
OUT OF AFRICA
THE GNOMES GO ON SAFARI
Alastair Burt

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous

- Atypical mycobacteria
- Malaria (pigment)
- Schistosomiasis (pigment)
- Leishmaniasis
- Others

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous
- Amyloid
- Light chain disease
- Diffuse sinusoidal fibrosis

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous

- CESD
- Cystinosis
- GM1 gangliosidosis type III
- Fabry disease
- Metachromatic leukodystrophy
- Niemann-Pick disease
- Hypervitaminosis A

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous

- Sinusoidal obstruction syndrome and NRH
- Peliosis hepatis
- Microvascular flow abnormalities: sickle cell anaemia etc

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous

- Angiosarcoma
- Epithelioid haemangioendothelioma
- ? Angiomyolipoma
- Sarcomas
- Non-Langerhans histiocytosis
- Lymphoproliferative disease: Tγδ lymphoma; EBV driven

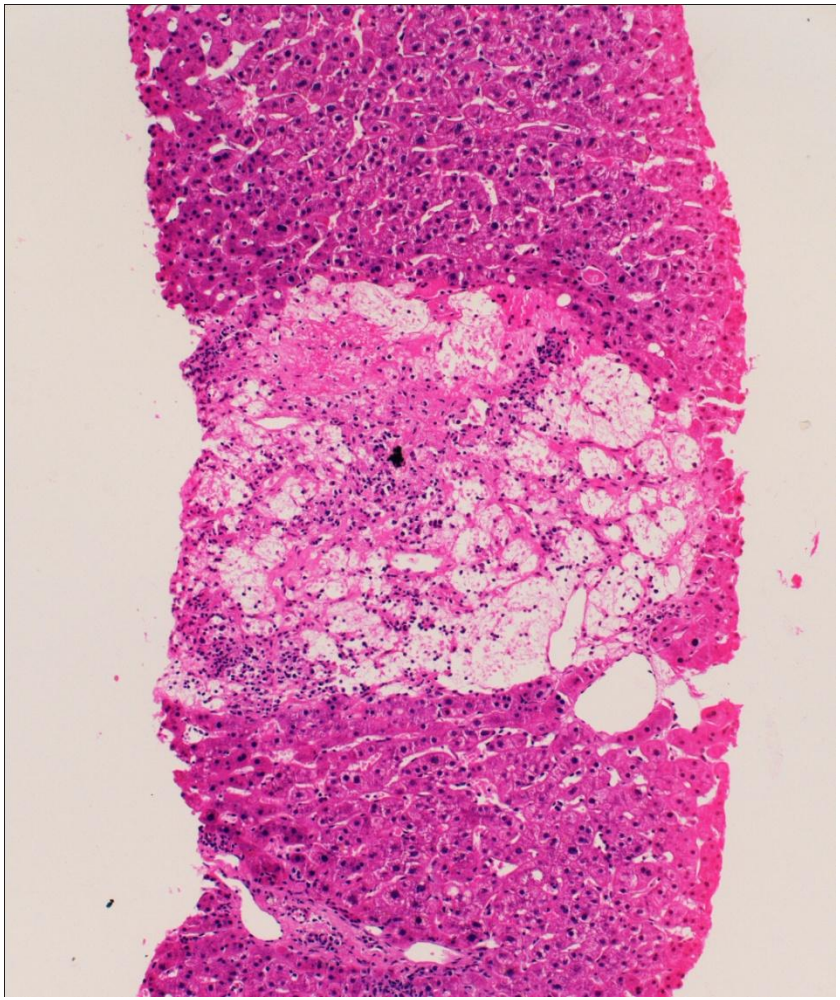
Table 1. Benign sinusoidal luminal accumulations

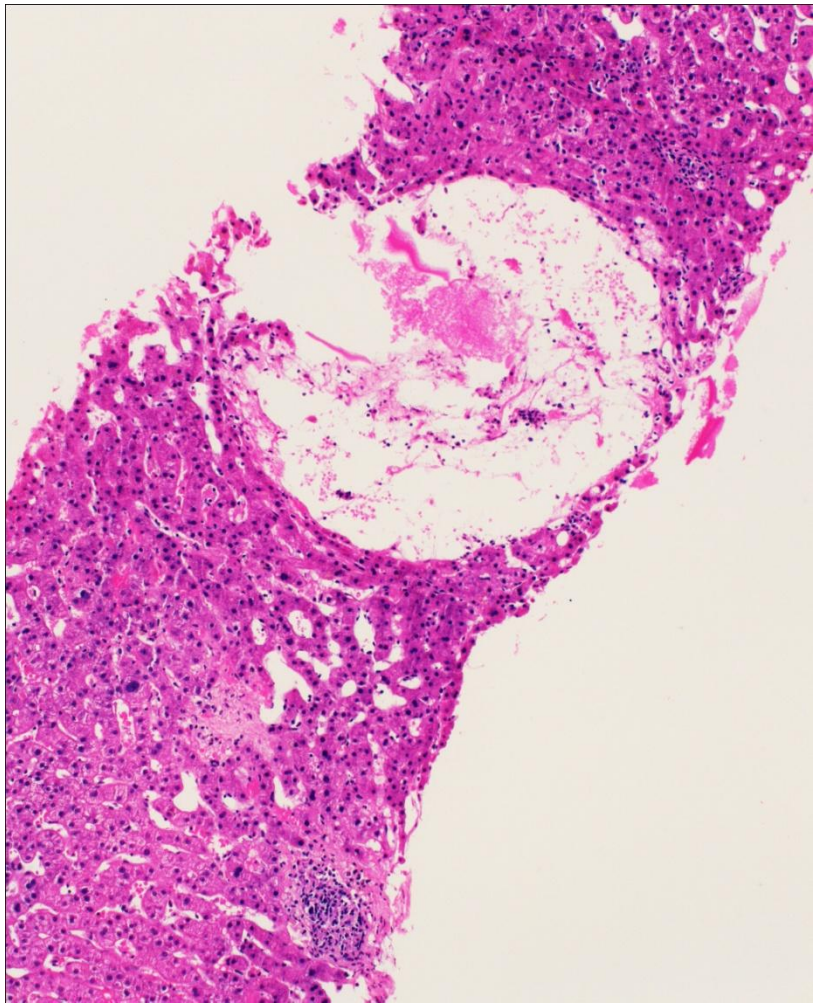
Erythrocytic	Lymphocytic	Histiocytic	Hemopoietic
Normal erythrocytes **Congestive heart failure** **Hepatic vein thrombosis** **Veno-occlusive disease** ***Abnormal erythrocytes*** **Sickled erythrocytes** - sickle cell disease **Spherocytes** - congenital spherocytosis - autoimmune hemolytic anemia **Acanthocytes** - abetalipoproteinemia - severe malnutrition	***Infectious diseases*** **EBV hepatitis** **Malaria** **HCV infection** ***Autoimmune hepatitis*** ***Phenytoin toxicity*** ***Allograft rejection*** ***Felty syndrome*** ***DRESS syndrome***	***Ceroid-laden histiocytes*** **Resolving hepatitis** **Drug-induced liver injury** ***Pigmented histiocytes*** **malaria** **visceral leishmaniasis** **schistosomiasis** **disorders of iron metabolism** **gold, titanium** **thorotrast** ***Hemophagocytic histiocytes*** **Macrophage activation syndrome/ secondary hemophagocytosis** **Familial haemophagocytic lymphohistiocytosis** ***Foamy histiocytes*** (see Table 2) ***Non foamy histiocytes*** **Infectious diseases** Disseminated histoplasmosis Disseminated cryptococcosis Penicilliosis **Disorders of lipoprotein & lipid metabolism** - Gaucher disease - Fabry disease - Sulfatide lipidosis (metachromatic leucodystrophy) **Disorders of aminoacid metabolism** - Cystinosis **Primary lymphohistiocytic disorders** - Langerhans cell histiocytosis* - Rosai-Dorfman disease	***Extramedullary haemopoiesis*** **Chronic myeloproliferative disorders** - myelofibrosis - primary polycythemia - essential thrombocythemia **Aplastic anaemia** **Marrow replacement syndromes** - tumor metastasis - myelomatosis - osteopetrosis ***Congenital erythropoietic porphyria***

Clinical history

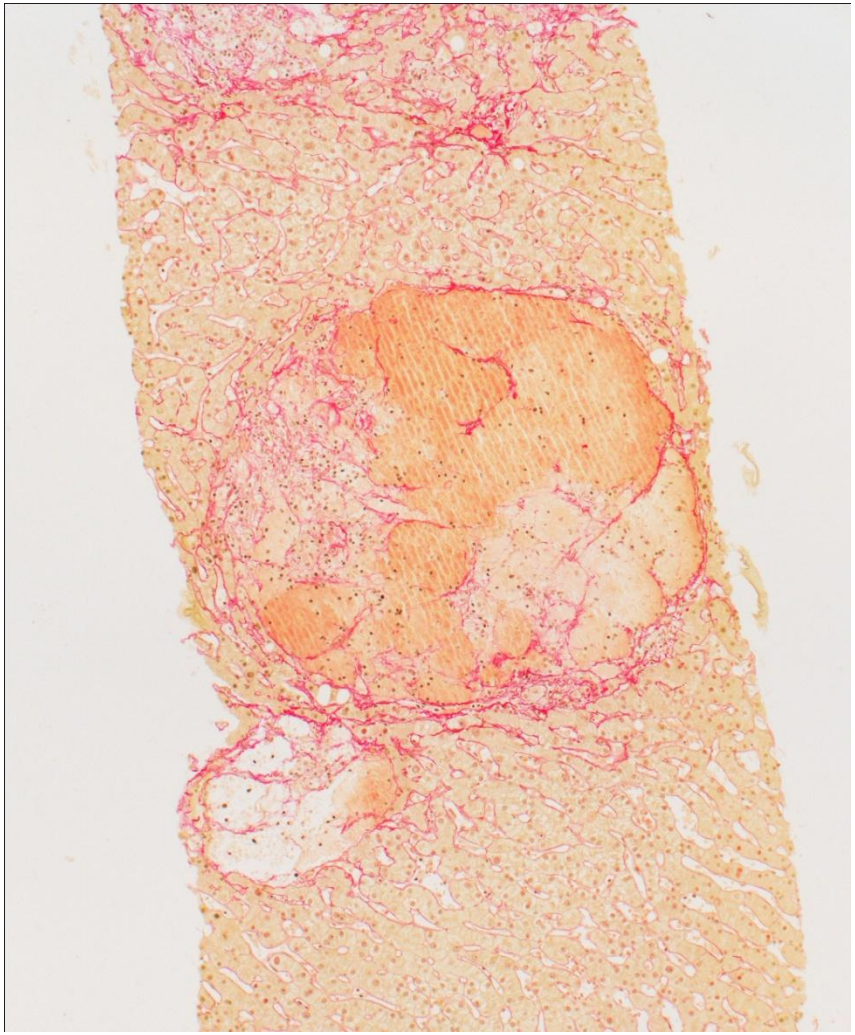
- 69-year-old caucasian female
- Renal transplantation in 1984 because of infectious (pyemic nephritis) and drug induced (Saridon) interstitial nephritis.
- Treatment with Imurek, CyA, steroids and statins.
- AST 43 U/l, ALT 60 U/l, GGT 767 U/l, ALP 692 U/l.
- Work up for causes of chronic liver disease was negative (i.e. HBV, HCV, hemochromatosis, autoantibodies).

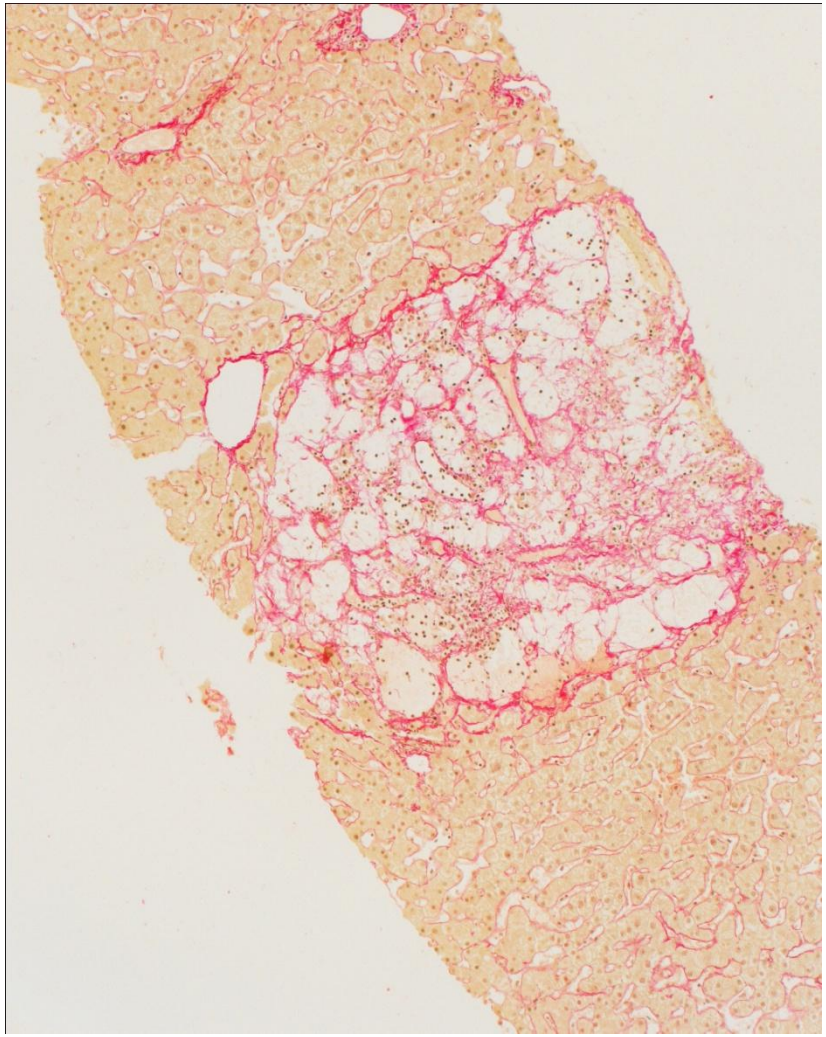
BASEL-A, 2012





BASEL-A, 2012





BASEL-A, 2012

Peliosis hepatis

Blood filled cysts present scattered within the parenchyma often communicating with the adjacent sinusoids. These cysts ranging in size from 1 mm to 2 cm in diameter.

The term arises from the greek *pelios*, i.e. discoloured by extravasated blood, livid, and the Latinized genitive case (hepatis) of the greek *hepar*.

Basel A

- Incomplete endothelial lining
- No zonality
- Fibrin and early collagen deposition
- Angioproliferative lesions associated with Bartonella henslae in AIDS
- Most asymptomatic but may rupture

Basel A

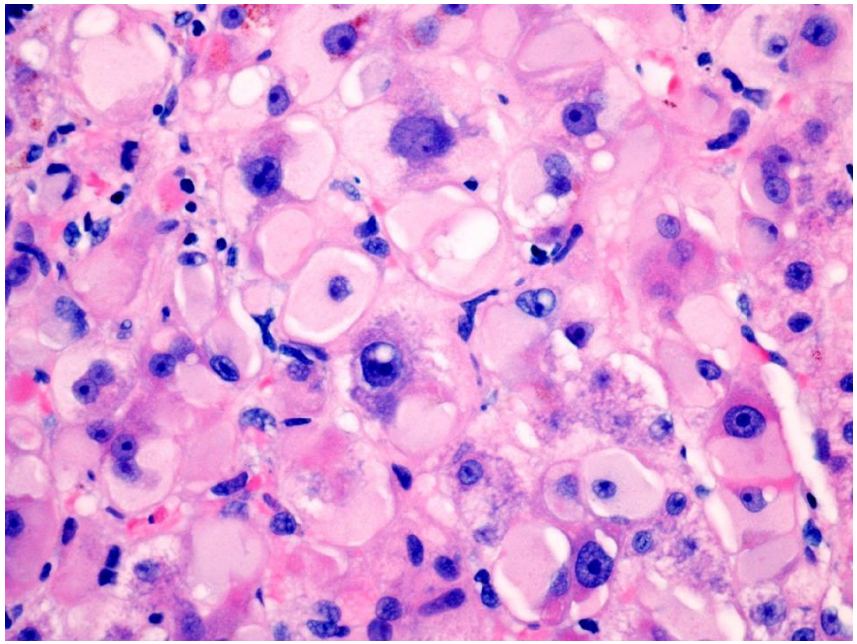
- Drugs
  - Steroids
  - AZA
  - Tamoxifen
- Renal transplantation
- TB
- Thorotrast and vinyl chloride
- AIDS

- Pathogenesis
  - Endothelial injury
  - Weakening of retic framework
  - Liver cell injury and ‘SOS’

Washington B 51 M

- Diabetes mellitus x many years
  - Diabetic neuropathy, gastroparesis, chronic renal disease
  - Meds: metoclopramide, pantoprazole, insulin, hydralazine
- Increasing ascites & renal failure x 1 week
- Labs: ALT/AST 50/104, alk phos 311, GGT 744, t. bili 0.6, creatinine 3.7

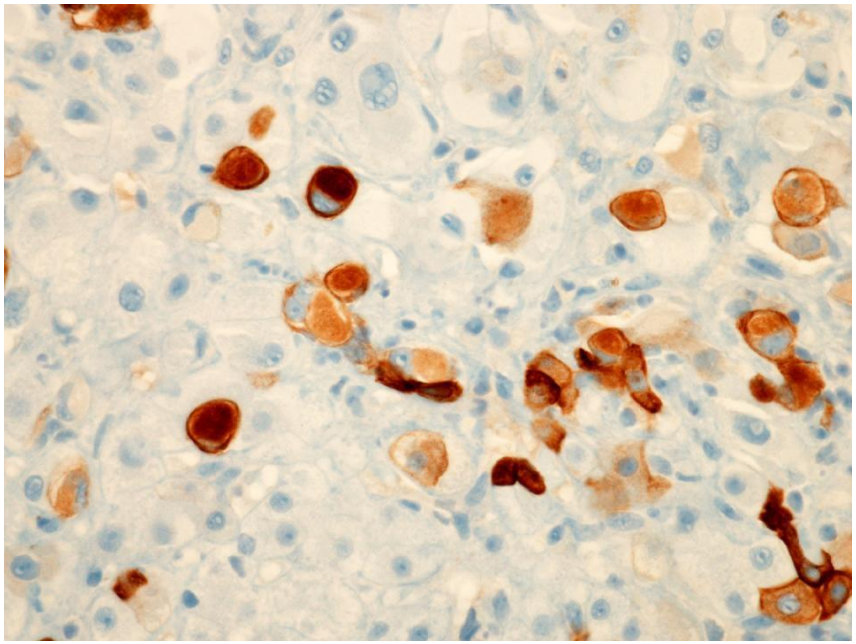
  Negative – anti-HAV, HBsAg, anti-HBC, anti-HCV, ANA, ASmA

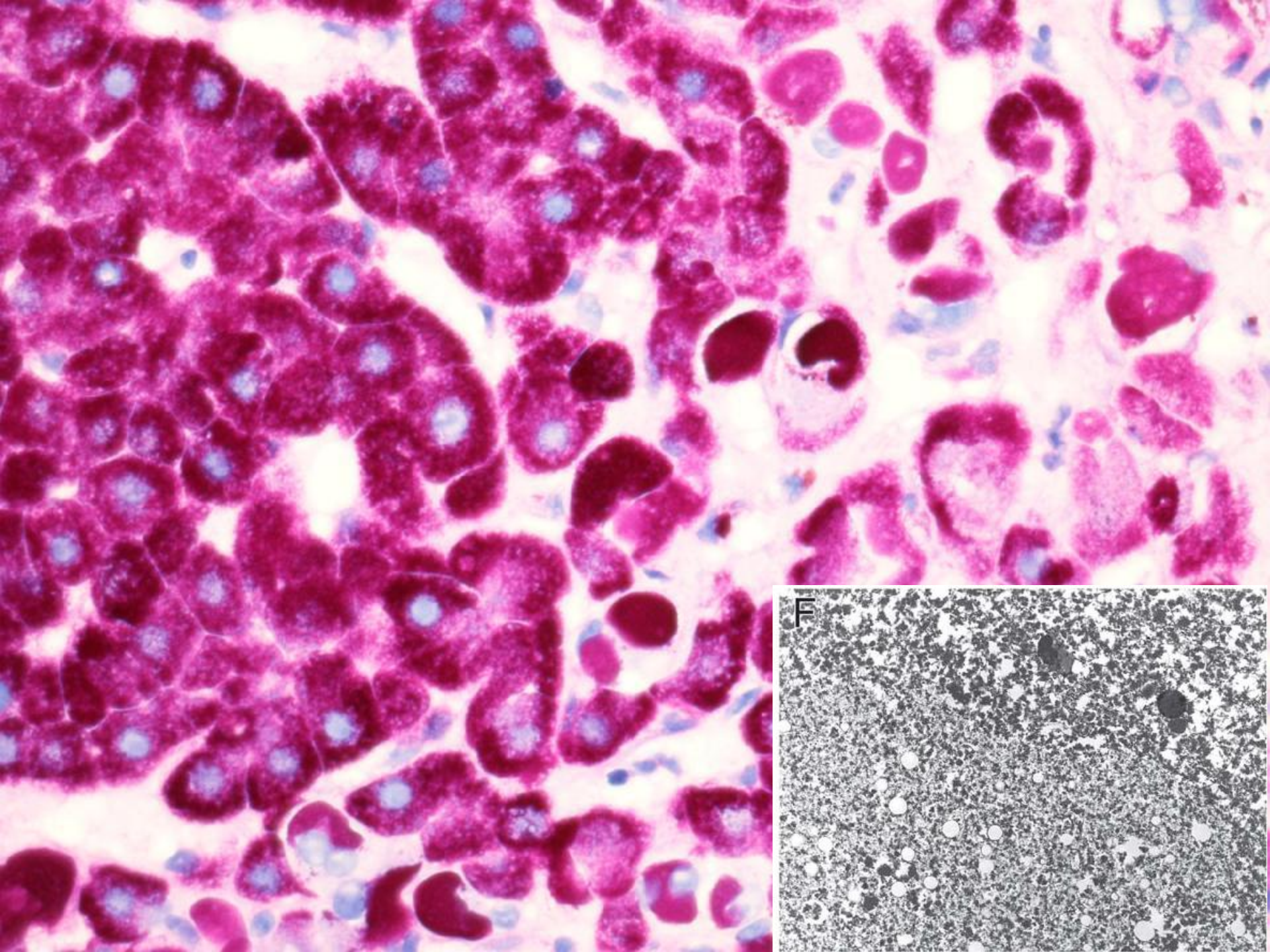


Differential diagnosis?

Ground-Glass & Ground-Glass-like Hepatocytes

- Hepatitis B
- Fibrinogen
- Plasma proteins
- Type IV glycogen storage disease
- LaFora's disease
- Cyanamide
- Glycogen-Polyglucosan




F

Ground-Glass, Polyglucosan-Like Hepatocellular Inclusions: A "New" Diagnostic Entity

JAY H. LEFKOWITCH,* STEVEN J. LOBRITTO,‡ ROBERT S. BROWN, Jr,‡ JEAN C. EMOND,‡ MICHAEL L. SCHILSKY,‡ LORI A. ROSENTHAL,‡ DIANE M. GEORGE,§ and MITCHELL S. CAIRO§

*Department of Pathology, ‡Center for Liver Disease and Transplantation, and §Department of Pediatrics, Columbia University Medical Center, New York, New York

Gastroenterology, Sept 2006

Glycogen Pseudoground Glass Change in Hepatocytes

Joshua Wisell, MD, John Boitnott, MD,* Mark Haas, MD, PhD,* Robert A. Anders, MD, PhD,* John Hart, MD,† Jason T. Lewis, MD,‡ Susan C. Abraham, MD,‡ and Michael Torbenson, MD**

Am J Surg Pathol, Sept 2006

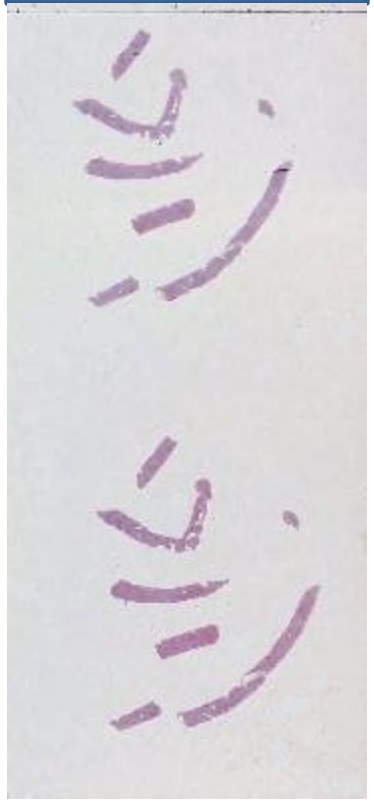
Athens B: Case History

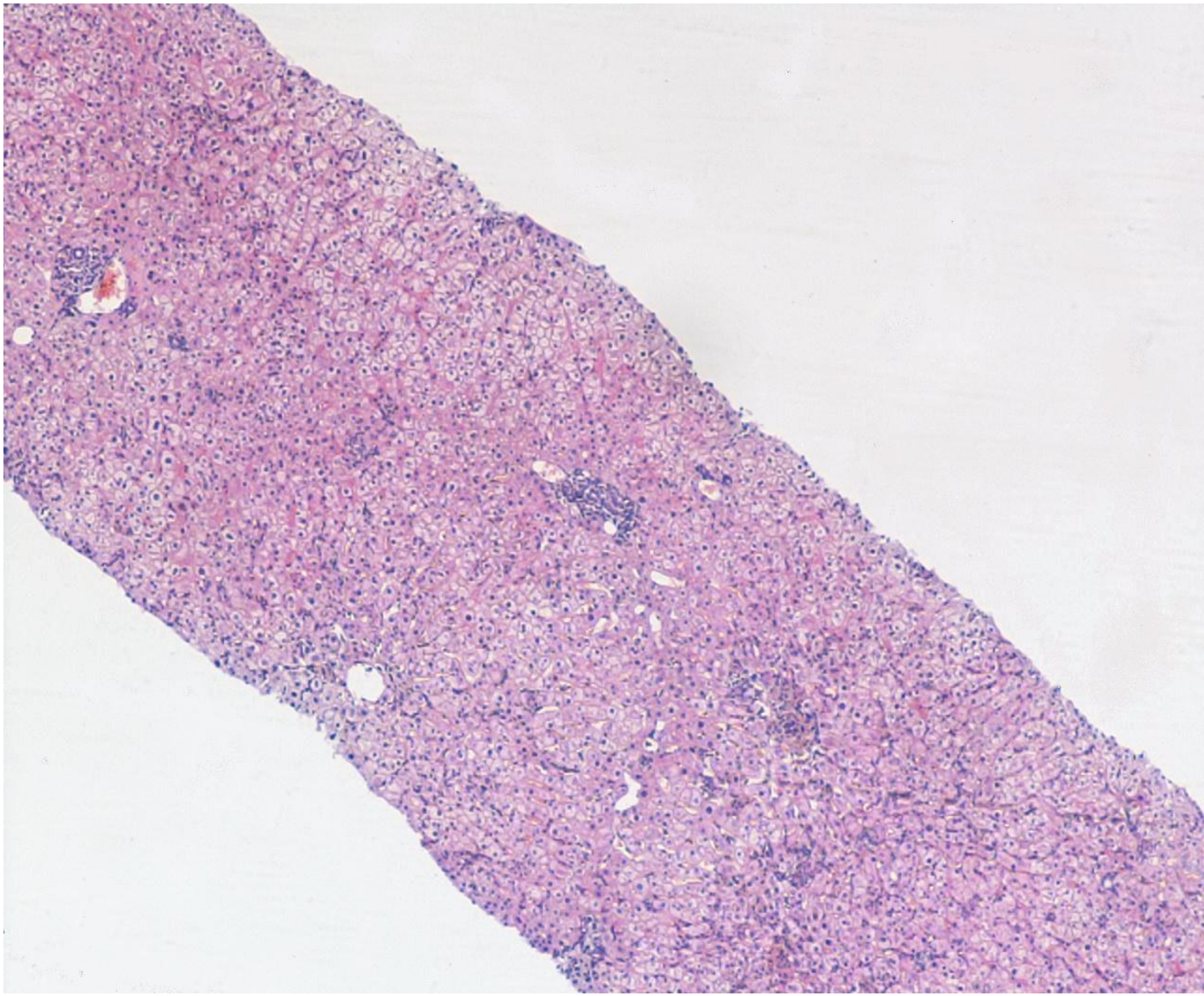
- 60-year-old woman
- no significant past medical history
- chronic back pain treated with numerous NSAIDs
- travelled to UK 3 months prior to admission

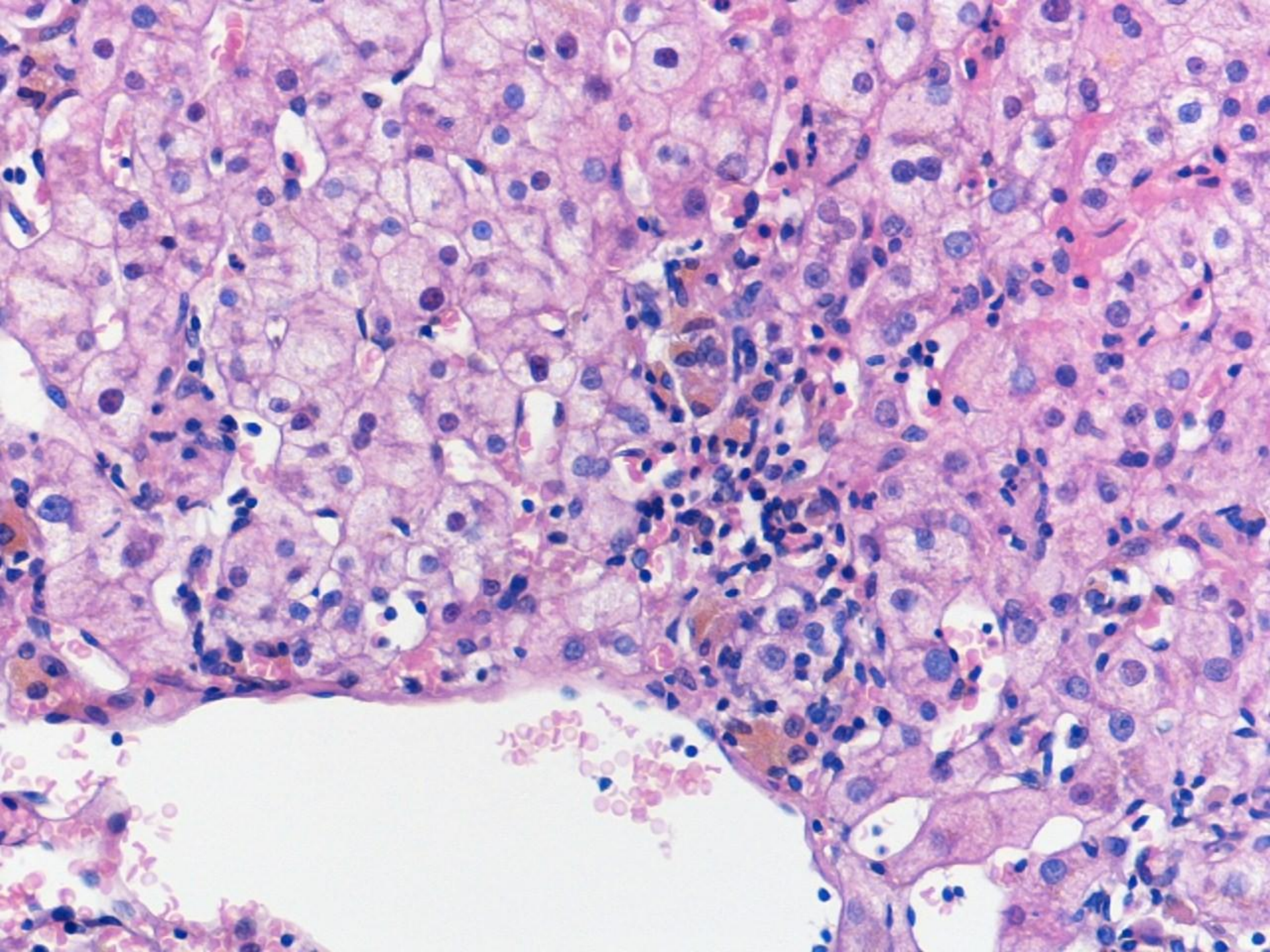
Presented with

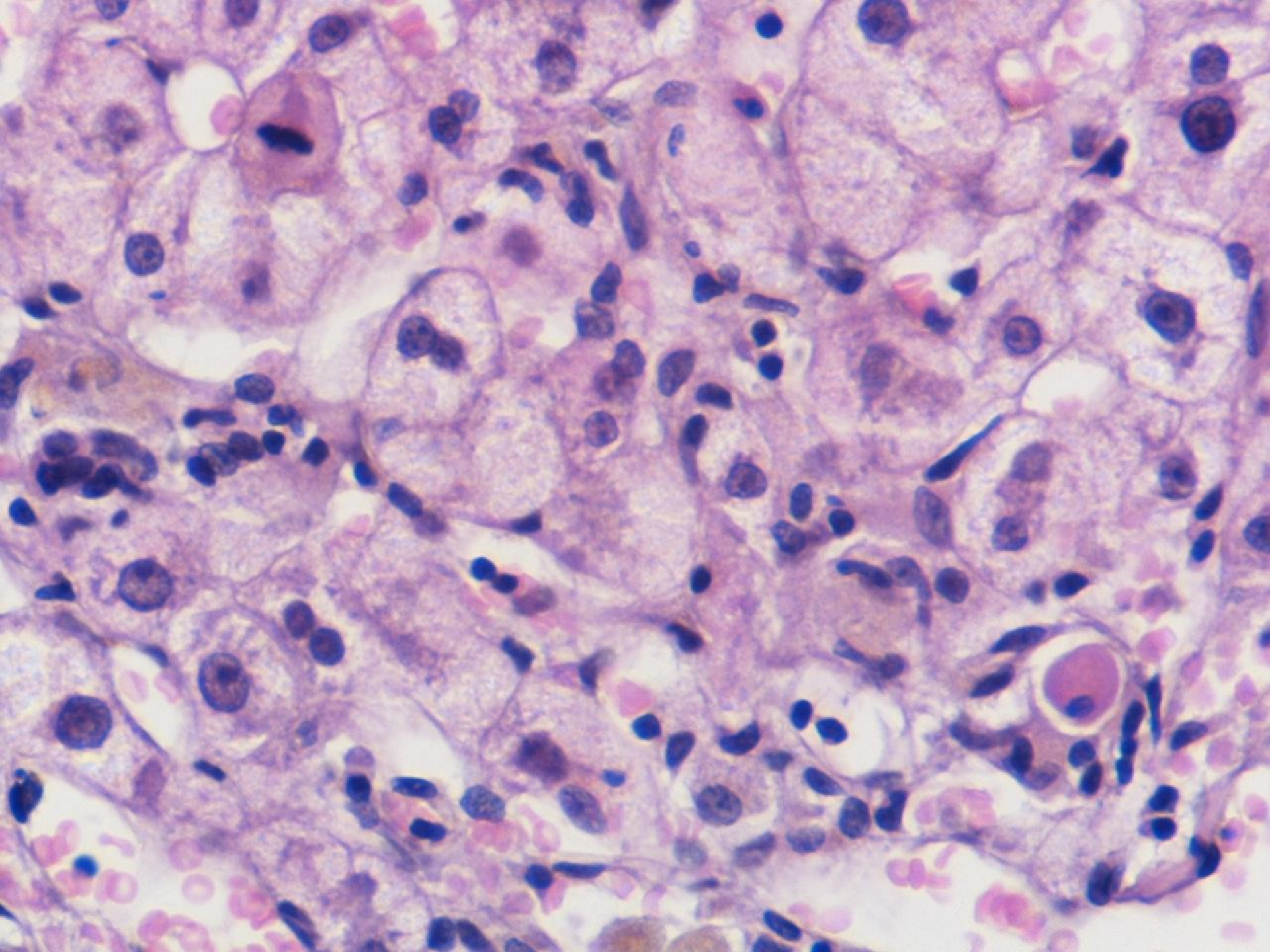
- **gradual ↑ of transaminases** for ~6 weeks
- γGT, ALP only mildly ↑
- bilirubin (total, direct) normal values

Athens B



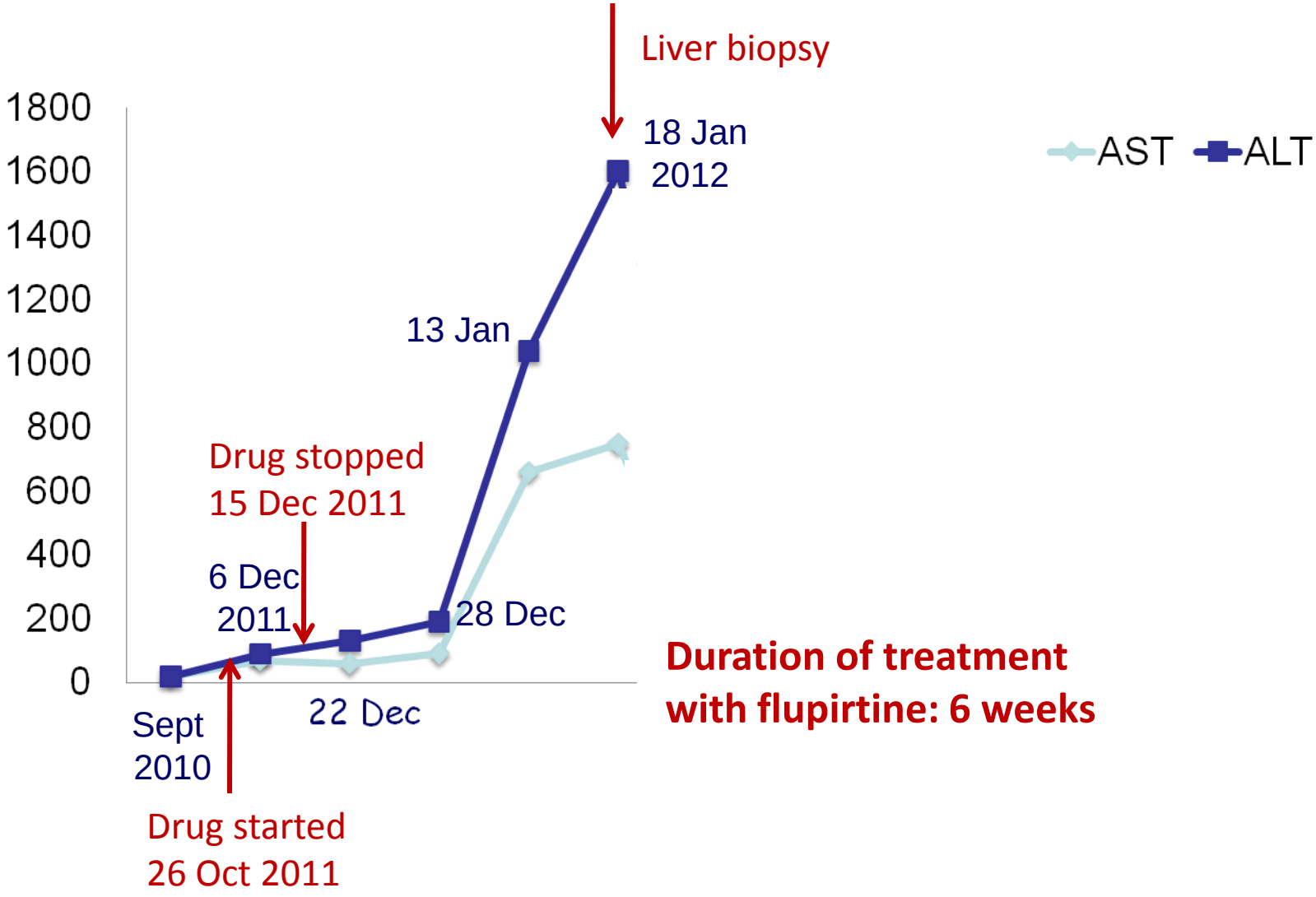






Differential diagnosis?

Levels of serum ALT, AST



Duration of treatment with flupirtine: 6 weeks

Flupirtine maleate

- centrally acting non-opioid, non-steroidal analgesic with muscle relaxant properties
- approved in Europe since 1984, Russia, China but never in U.S.
  - **acute and chronic musculoskeletal pain**
  - headache, migraine
  - dysmenorrhea
  - postoperative pain
  - pain in metastatic malignancies
  - neuralgia
- increasing importance in pain management
- recent new indications for use
  - neurodegenerative &
  - neuroinflammatory diseases

Unexpected frequent hepatotoxicity of a prescription drug, flupirtine, marketed for about 30 years

Martin C. Michel,[1] Piotr Radziszewski,[2] Christian Falconer,[3] Daniela Marschall-Kehrel[4] & Koenraad Blot[5]

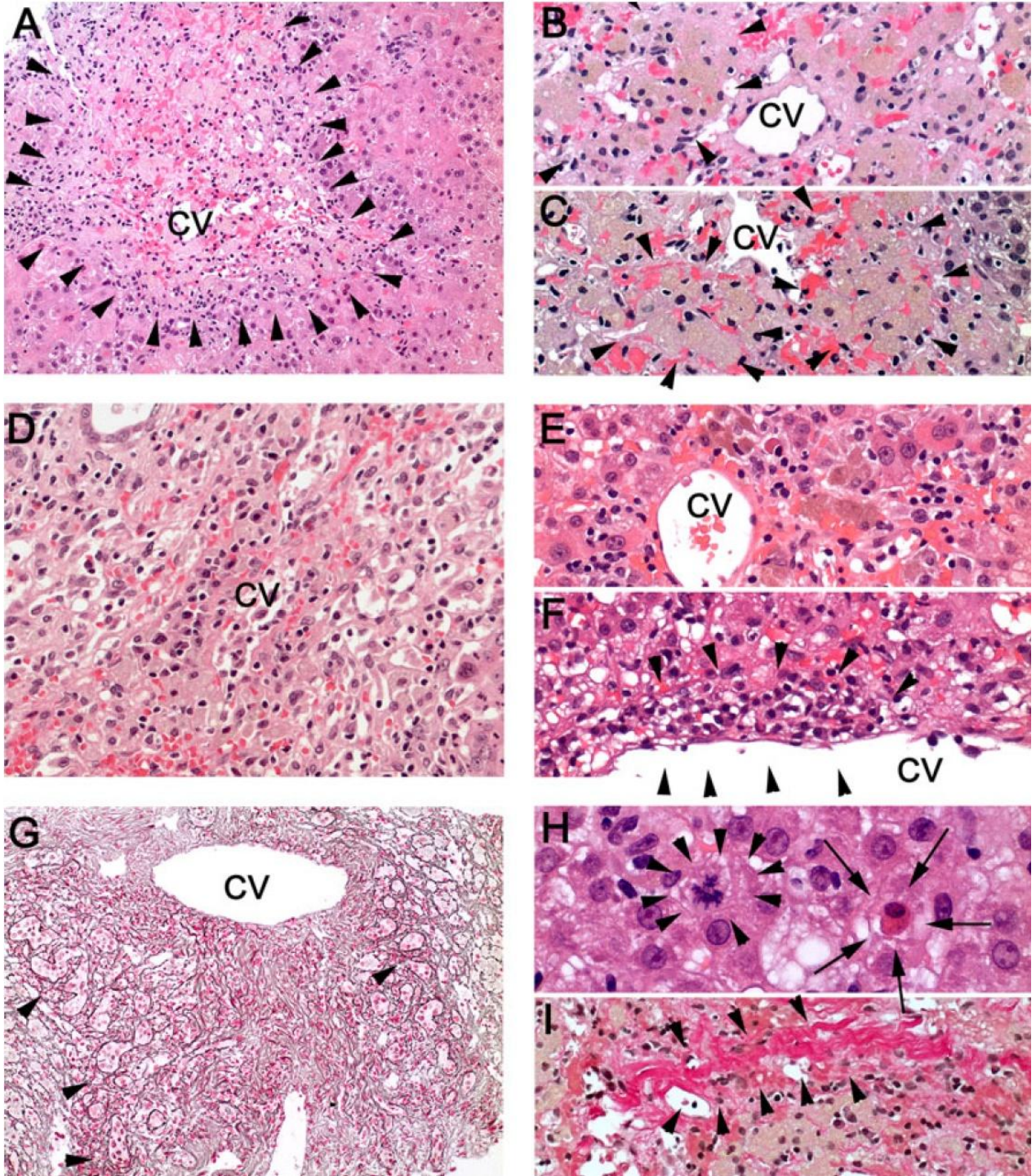
[1]Department of Pharmacology & Pharmacotherapy, Academic Medical Center, Amsterdam, The Netherlands, [2]Department of Urology, Medical University of Warsaw, Poland, [3]Division of Obstetrics & Gynecology, Danderyt Hospital, Sweden, [4]Urological Practice, Frankfurt, Germany and [5]elbion, Leuven, Belgium

BJCP British Journal of Clinical Pharmacology

Published Online
2 October 2011

- Major elevations of liver enzymes (>3xULN) in 31% of patients treated with flupirtine (>6 weeks) for overactive bladder syndrome

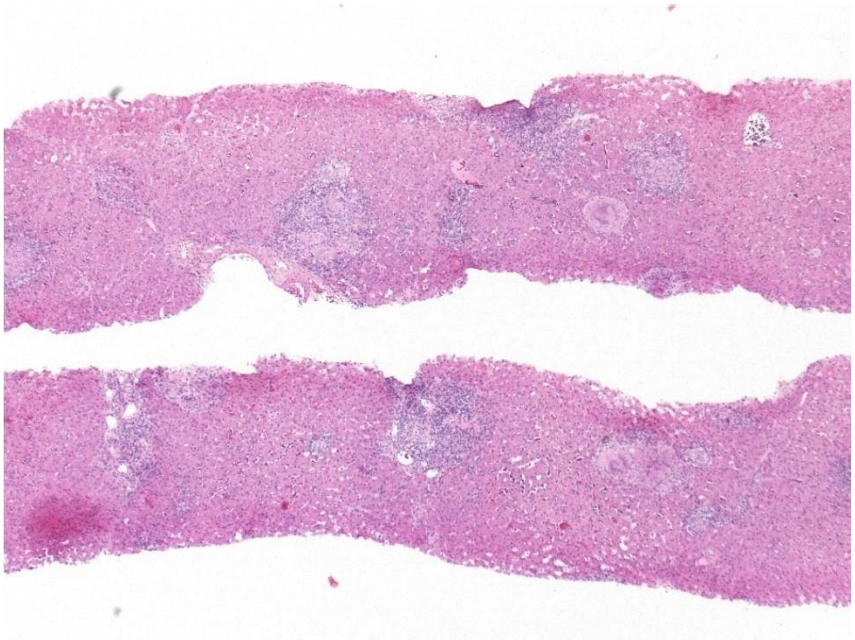
- suggested immuno-allergic type of hepatotoxicity

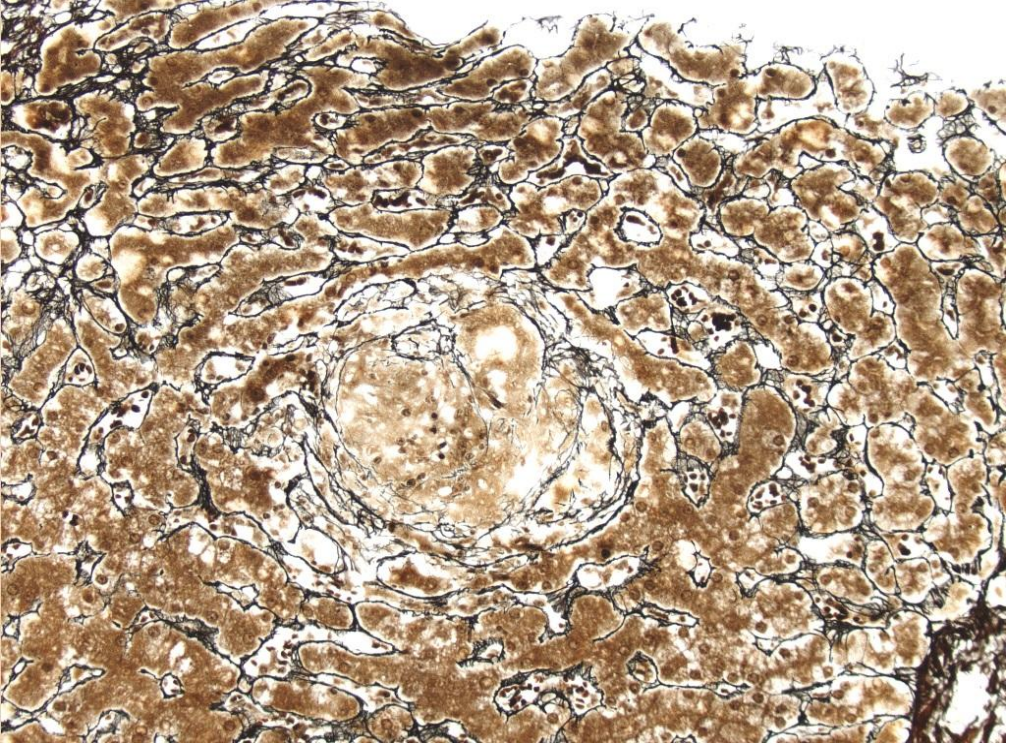


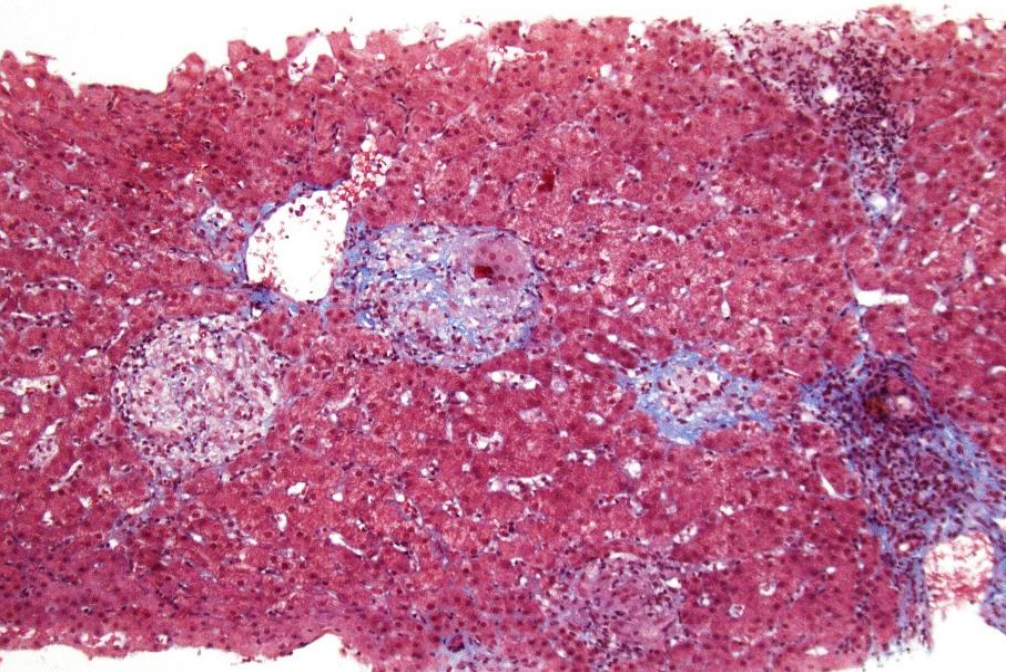
Puls et al
Virchows Archiv 2011

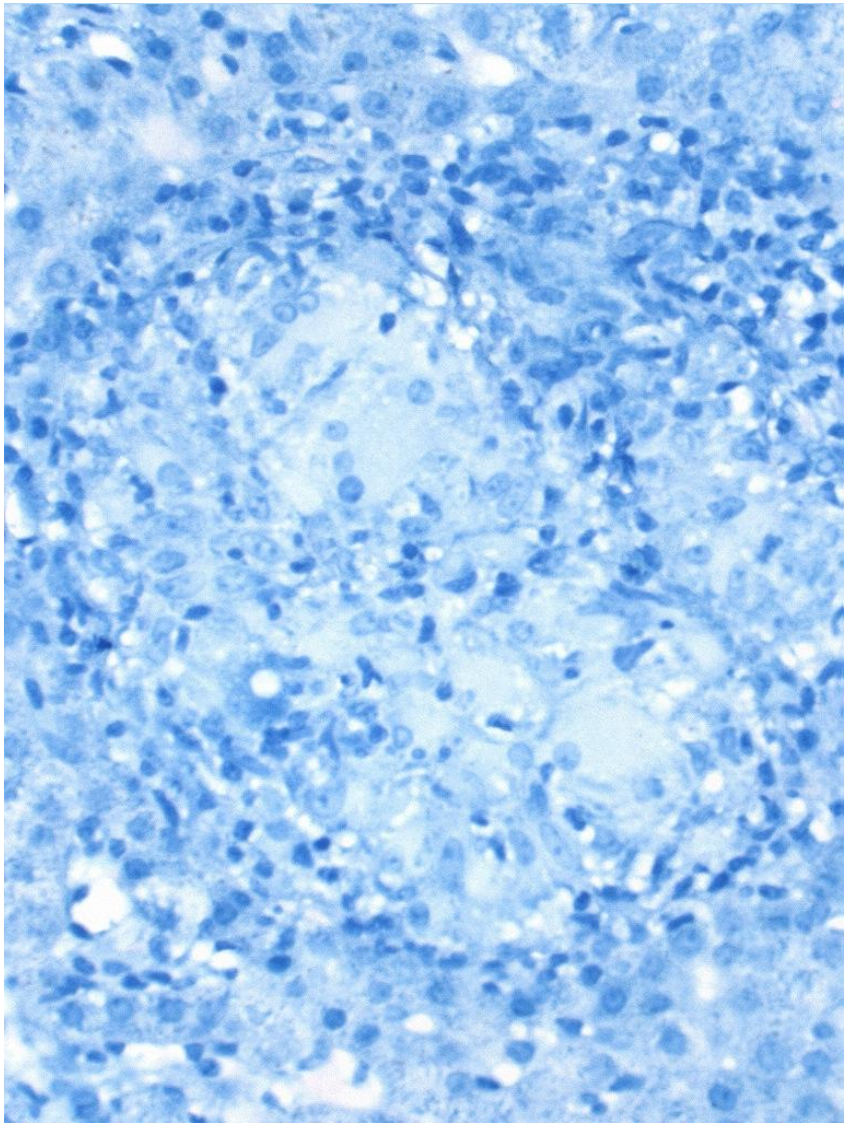
Brisbane B

- 35yo male
- “Hepatitis C” – from radiology
- Abnormal LFTs





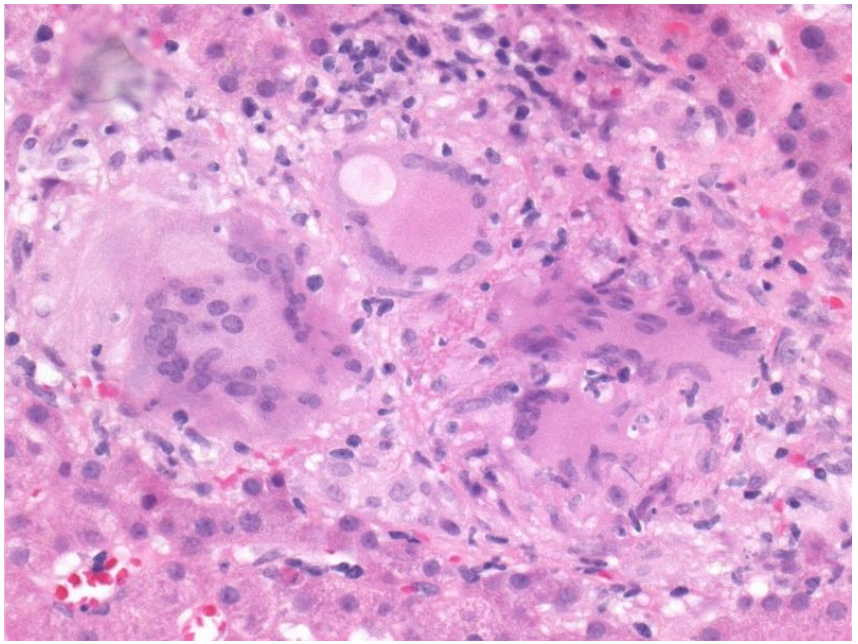




Differential diagnosis?

“Orange juice” granuloma

- IV drug users on Rx
- inject methadone
- sequester in mouth, regurgitate or more “committed” manoeuvres
- *>> disseminated granulomas*



Can be associated with spontaneous clearance of HCV

Newcastle B

- 77 yr male, retired supply manager
- PMHx: Alzheimers dementia, hypertension, prostate cancer, IHD
- Holiday cruise – first stop Barcelona – arrived at Egypt 17.1.2012
- Felt unwell with nausea, diarrhoea and jaundice – admitted to Nile hospital
- Drug history –
  - Rivastigmine 1 mg bd started in Nov 11 and increased to 3.5 mg bd in Dec 11
  - Aspirin 75 mg od, Atenolol 25 mg od, Atorvastatin 40 mg od

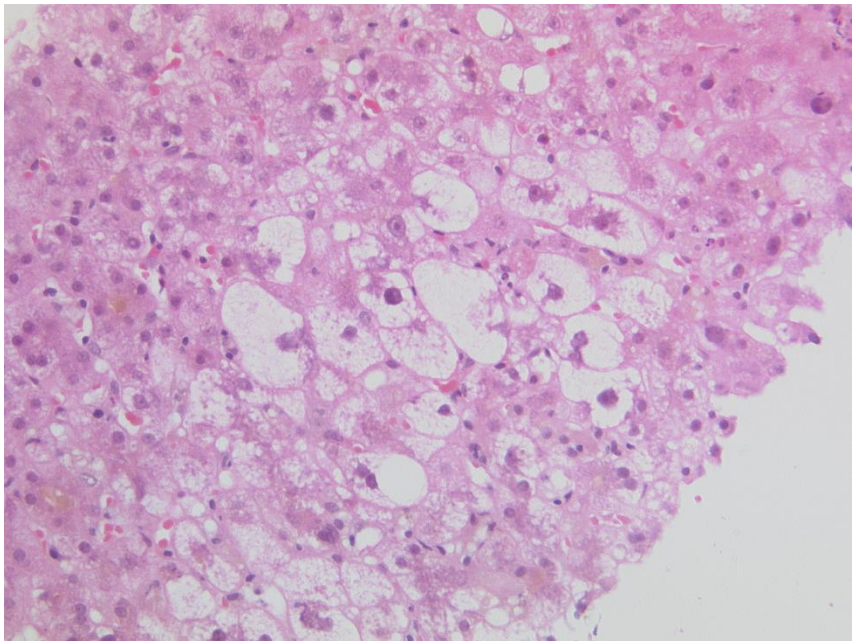
Investigations

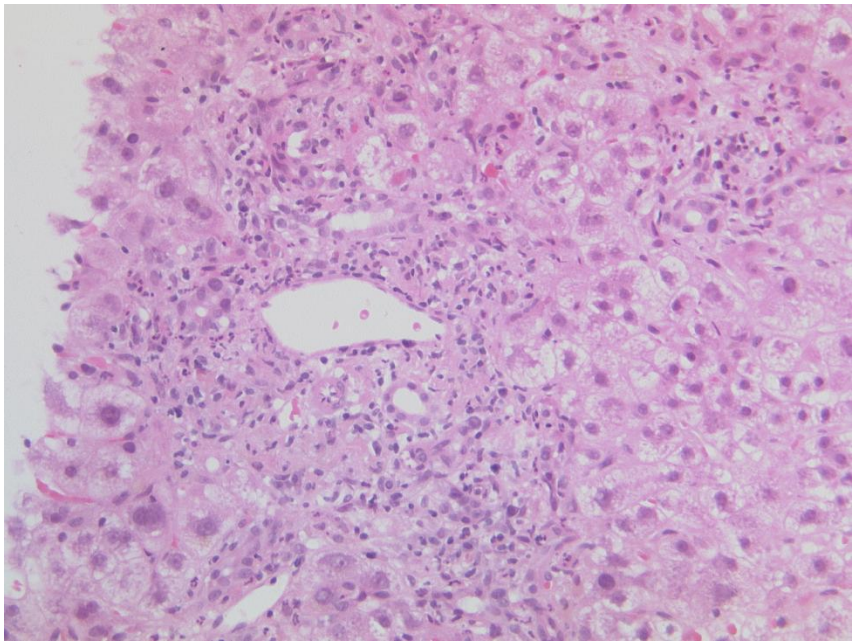
- Blood tests in Egypt - ALP: 169, ALT >2000, AST 1935, Bili 89
- Hep A, B, C – negative
- USS - chronic parenchymatous liver changes with mild splenomegaly and chronic calcular cholecystitis
- Rivastigmine and Atorvastatin stopped, started on NAC and Urso

Blood results

	21.1.12 (nile hospital)	2.2.12 (admitted to FRH)	7.2.12 (liver biopsy)	10.2.12 (peak LFTs)
Bi	89	350	462	500
ALT	2100	515	242	199
AST	1935	216		
Alk phos	169	169	153	173
GGT		186		

Newcastle B





Differential diagnosis?

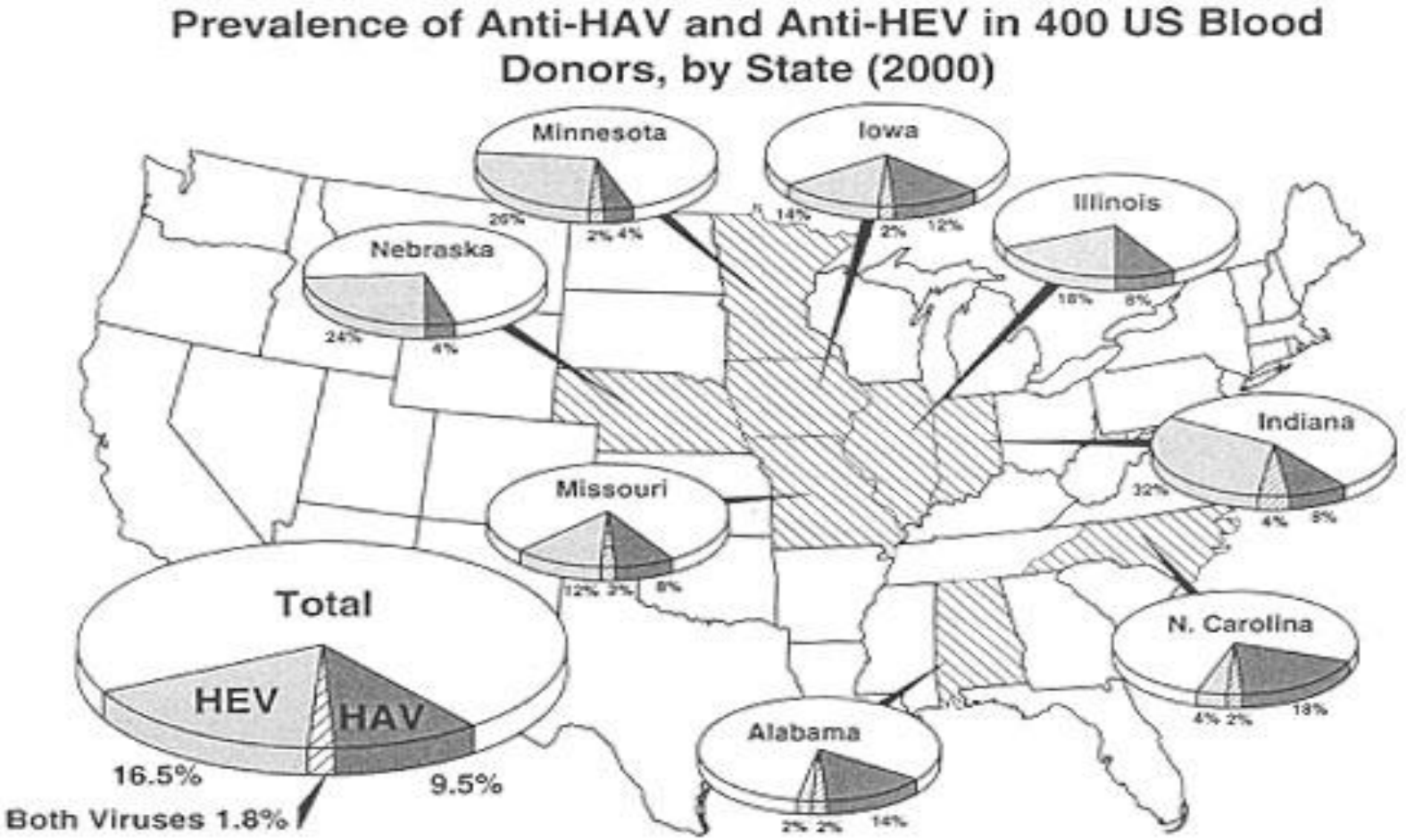
Further progress

- Anti-HEV IgM positive [result back after a few weeks]
- Further history – had pork meat during Christmas - possible source of HEV [incubation period 15-60days, mean 40 days]
- HEV viral RNA arranged - negative in stool and blood (too late ?)
- LFTs resolved on FU in clinic
- Advised could restart rivastigmine in 6 months time

Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury

- 318 patients with suspected DILI
- 50 (16%) tested positive for anti-HEV IgG and 9 (3%) for anti-HEV IgM
- In 9 patients with positive anti-HEV IgM, acute hepatitis E was the most likely diagnosis in 7 pts and primary diagnosis in 2 patients
- 4 out of 9 with positive anti-HEV IgM were positive for genotype 3
- Patients with positive anti-HEV IgM positive were mostly older men (89%, mean age 67 yrs)

Gastroenterology 2011;141:1665-1672



Surprisingly, in the USA, the prevalence of anti-HEV is equal to or greater than the prevalence of anti-HAV in some regions, especially in the states that are large producers of swine

Purcell & Emerson J Hepatol 2008,48:494-503

Histopathology of HEV

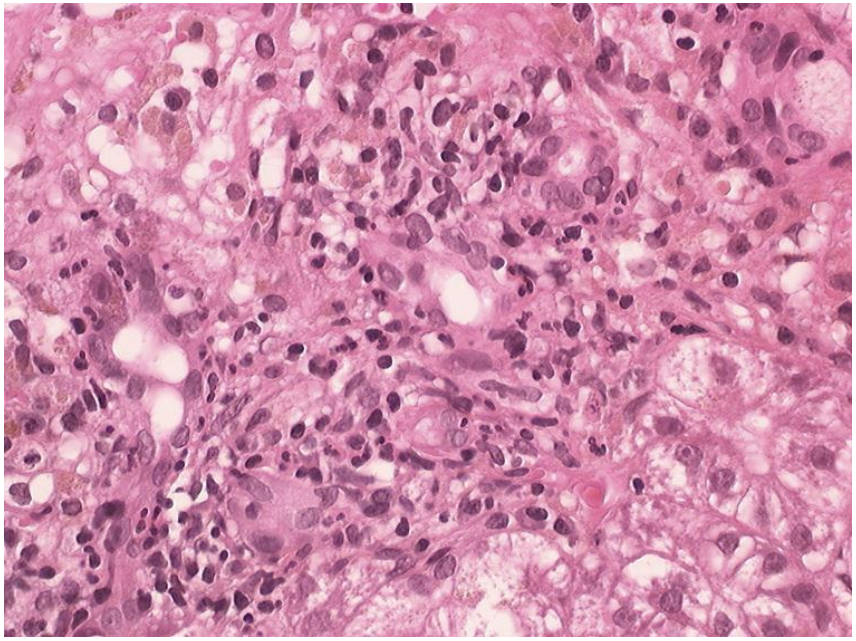
- Lobular hepatitis
- Cholestatic features with varying degrees of bilirubinostasis
- Portal inflammation with plasma cells
- Polymorph rich infiltrates

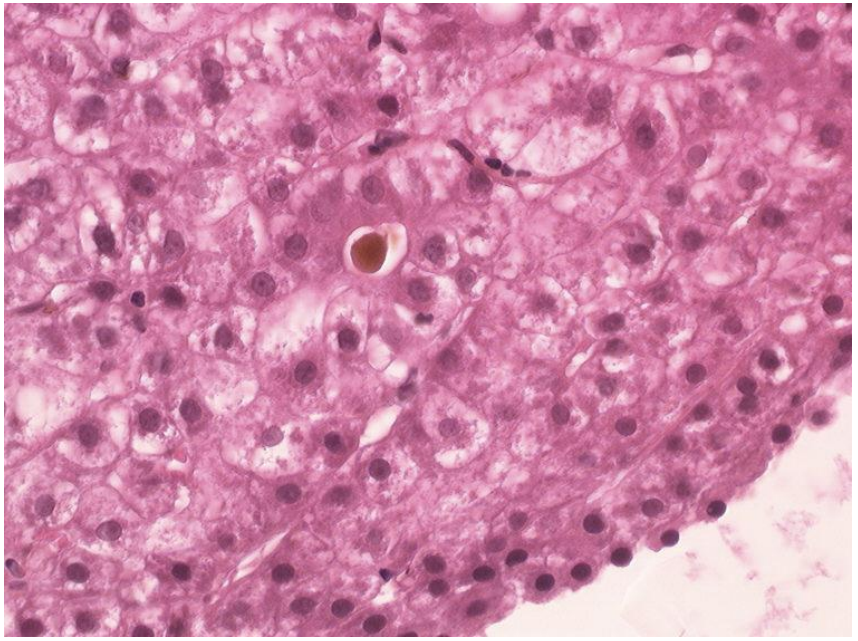
Malcolm et al 2007; Moncari et al 2007

Paris B

- 65-years-old male
- One of the candidates for the past presidential election in France
- Progressive onset of fever, fatigue, loss of appetite, upper abdominal discomfort and dark-coloured urine.
- At admission, liver function tests showed :
  - AST 1458 U/l - ALT ; 2232U/l,
- Hepatitis A to C and AIH excluded as well as HSV, Q-fever and Brucella.
- Progressive deterioration of biological and clinical condition, a liver biopsy was performed.
-

Paris B





Follow-up

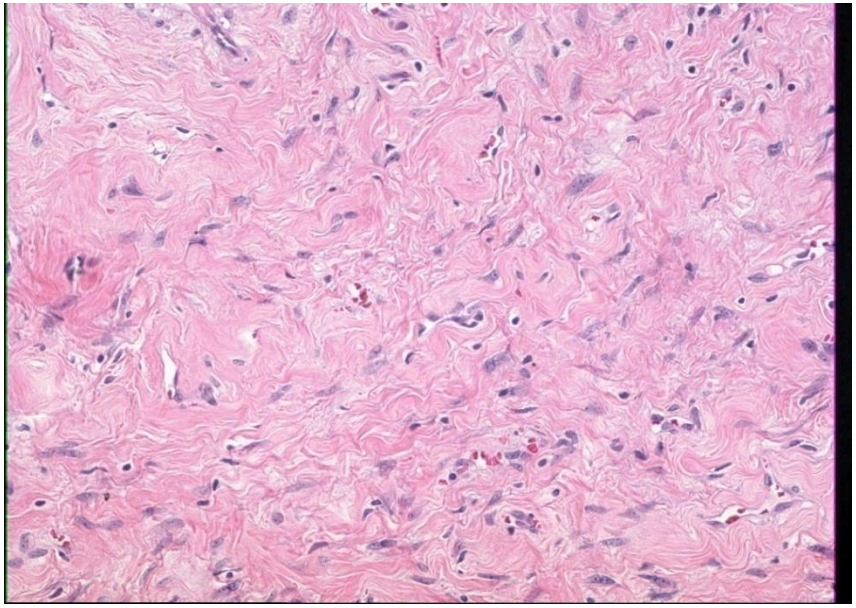
- IgM HEV ++, PCR HEV (blood) +
- **Diagnosis : Acute HEV hepatitis (autochtonous in an immunocompetent patient)**
- Quick complete recovery

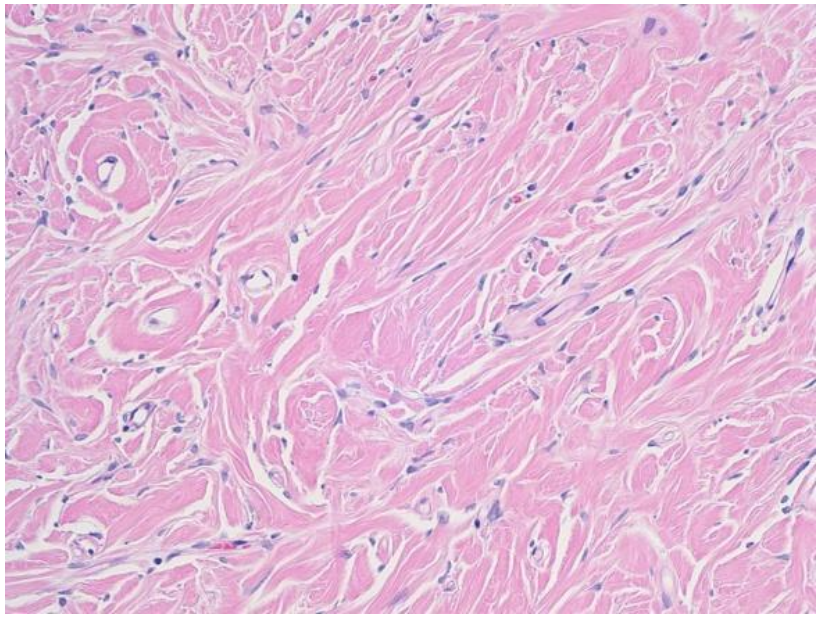
Hepatitis E Virus

Baltimore B

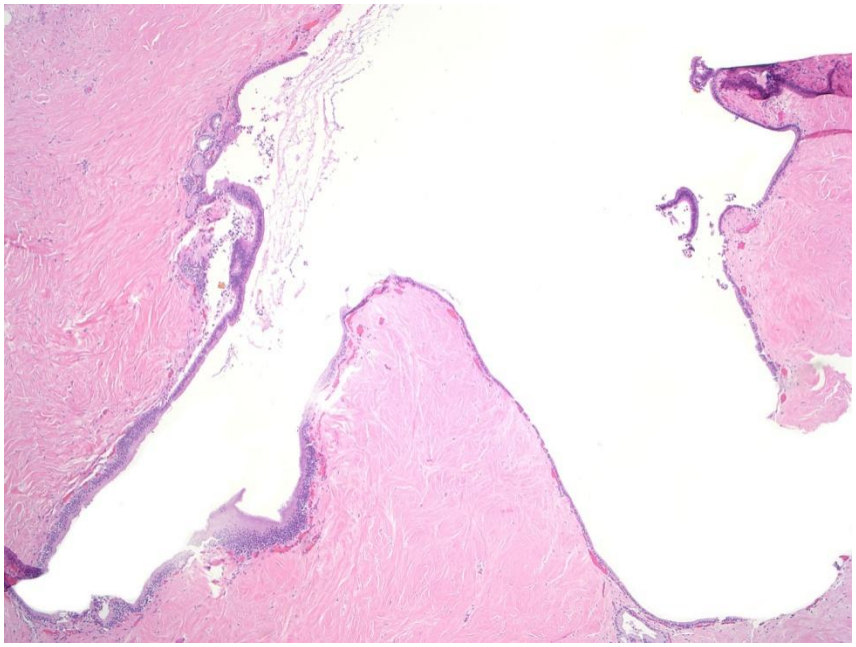
- 50 year old female presented with acute cholecystitis.
- No other medical history is relevant to the liver lesion.
- Imaging showed an “indeterminate” 2.8 cm lesion in the central right liver (segment 8) that “wraps around a 5 mm tubular cystic structure”.
- In addition, small scattered hepatic cysts are noted (at least 6), ranging from sub cm to 2 cm.
- The central right liver lesion was resected.

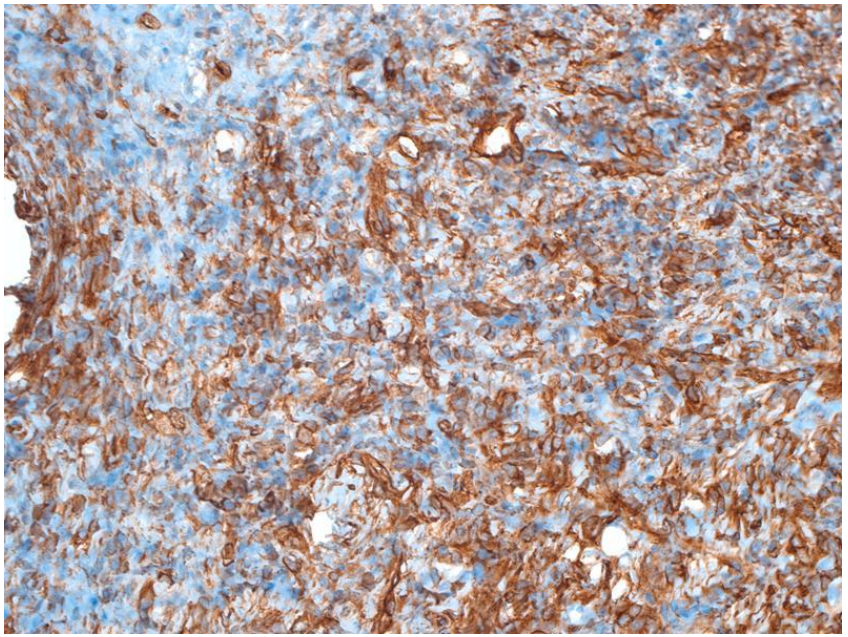
Baltimore B





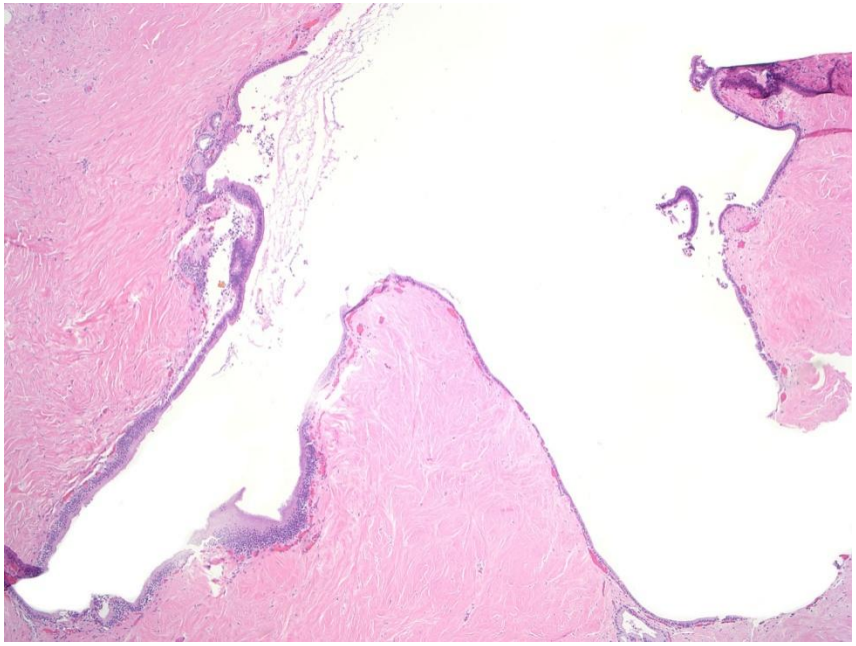
Baltimore B

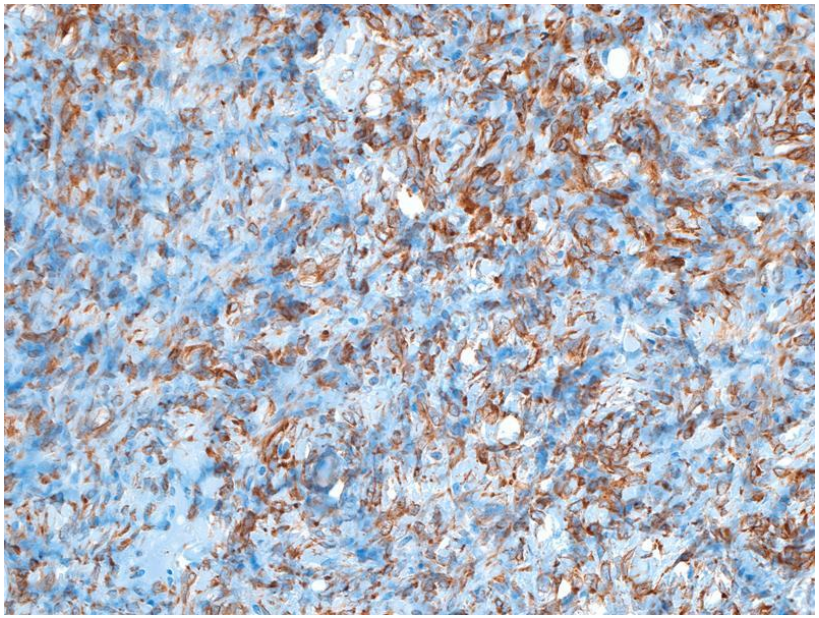




CD34

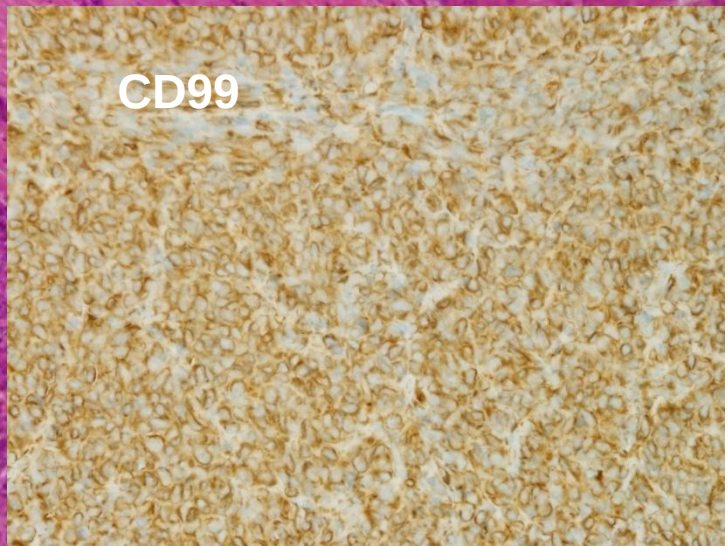
Baltimore B





Bcl2

Ex-vivo resection; segments 2,3 re-implanted
IVC reconstruction; hepatico-jejunostomy
Segments 1; 4-8 removed
30 x 25 x 15 cm, 6600 g resection
Mass: 35 x 22.5 x 12 cm; foci of hemorrhage and necrosis



Diagnoses?

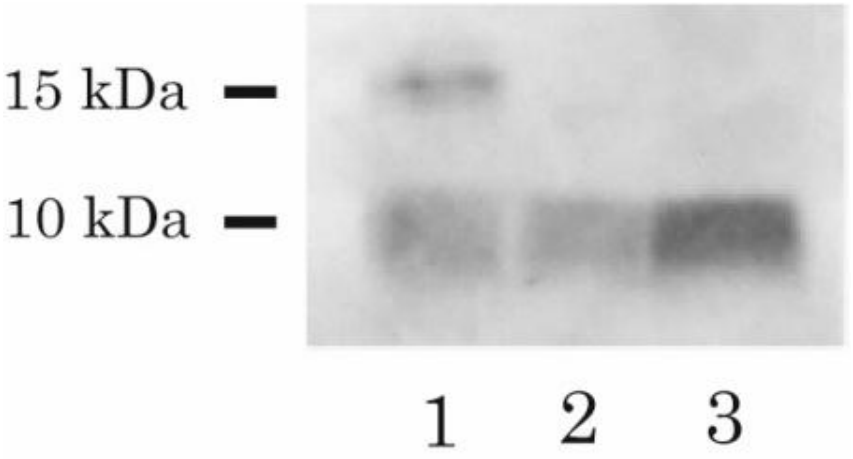
Hemangiopericytoma/SFT

- Now considered a “spectrum” of tumours that arise from fibroblasts
- HPC/SFT spectrum: can occur at any site; M = F; middle-age
  - Can be “benign” or “malignant”
  - If completely resected, long-term outcome is “good”
  - If not resectable, recurrent or metastatic: poor prognosis
- HPC elements can occur in many sarcomas
  - Staghorn vessels; CD34
- SFT “patternless pattern”; CD34, CD99, bcl-2, vimentin

Park, Curr Opin Oncol 2009; 21:327

SFT

- Doege-Potter syndrome: hypoglycemia associated with large SFT
- Uncommon paraneoplastic process; ~ 5% of SFT
  - Associated with IGF's produced by tumor
    - IGF -2, HMW…aka "BIG" IGF-2
  - Seen when tumours are large (~ 20 cm)
  - Due to altered expression of "BIG" IGF 2
  - Disappears after surgical resection




T 465 AQT

Next year:

Aussie rule gnomes

alastair.burt@adelaide.edu.au