The liver in systemic diseases

Chris Bellamy
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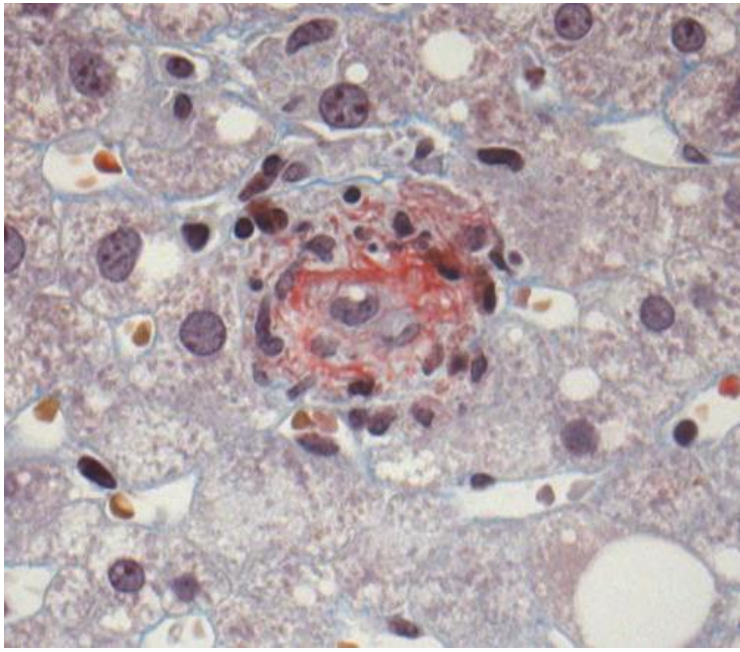
- Granulomas
- GI
- Diabetes & Nutritional
- Endocrine
- Amyloid
- Haemophagocytosis
- Metastasis
- Insulting the fatty liver

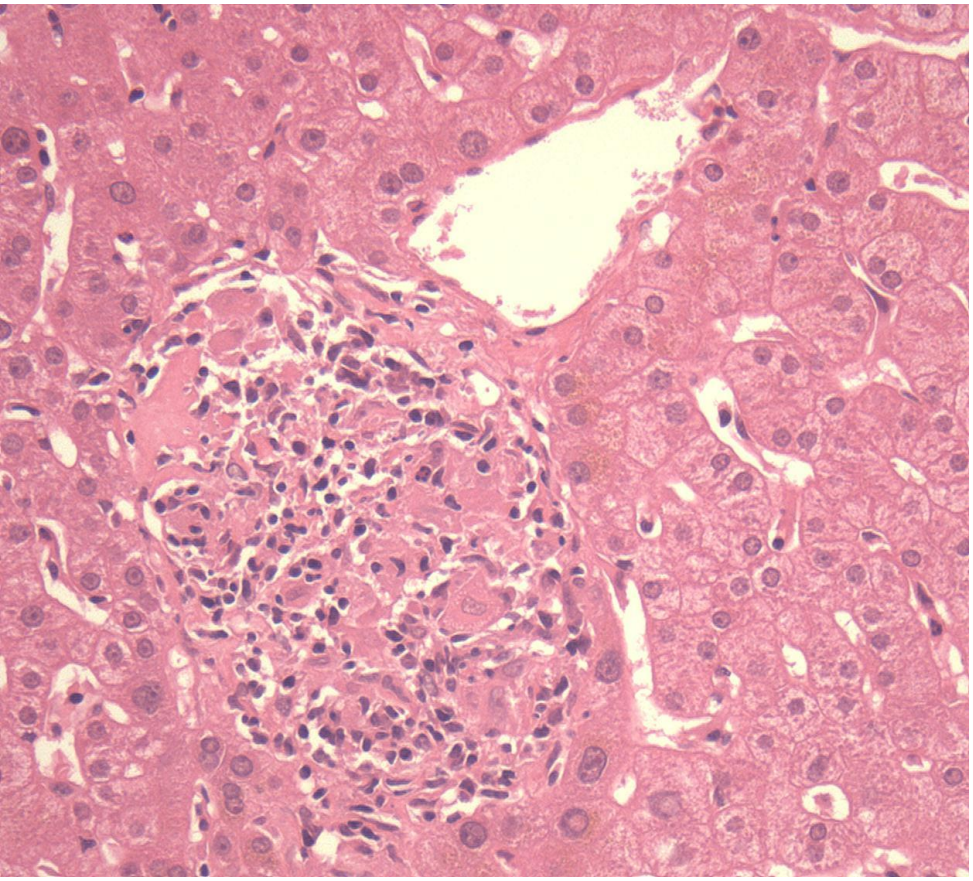
SahinM2014: granulomas in 1.3% of 2662 liver bx

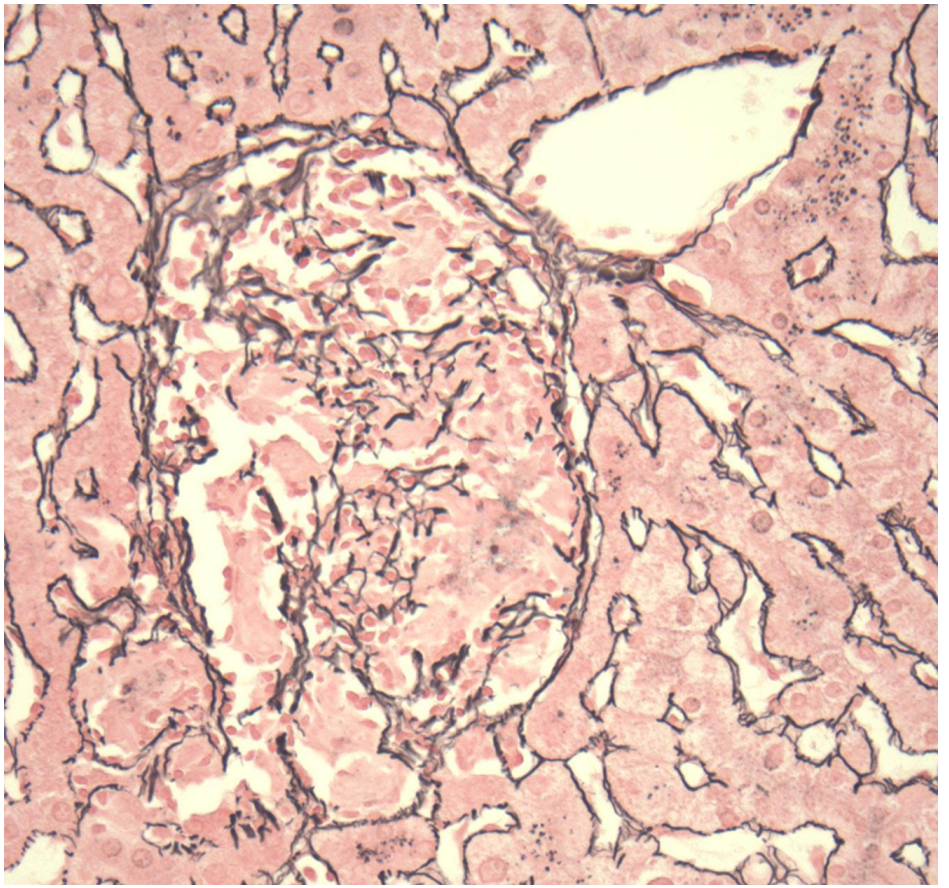
Granulomas

- Organised clusters of mature macrophages
  - response to persistent stimuli, which are required to maintain them
- Case mix/Area/Era
  - PBC, sarcoid, drug…
  - >20% unknown
    - Long term follow-up
- High/Low turnover
  - lipogranulomas
    - gold granules in RA LandasSK1992
  - fibrin-ring granulomas
  - epithelioid granulomas



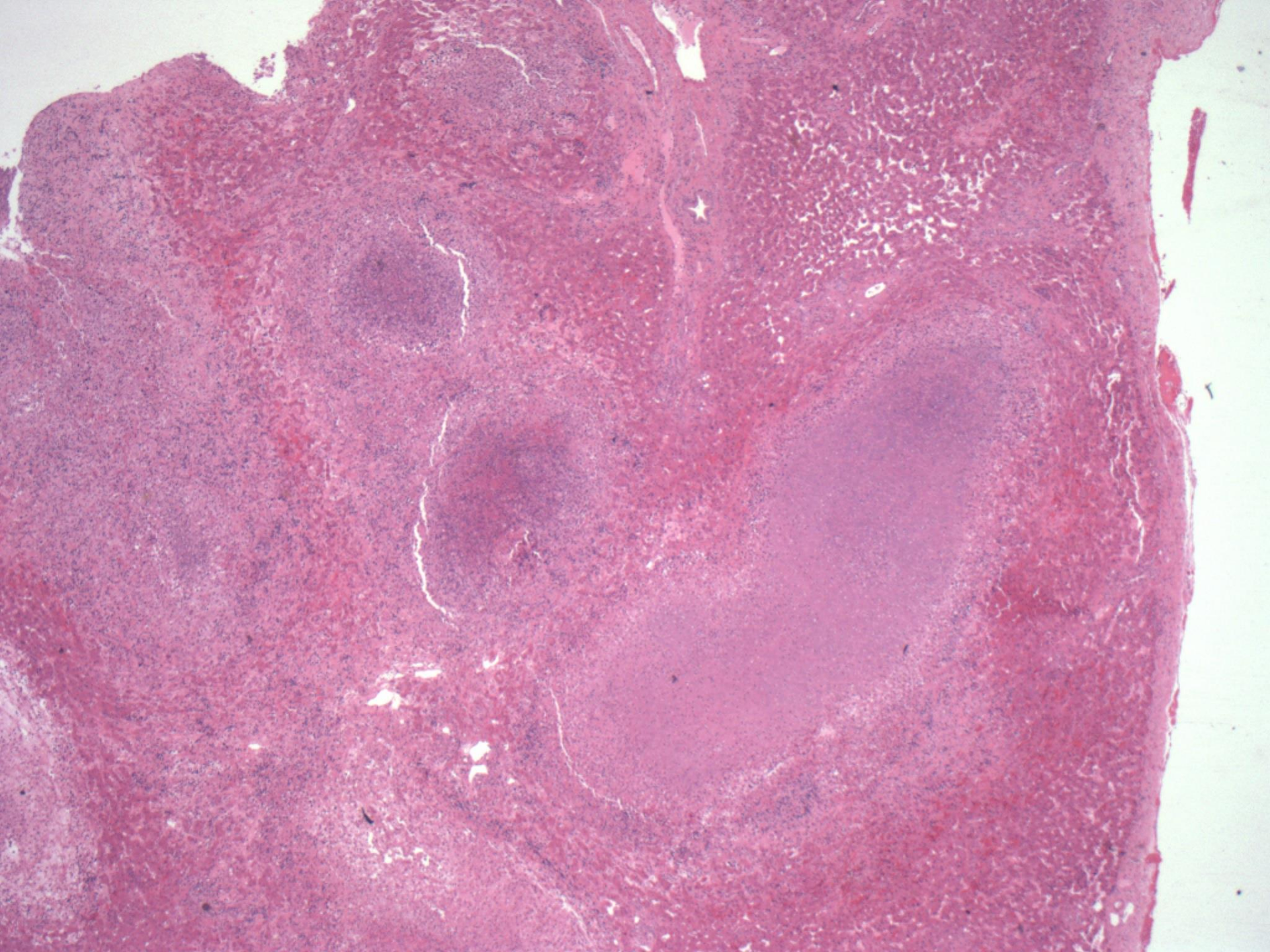
tuberculosis

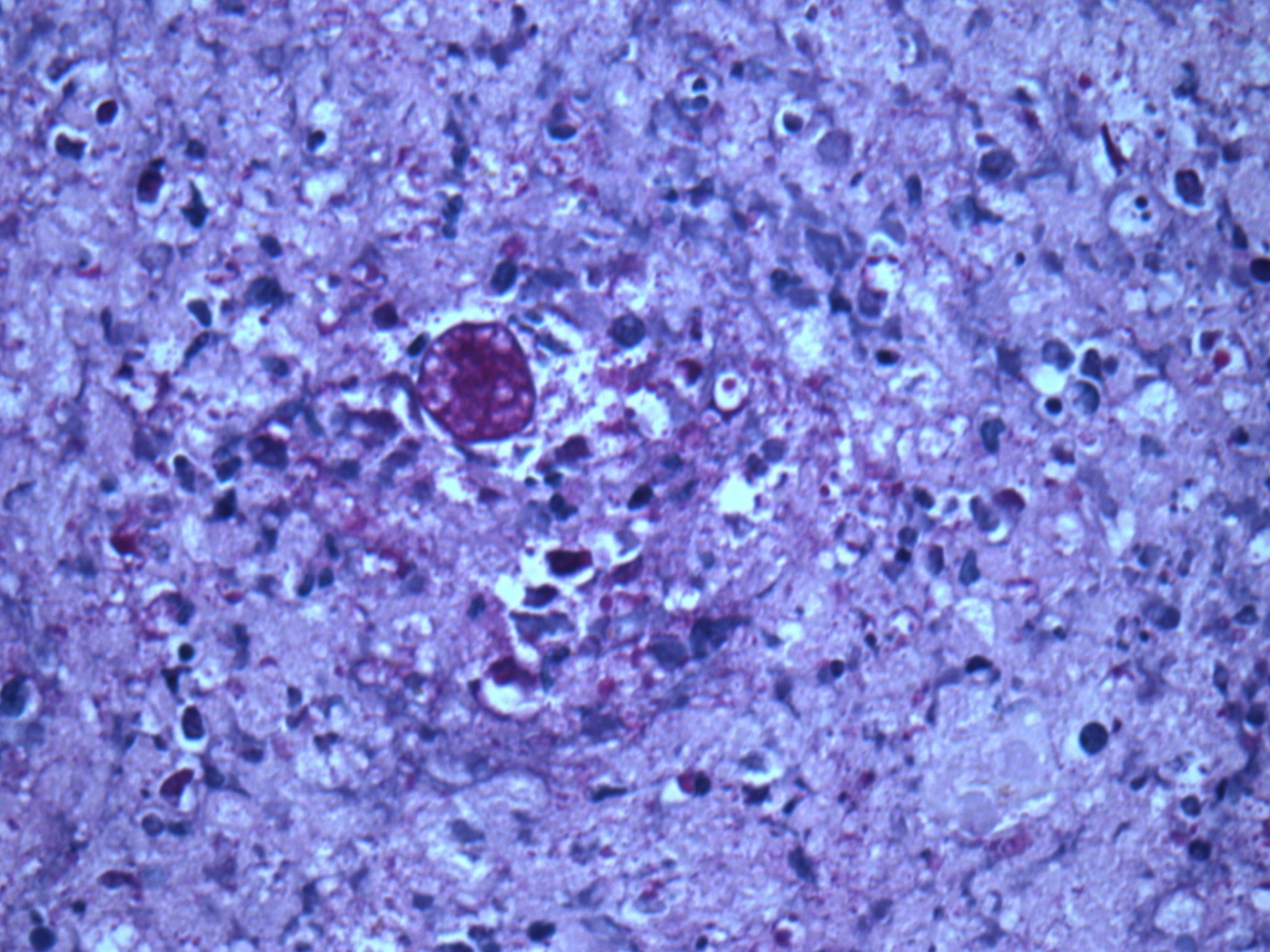




Hepatic sarcoid

- 15-70 (25-45, >50)
  - genetic predisposition to exaggerated granulomatous response to PAMP (persistent mycobacterial/propionobacterial products)
  - Ifn for HCV
  - TNFα-blockade
  - CVID: sarcoid-like ~15%: 40% liver involvment; BoursiquotJ-N2013
- liver 3rd after lung, nodes
  - cholestatic LFT in 25%:
  - liver sarcoid in 15%
  - FDG uptake scan
- Portal hypertension
  - usually *non*-cirrhotic
  - pre-sinusoidal obstructive
  - sinusoidal fibrosis/NRH/portal venopathy
  - Budd-Chiari rare
- Ductopenia (± PBC-like bile duct lesions)





Inflammatory bowel disease

  - unbalanced mucosal immune response to gut contents in genetically predisposed individuals
  - 3 genotype-phenotype groups:
    - colonic Crohn, UC, ileal Crohn Cleynenl2015
  - Abnormal LFT in 50% IBD
    - abnormal biopsy in ~10%UC, 20%Crohn
    - more common in colonic Crohn
- common hepatic pathology
    - Steatosis
    - Drug
    - Cholelithiasis (esp ileal Crohn 5-10x)
    - PSC
      - UC (1-5%)>Crohn (1-3%)
      - distinct colitis (R/pancolonic, dysplasia, quiescent)

Inflammatory bowel disease

Less common hepatic pathology

- Granulomas (5%)
  - also: TNFα antagonists, sulfasalazine, mesalazine BruanM1999
- Portal venous thromboembolism
  - flares; 40% of post-proctocolectomy, non-occulsive GizardE2014
  - pouchitis BallCG2007
- Abscess
  - multiple, R lobe, bacteraemia
  - "aseptic abscesses": multi-organ necrobiosis, relapsing, steroid-sensitive AndreMFJ2007
- AA Amyloid (0.5%)
  - hepatomegaly in Crohn
  - regression after colectomy

Coeliac disease

- extra-intestinal presentations

- transaminitis (20-40%)
  - differential for transaminitis of unknown cause
    - altered intestinal permeability/microbiome
    - reverses
  - specific autoimmune liver disease:
    - PBC (6%) > AIH > PSC
  - non-cirrhotic portal HT

Whipple disease

- *Tropheryma whipplei*
  - 4% population are carriers
    - 10-20% of sewage workers
    - 40% of relatives
  - non-intestinal involvement common
    - 7 years prior to diagnosis
    - chronic arthropathy
    - hepatic epithelioid granulomas may precede GI symptoms
- immunosuppressive-excacerbation
    - pyrexia, sepsis & dissemination
    - endocarditis
    - organism-laden macrophages/Kupffer cells
    - pcr is a better test

Nutritional liver disease

- Bariatric surgery
  - restrictive and/or malabsorbtive procedures
    - roux-en Y gastric bypass
      - protein deficiency (‘2^{o} kwashiorkor’)
      - micronutrient deficiencies BalBS2012
    - 1 & 5 year biopsy follow-up MathurinP2009
      - reduced steatosis (& metabolic syndrome metrics)
      - mild increase fibrosis

Nutritional liver disease

Total parenteral nutrition in older children & adults NainiBV2012

- complex settings
  - sepsis, malnutrition, antibiotics, transfusions, surgery
- biliary sludge, cholelithiasis, acalculous cholecystitis (esp. ileal resection)
- abnormal LFT within 3 weeks (20-60%)
  - transaminases, ALP, GGT, mild bilirubin
- cholestasis after 2-3 weeks (z3 canalicular; chronic)
- steatosis/steatohepatitis
- ductopaenia (25%)
- fibrosis after 6 weeks
  - biliary periportal + peri-venular characteristic
  - can regress; cirrhosis uncommon vs infants

Nutritional liver disease

- protein malnutrition (kwashiorkor)
  - reversible macrosteatosis (z1➔panlobular)
  - fibrosis/necroinflammation imply a 2nd diagnosis
  - UK case LunnPG1998
- caloric starvation (marasmus)
  - hepatocyte atrophy ± sinusoid dilation

Case 21-2012: A 27-Year-Old Man with Fatigue, Weakness, Weight Loss, and Decreased Libido

Daniel P. Hunt, M.D., Anne E. Becker, M.D., Ph.D.,
Alexander R. Guimaraes, M.D., Ph.D., Anat Stemmer-Rachamimov, M.D.,
and Joseph Misdraji, M.D.

PRESENTATION OF CASE

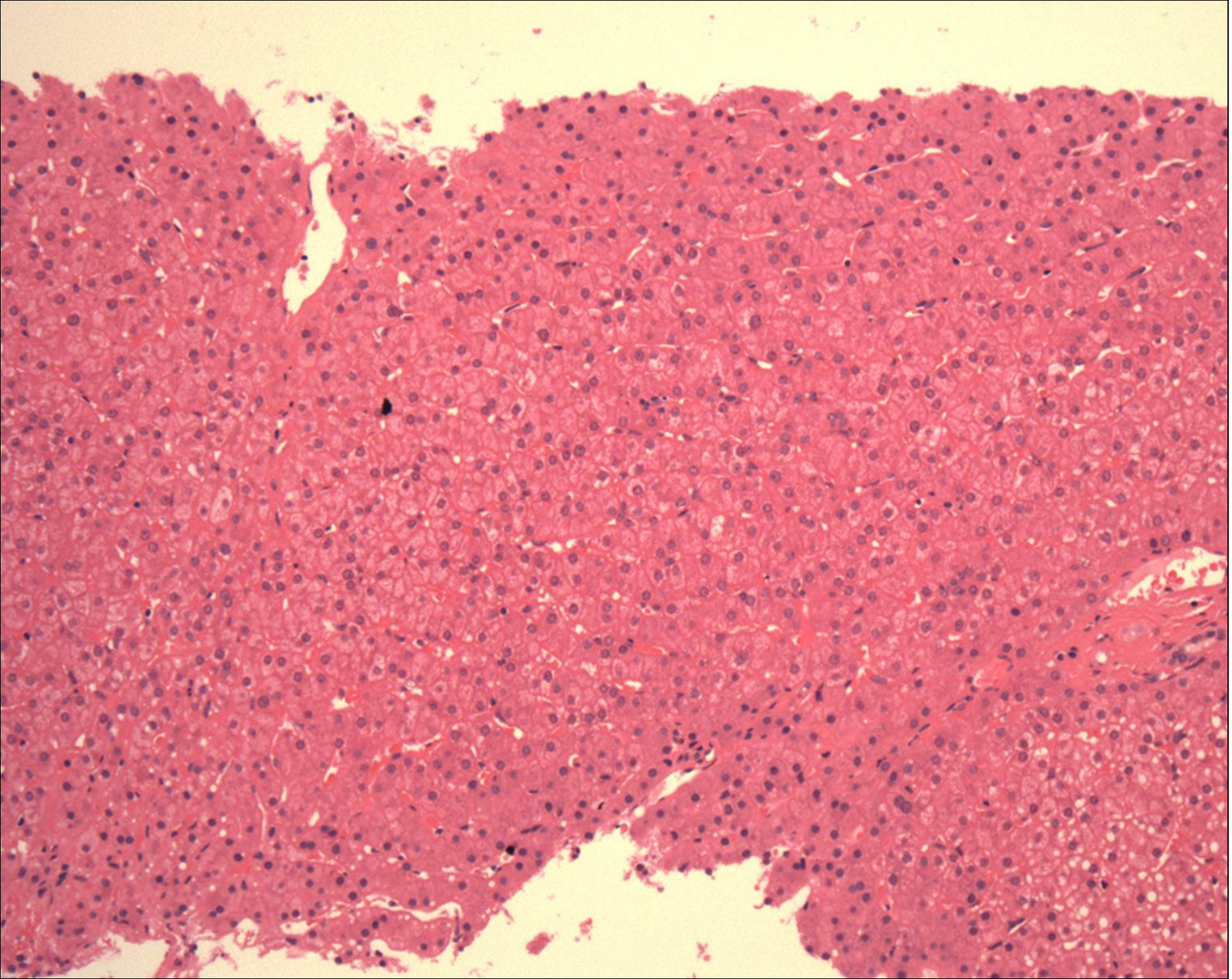
Dr. Fernando M. Contreras (Medicine): A 27-year-old man with a history of obesity was seen in the endocrinology clinic at this hospital because of fatigue, myalgias, weakness, weight loss, and loss of libido.

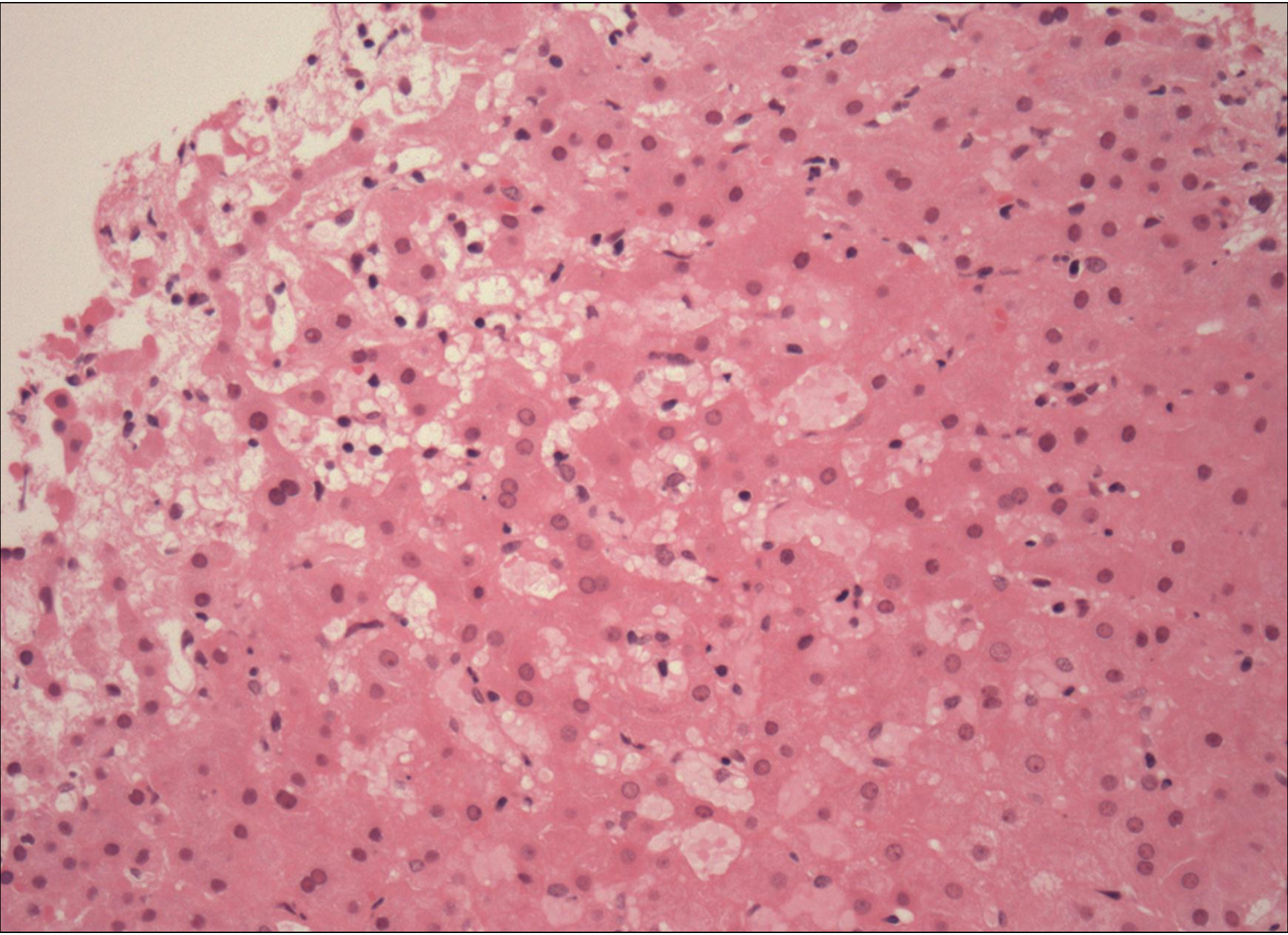
Thirteen months before presentation, the patient reported weighing 108.9 kg

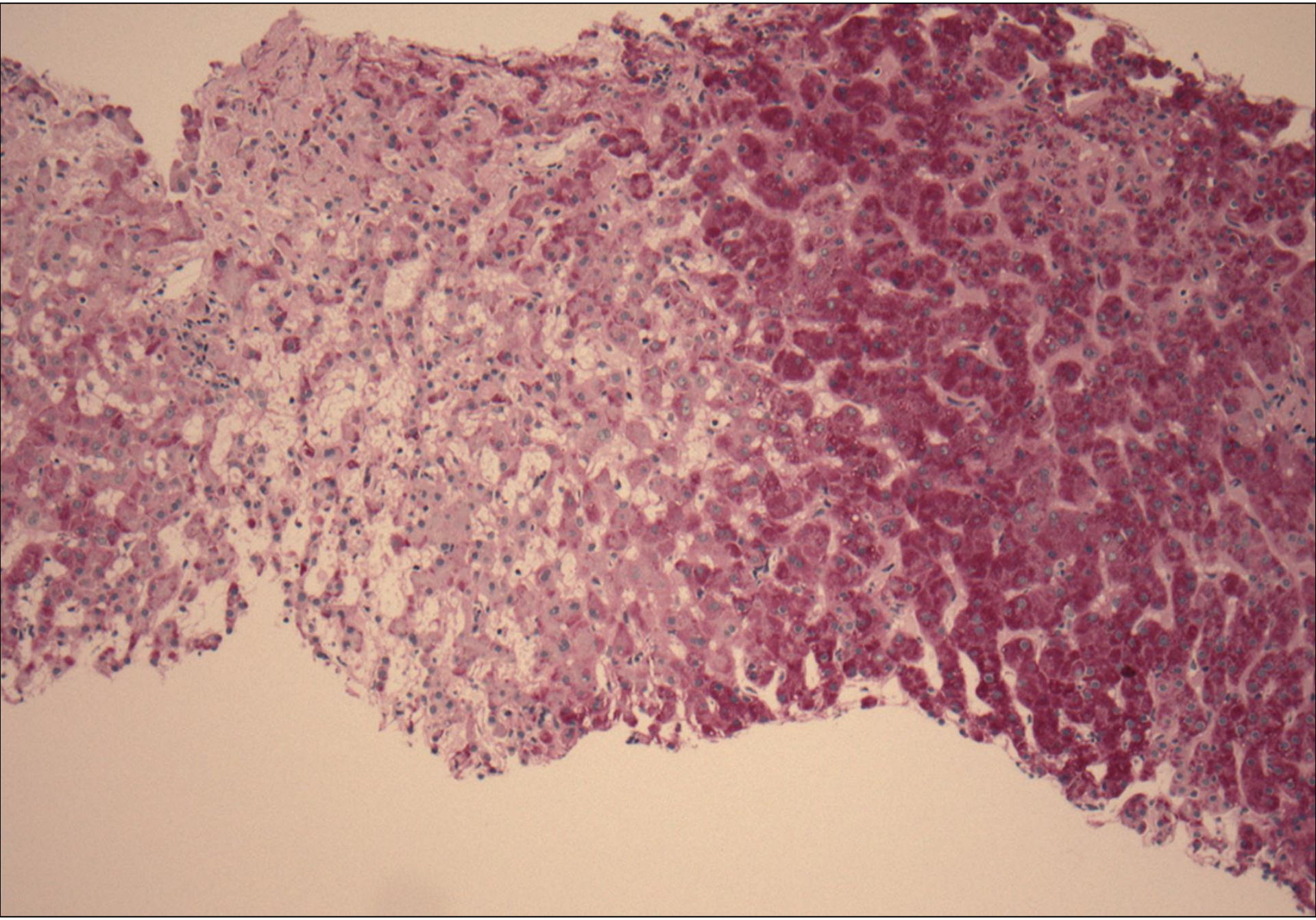
Liver disease in anorexia nervosa

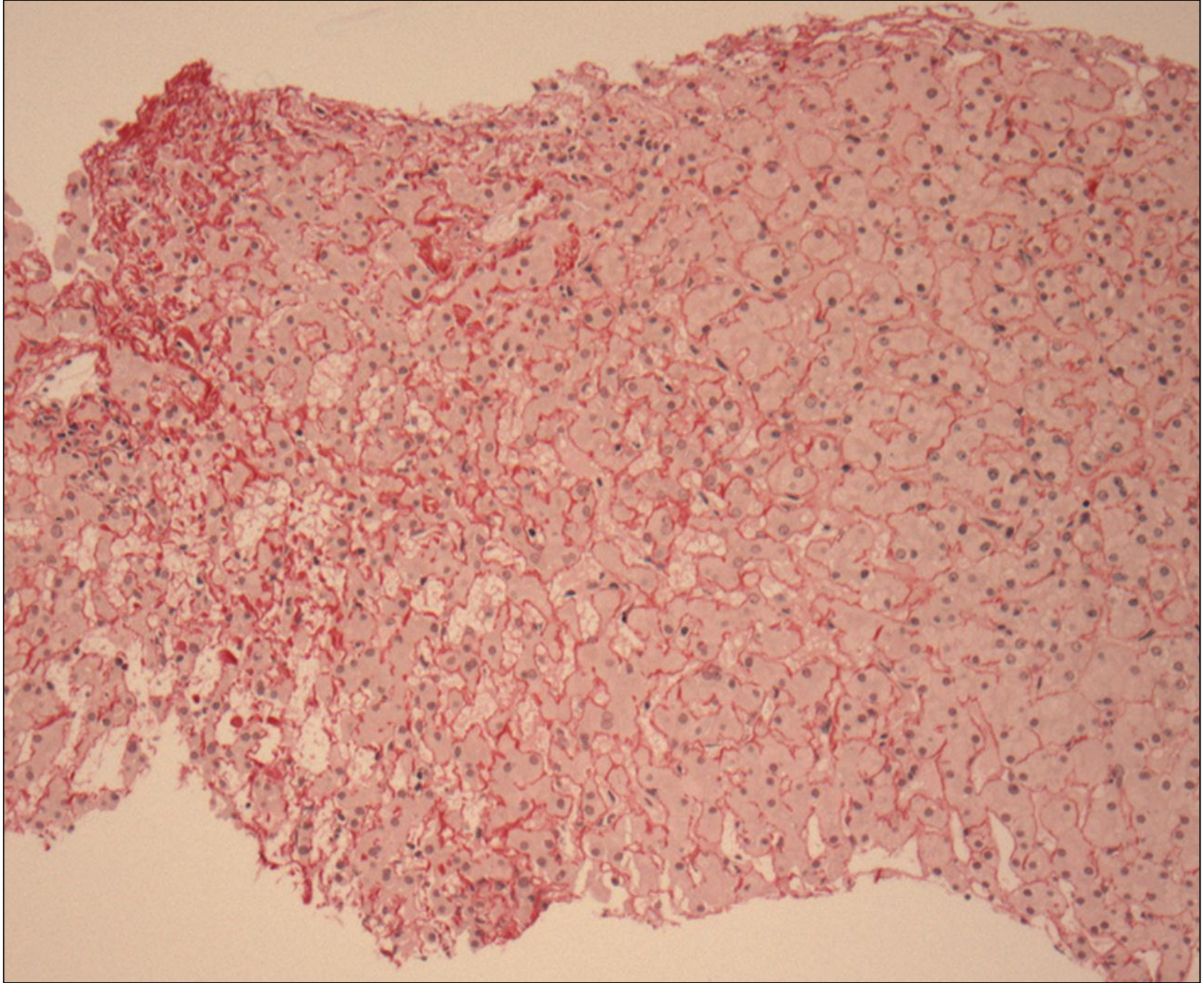
- transaminitis episodes in 40% HanachiM2013
  - >50 fold when BMI very low (~11)
  - resolves with refeeding, unless refeeding syndrome
- acute liver failure
  - ascites
- hypoglycaemic coma

- acute starvation-induced autophagic liver injury RatouPE2008
  - glycogen rebound during refeeding KomutaM1998







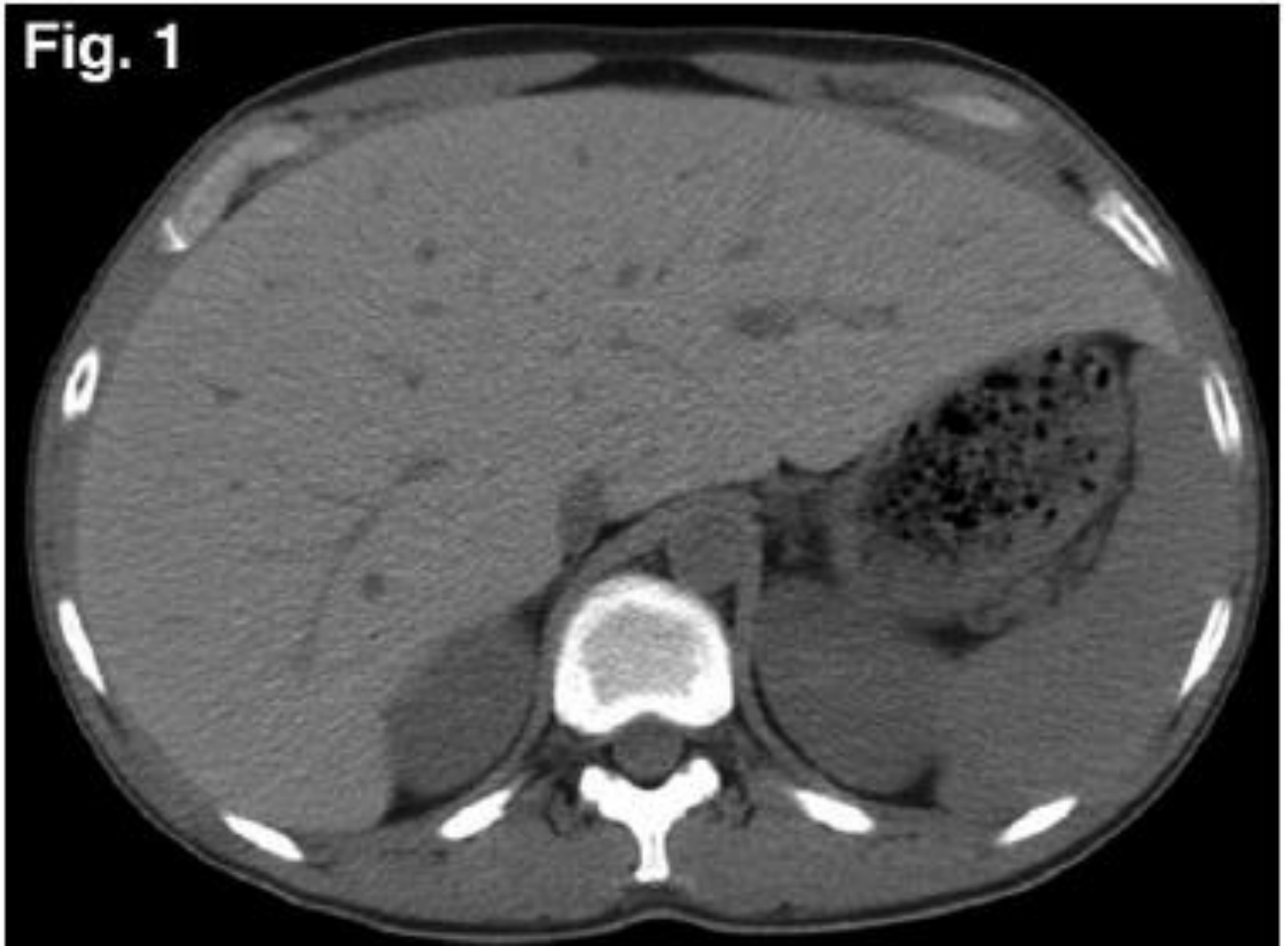


Diabetes mellitus, type I

- Hyperglycaemia
  - increased hepatic output (no feedback on GNG)
  - reduced hepatic trapping (glucokinase)
  - reduced peripheral uptake

- Insulin dosing in hyperglycaemia (adults/children)
  - hepatic glycogen loading Mauriac1930, Evans1955
    - vigorous Rx of acute diabetic presentation
    - repeated insulin excess corrected with sugar
    - chronic hyperglycaemia + intermittent insulin dosing

Sweetser2010: Hepatology, Image of the month



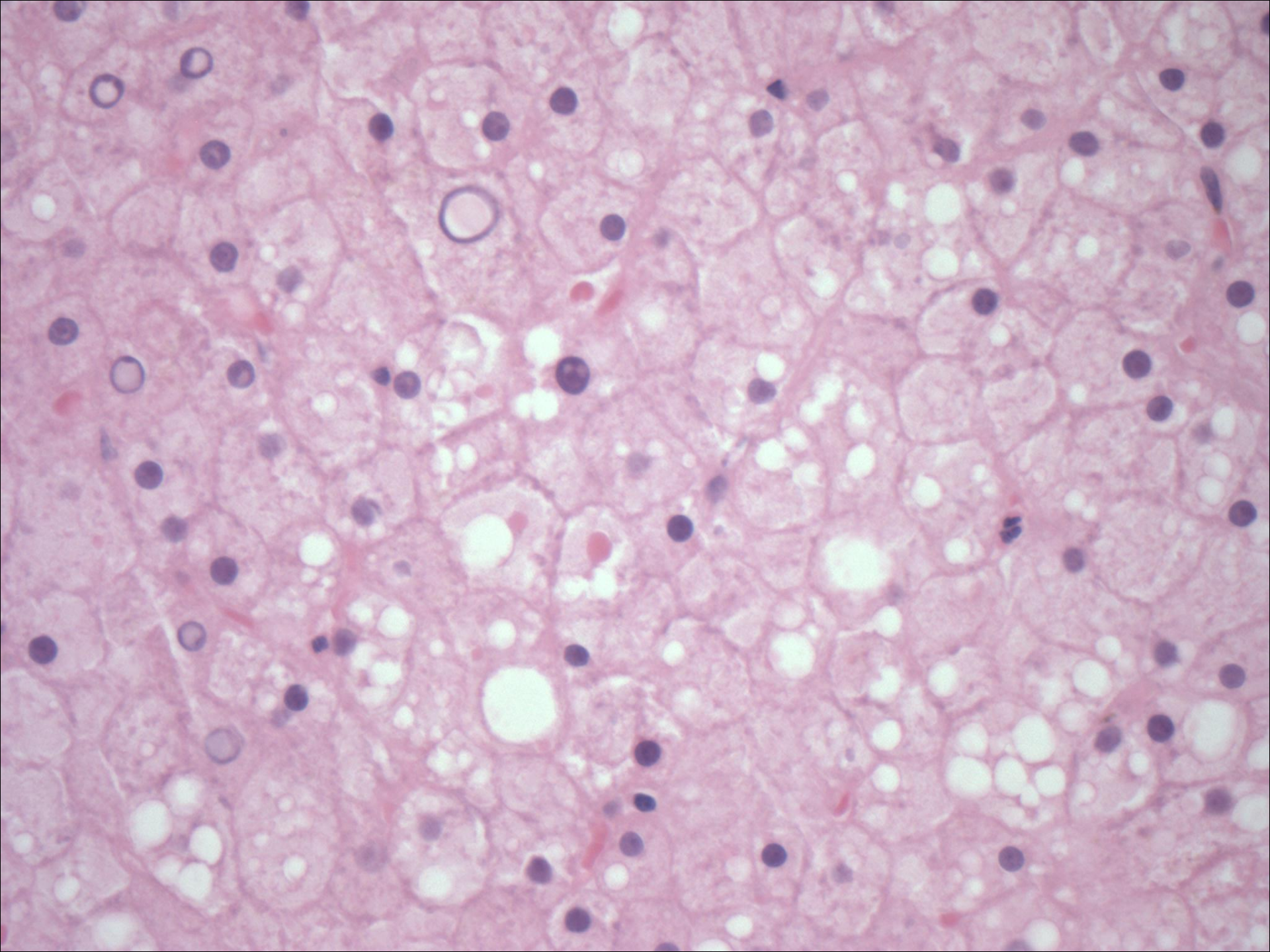
“Glycogenic hepatopathy”

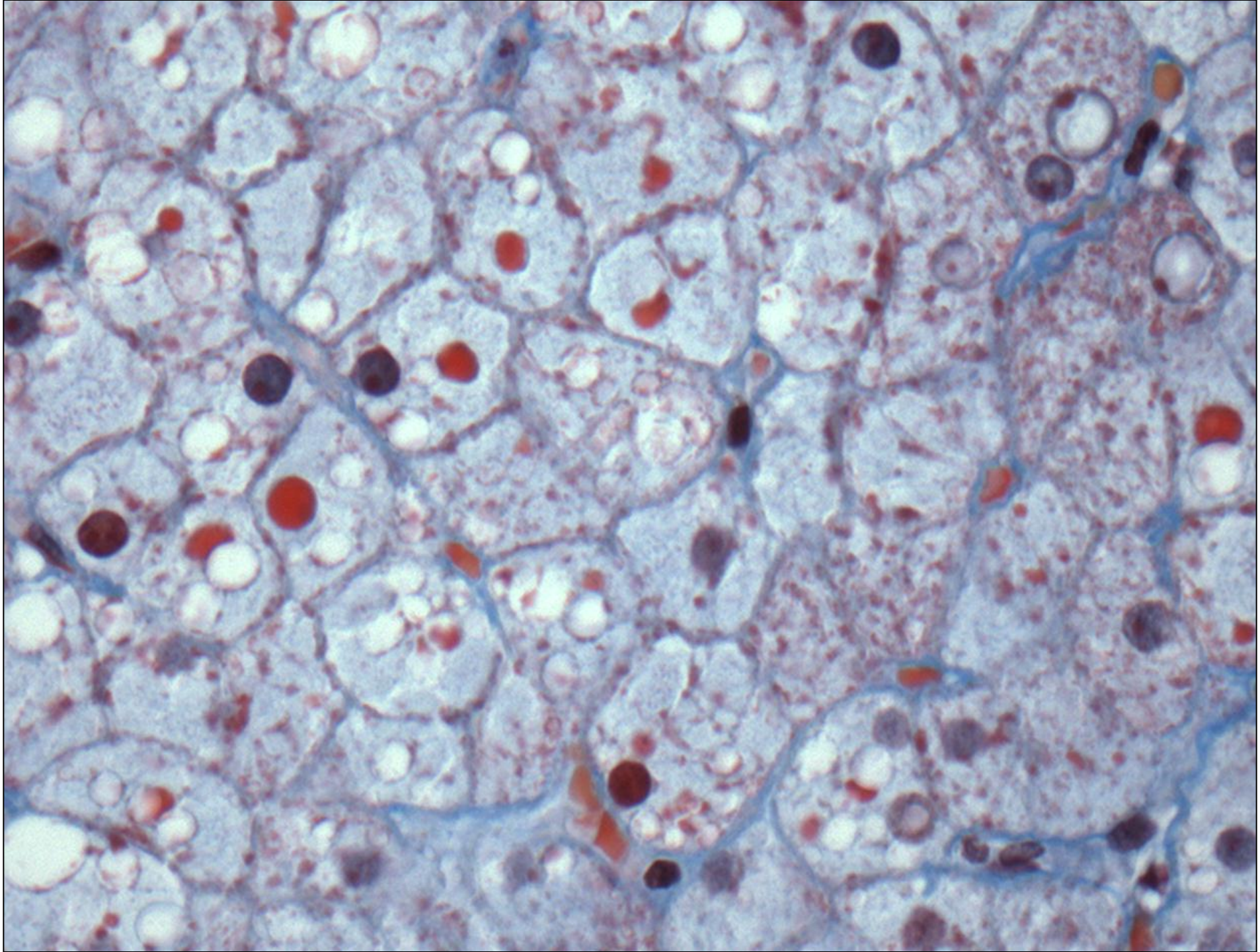
Torbenson2006

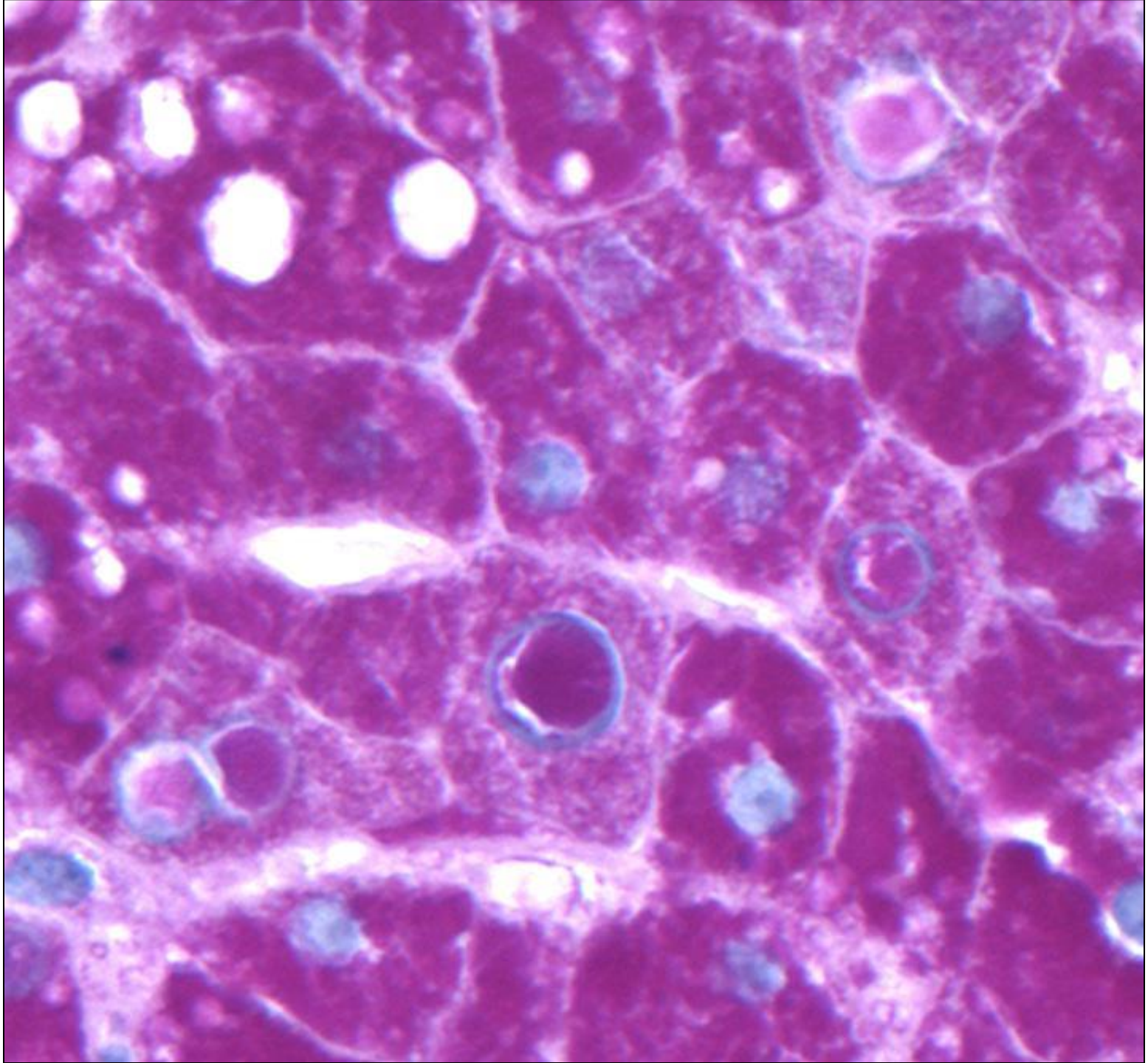
reversible glycogen-loading in insulin-dependent diabetics

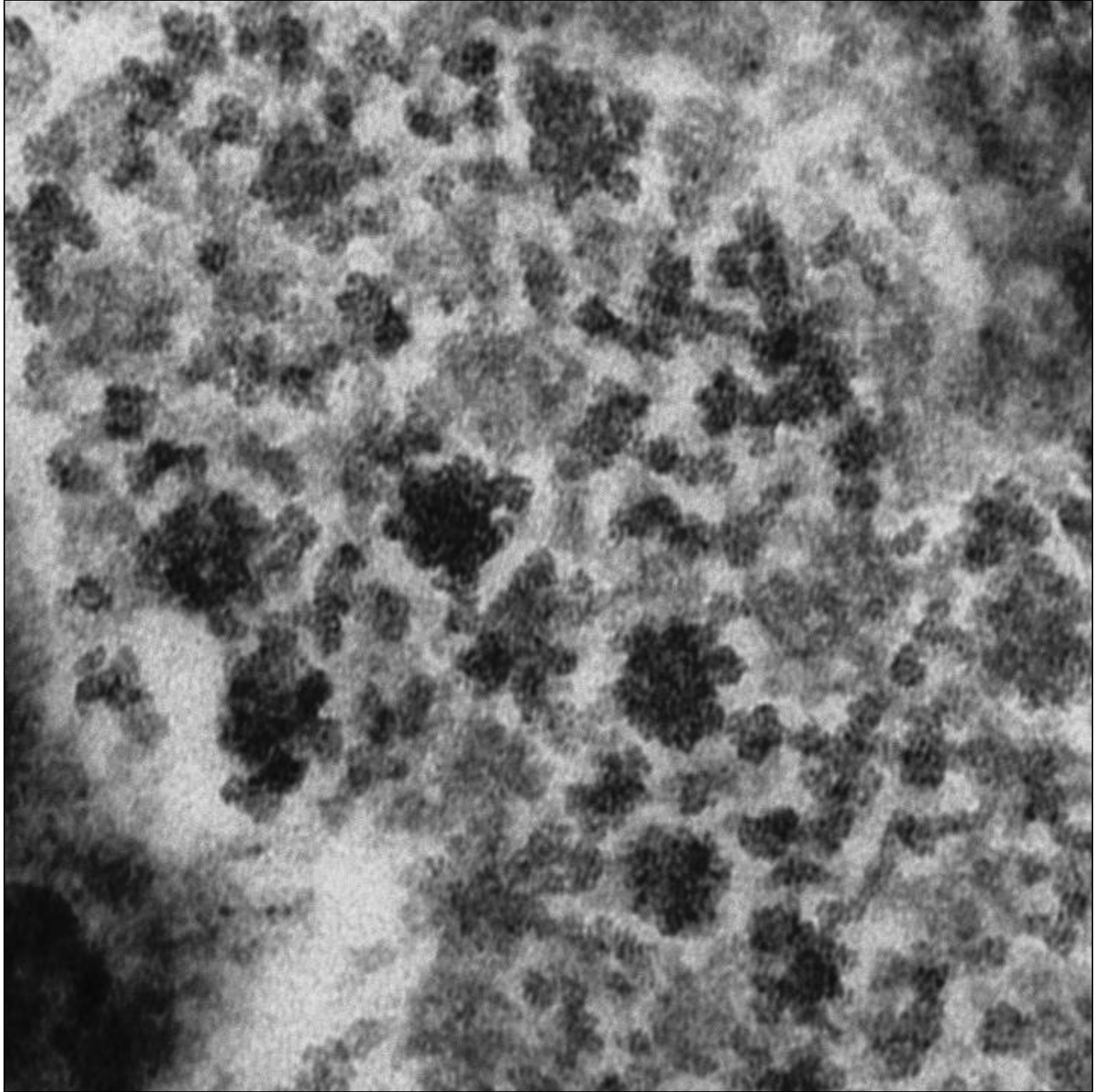
- painful hepatomegaly
- transaminitis, ↑ALP

- Pale hepatocytes with prominent membranes, compressed sinusoids, glycogenated nuclei, PAS replete, giant mitochondria
- Minimal fat/fibrosis
  - Steatosis is not a feature of type 1 diabetes
    - MRI screen, PetitJM2015,
    - 155 children with steatosis on biopsy, Hourigan2015





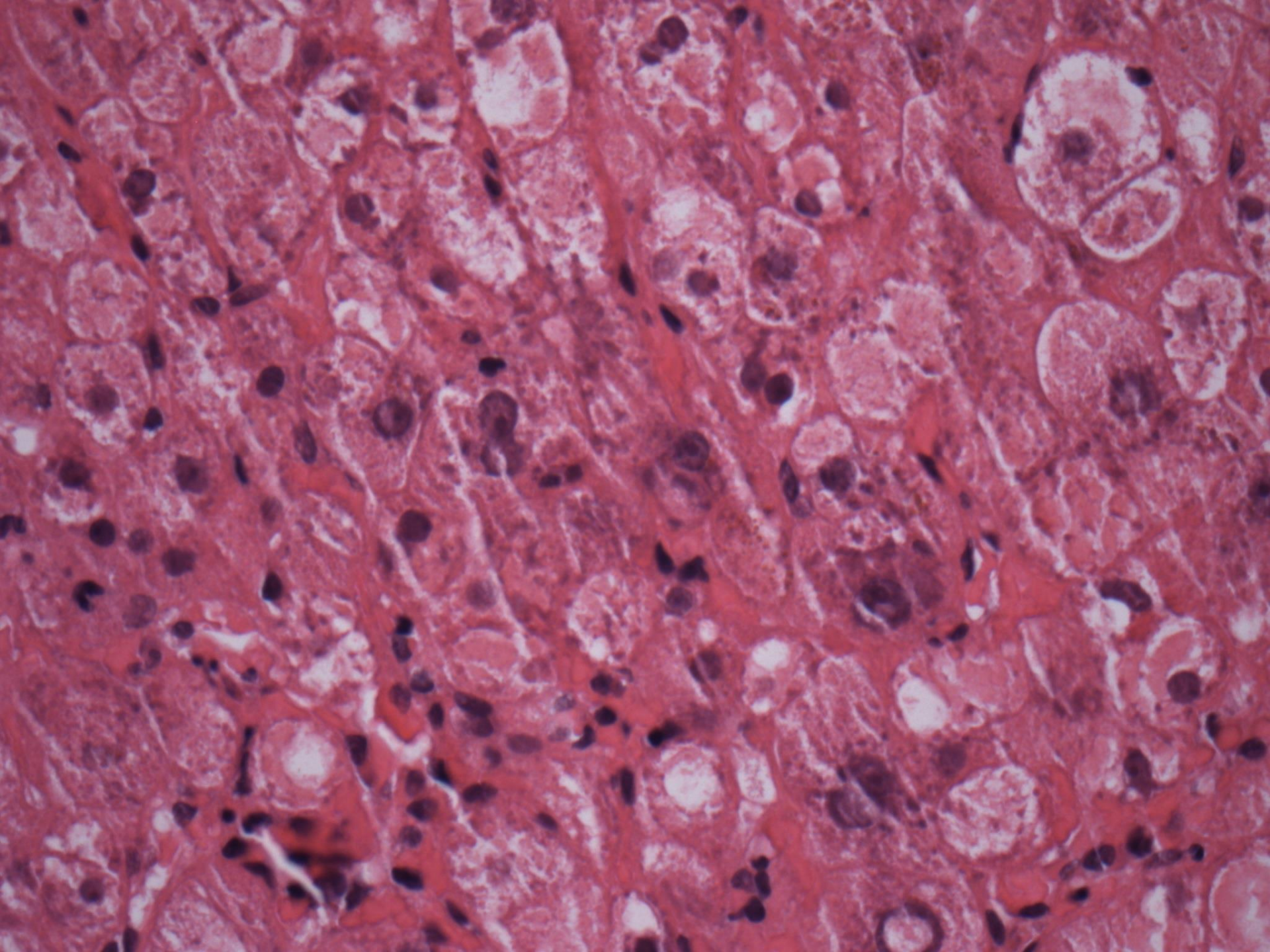


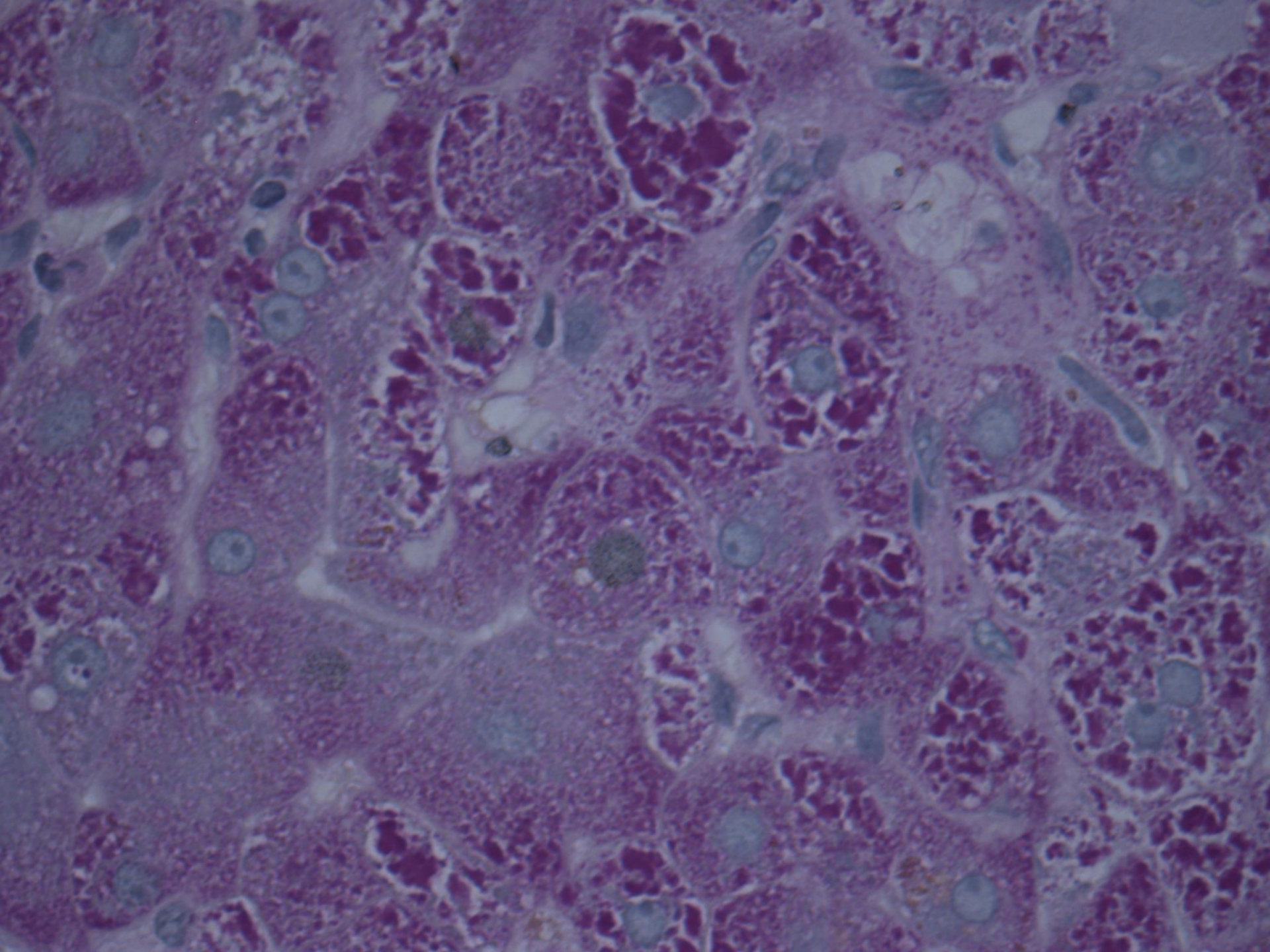


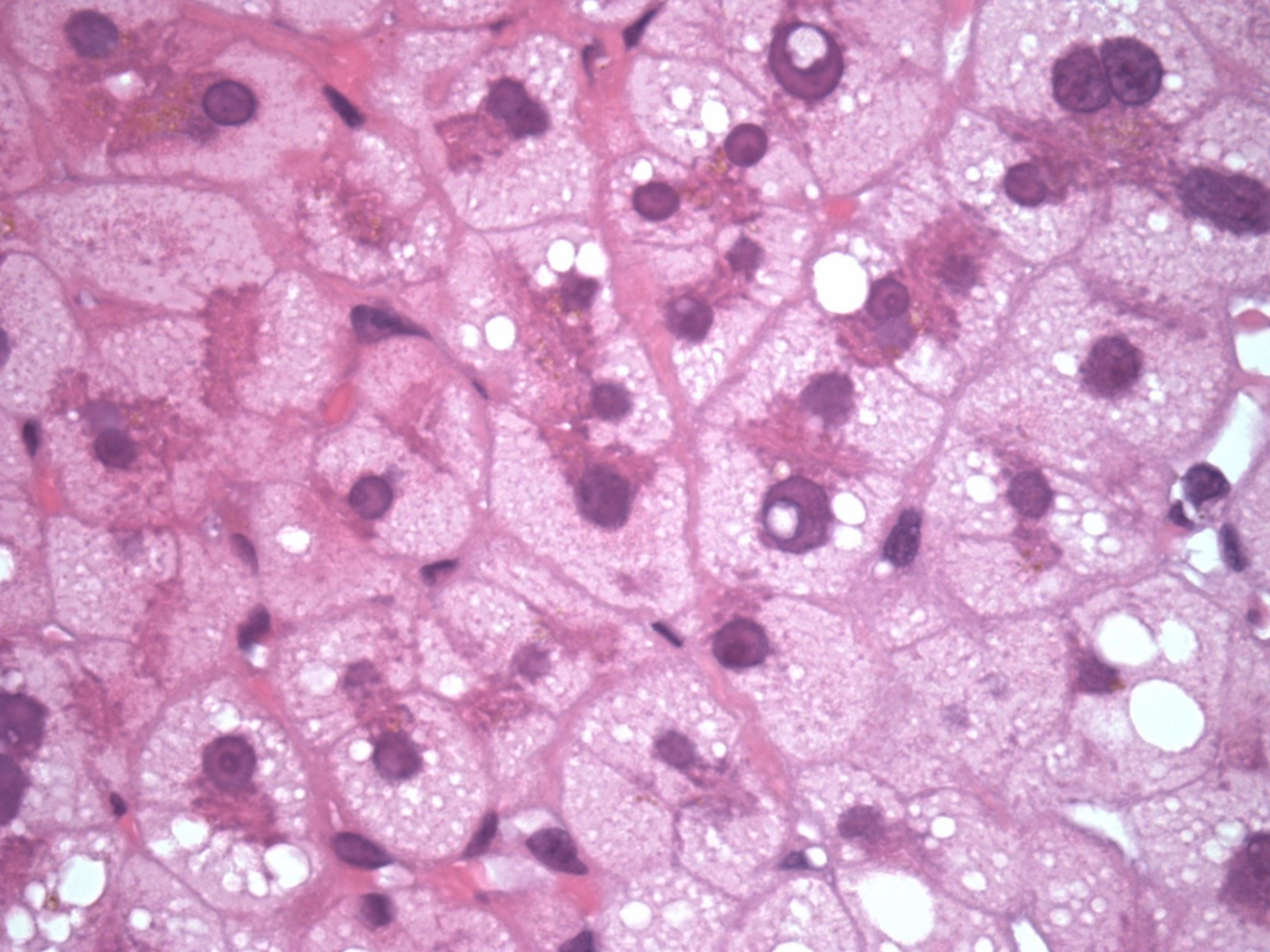
Poorly branched glycogen (“polyglucosan”)

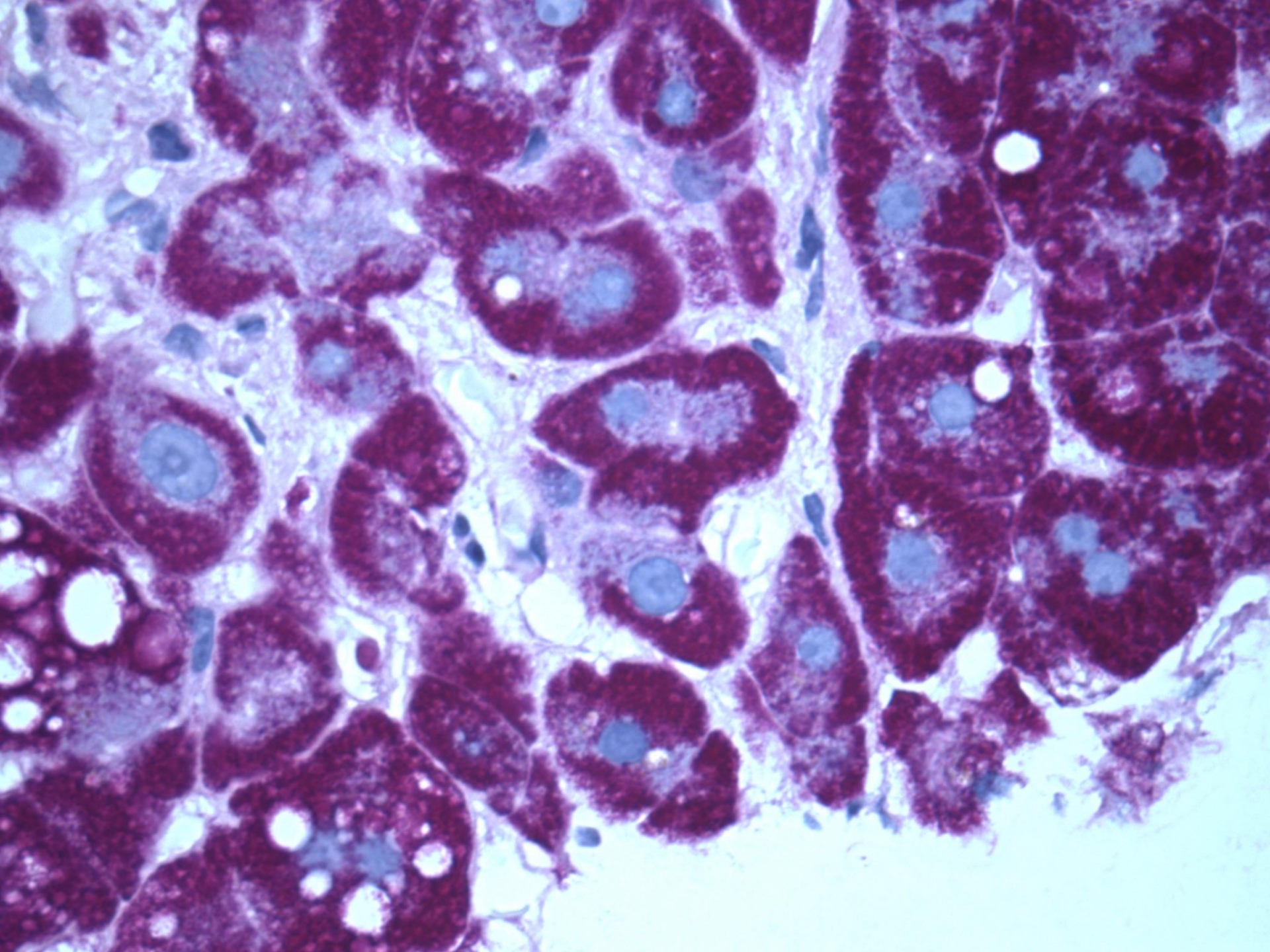
- Glycogen synthesis
  - glycogen synthase (insulin stimulated) builds linear chain; then GBE attaches short branches of ~4 Glc
  - insufficient GBE causes polyglucosan accumulation
  - Unbranched glycogen is a poor source of free glucose
- Genetic (multisystem)
  - GSD IV (variable activity); Juvenile myoclonic epilepsy (indirect)
- Acquired hepatic
  - stressed glucose metabolism:
    - short term high dose corticosteroids: hepatomegaly within days IancuTC1986;
    - diabetes type II on insulin, transplant recipients (immunosuppression e.g. MMF, tacro), beta blockers, TPN
  - cyanamide
  - No consistent relationship with LFT

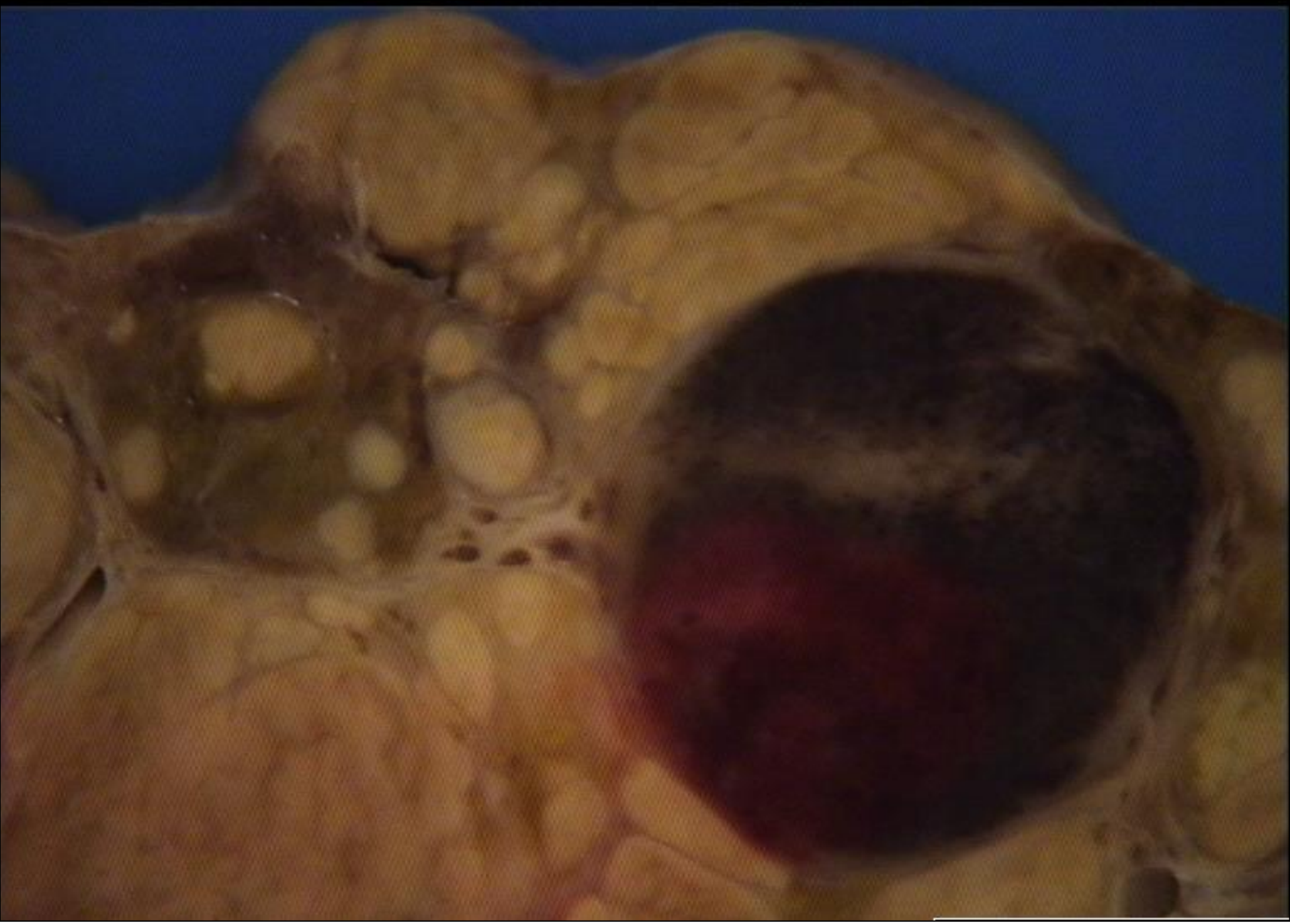
BrugueraM1986; YokotaT1988; WissellJ2006; LefkowitchJH2006; BejaranoPA2006;

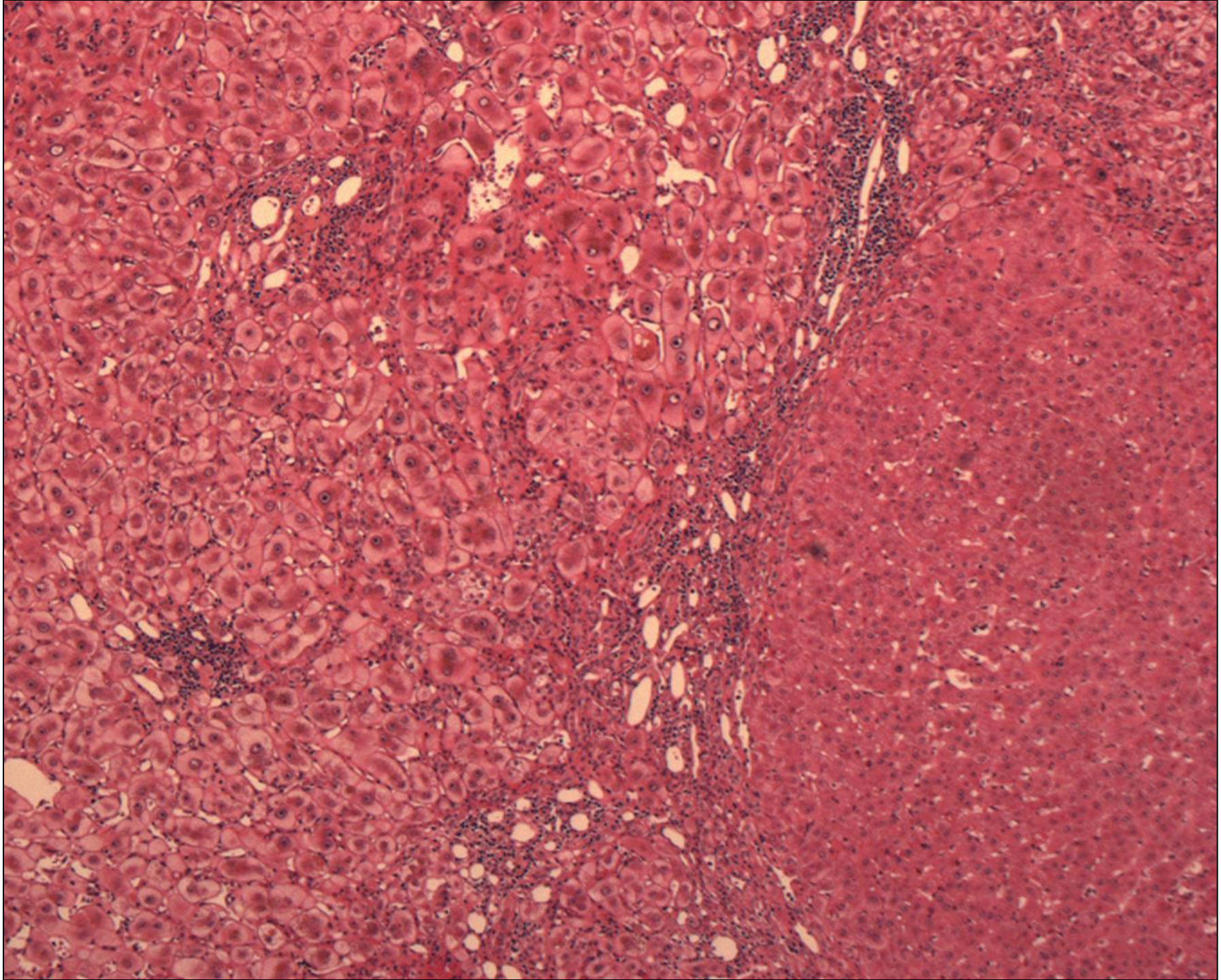






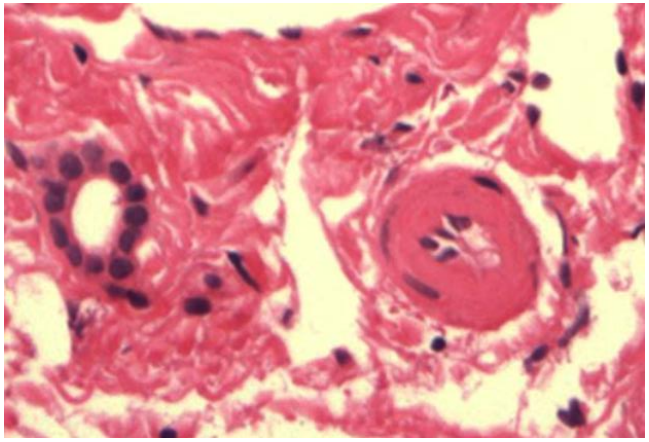






Diabetic microangiopathy of the liver

- Chronic diabetics with retinopathy/nephropathy
- “diabetic hepatosclerosis”
  - Collagenisation of space of Disse with basement membrane components (laminin, collagen IV)
  - perisinusoidal + perivenular fibrosis + arteriolosclerosis
    - Latry1987, Bernuau1982, Harrison2006, Chen2008
- arteriolosclerosis
  - more prevalent in hypertensive diabetics
  - no correlation with sinusoidal fibrosis
    - Balakrishnan2015



Endocrine disease

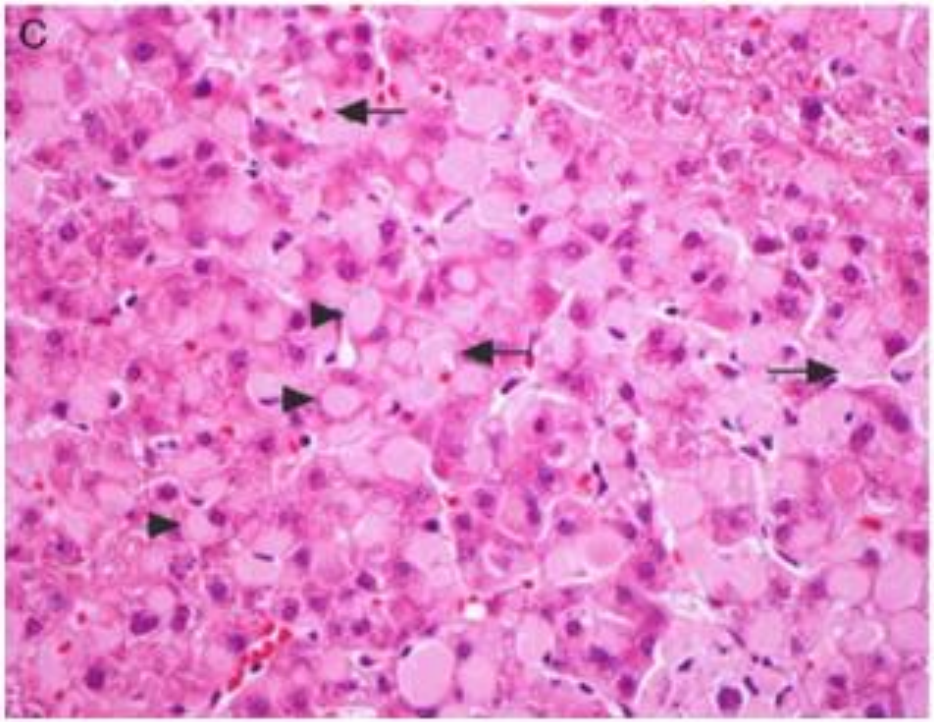
- Polycystic ovary syndrome
  - commonest endocrine abnormality in premenopausal women
  - insulin resistance, metabolic syndrome inc NAFLD
- Hyperthyroidism
  - pure cholestasis
    - in thyroid storm, heart failure
    - liver disease (PBC): role of thyroid can be overlooked – test TFT in transplant assessment!
- Hypothyroidism
  - high protein ascites may misdirect investigation to liver/Meig

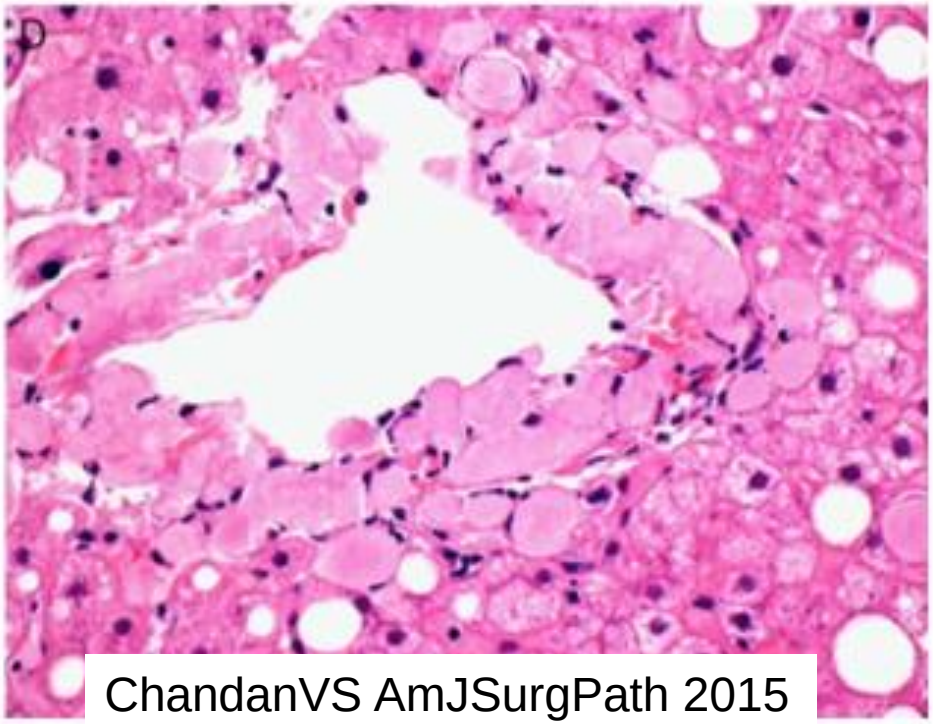
Amyloid

- 90% liver involvement
  - linear peri-sinusoidal
  - mural arterial/venous +/- portal connective tissue, large ducts/peribiliary glands
  - globular (portal/sinusoidal)
- >28 precursor proteins
  - AL
    - SAA
    - transthyretins
    - fibrinogen A alpha
    - apolipoprotein AI/II
    - leucocyte cell-derived chemotaxin 2, MereutaOM2014
      - Hispanic; incidental liver finding; 25% of liver amyloid; globular pattern characteristic; ihc possible
      - can cause symptomatic portal hypertension, DamlajM2014

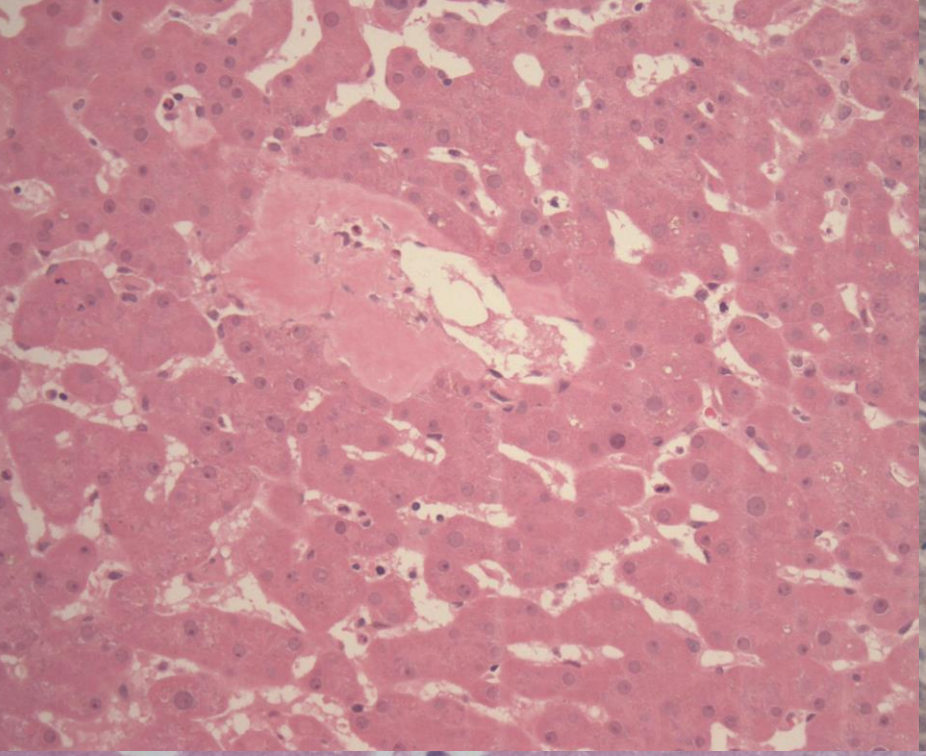
Amyloid

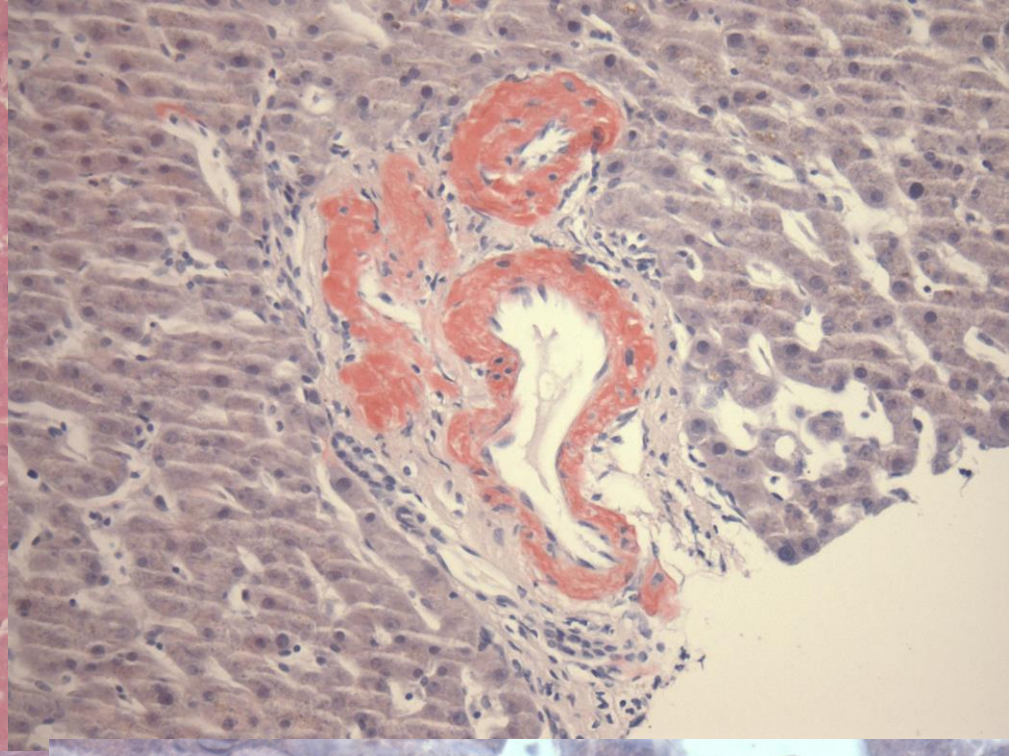
- *leucocyte cell-derived chemotaxin 2 amyloid*
  - globular deposition (without linear sinusoidal) may be specific
  - 4% of amyloid liver bx
  - (+/- mural arterial)
  - of other types, only 7% AL showed focal globular (with linear sinusoidal)

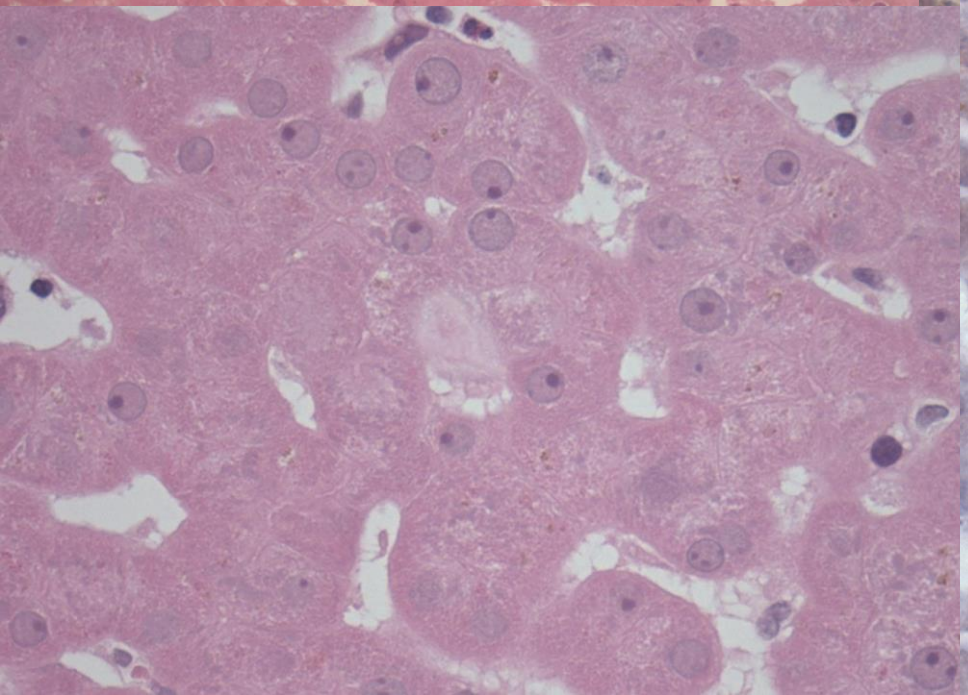


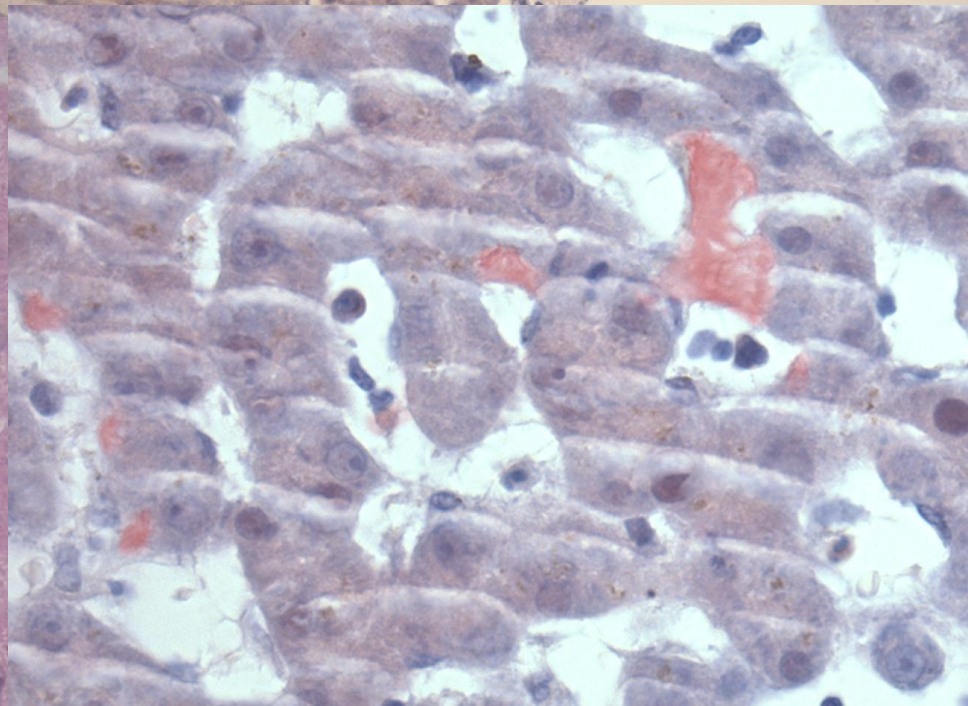


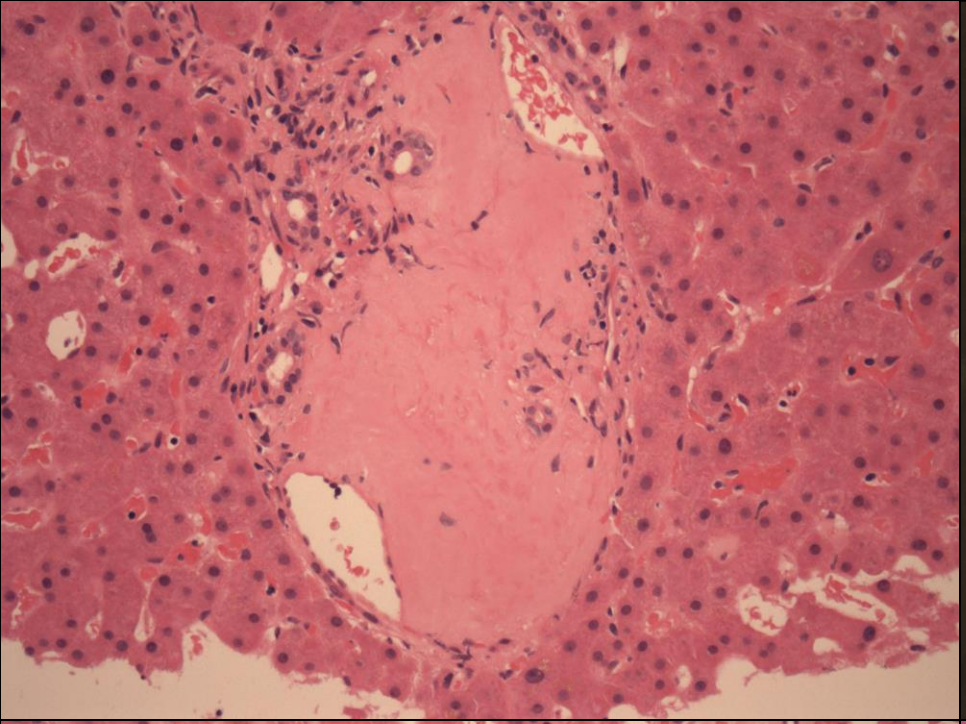
ChandanVS AmJSurgPath 2015

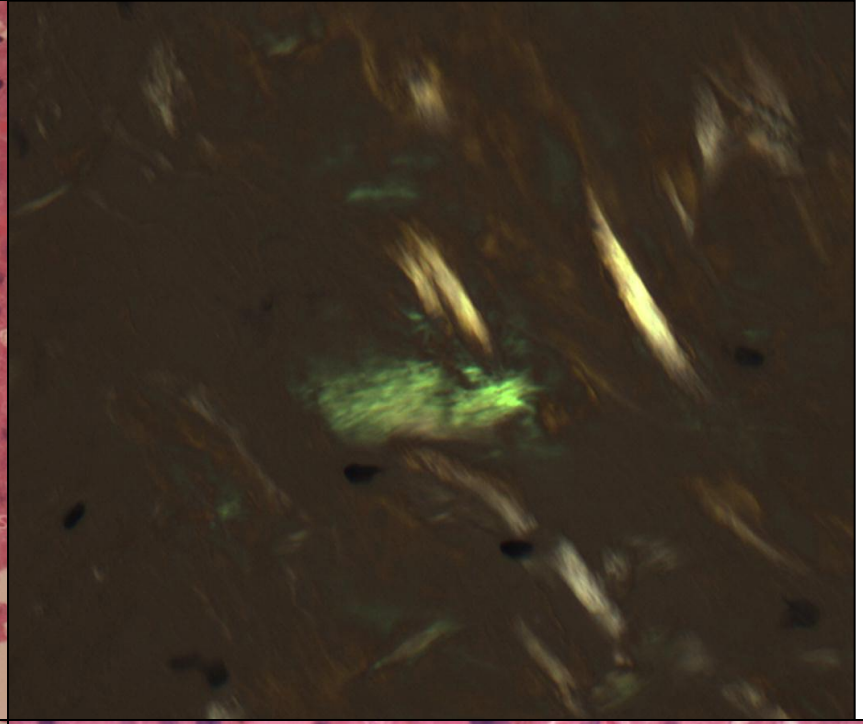


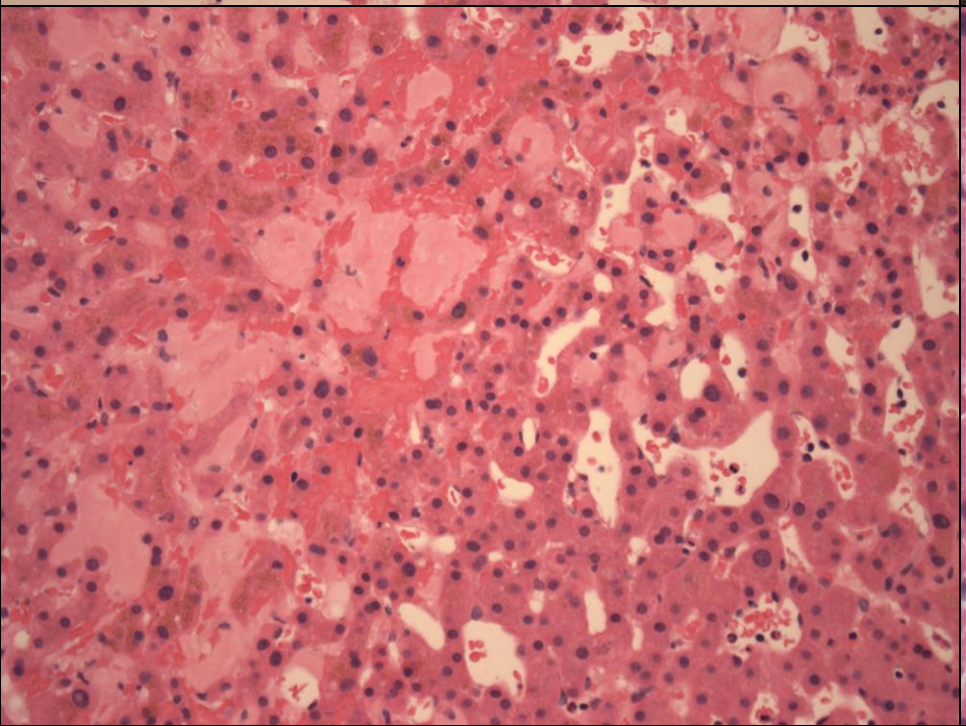


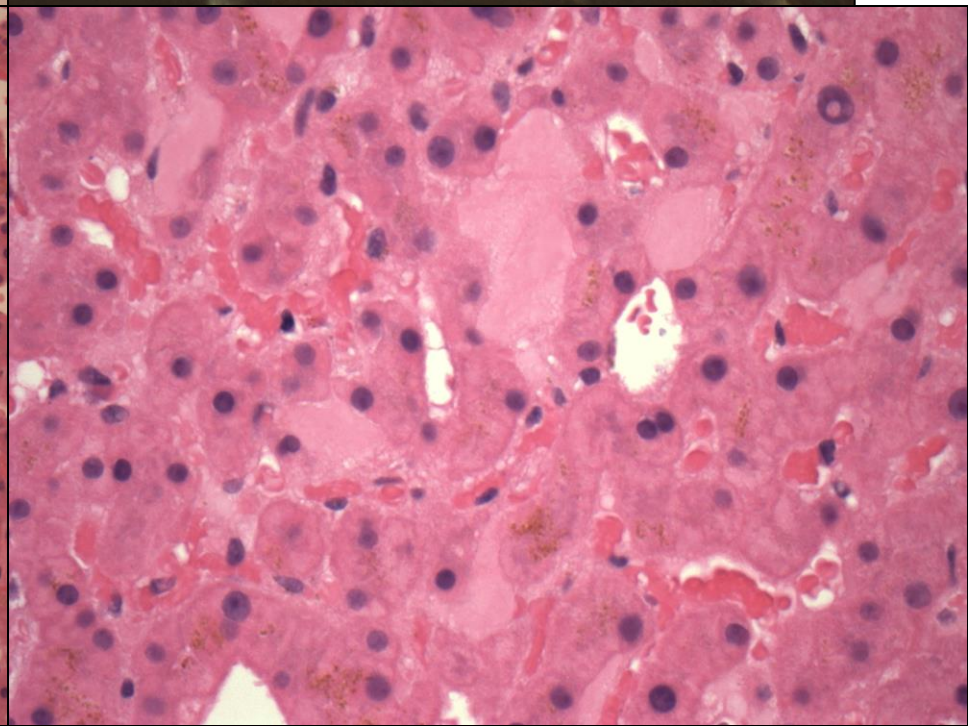








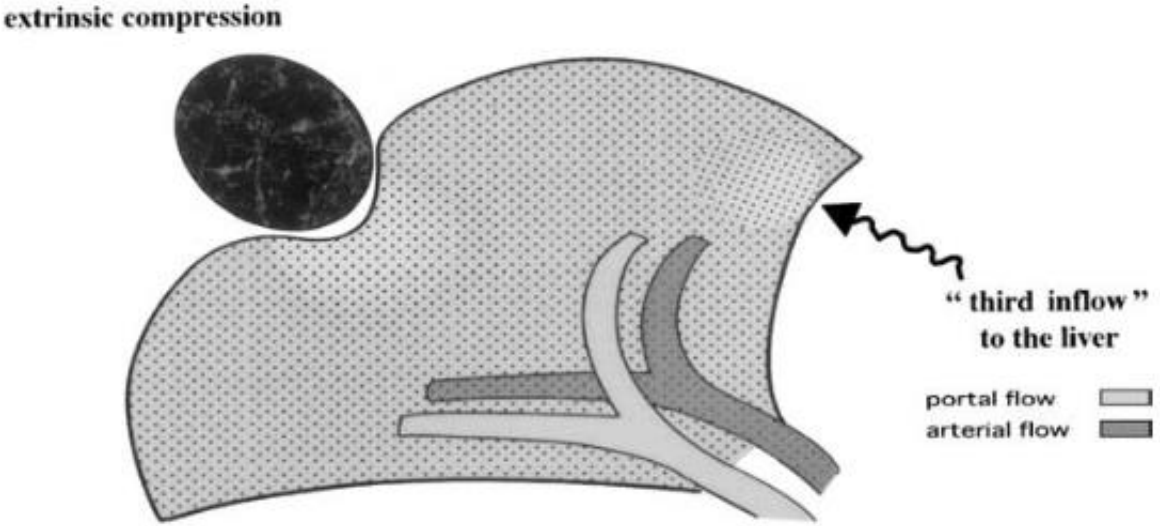




- Amyloid differential: light/heavy chain disease
  - peri-sinusoidal
  - kidney mainly, incidental liver
  - granular (not fibrils)
    - congo red negative
    - no component P
  - PAS, PAS/D positive

Liver and metastases

- “pressure/haemodynamic”
  - z3 sinusoid dilation, cholangiolitis+oedema

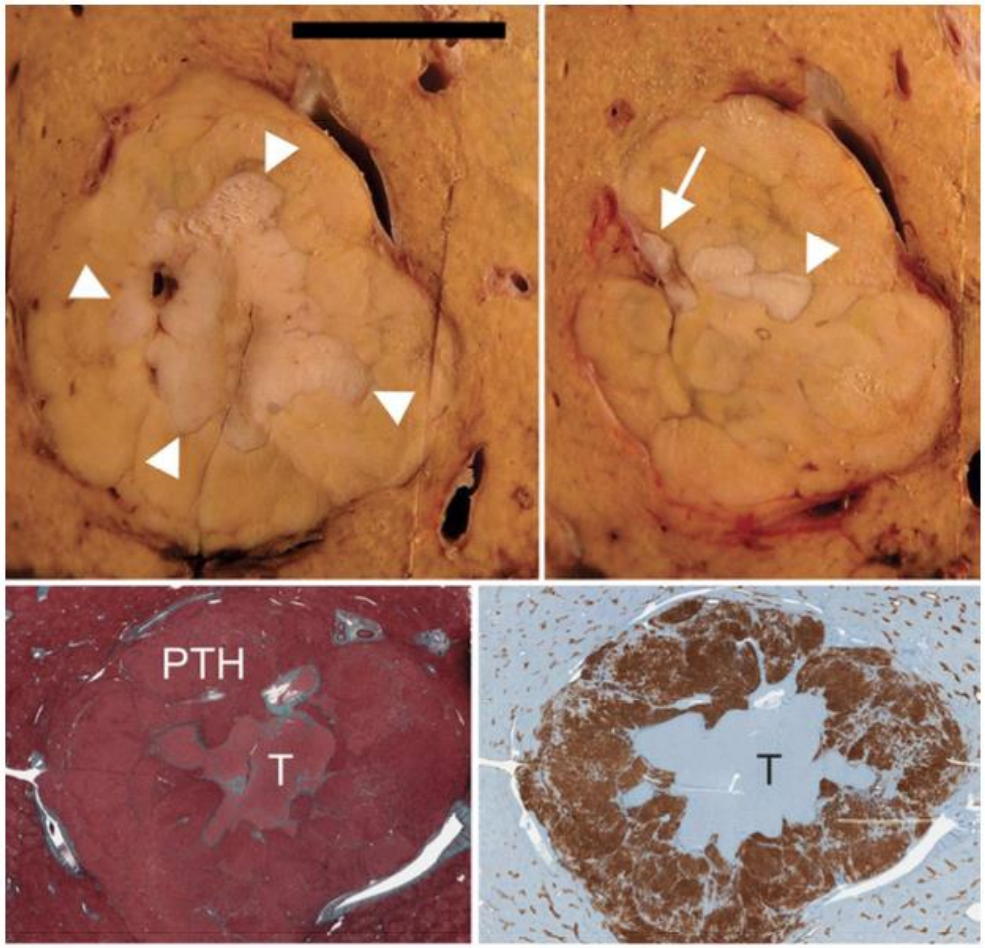


cholecystic v; parabiliary v;
aberrant v; epigastric-paraumbilical

YoshimitsuK2001

Metastases

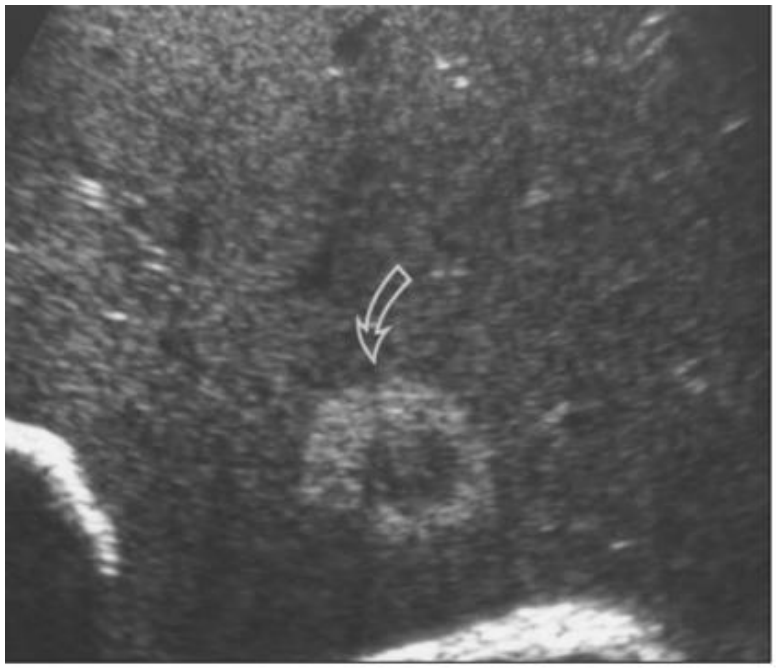
- peri-tumoural hyperplasia
  - capillarised GS+ hyperplastic plates



ArnasonT2012

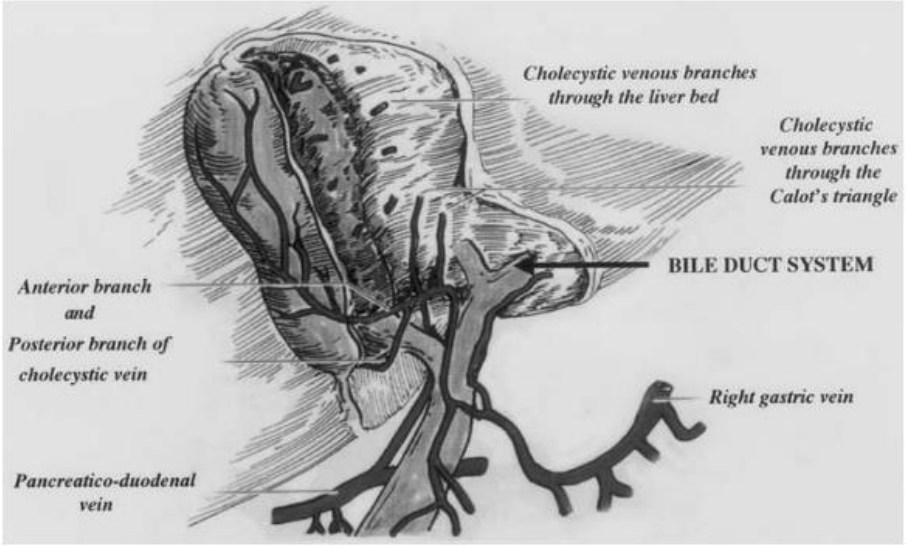
Metastases

- peri-tumoural steatosis
  - insulinoma SohnJ2001

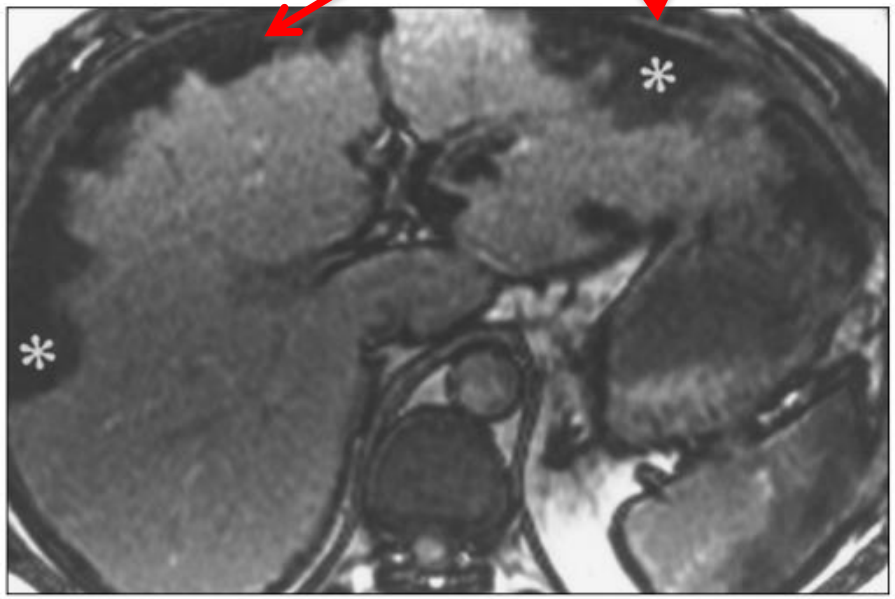


Differential diagnosis

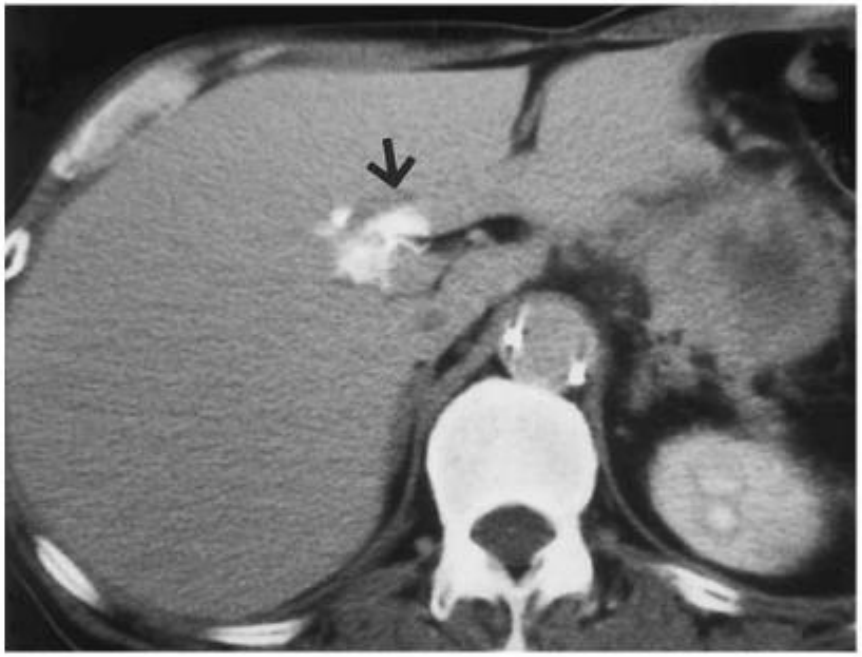
- focal fatty change BattagliaDM1995
- focal fatty sparing YoshimitsuK2001



- sub-capsular steatosis WanlessIR1989, BurrowsCJ1994
- adrenal rest



SohnJ2001

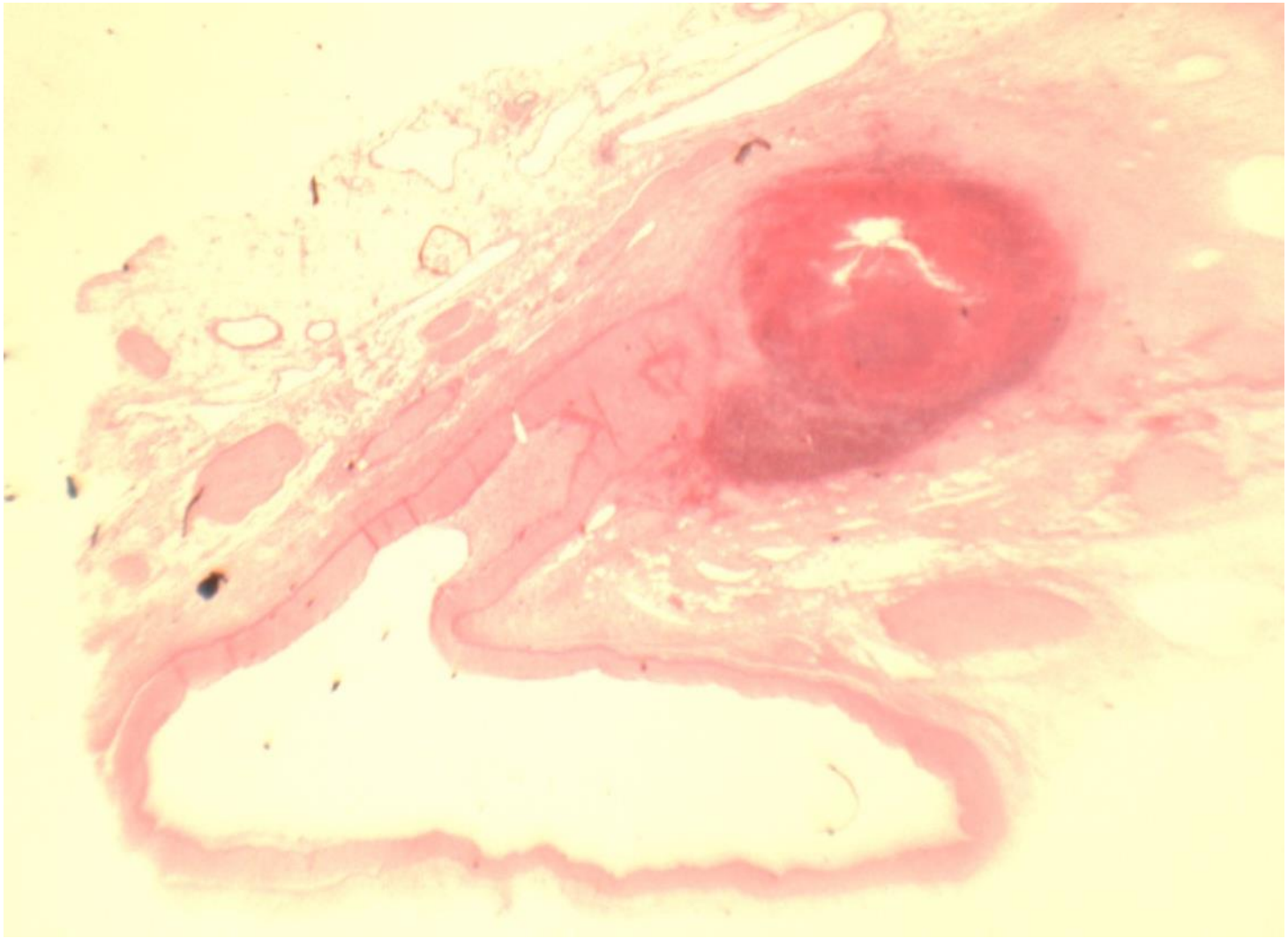


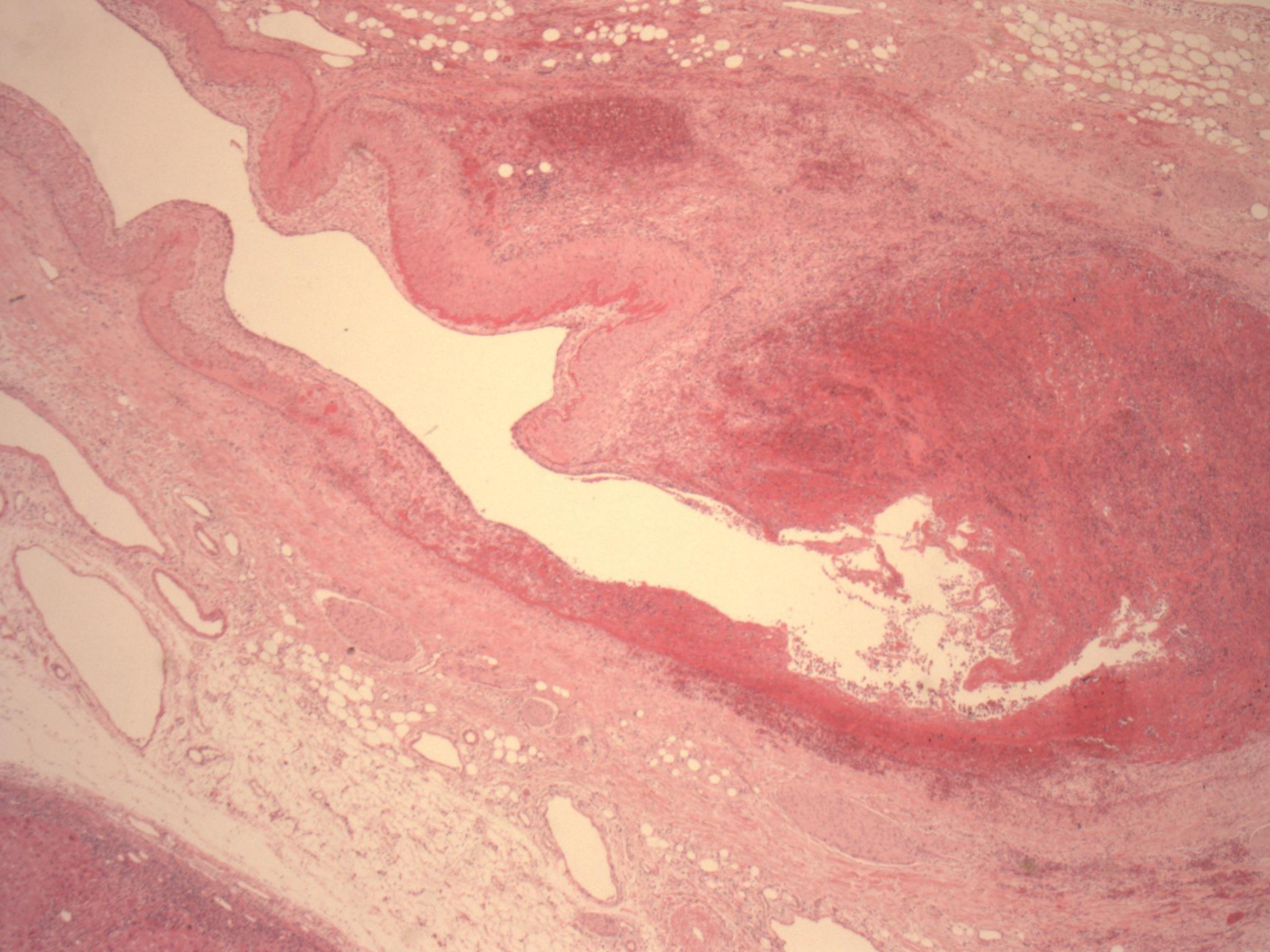
YoshimitsuK2001

Malignancy-related

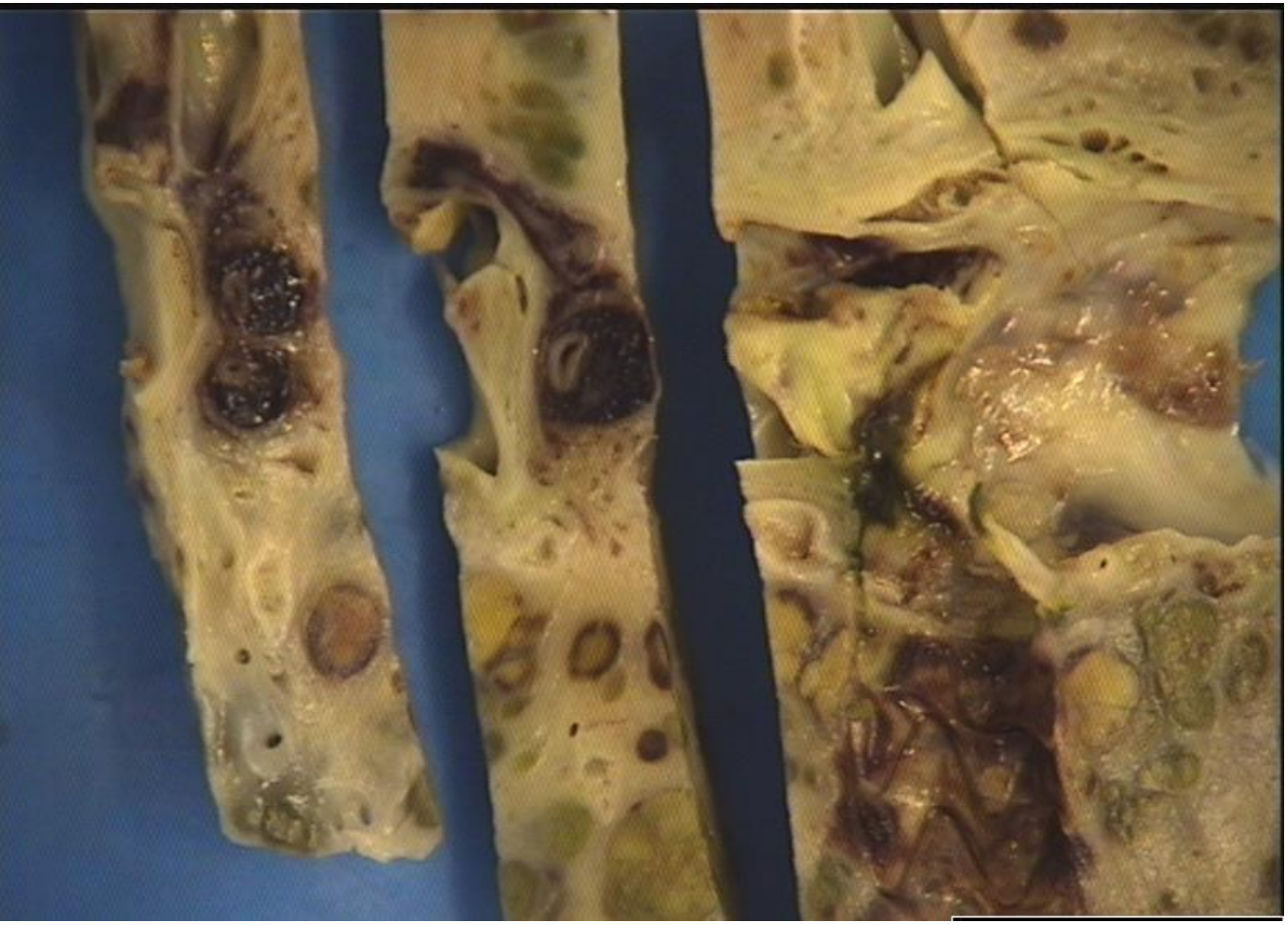
- paraneoplastic
  - ductopenia
- therapy-related
  - steatohepatitis
  - sinusoidal obstruction syndrome
  - FNH-like nodules
  - TACE
    - hepatic artery occlusion/rupture: ischaemic, abscess
    - portal vein branch thrombosis
  - Portal vein branch embolisation

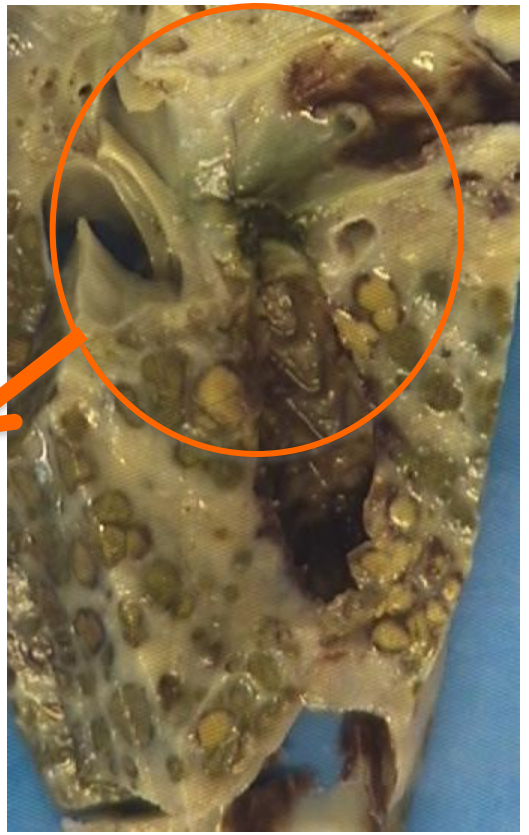
TACE trauma

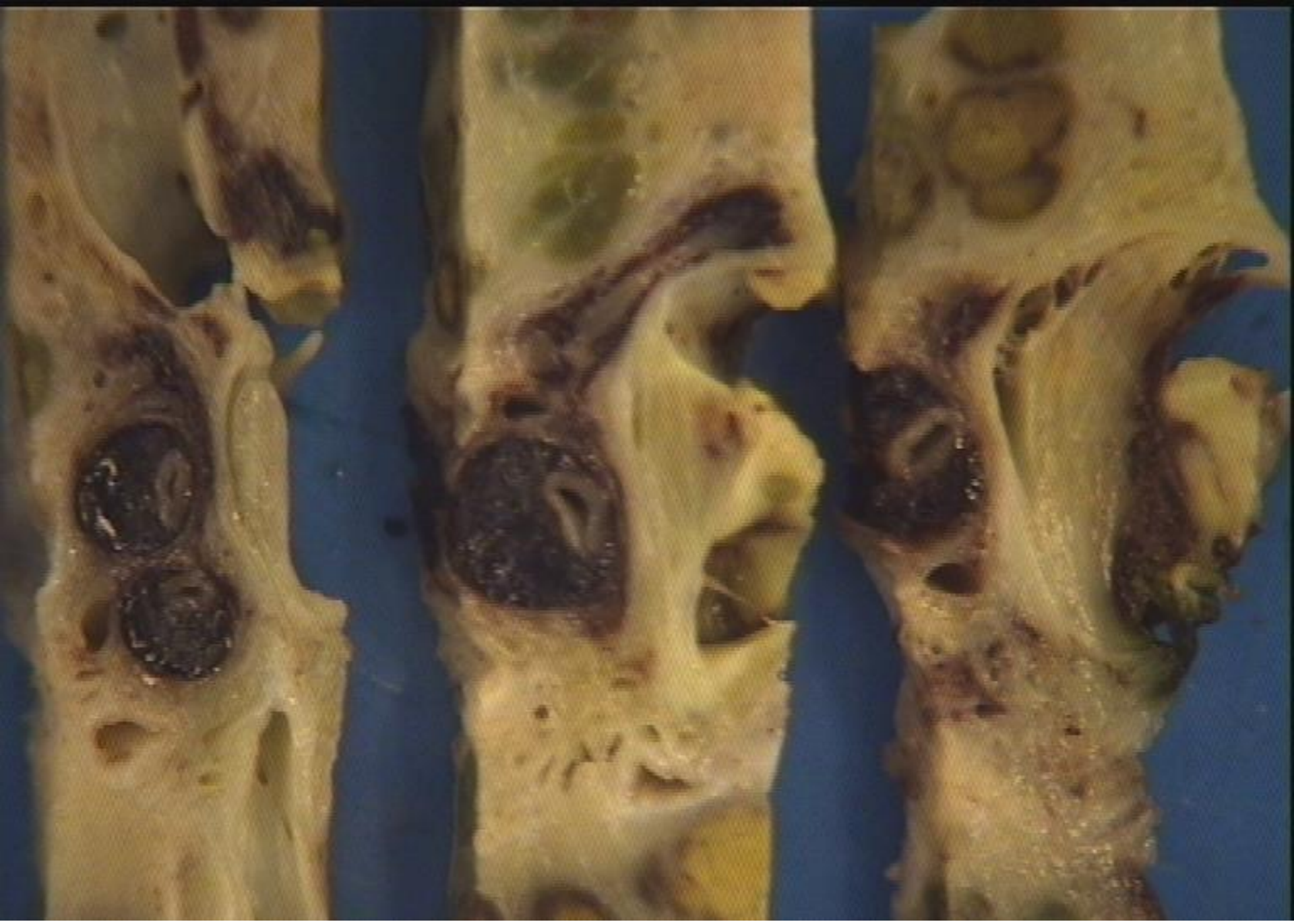


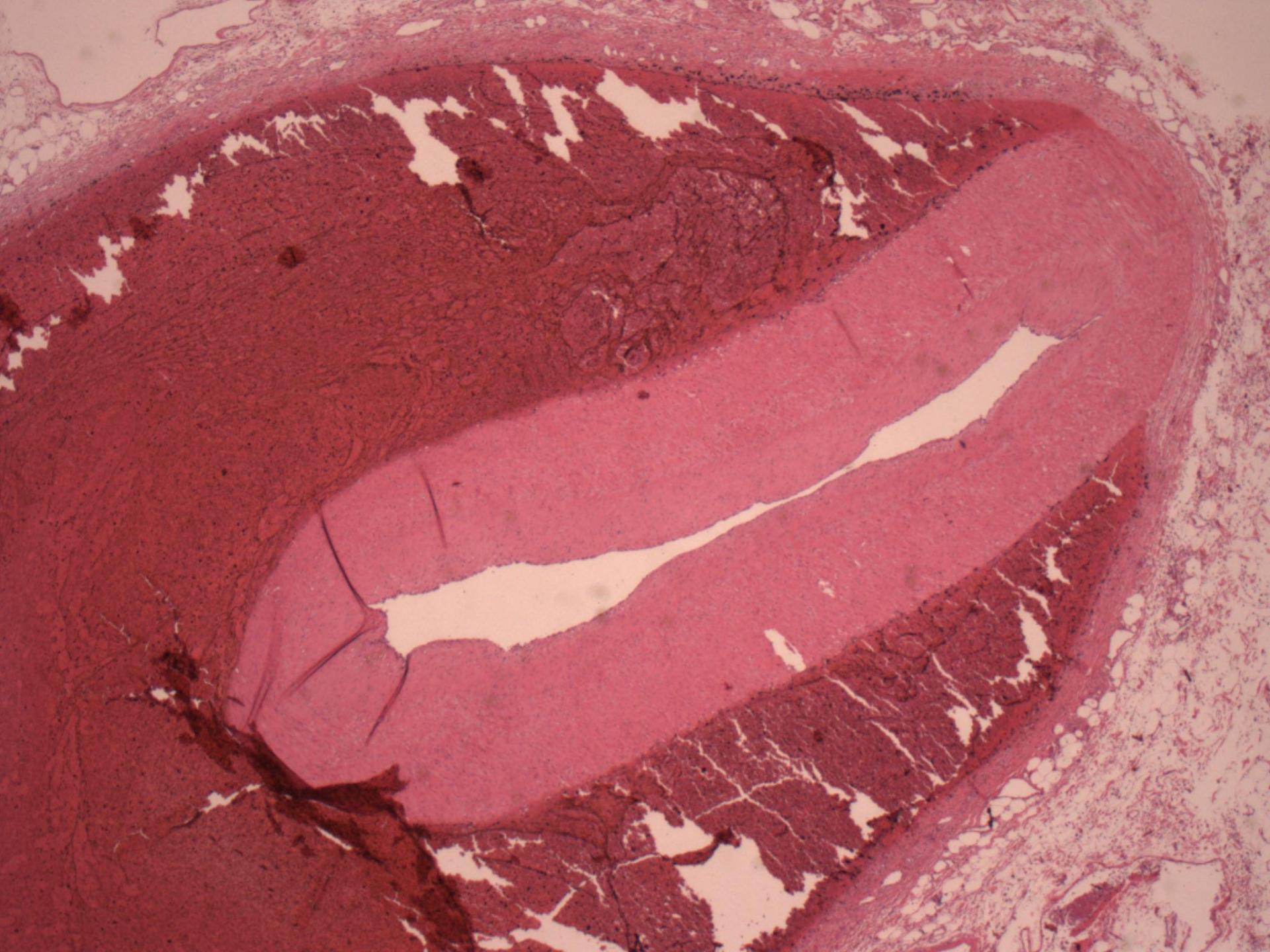


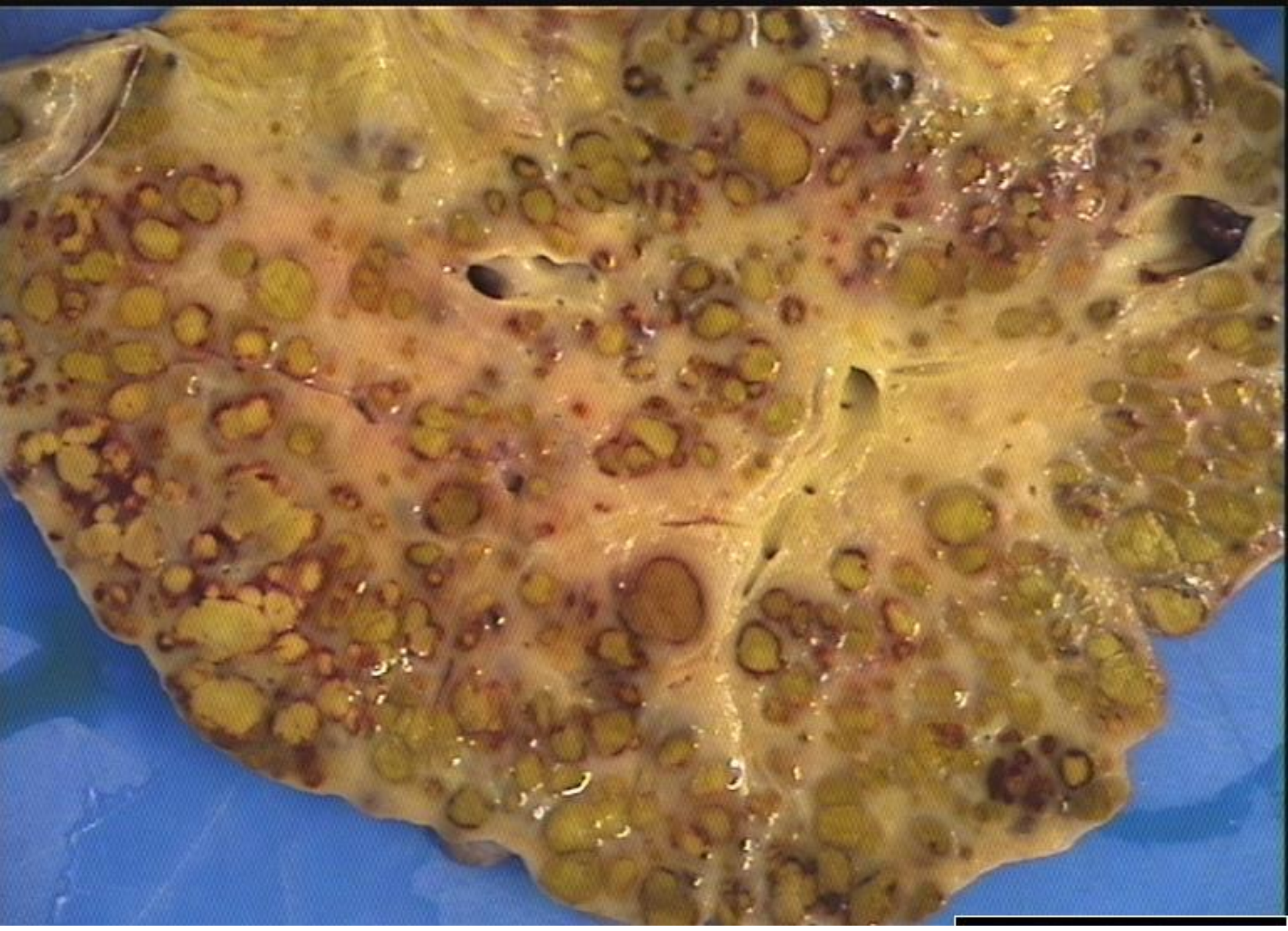
TIPSS trauma







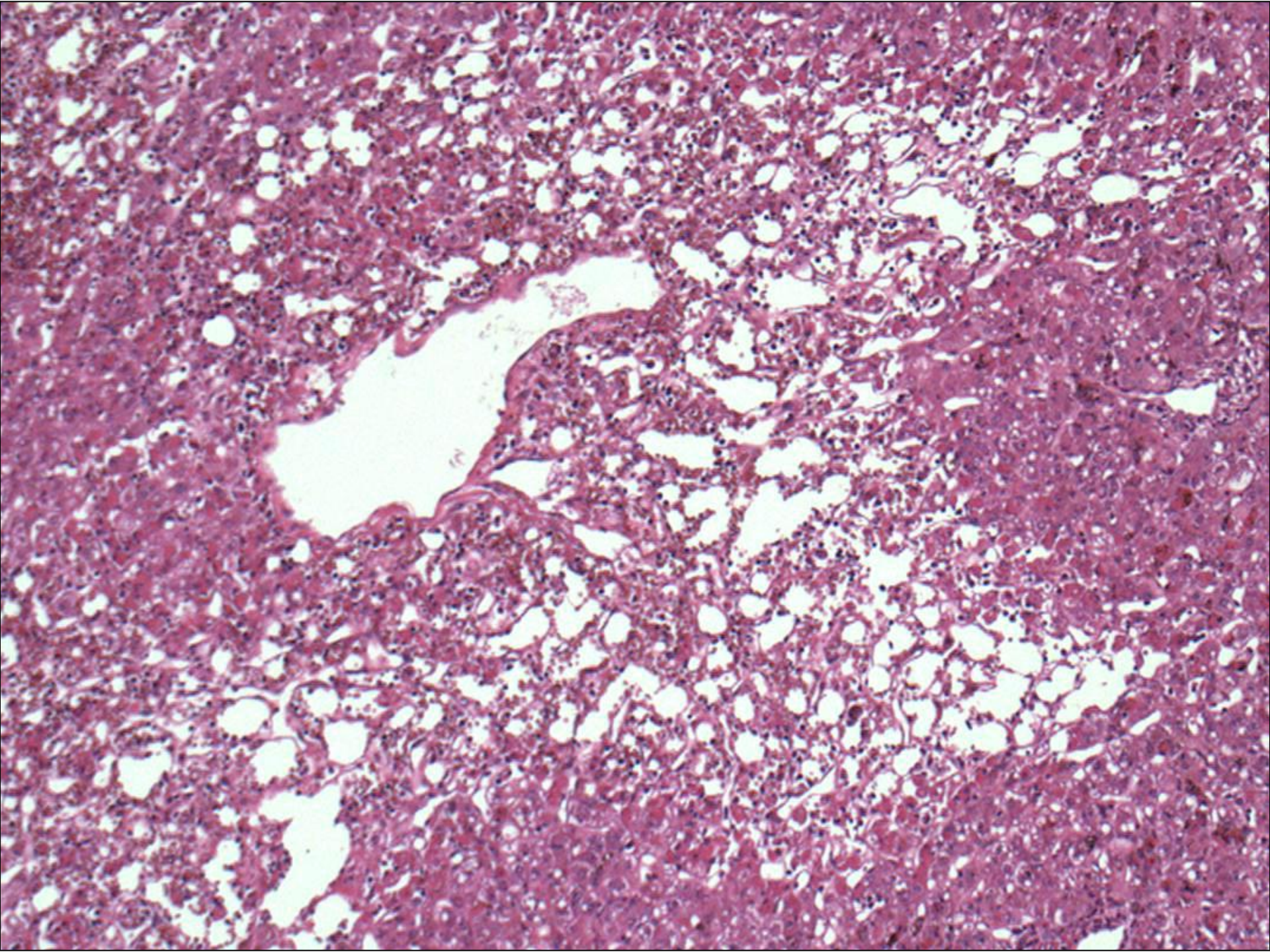


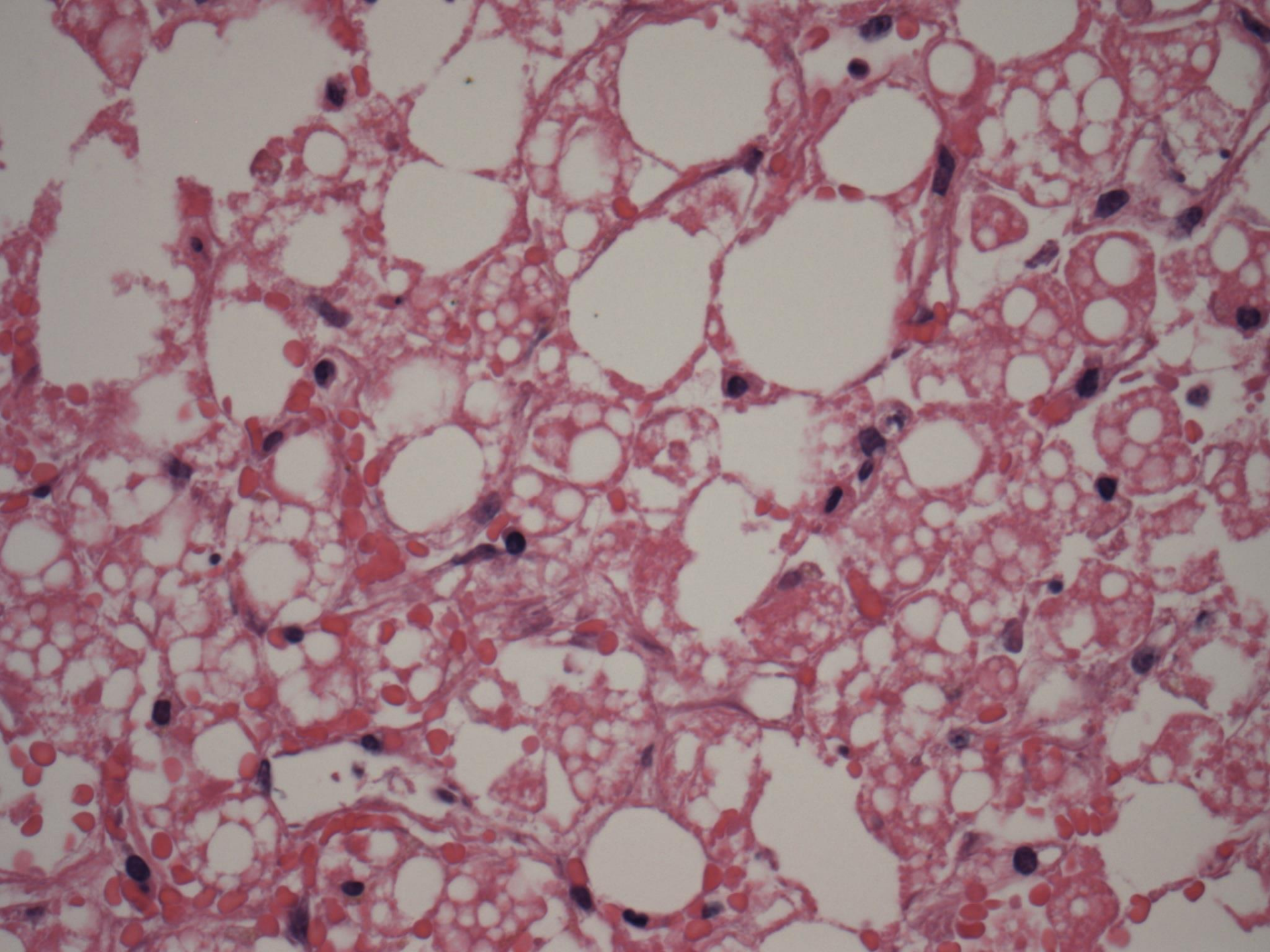


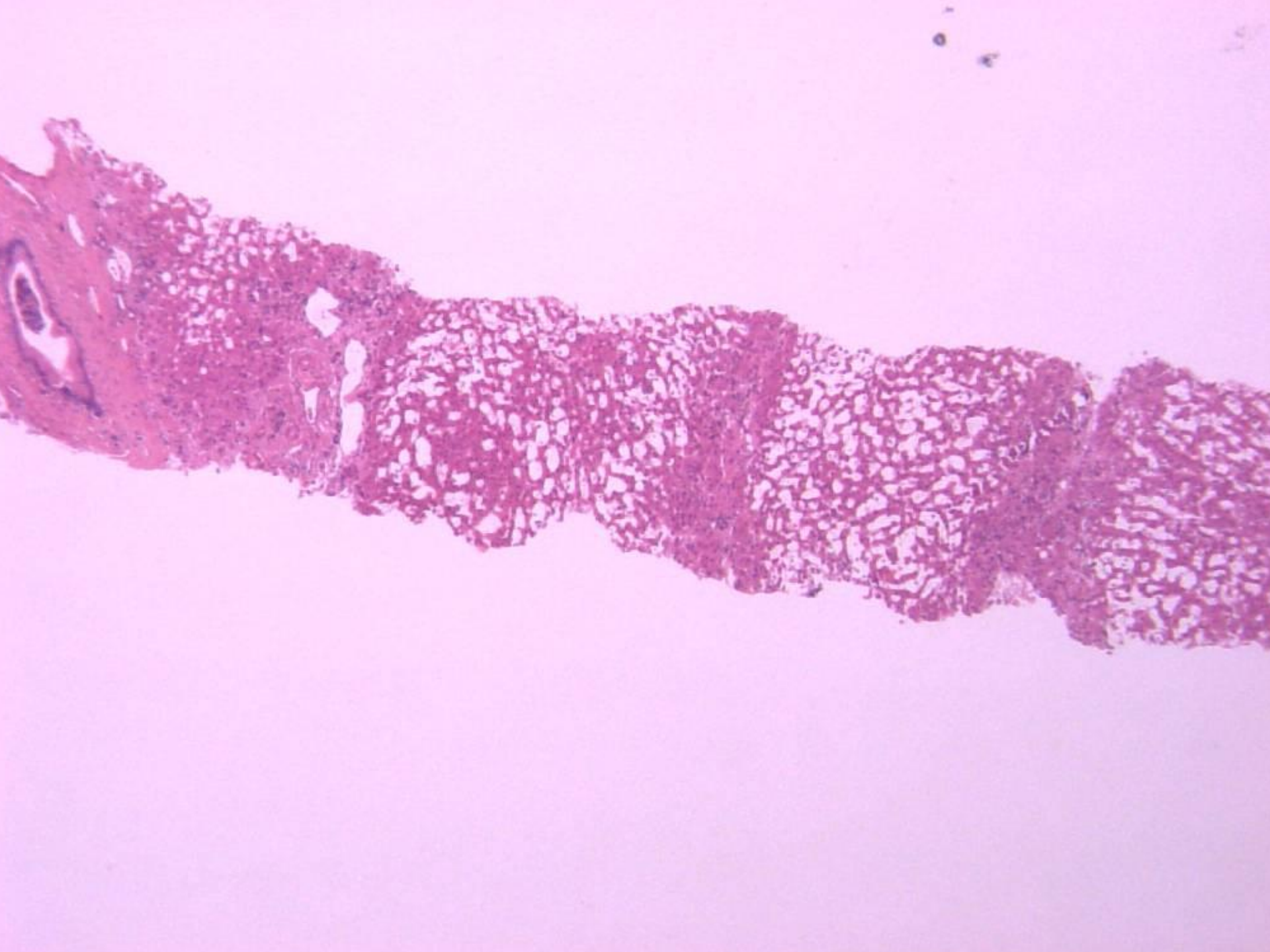
- Hypotension (surgery, shock)
- Necroinflammation (fulminant hepatitis)
- Toxic necrosis

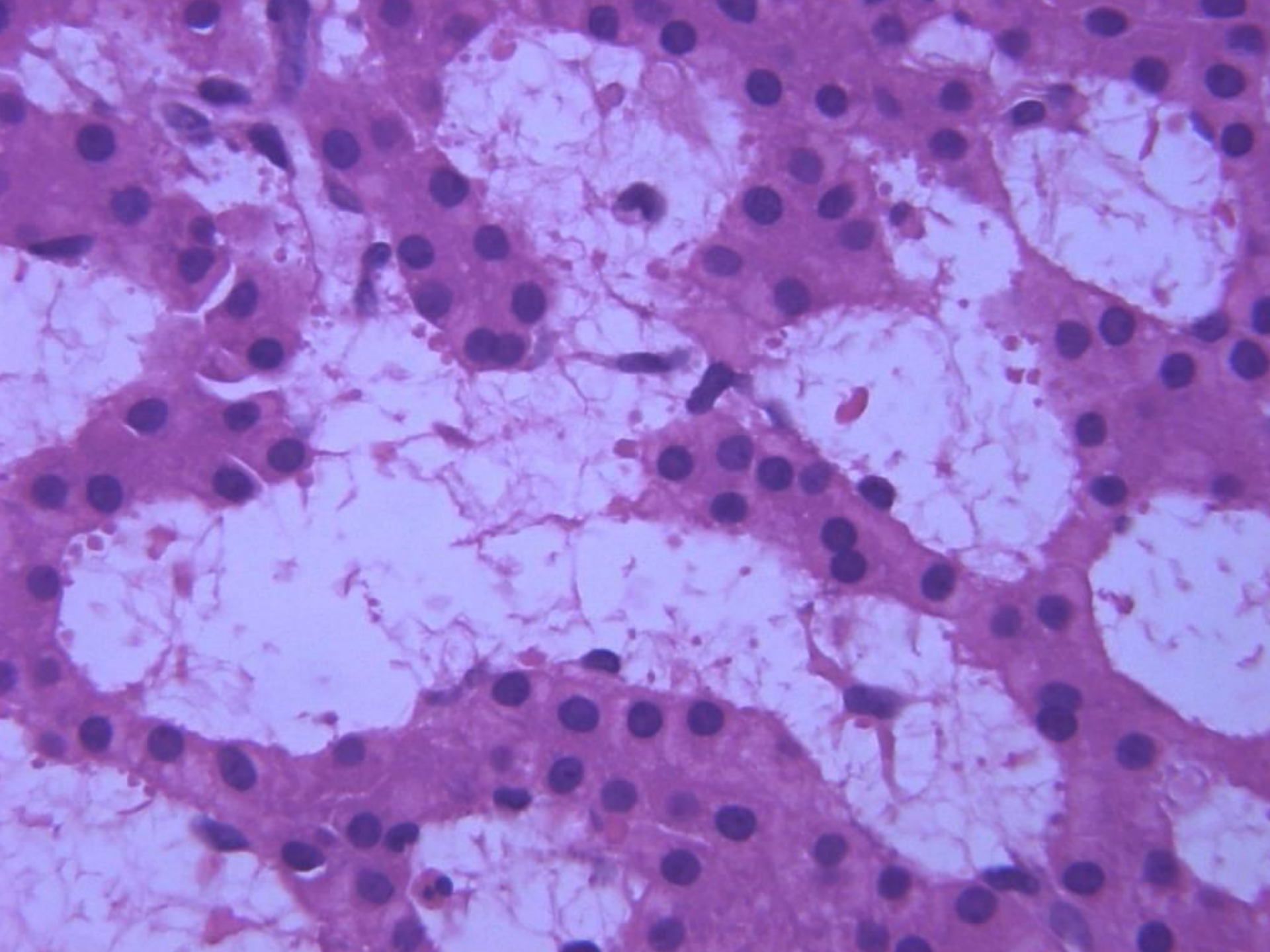
  +
- Severely fatty liver (incl. fatty liver of pregnancy)

  =
- fat embolism (hepatogenic)









Haemophagocytic syndrome

- Impaired NK & Tc function
  - Genetic predisposition in some: perforin 40%
- proinflammatory cytokine storm
  - Intravascular λc, mφ activation (via TLR)

- Any age
- Triggers
  - infection, malignancy, autoimmune (MAS)
- Fatal untreated
  - Good response to specific Rx

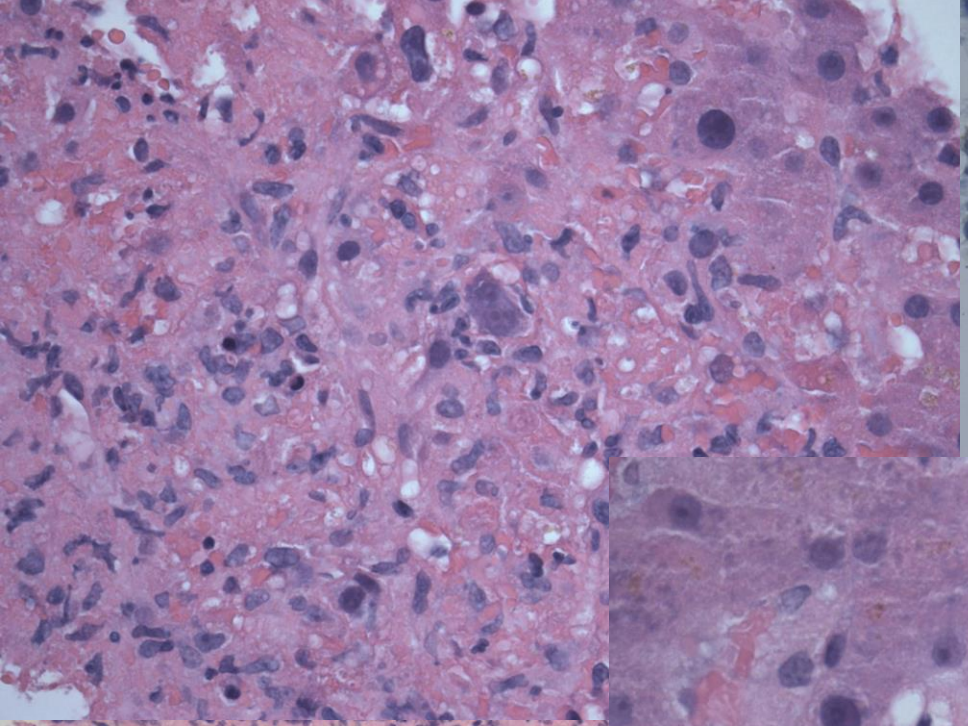
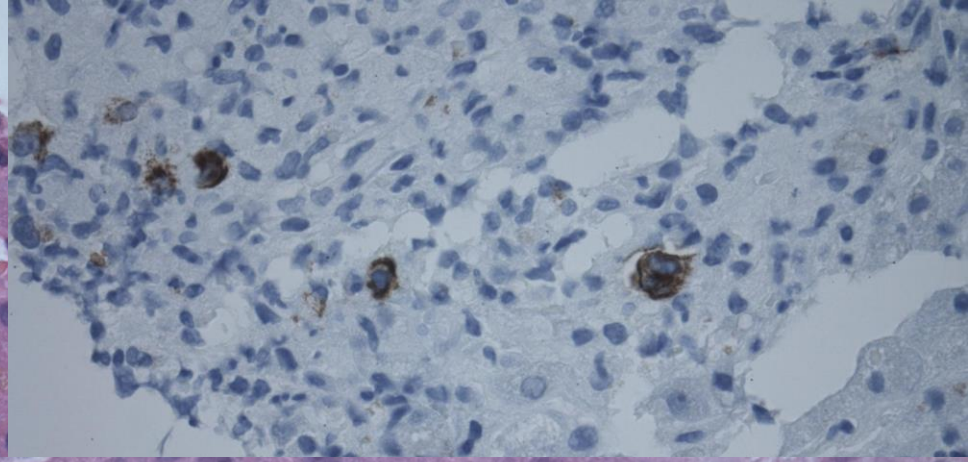
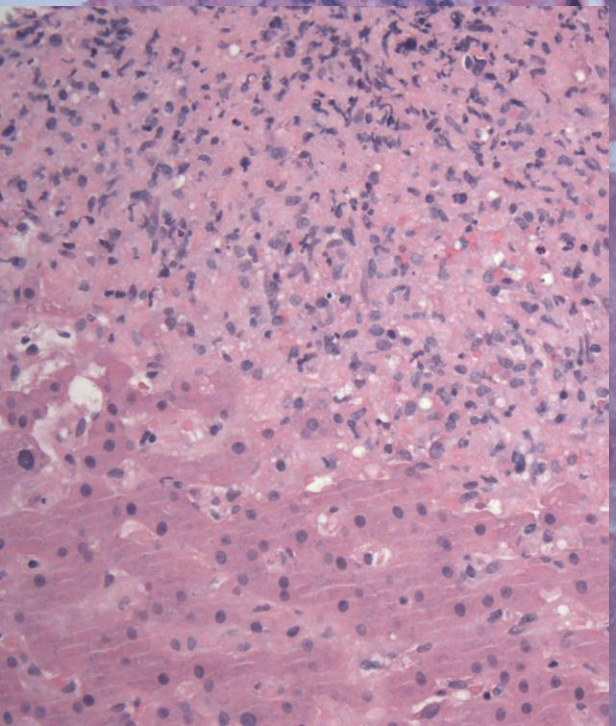
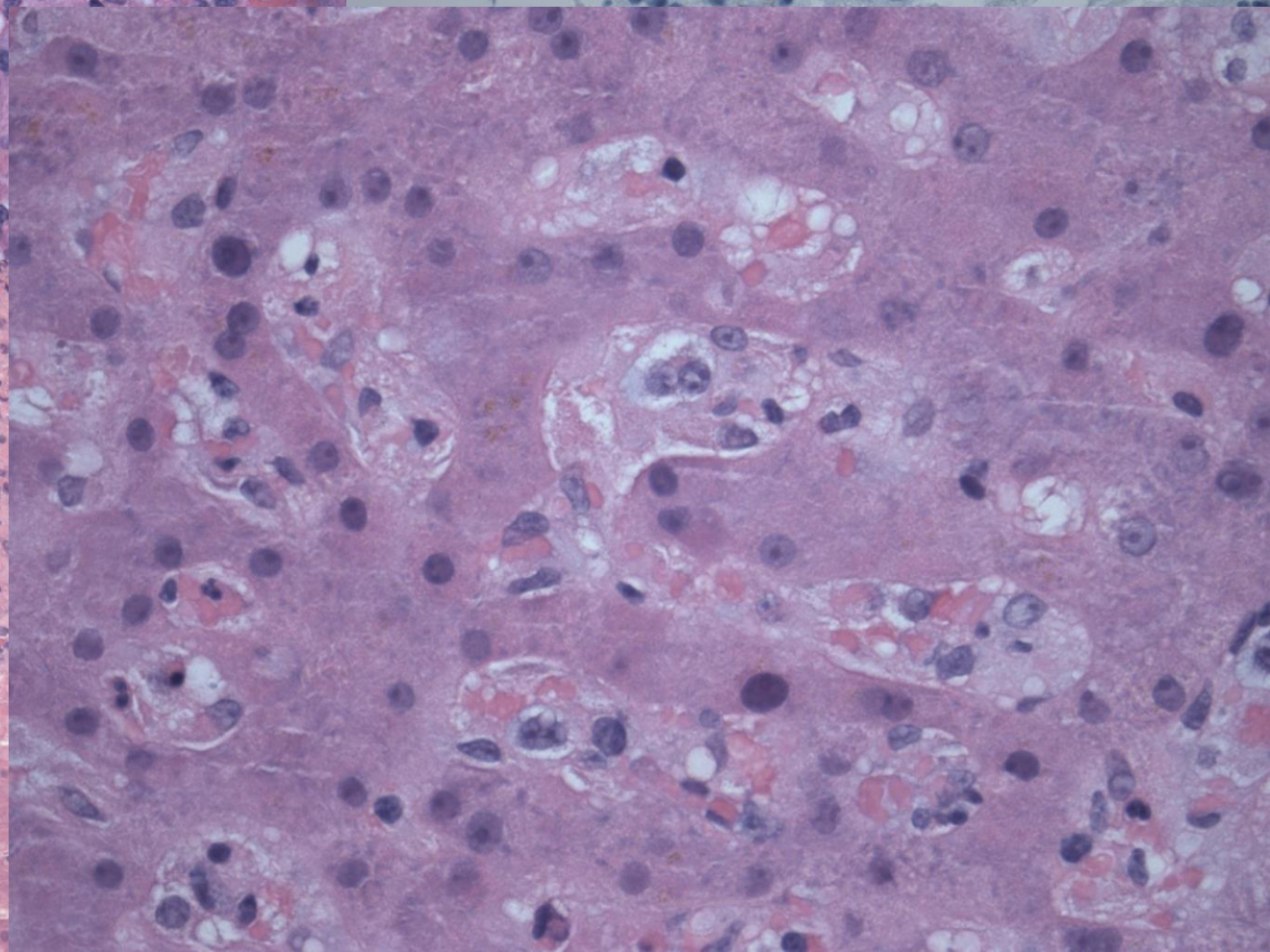
Rouphael NG, 2007
Janka GE, 2007

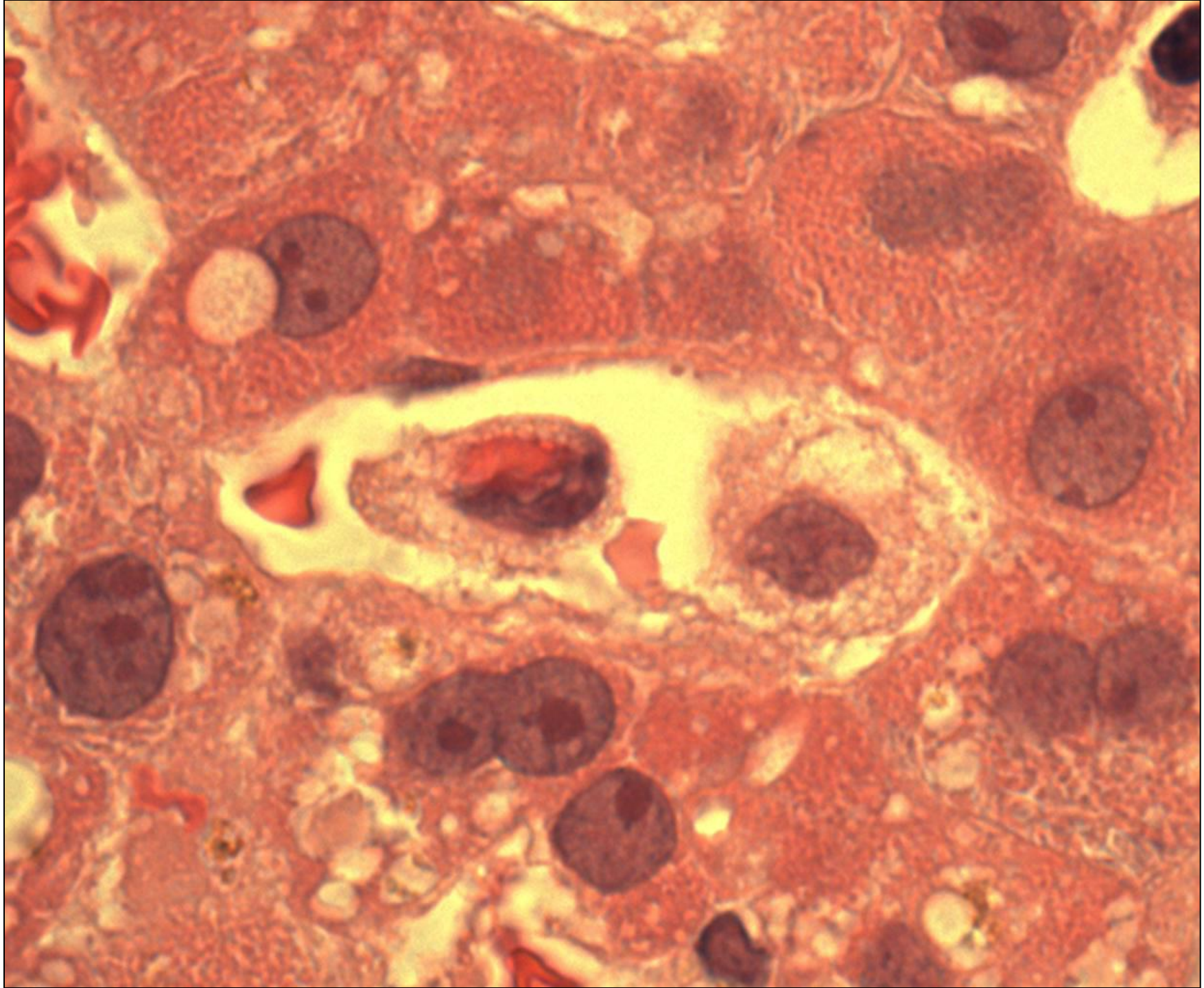
Viral triggered haemophagocytic syndrome

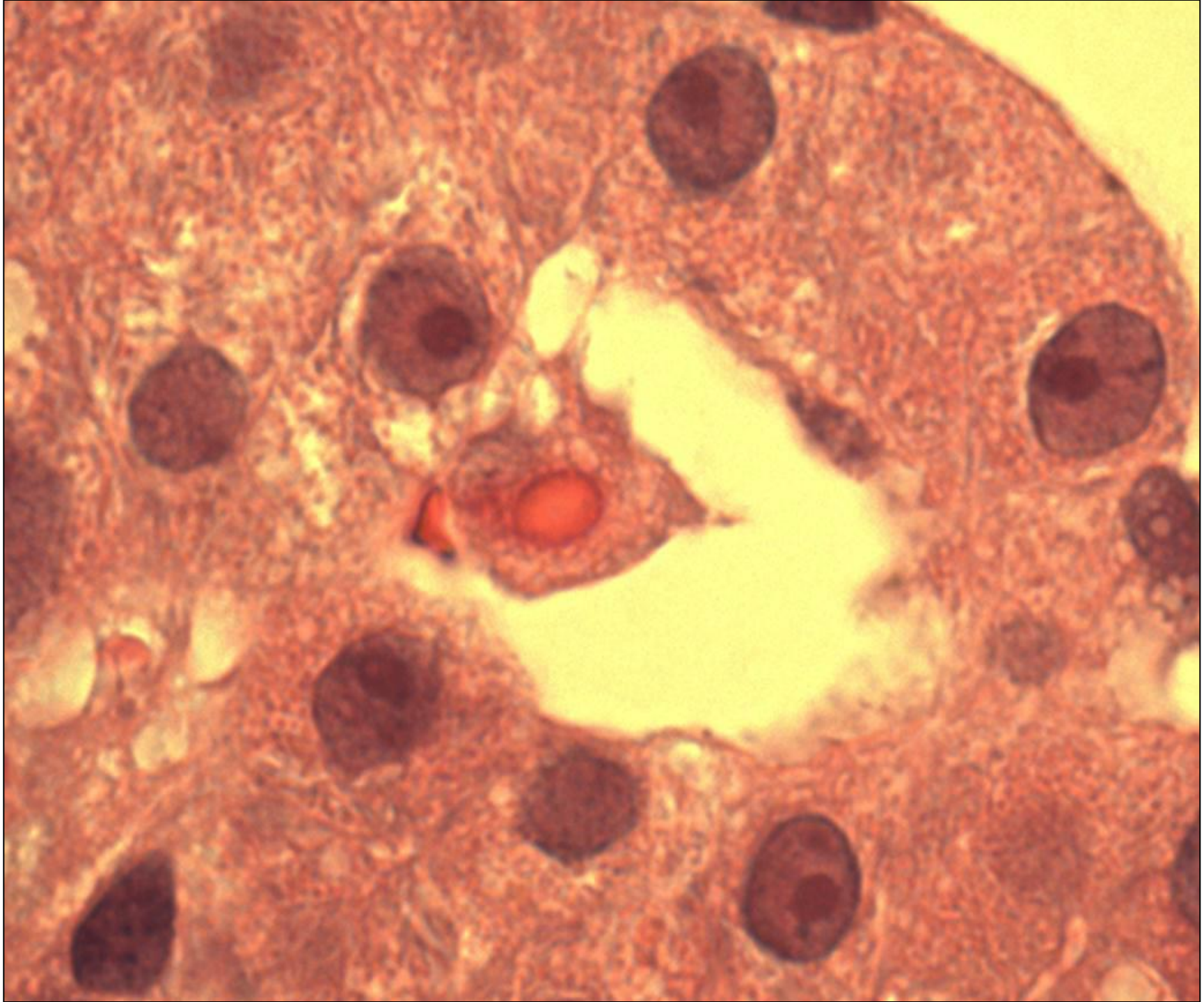
- Herpes viruses
  - EBV
    - Poorest prognosis: severer
    - Reactivation typical setting
  - CMV
    - Healthy, IBD, transplant…
  - HHV6, HHV8
- HIV
- Hepatitis A
- Parvovirus
- Influenza A
  - H1N1 swine, H5N1 avian
- Adenovirus, measles, SARS, dengue…

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]

Portal venopathy/NRH

- Low observer agreement for diagnosing “NRH”

  JharapB2015

- Obliterative portal venopathy

  GuidoM2015

  –common cause of cryptogenic liver disease *without* clinical portal hypertension (20% of 482 biopsies)

  - not histologically separable from NCPHT, but
  - NRH (10% vs 40%) & incomplete septa (6% vs 30%) less common