

# Other viral infections...

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not transplant, not HIV, not neonatal, not congenital immunodeficiency...

# plan

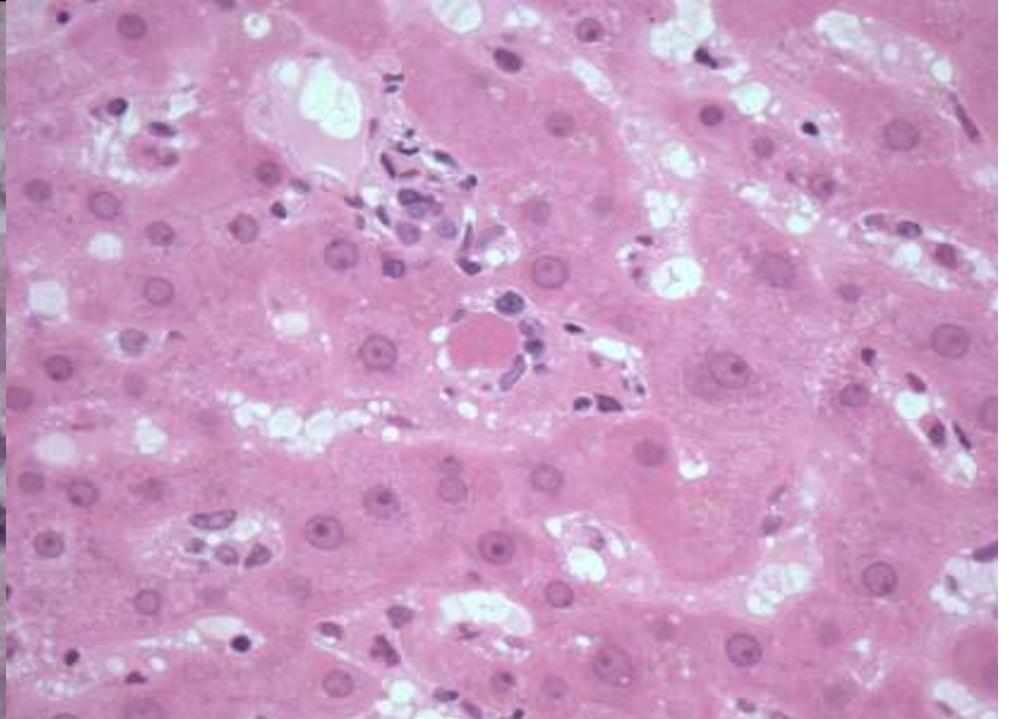
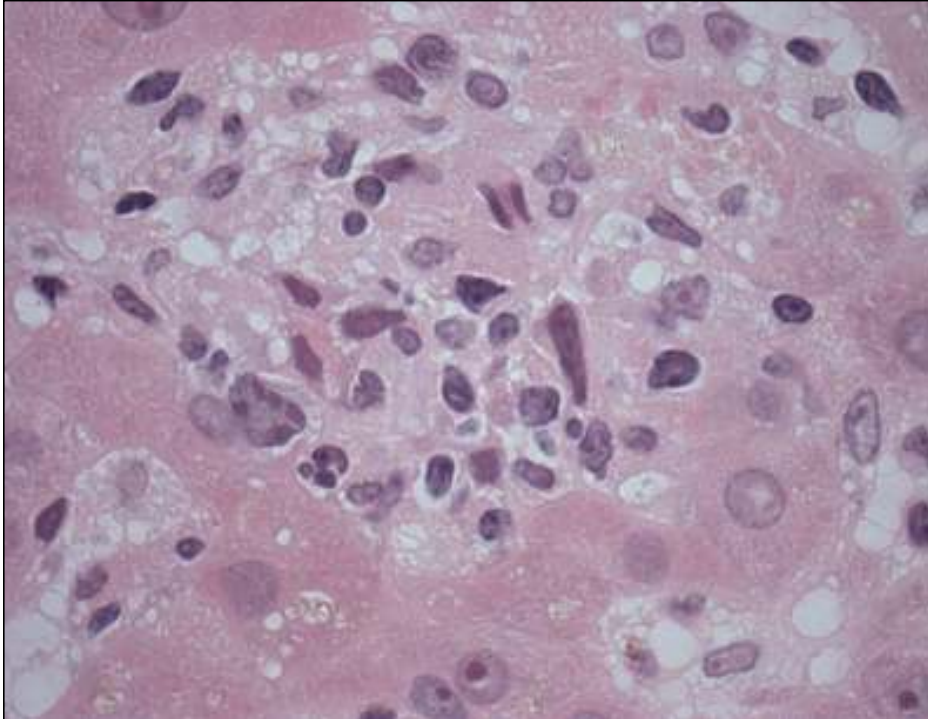
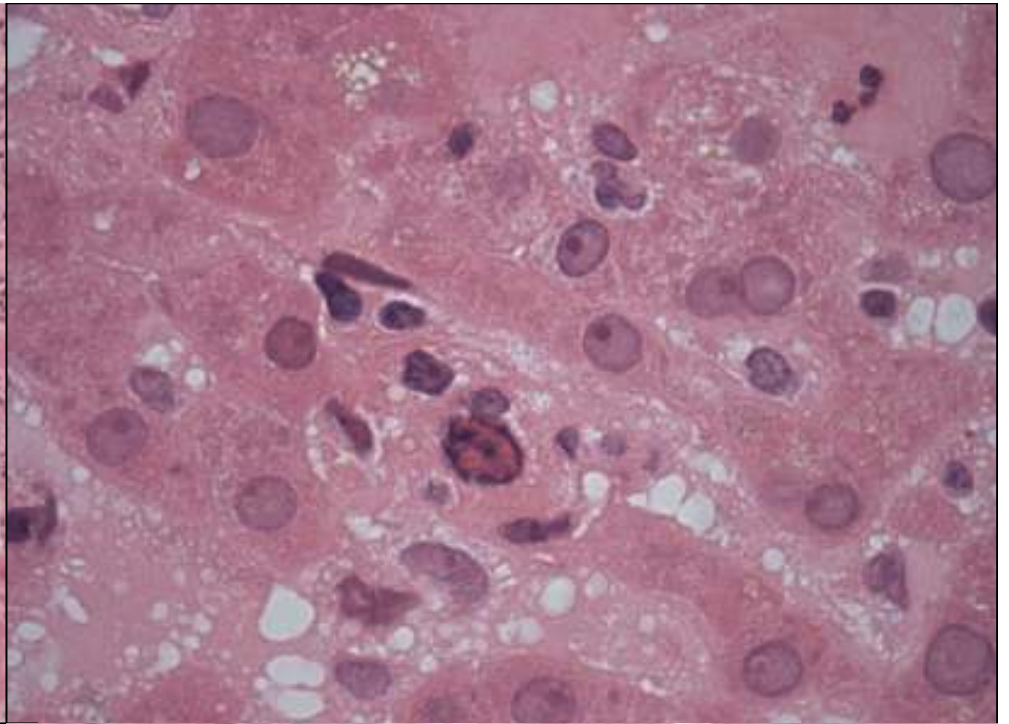
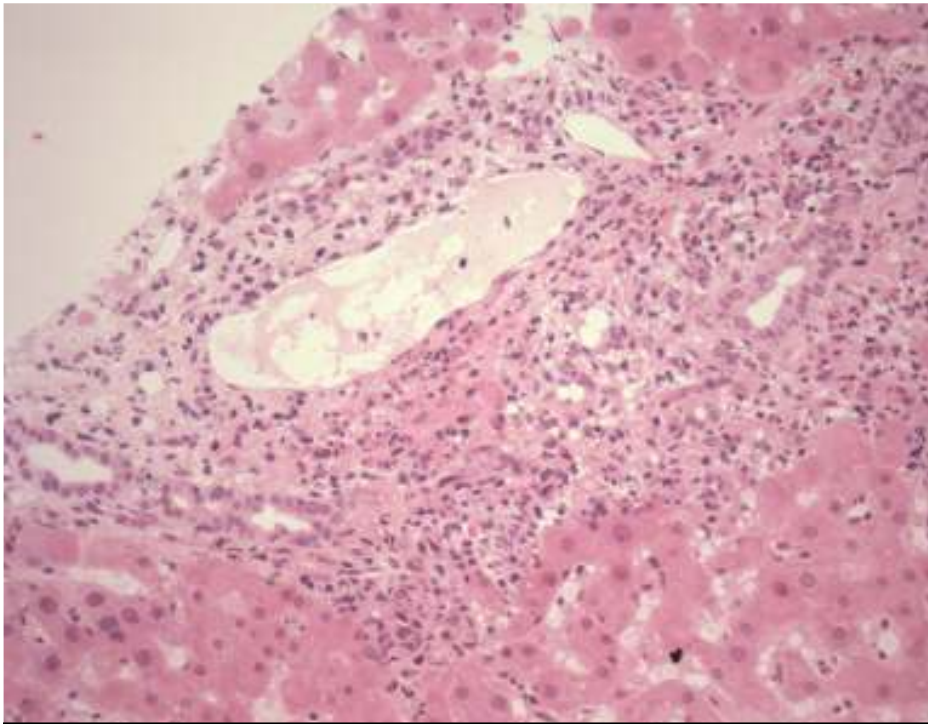
- Post-infantile viral hepatitis in the immunocompetent
- “Bystander” hepatitis
- Viral haemophagocytic syndrome

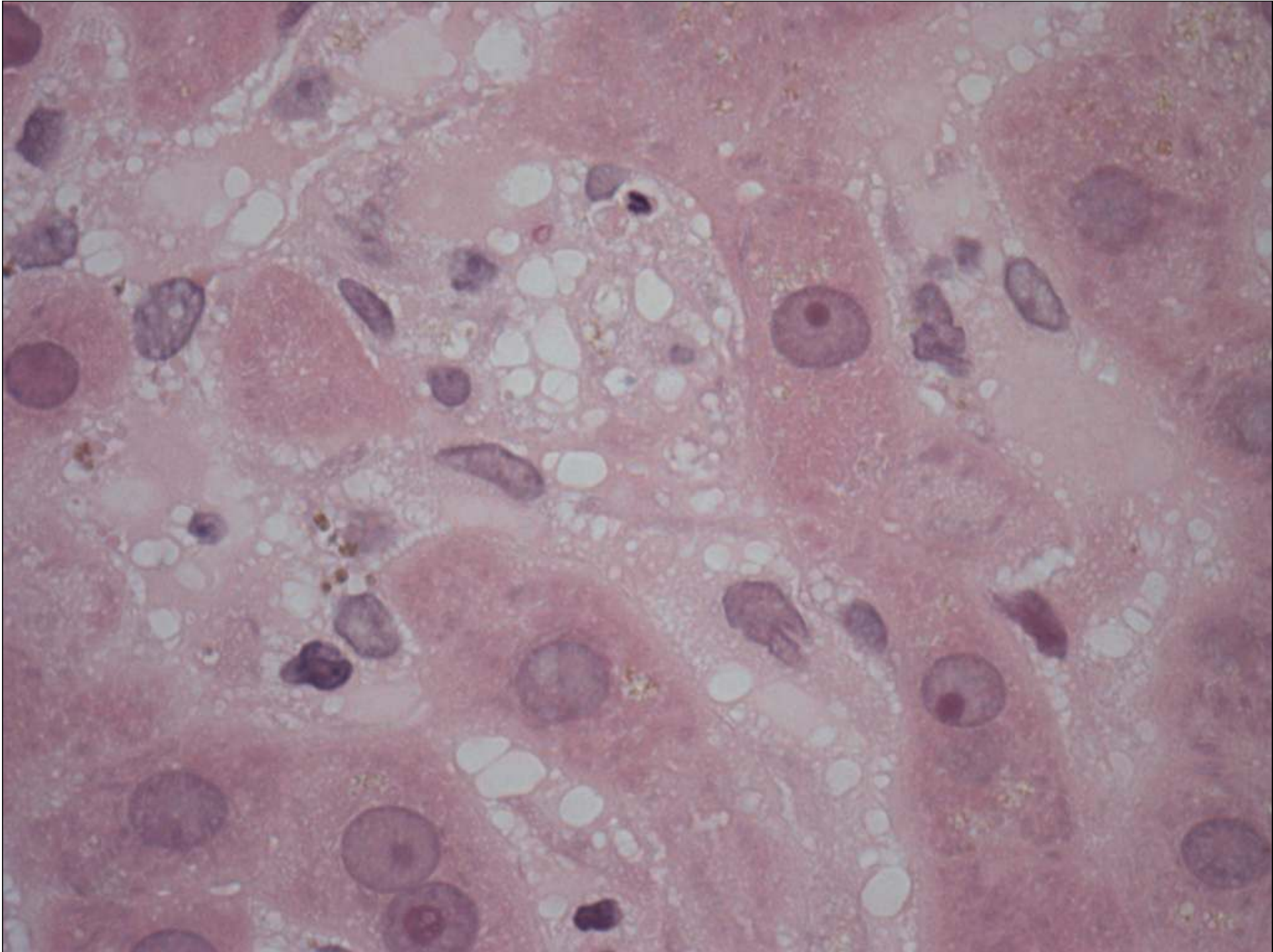
# post-infantile viral hepatitis

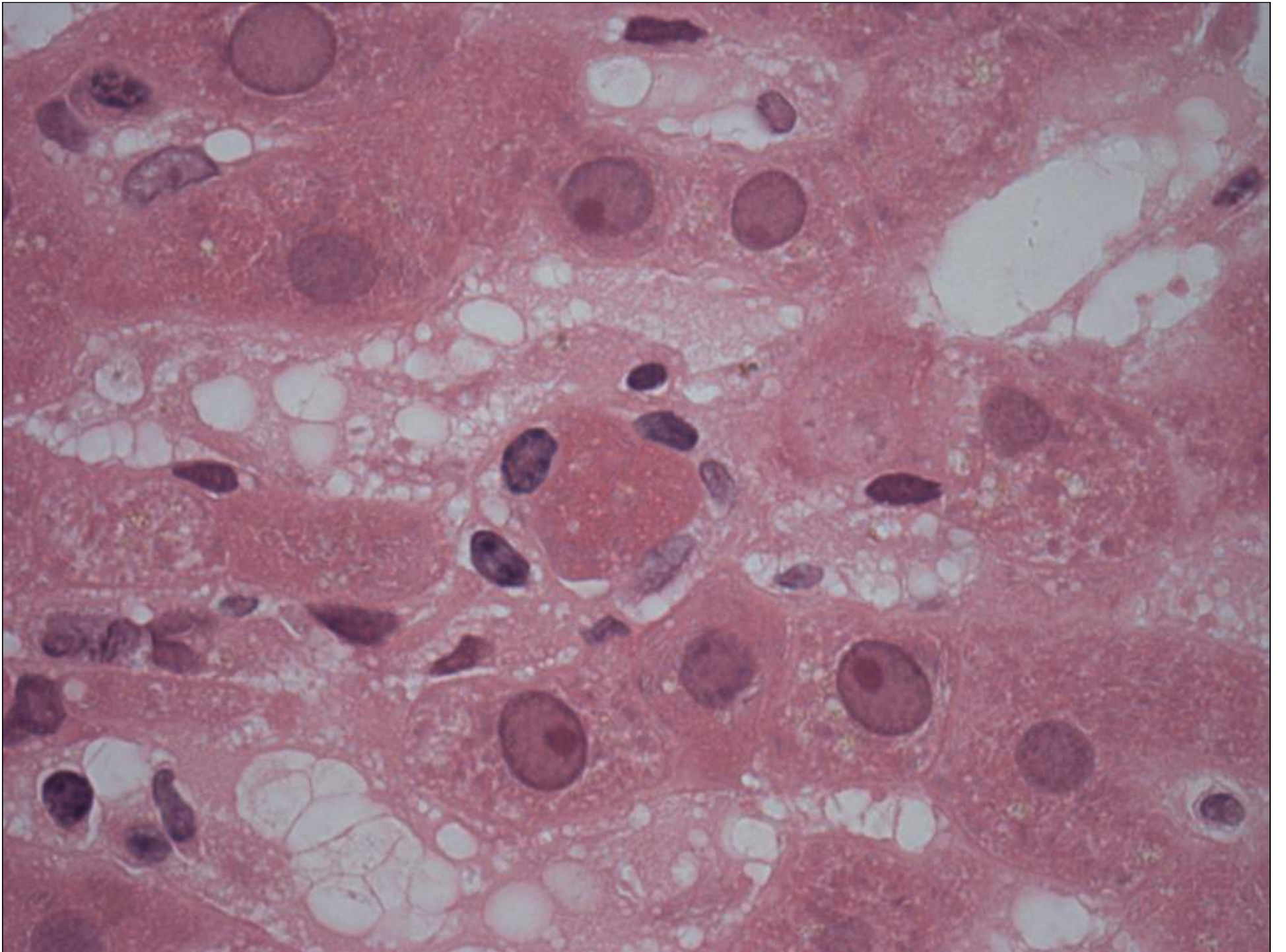
- Herpes viruses
  - EBV
  - CMV
- Adenovirus
- Measles (rubeola)
- Parvovirus B19
- Yellow fever

# Herpes viruses

- Prevalent; life-long latency
- EBV
  - Abnormal LFT common, <5% jaundiced
  - Infectious mononucleosis syndrome
    - Acute fever, pharyngitis, lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis
    - Infected B cells
    - T cell-mediated injury







# EBV

## – Hepatitis

- portal mixed inflammation, bd damage, venulitis
- ?ductopenia (Kikuchi K 2000)
- sinusoidal T lymphocytes (atypical; beading)
- lobular disarray
- plasma cells
- microgranulomas
- spotty necrosis to fulminant failure (Kimura 2001)
  
- value of EBER? [HubscherSG1994, SuhN 2007 ]
  
- Shaw1988, Markin 1994,

- 1° cytomegalovirus in the immunocompetent

- Mononucleosis syndrome

- Prolonged fever precedes (1-2 months)
- Moderate transaminitis
- Not jaundiced, less pharyngitis, not vasculitic

- Hepatitis

- Sinusoidal mononuclear cells, perivenular
- bile duct damage
- Apoptosis; no confluent necrosis
- No inclusions
- Lobular microgranulomas
- Negative for late structural Ag

Bonkowsky HL 1975

Snover DC 1984

Ten Napel HH 1984

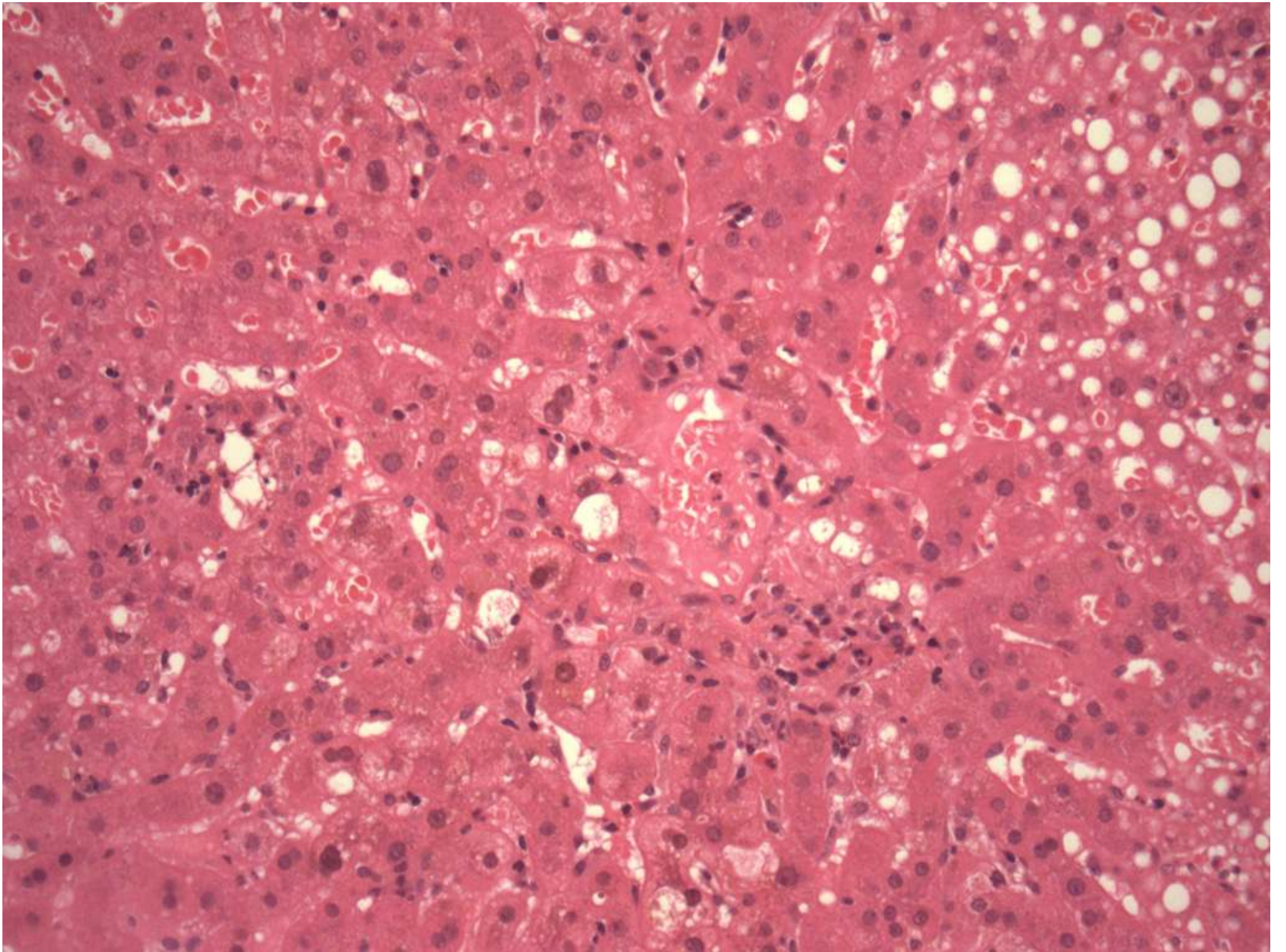
Cohen JI 1985

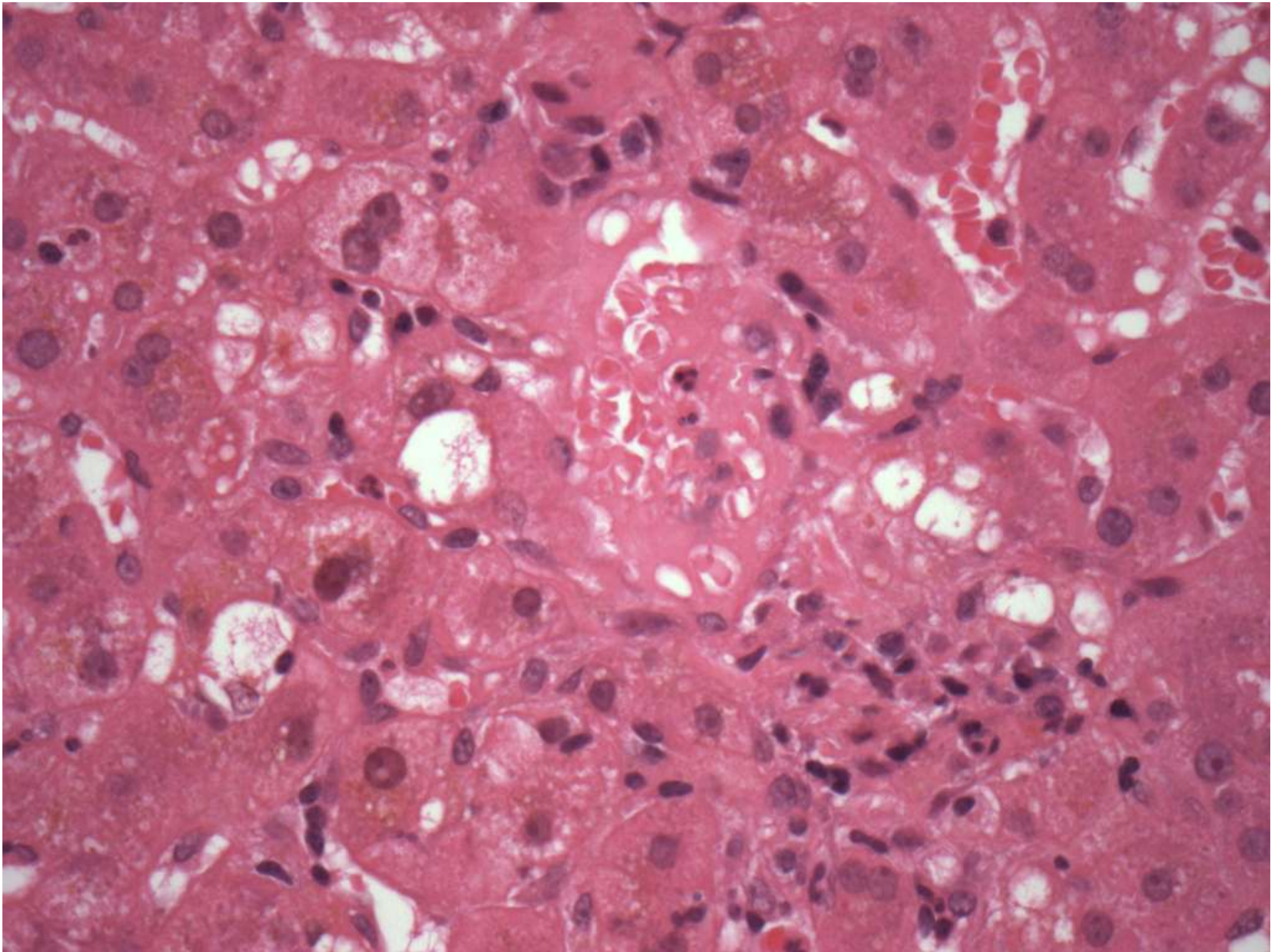
Vujacich C 2006

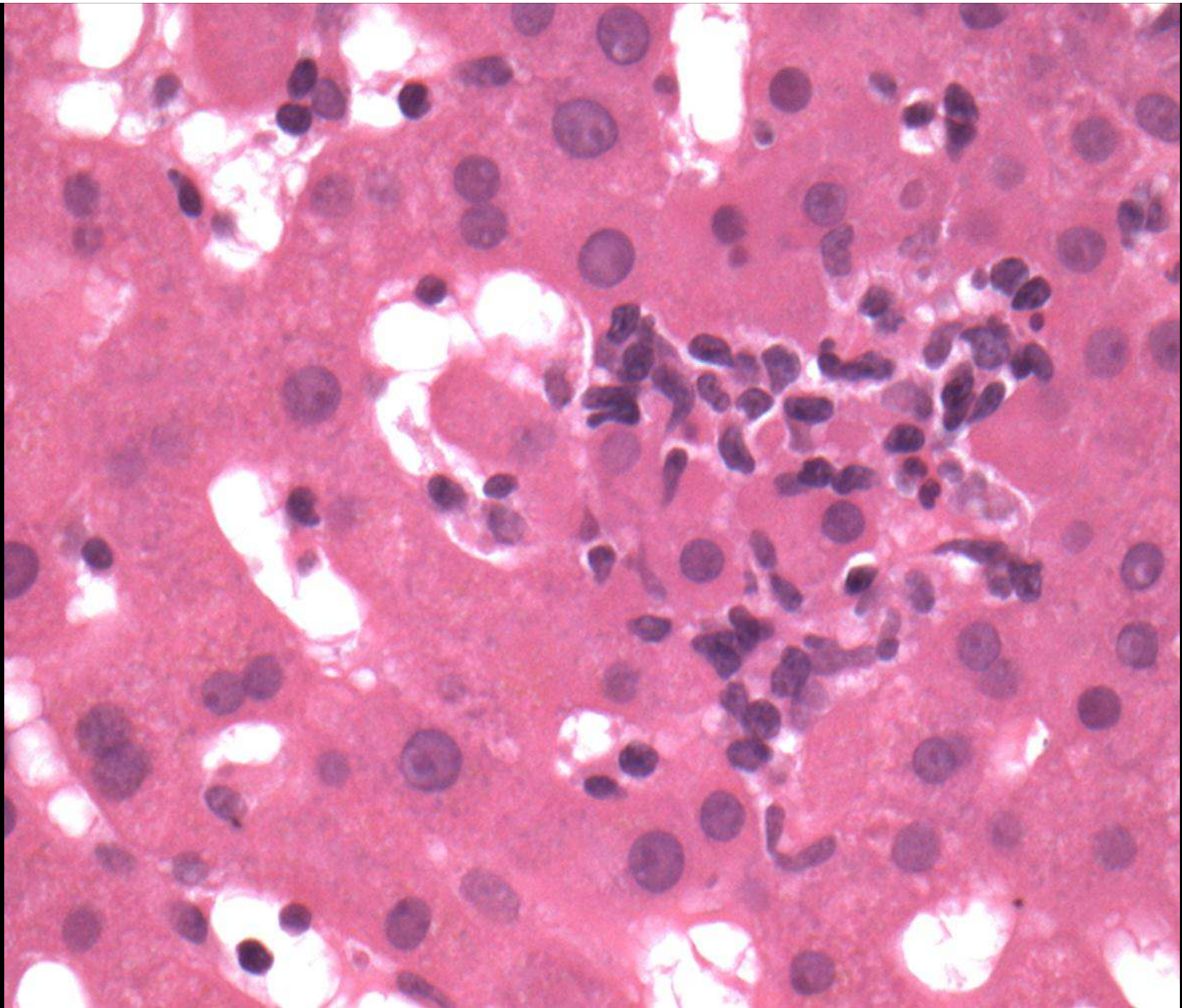
Bentata-Pessayre M 1987

- Portal vein thrombosis [Squizzato A 2007]

- 36yr woman
- some weeks fever, splenomegaly, rash, pleurisy, no drugs, normal liver US, other liver screen negative
- CMV IgM and pcr ?positive
- Bilirubin 12, ALT 174, ALP 356, GGT 387, albumin 42 (slowly improved)







# HSV hepatitis

- “septic shock”-like
- Gestational (3<sup>rd</sup> trimester)
  - Severe anicteric liver failure
  - Patchy/diffuse necrosis +/- neutrophils
  - Ground glass inclusions, em, ihc +ve
    - (varicella zoster similar)
  - Viral culture +ve when ihc negative

Jacques SM 1992

Yaziji H 1997

Goodman ZD 1986

# Measles hepatitis

## – Acute hepatitis syndrome

- More frequent & severe in adults ( $\frac{2}{3}$ )
- Jaundice uncommon (5%)
- Self limited (2-4 weeks)
- Therapeutic paracetamol interaction (Ackerman 1989)
  
- Portal inflammation, lobular hepatitis
- No inclusions

McLellan RA 1982

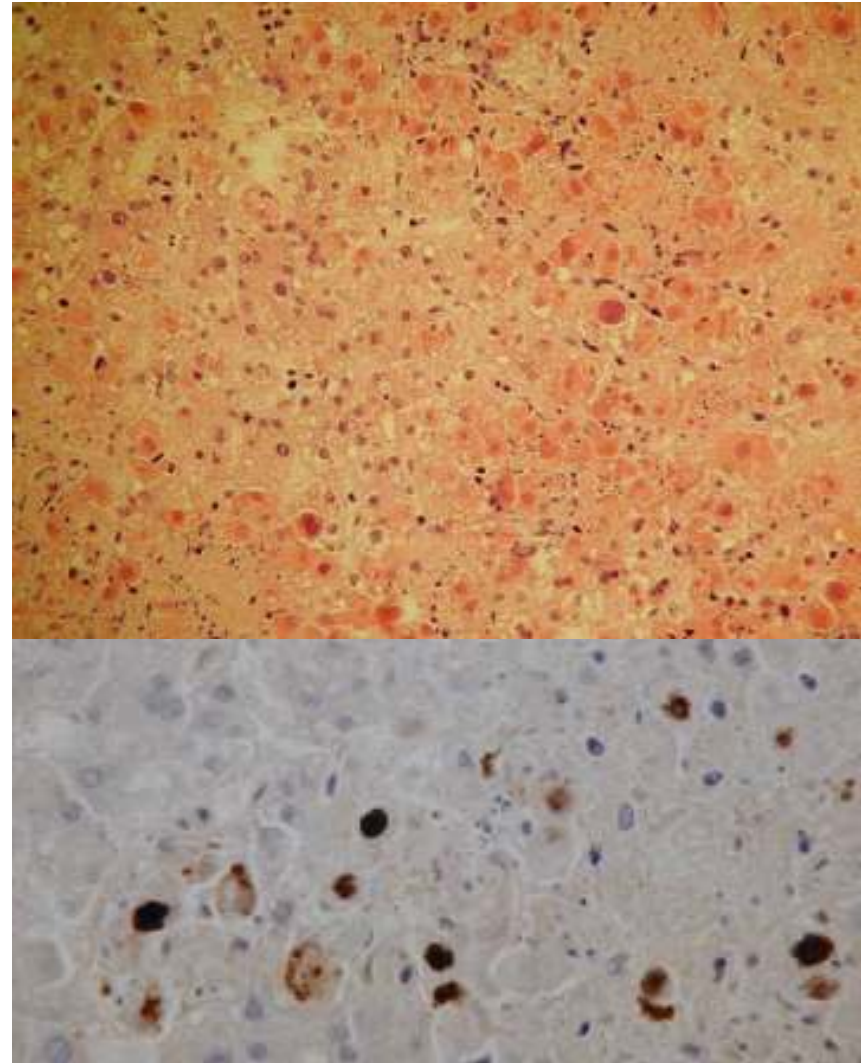
Ackerman Z 1989

Shalev-Zimels H 1988

Tishler M 1983

# Adenovirus hepatitis

- Respiratory tract/conjunctivitis
- Hepatitis rare in immunocompetent children
  - 1/143 acute ADV inpatients (Rocholl C 2004)



# “Collateral damage”

- extrahepatic virus
- effector T<sub>CD8</sub> cells accrue in liver
- Kupffer cells
- collateral **hepatocyte damage**
  - ?cytokine storm, autoinflammation...
- patchy lobulitis
- **influenza A virus (H1N1)**
  - liver T cells parallel lung inflammation [Belz GT PNAS 1998]
- **?other “reactive” hepatitis** [AdamsDH, 2006 editorial]
  - RSV bronchiolitis [Eisenhut M 2004]

# Parvovirus B19

- Childhood infection
- Droplets/blood products
- Persists in several tissues
- occasional acute hepatitis (+/- anaemia)
  - Self limited even if severe, milder in adults
  - Rarely fulminant [Langnas AN 1995]
  - Disputed association [Wong S 2003]
- mimicks & triggers SLE in adults
- Haemophagocytic syndrome (esp hered spherocytosis)...

So K, 2007

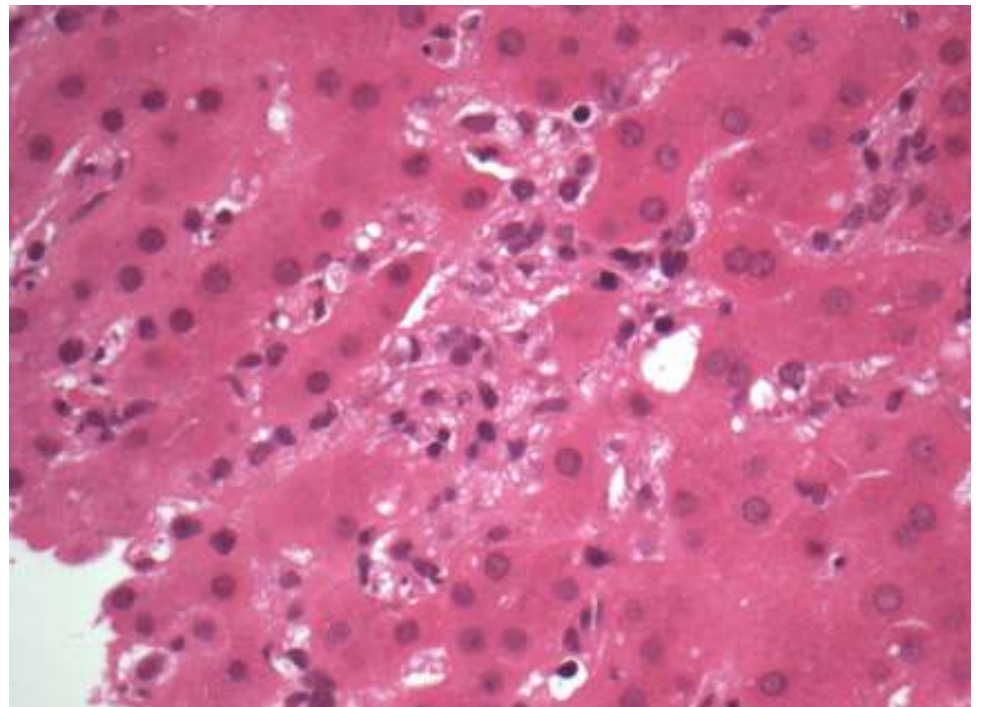
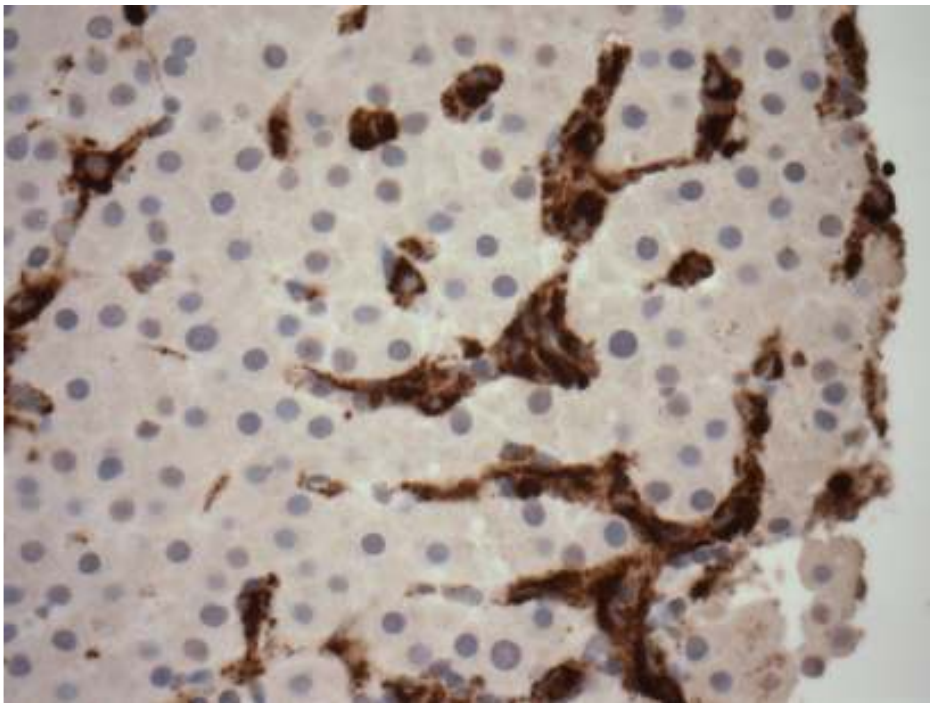
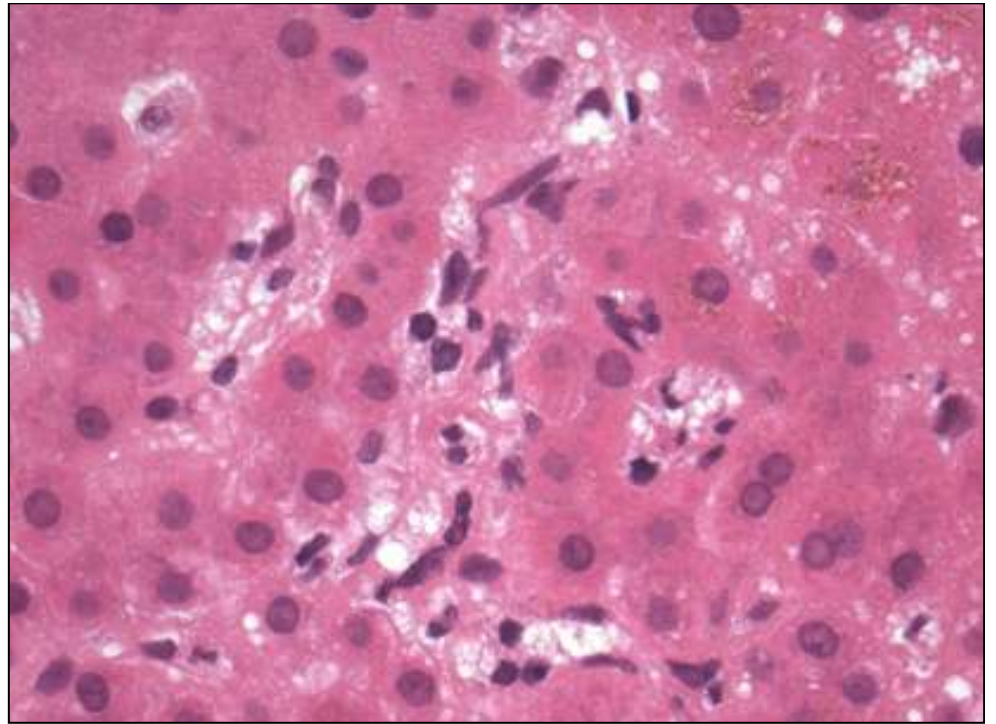
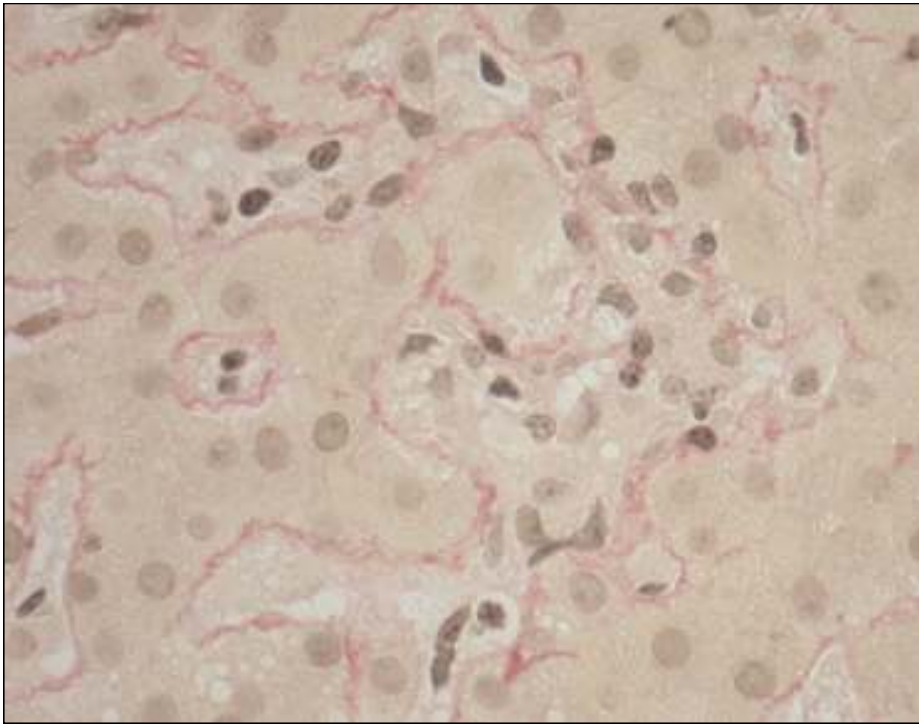
Young NS, 2004

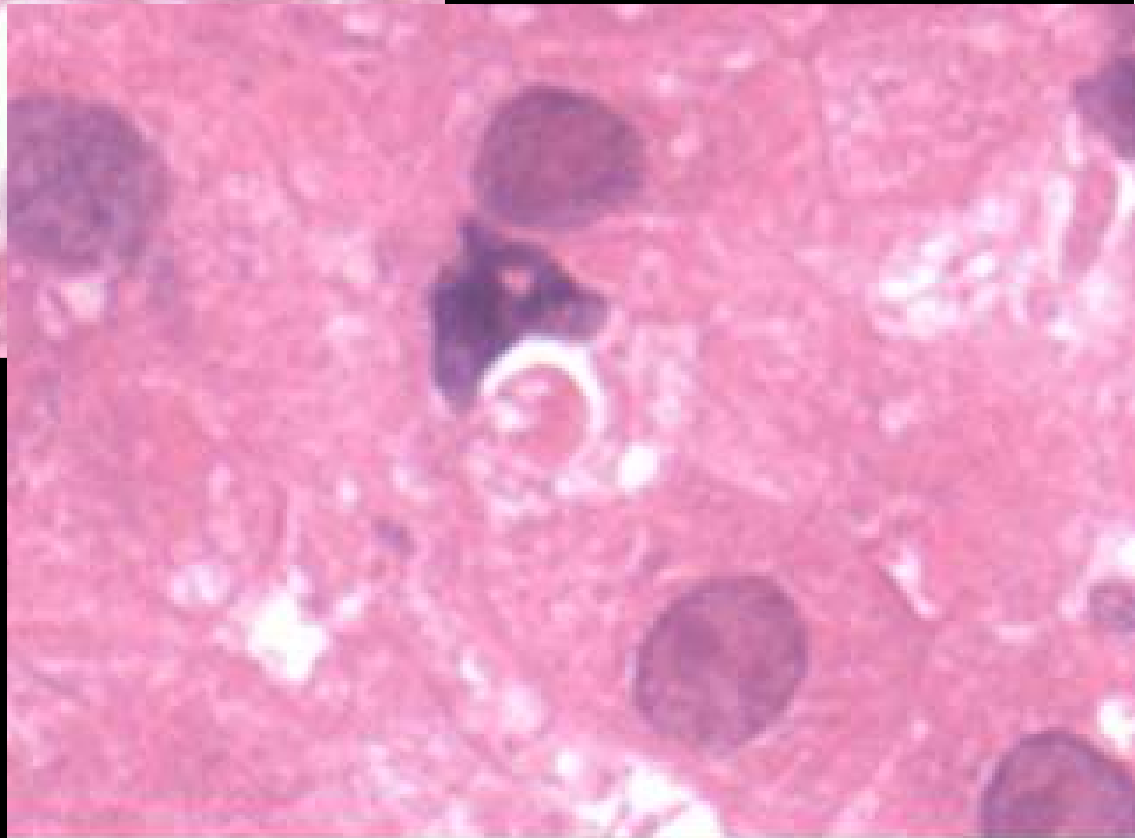
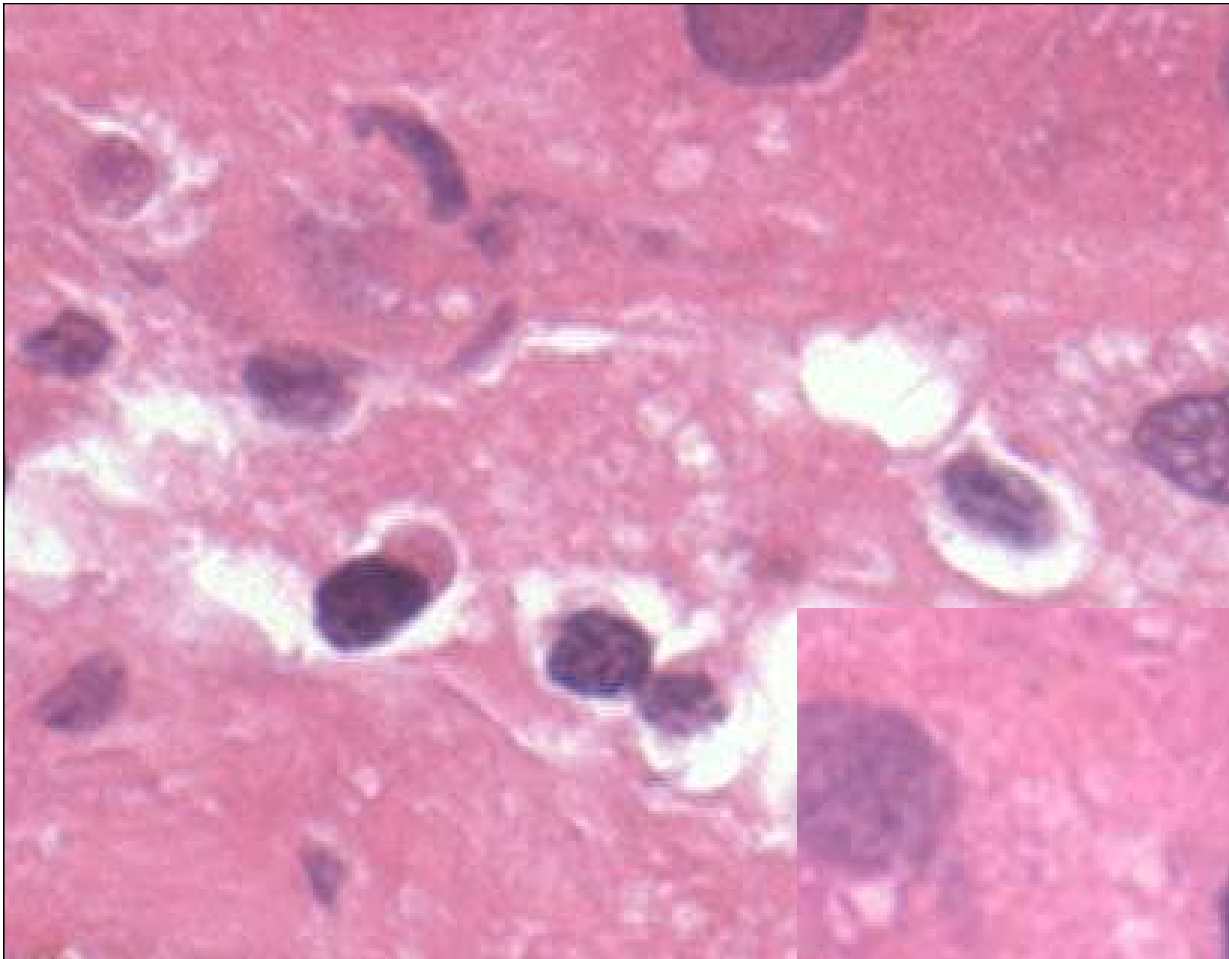
Ramos-Casals, 2008

Krygier DS, 2009

Wang C, 2009

- 41 yr fever, massive splenomegaly, jaundice, red cell aplasia, parvovirus infection (IgM)





# Haemophagocytic syndrome

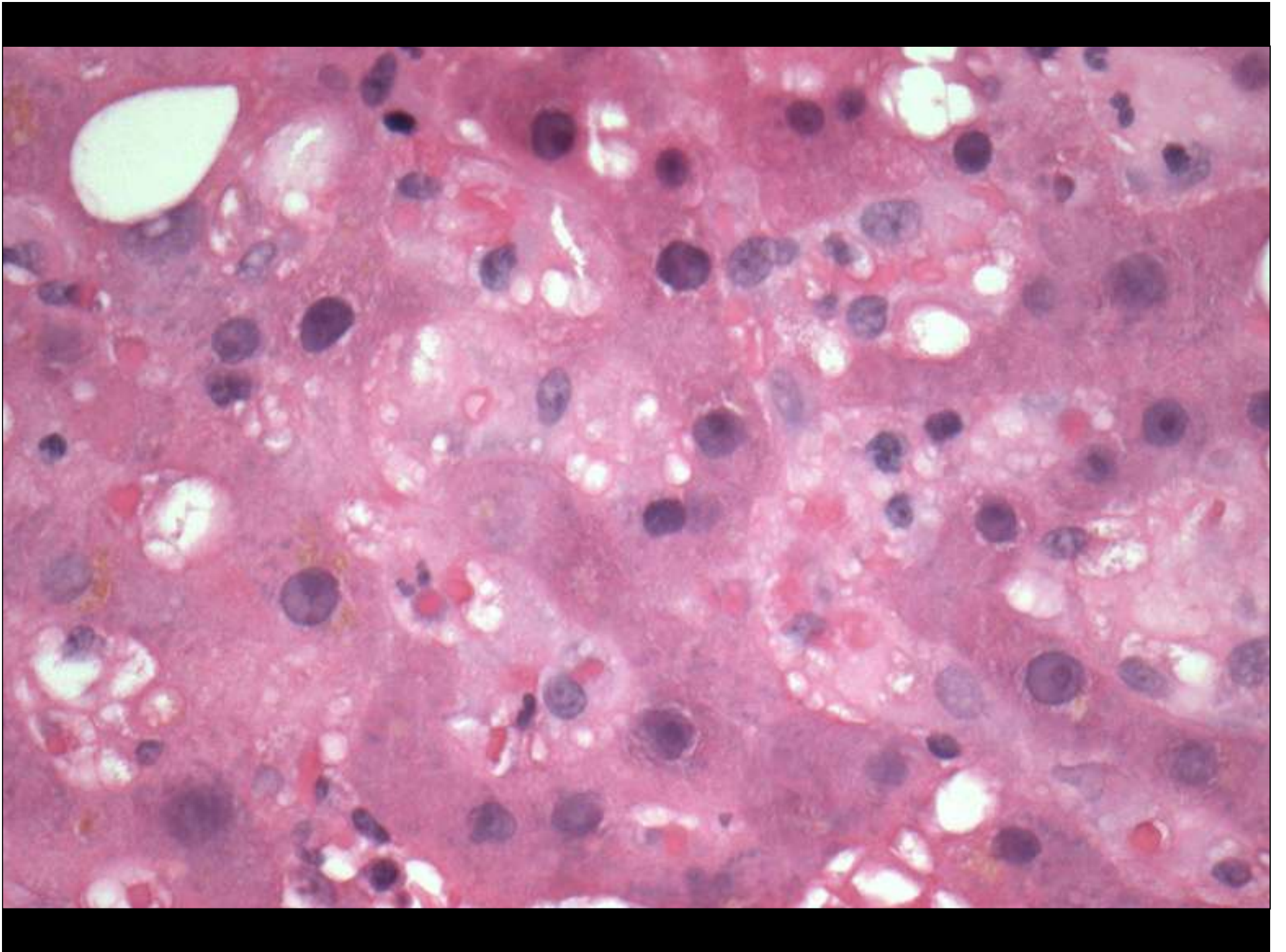
- Impaired NK & Tc function
  - Genetic predisposition in some: perforin 40%
- Intravascular  $\lambda$ c, m $\phi$  overactivation
  
- Any age
- Triggers
  - infection, malignancy, autoimmune
- Fatal untreated
  - Good response to specific Rx

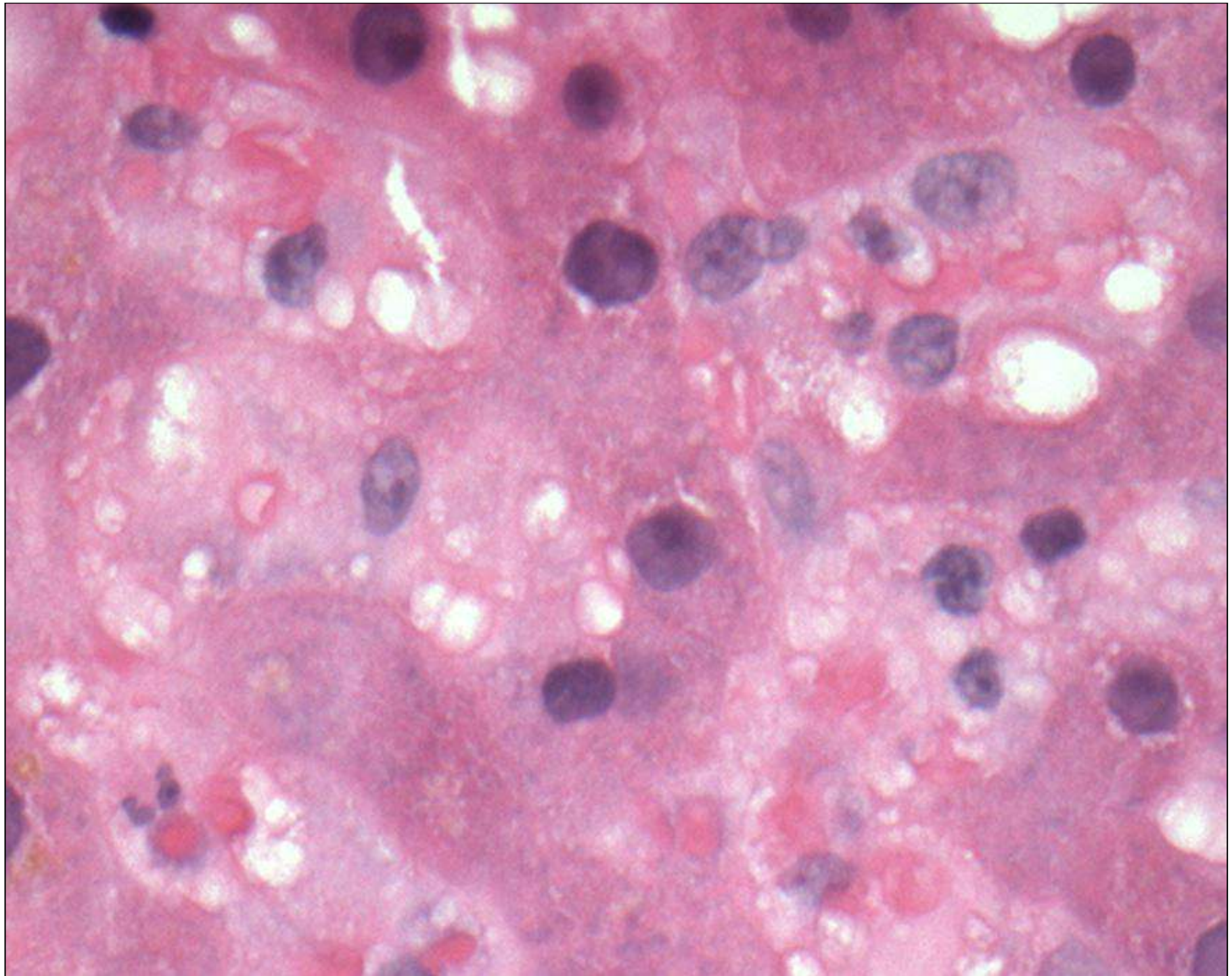
# Viral triggered haemophagocytic syndrome

- Herpes viruses
  - EBV
    - Poorest prognosis: severer
    - Reactivation typical setting
  - CMV
    - Healthy, IBD, transplant...
  - HHV6, HHV8
- HIV
- Hepatitis A
- Parvovirus
- Influenza A
  - H1N1 swine, H5N1 avian
- Adenovirus, measles, SARS, dengue...

# Clinical Diagnosis

- Genetic diagnosis
- 5 of
  - Fever
  - Splenomegaly
  - Cytopenias (2)
  - Ferritin >500ng/ml
  - Increased TG/ decreased fibrinogen
  - Haemophagocytosis w/o malignancy
  - Low NK cytotoxicity
  - Increased soluble CD25





Tsui WM, 1992  
Ost A, 1998  
Favara BE, 1996  
De Kerguenec C, 2001  
Billiau AD, 2005  
Bihl F, 2006

- Liver changes
  - Variable portal infiltrates
  - (bile duct damage)
  - Sinusoid dilation
  - Sinusoidal macrophage hypertrophy, hyperplasia, haemophagocytosis
  - Focal necrosis
  - Lobular microgranulomas
  - Steatosis
- Liver biopsy diagnostic in 15/30 (8 NOS marrow)
  - 19 admitted for liver reasons (16-85 years)
  - [De Kerguenec C 2001]

- Post-infantile non-hepatotropic viral hepatitis is rarely a clinical problem in the immunocompetent
- Bystander “non-specific” hepatitis may accompany a distant viral infection
- Haemophagocytic syndrome can be triggered by a variety of viral infections (EBV in normal children/adolescents), is often fatal untreated, but is often responsive to early therapy