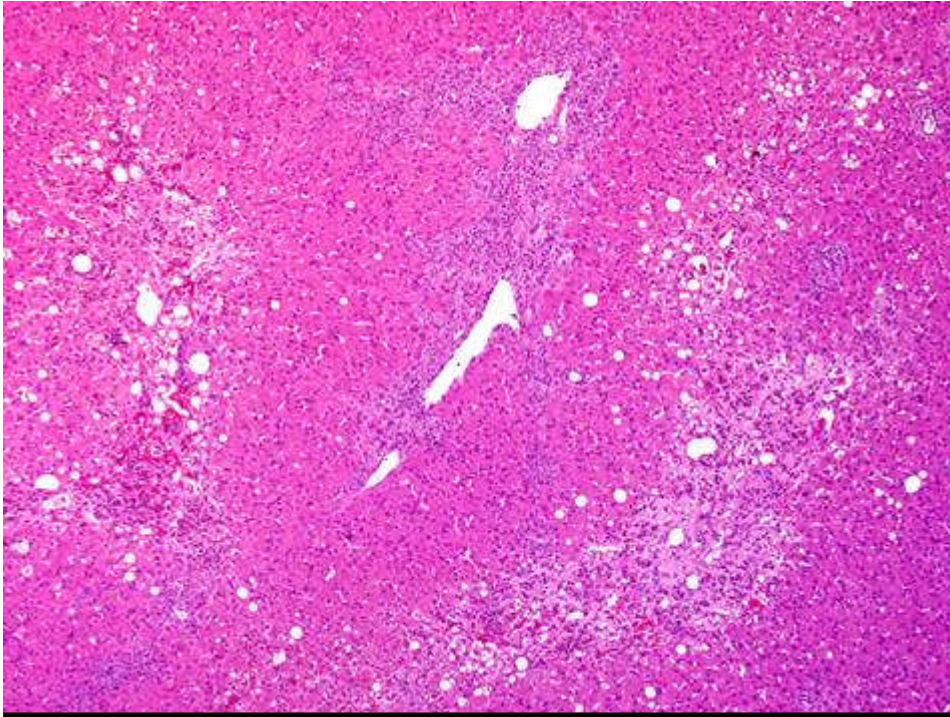
# Liver injury following multiple trauma



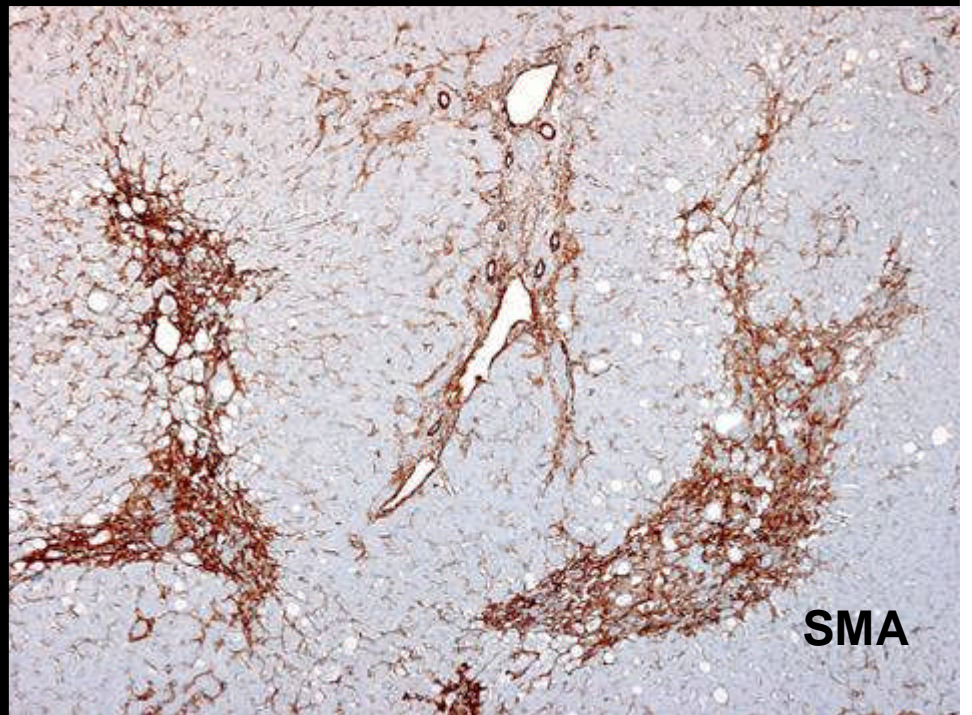
- Severe trauma, hypotension, mult blood transfusions, acute renal failure
- 25 days in ICU
  - Ventilator-dependent, dialysis, wound infections, sepsis, pneumonia, open abdomen, mult antibiotics, TPN
- Jaundice; cholecystectomy, day 16
  - Liver biopsy (? day 16-23)

Acknowledgement: Dr Zac Goodman; AFIP





**CK7**



**SMA**



- **Cholestasis with acute cholangitis and ductular reaction, secondary to sepsis ± other factors**
- **Zone 3 fibrosis (stellate cell activation) secondary to cholestasis ± ischemia**
- **Zone 1 fibrosis (portal myofibroblast activation) secondary to ductular reaction**



# Patterns of hepatic fibrosis

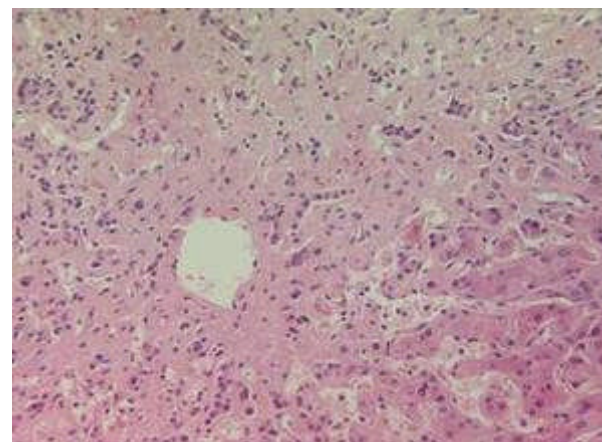
- **Localised**

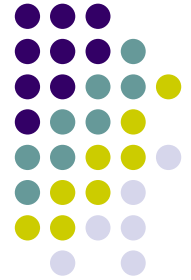
- Abscess
- Inflammatory pseudotumour
- Intra and peri-tumoral including FNH
- Trauma



- **Generalised**

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





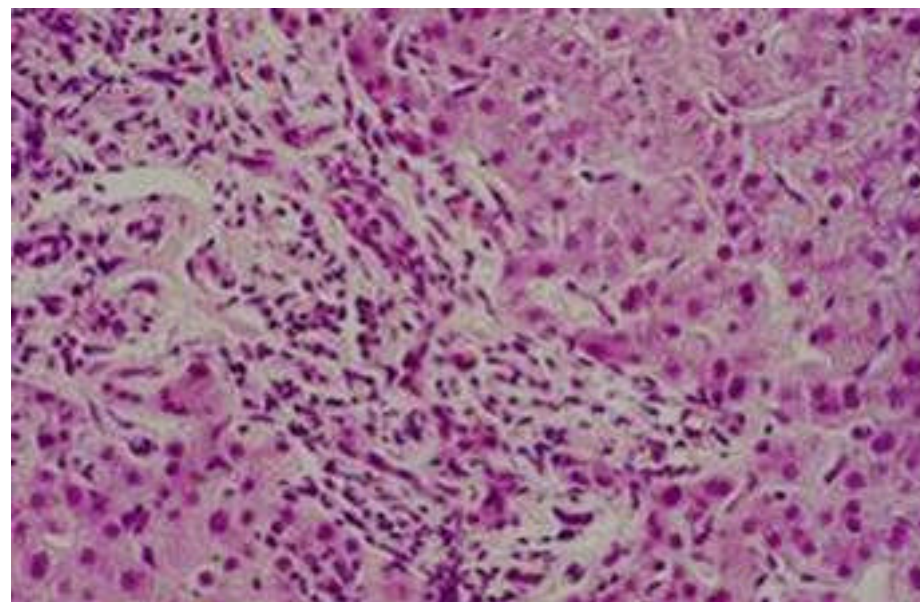
# Patterns of liver fibrosis

- Portal
  - Expansive
  - Periductal
  - Peri or intravascular
- Periportal
  - Interface hepatitis-associated
  - Ductular reaction-associated
  - Spikes
  - Perinodular



# Patterns of liver fibrosis

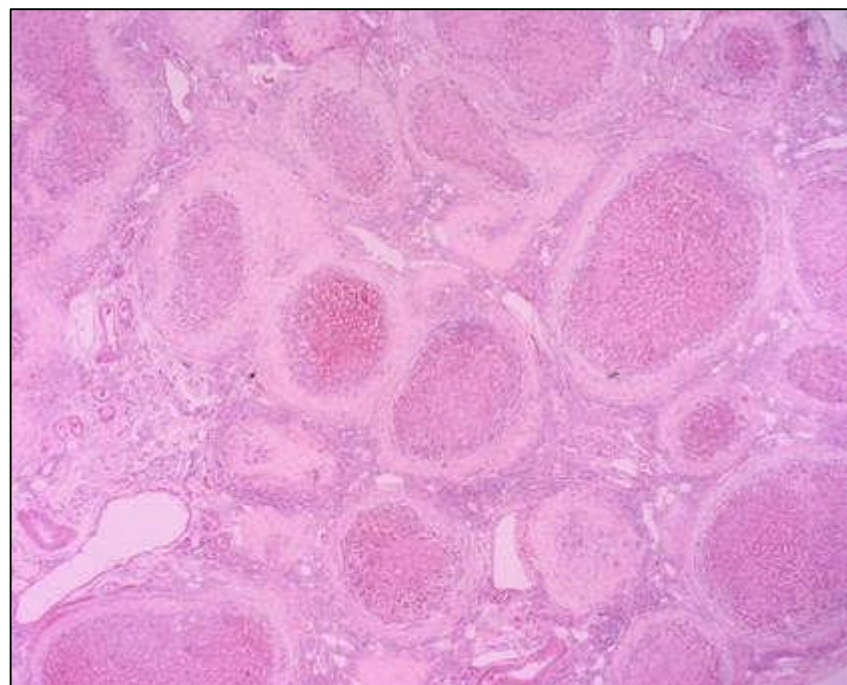
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  - **Perinodular**





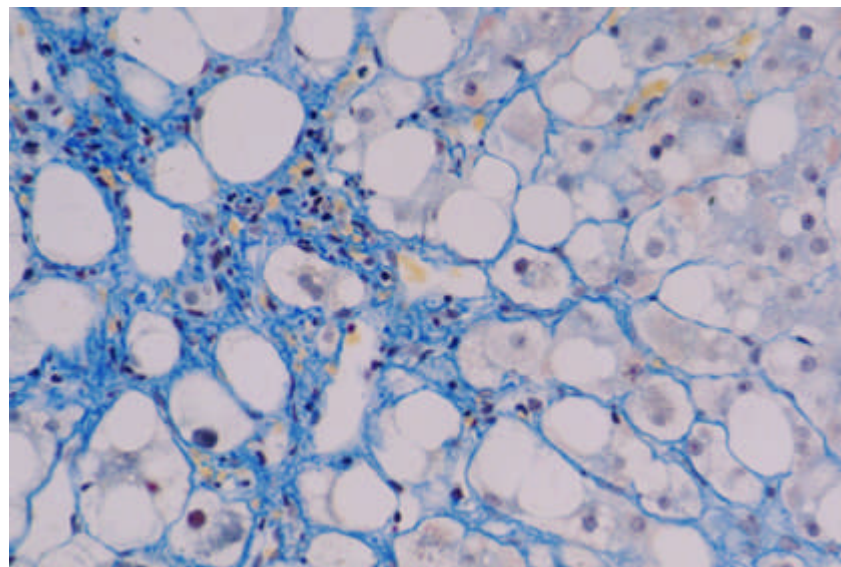
# Patterns of liver fibrosis

- Perisinusoidal
  - Diffuse
  - Zonal
  - Focal
- Pericellular
  - Diffuse
  - Zonal
  - Focal
- Perivenular
  - 'Typical'
  - Sclerosing hyaline necrosis
  - Intravenular

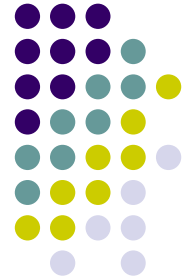


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# Patterns of liver fibrosis

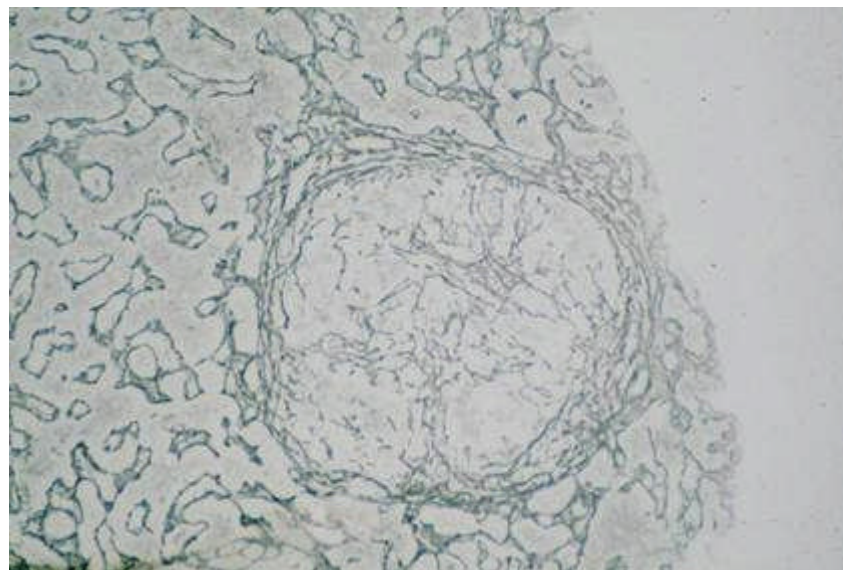


- Intra or peri-lesional
- Granulomatous
- Glissons capsule
- Developmental abnormality



# Patterns of liver fibrosis

- Intra or peri-lesional
- **Granulomatous**
- Glissons capsule
- Developmental abnormality

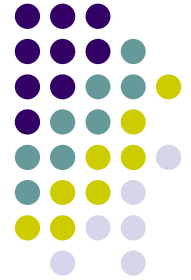




# Patterns of liver fibrosis

- Intra or peri-lesional
- Granulomatous
- **Glisson's capsule**
- Developmental abnormality





# Patterns of cirrhosis

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