Assessing liver biopsies with more than one diagnosis

Dr Susan E Davies

Addenbrookes, Cambridge University Hospitals NHS Foundation Trust.

Occam's Razor

Occam's Razor: No more things should be presumed to exist than are absolutely necessary, i.e., the fewer assumptions an explanation of a phenomenon depends on, the better the explanation.

(William of Occam)

izquotes.com

Evolving role of Liver biopsy

- BASL, EASL, AASLD, BSG guidelines on **when to liver biopsy**
- Many ancillary tests now available
  - genetics, viruses, HFE, HEV, TB, 2nd and 3rd line auto-antibodies
- Increasingly other strategies for staging
  - Firboscan, Fibrotest, ELF test, etc
- Decreasingly used to make the diagnosis

Increasing number of less straightforward cases are being biopsied

More is being expected ,
sometimes from less tissue too!

Known incidence of 2nd diagnosis?

- Decreased as more diagnostic tests available
- Not much recent literature – some state 3-<6% additional findings in HCV
  - Andriulli, Dig Dis Sci 2001, Castellano 2002
- All bxs 90s; 10 % with additional diagnosis
  - Spycher BMS Gastro, 2001

Consequences of more than one diagnosis

- Different treatment strategies – steroids, ursodeoxycholic acid, venesect iron, lifestyle
- Different follow-up strategies

  – clear HCV or HBV but still with N/AFLD, genetic implications
- Symbiotic effect of more than one ‘hit’ to accelerating CLD, decompensation and HCC

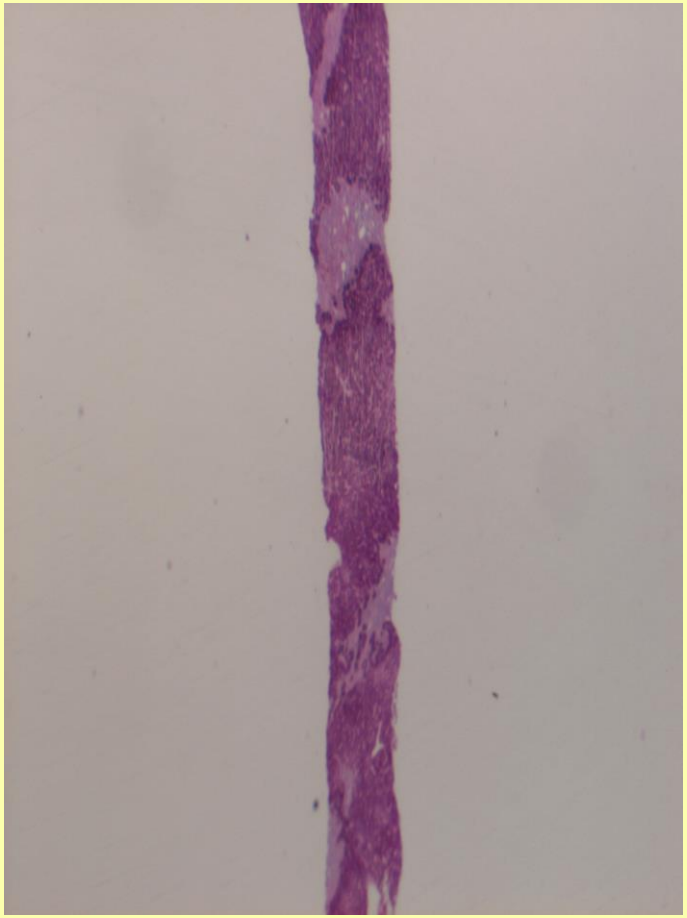
When could there be a 2nd pathology?

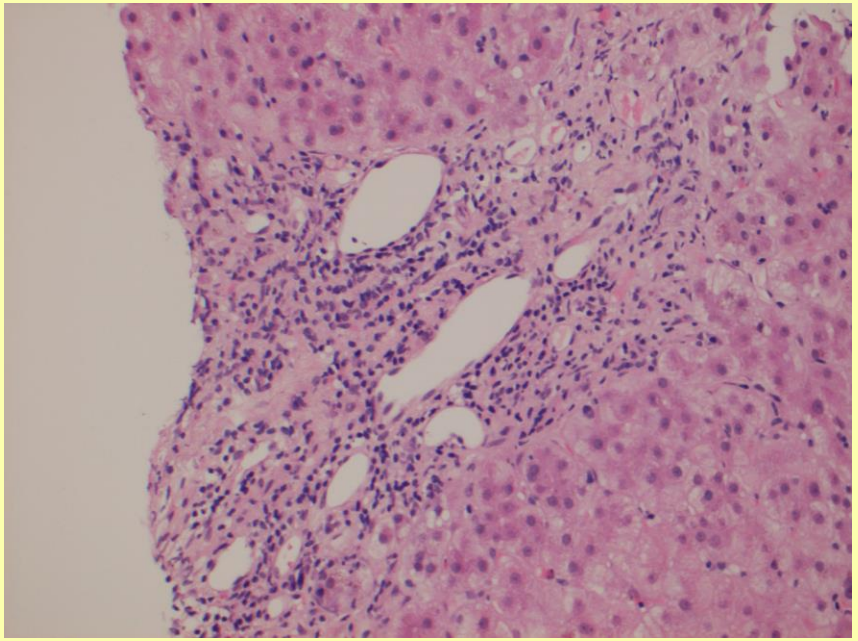
- Natural history or complication of the disease
- Same risk factors for other diseases
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

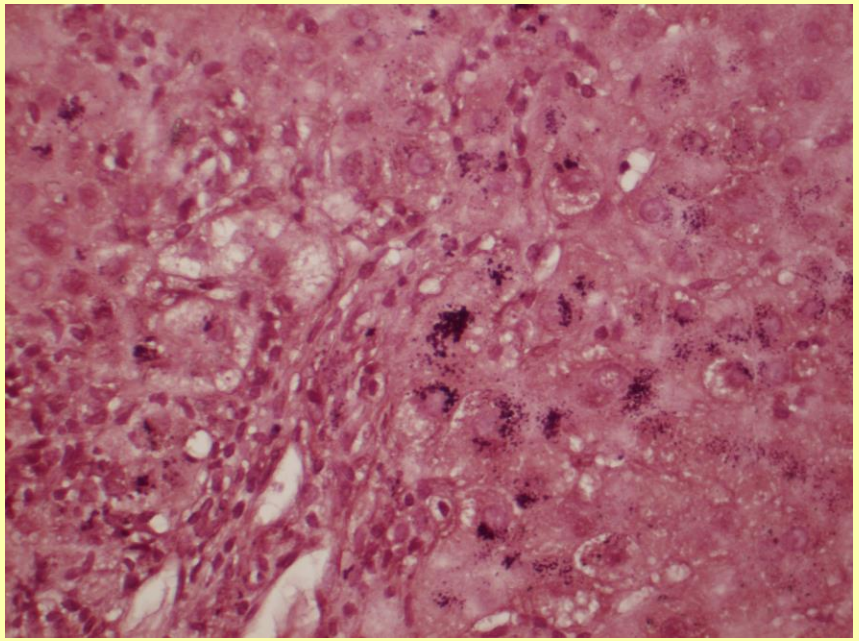
When could there be a 2nd pathology?

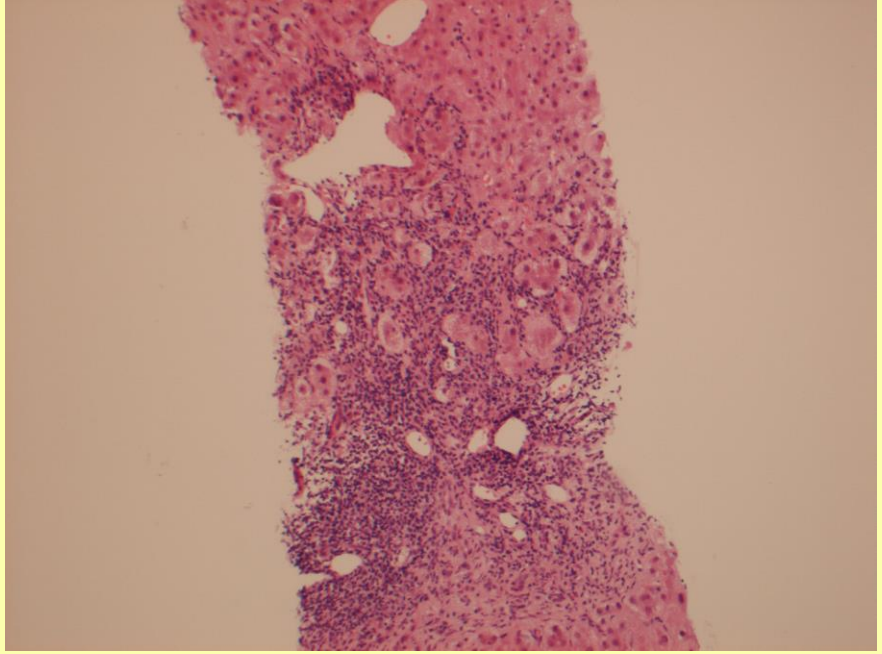
- Natural history or complication of the disease
- Common risk factors for other disease
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

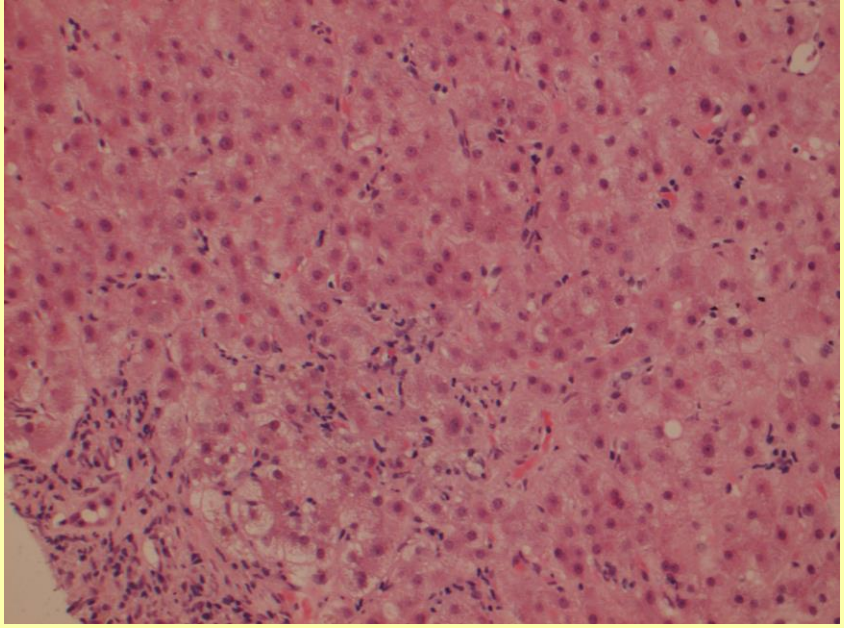
55yr female PBC diagnosis

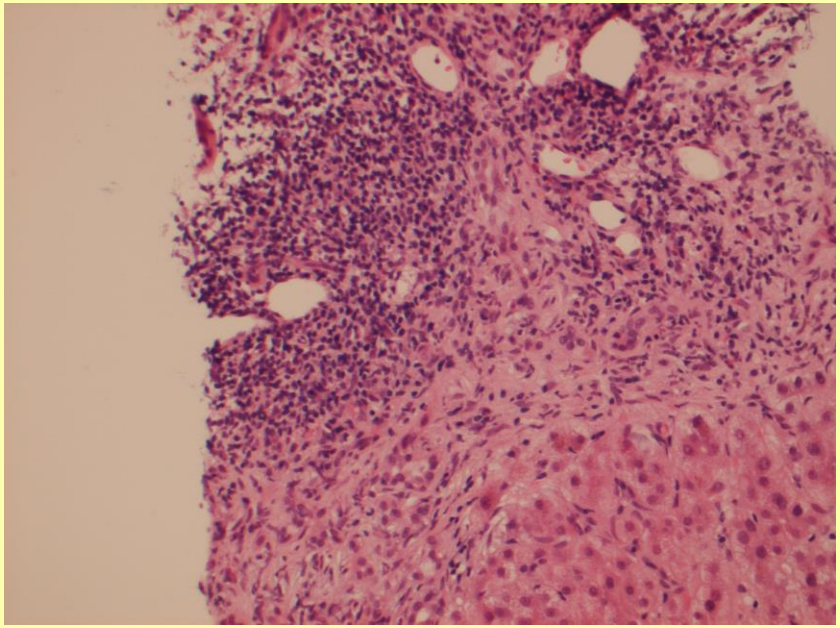


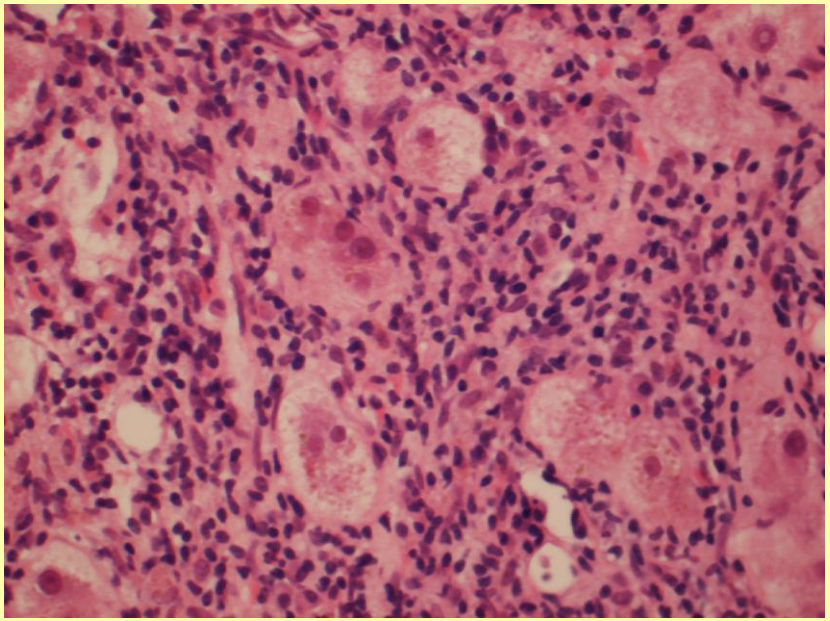




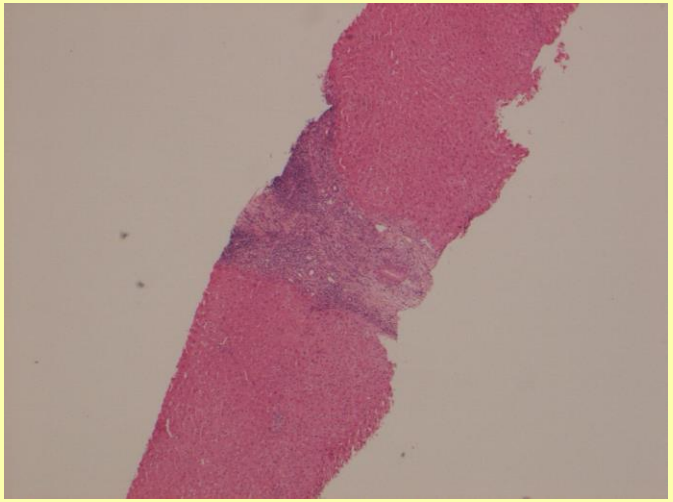


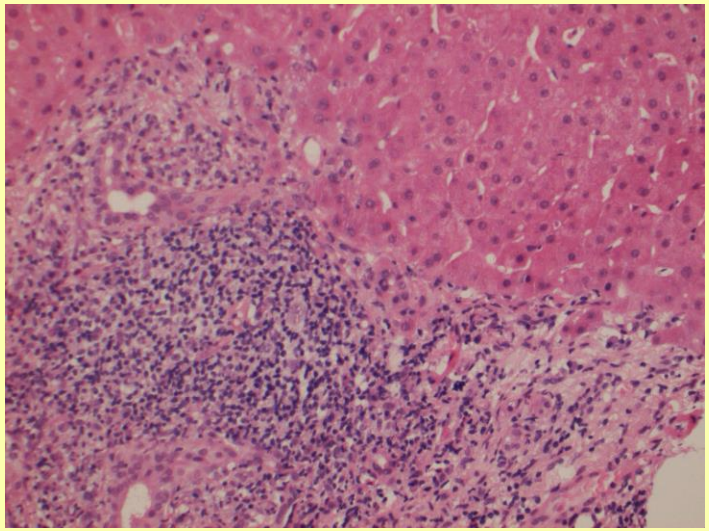


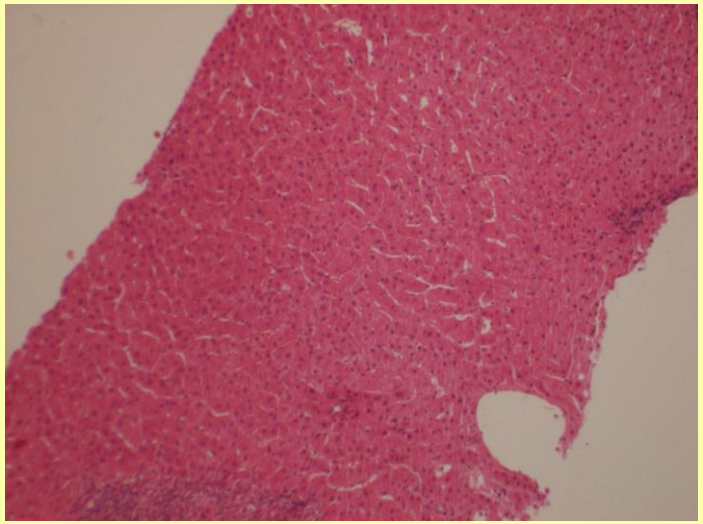


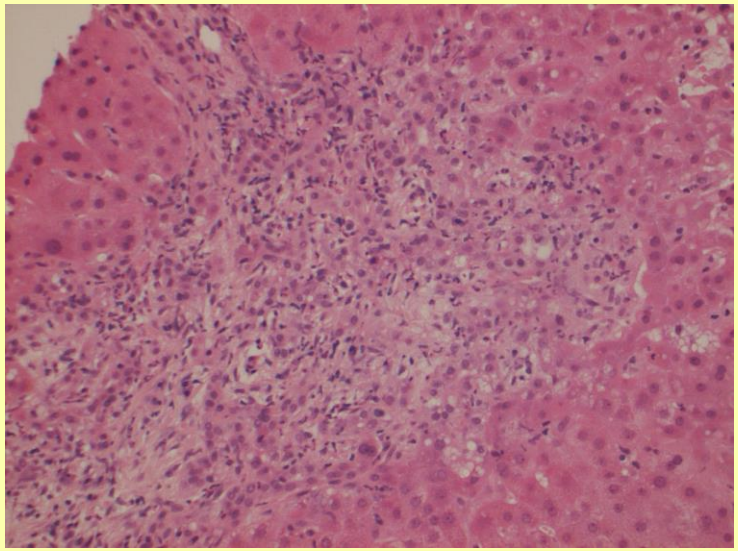


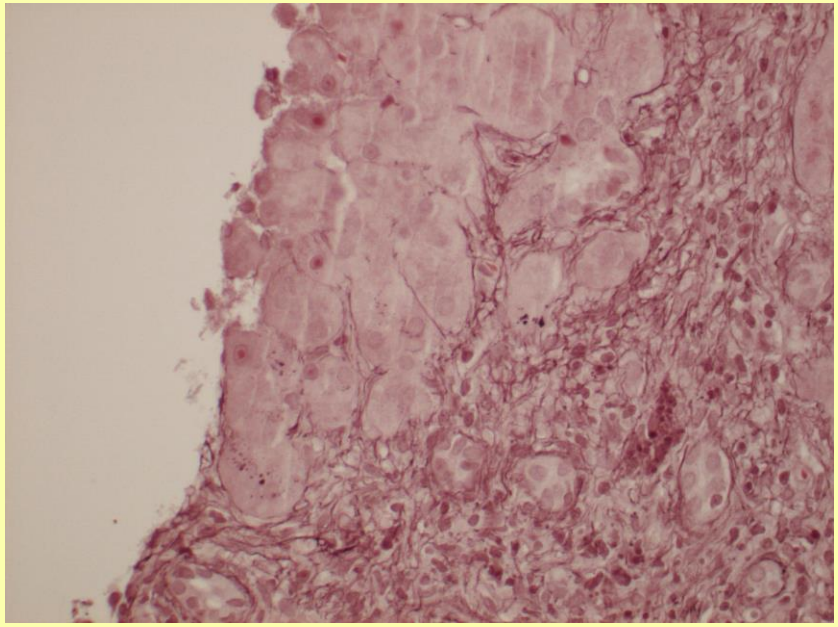
28yr male treatment for AIH

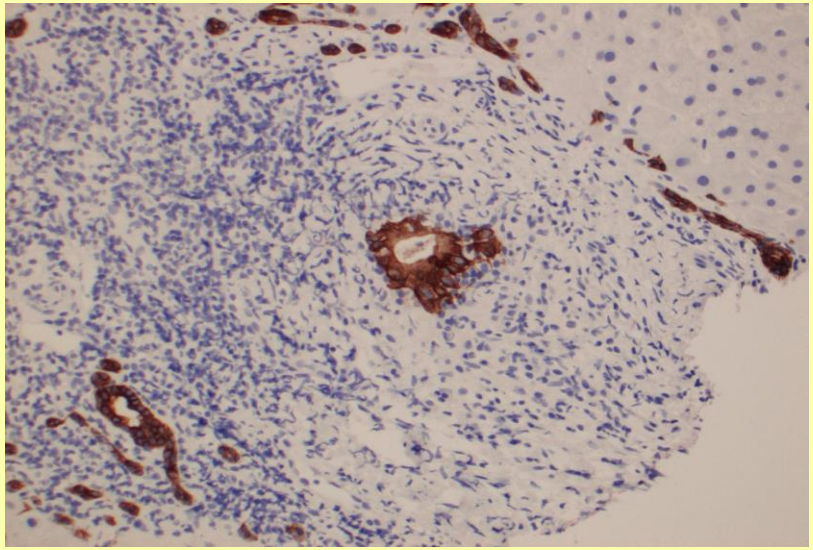


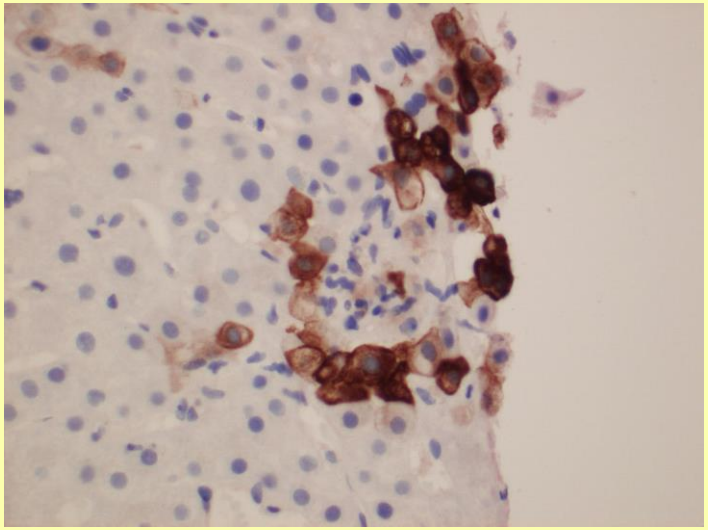


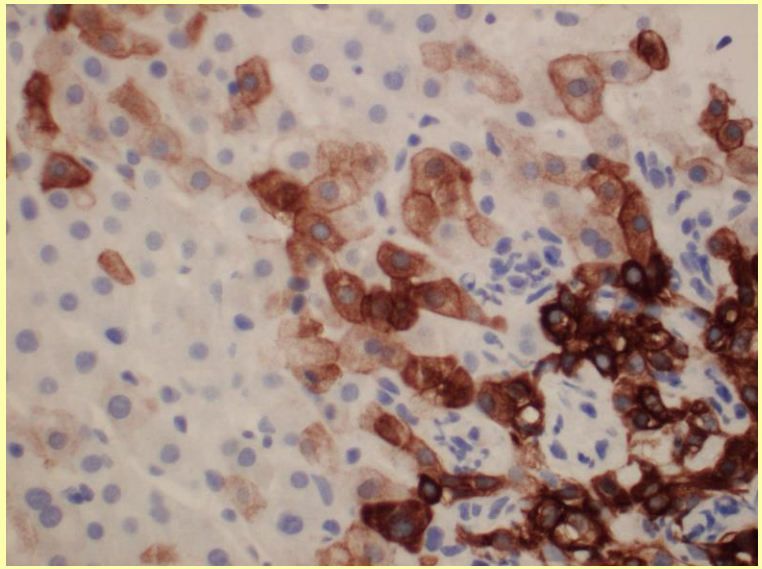










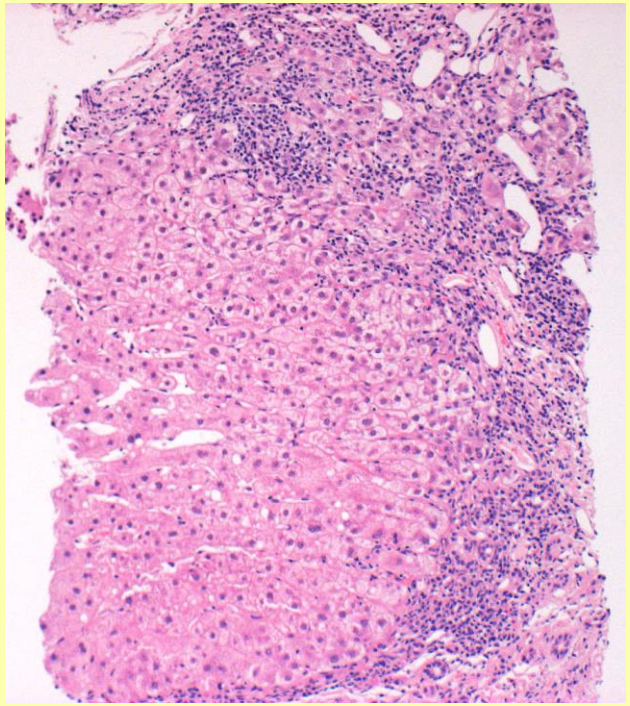


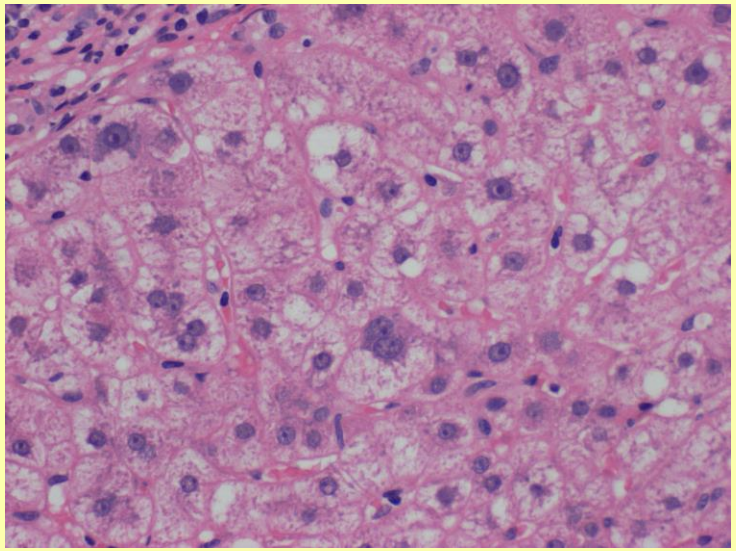
Overlap AIH/PBC/PSC

- IAIHG – histology 3 categories of AIH
  - Interface hepatitis, lymphoplasmacytic infiltrate, rosetting
- Paris criteria for overlap - 2 of 3 diagnostic from each
  - AP >x2, AMA +ve, histology - florid duct lesions
  - ALT >x5, IgG >x2 or SMA+ve, histology – mod/severe piecemeal necrosis
- Anti-ds DNA seem more common in overlap.

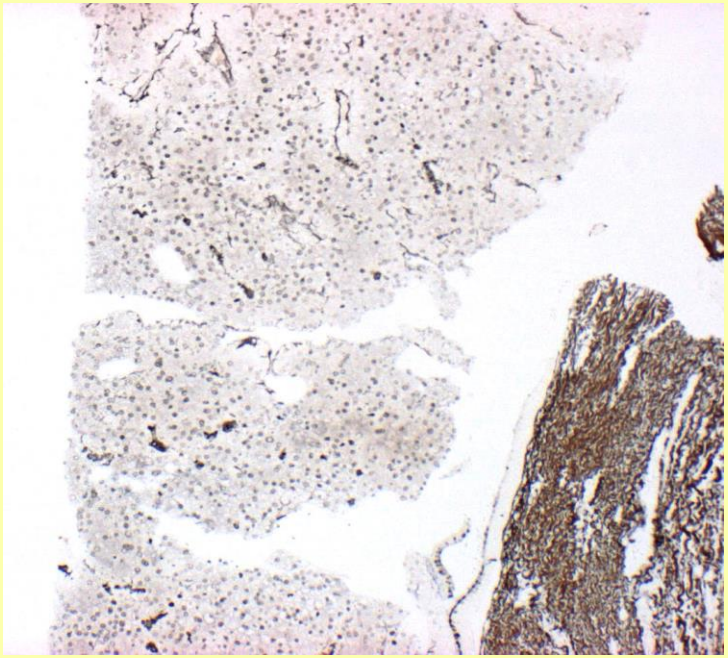
Caution

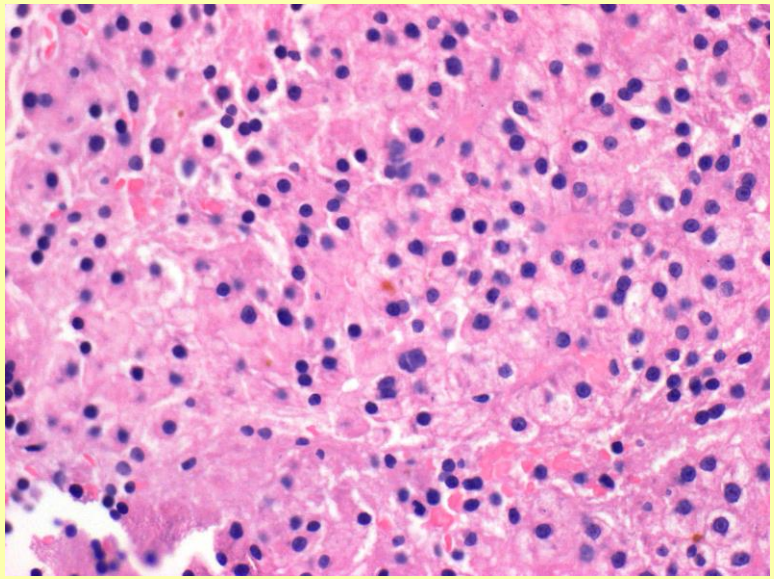
- Auto-antibodies are more common in chronic liver disease than general population
- Often low titre, non-organ specific
- 20-40% of FLD have ANA or SMA Ab; 25% HCV
- Raised IgG in cirrhosis, IgA with ALD &PSC, IgM PBC
- ~20% of NASH meet IAIG diagnostic/probable criteria for AIH without a biopsy

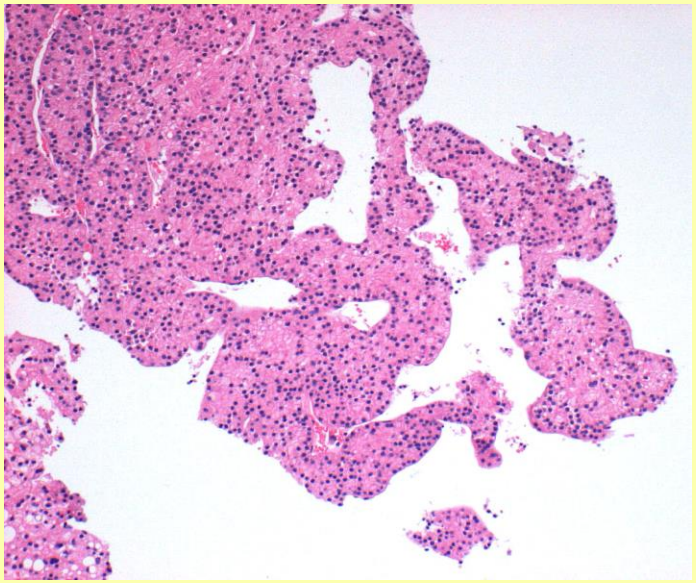


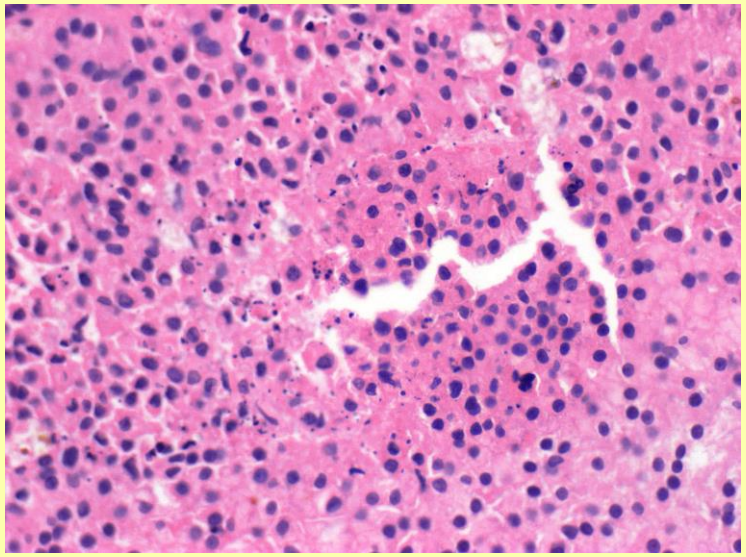


65yr female
abnormal LFTs and imaging





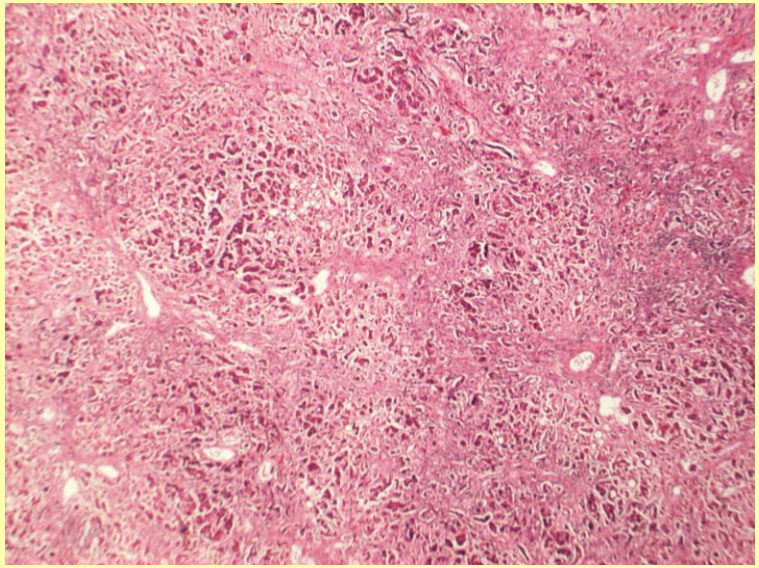


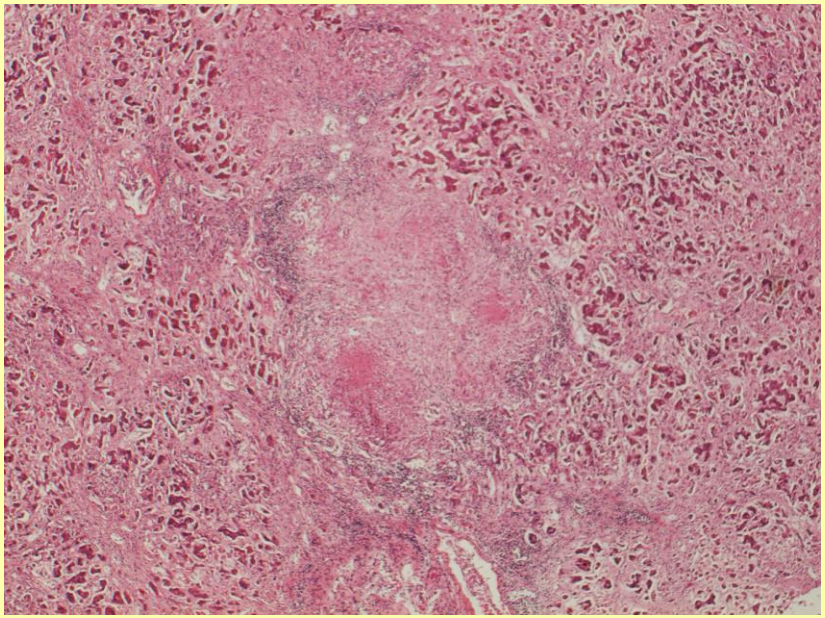


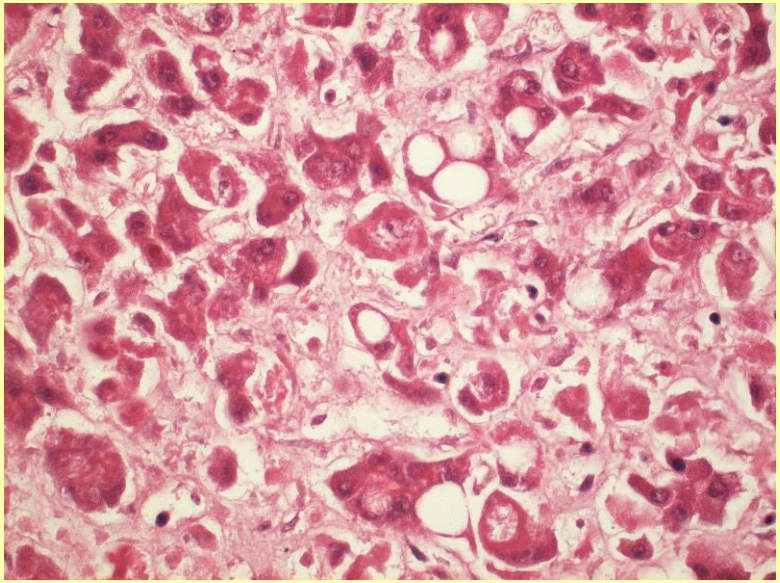
When could there be a 2nd pathology?

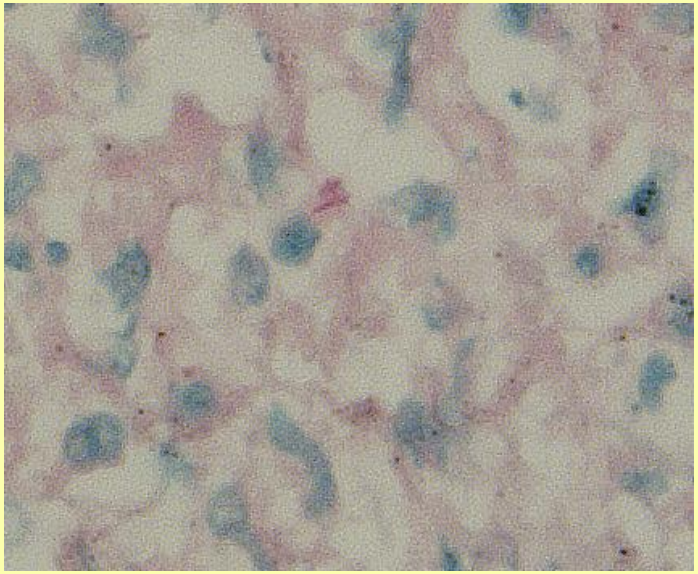
- Natural history or complication of the disease
- Common risk factors for other disease
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

65yr male alcoholic,

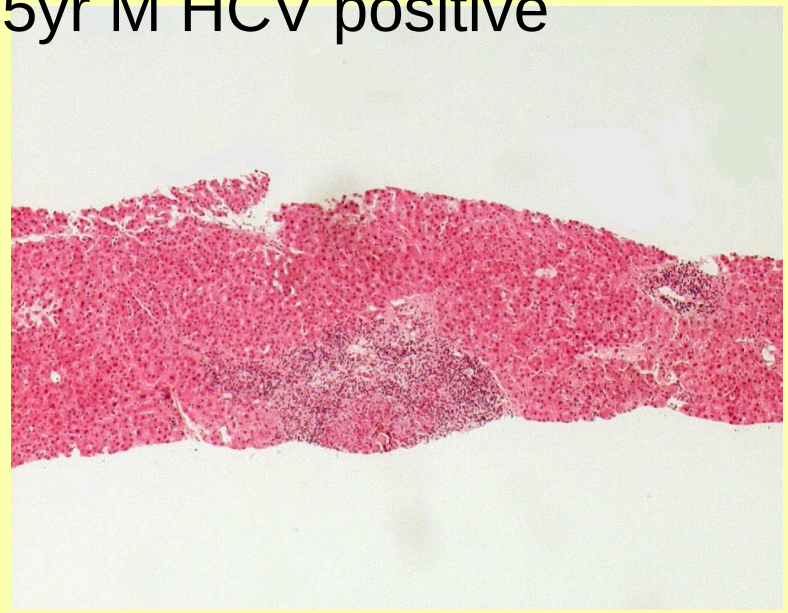


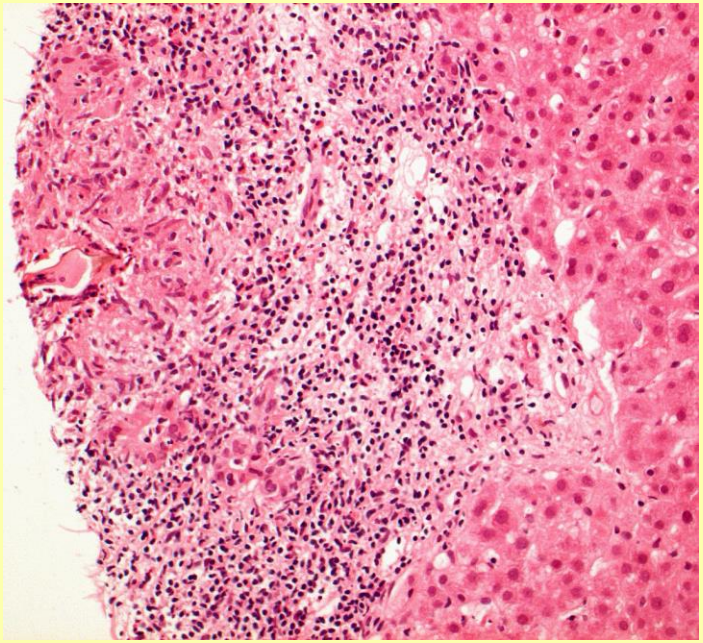


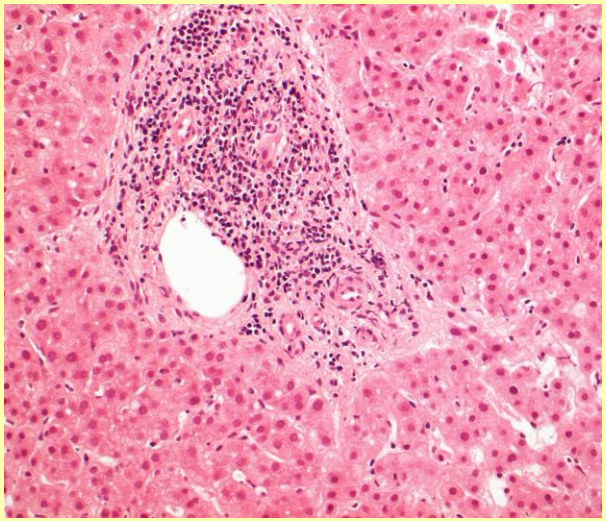


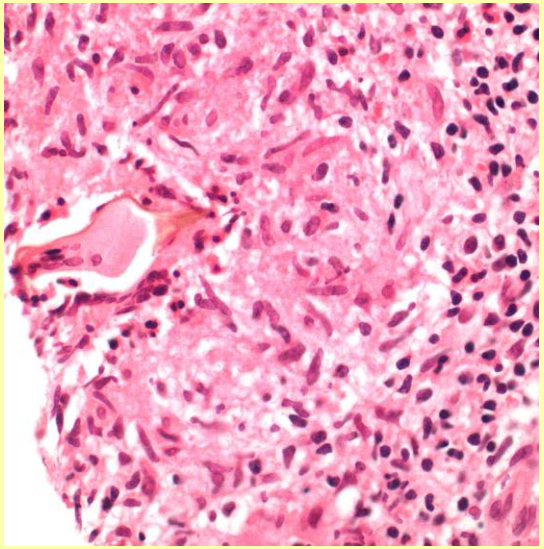


45yr M HCV positive

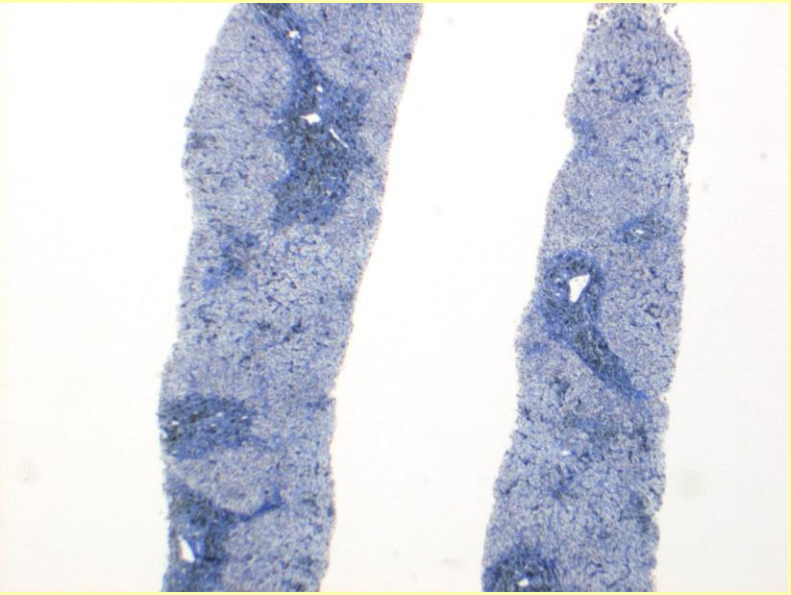


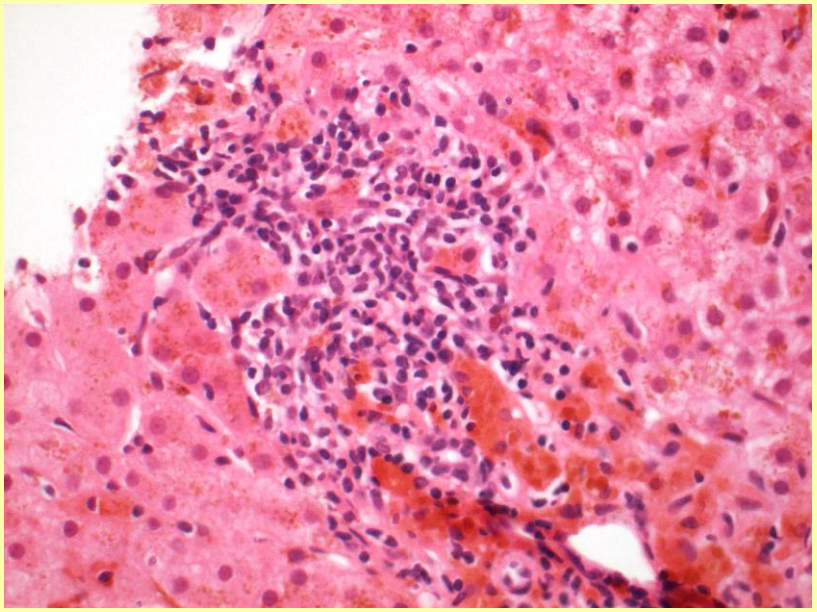


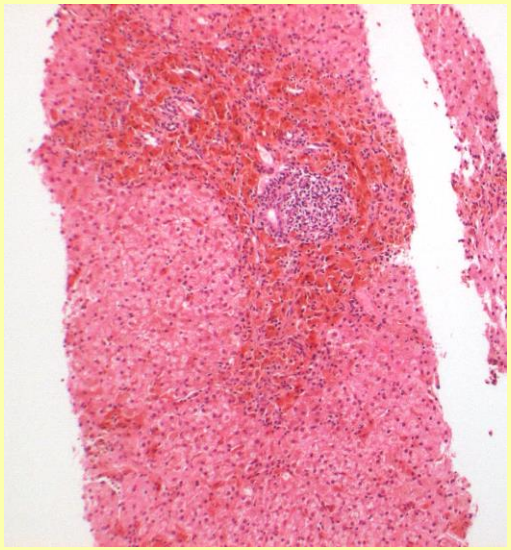


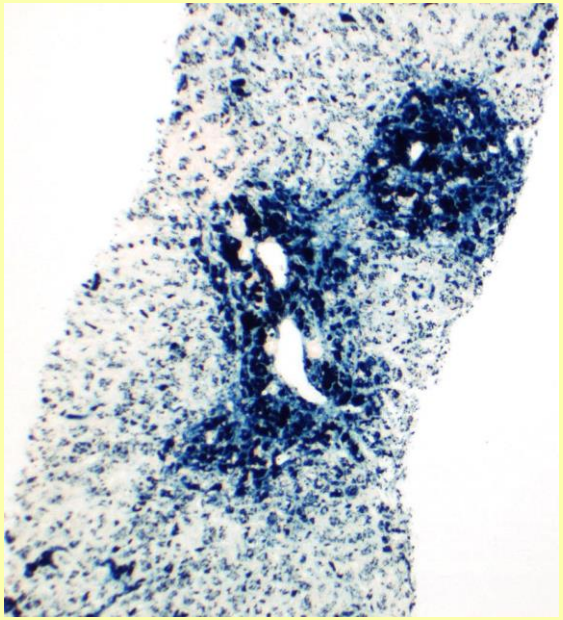


15yr M haemophiliac

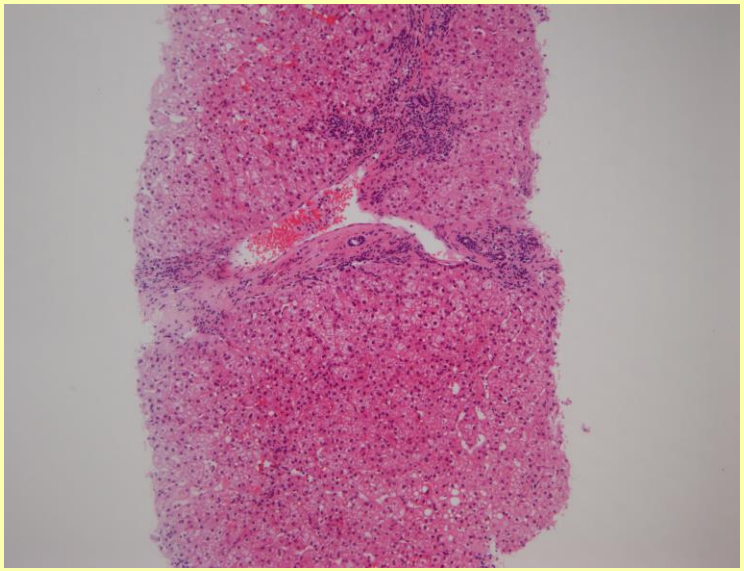


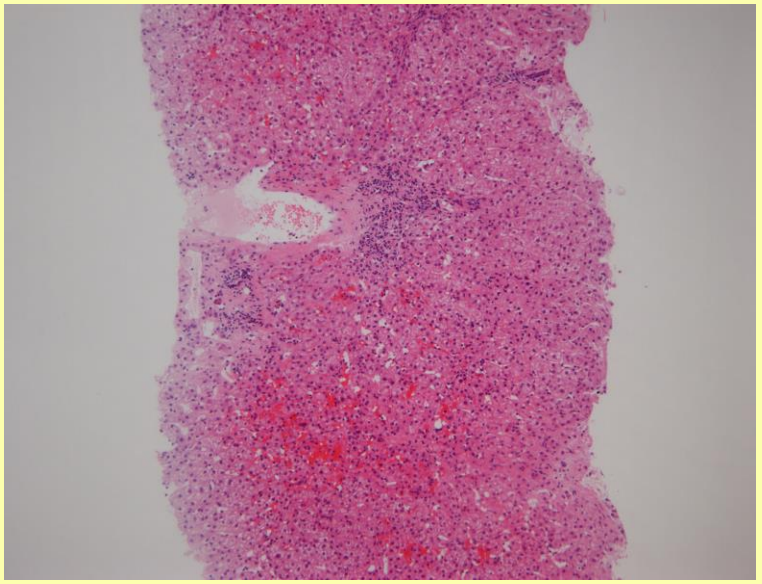


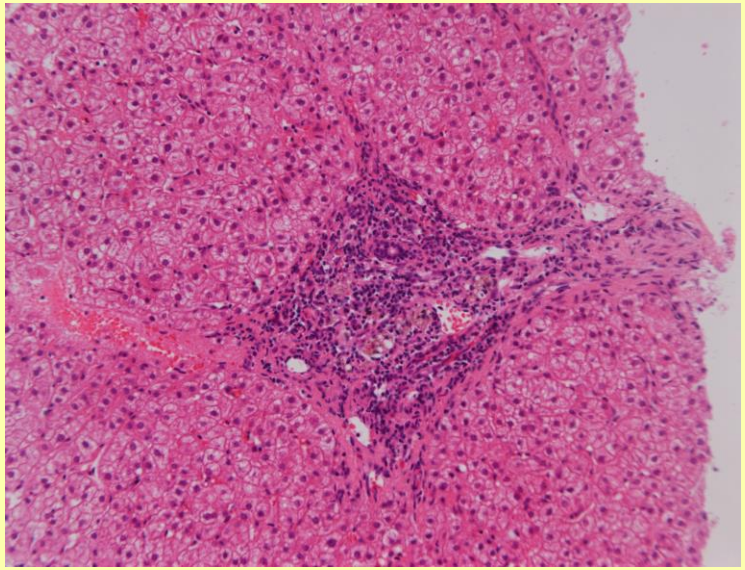


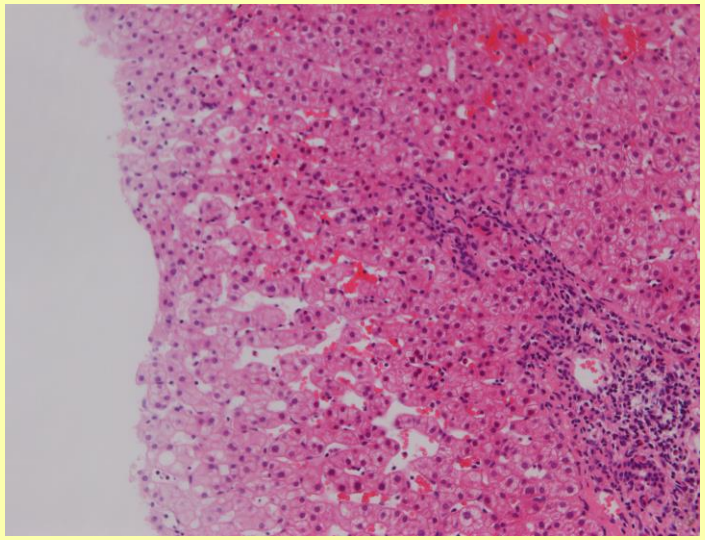


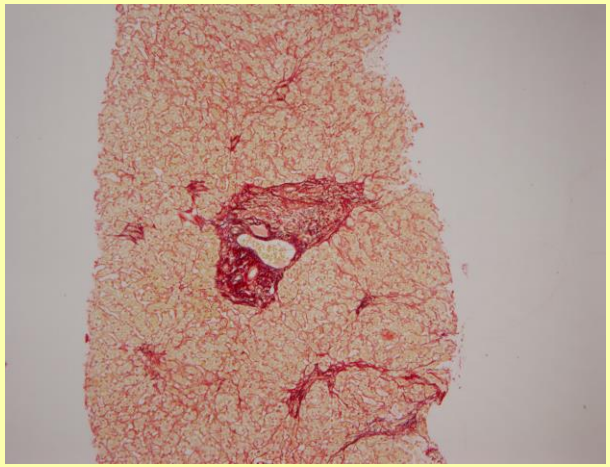
38yr F HCV

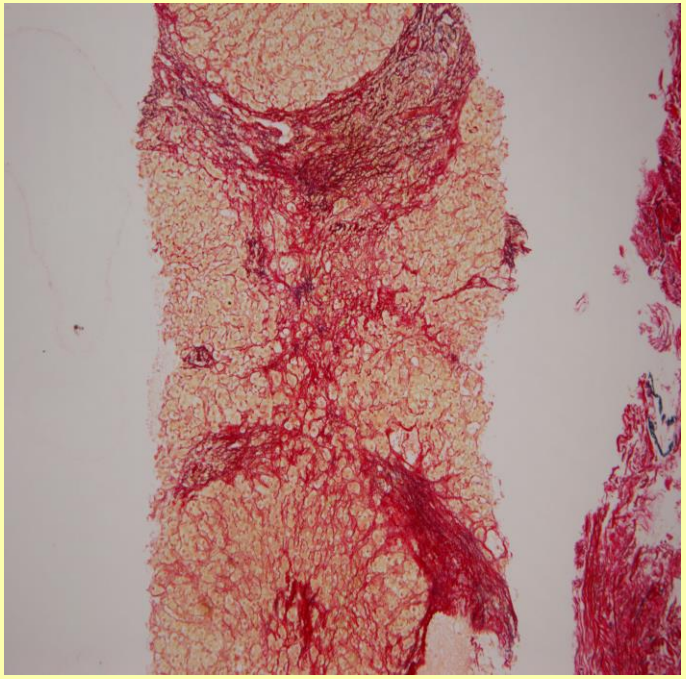


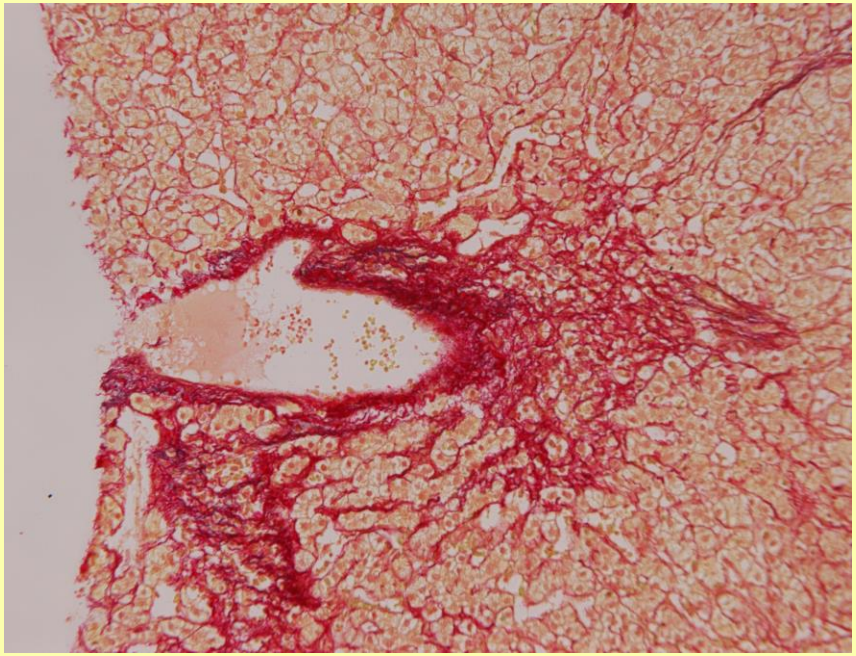












- Multiple viruses
- Geographical areas of infections
- Shared lifestyle
- Multi-treatment modalities for severe disease.

When could there be a 2nd pathology?

- Natural history or complication of the disease
- Common risk factors for other disease
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

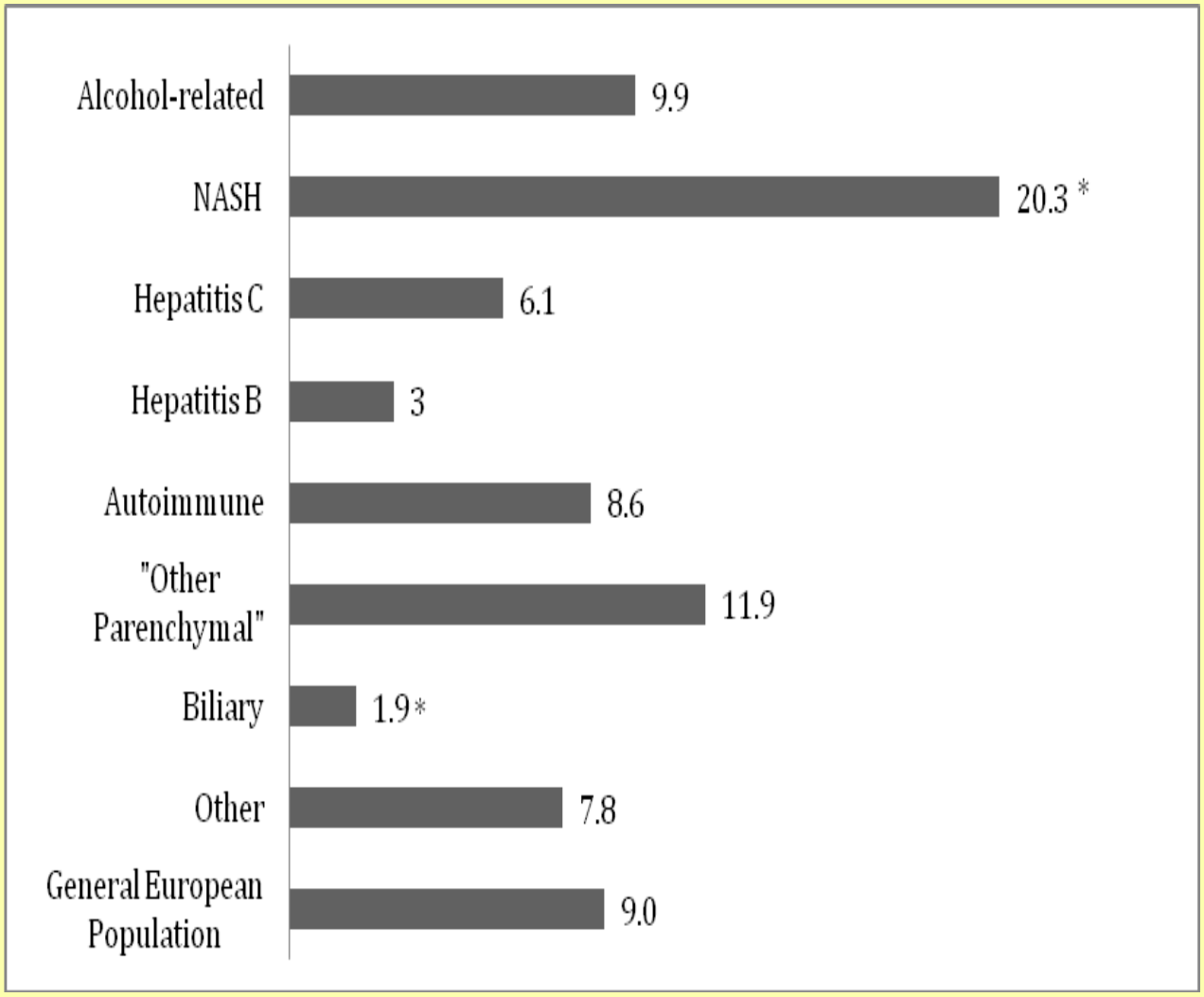
When could there be a 2nd pathology?

- Natural history or complication of the disease
- Common risk factors for other disease
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

Alpha-1-Antitrypsin

- Two main variants; S (60% of wild type) ~ 6.2% prevalence, Z (10% activity) ~ 2.7%
- Homozygous PiZZ – clear disorder with emphysema and cirrhosis
  - Heterozygous higher prevalence in some studies of chronic liver disease
- CUH analysed >1000 pts OLT assesment
  - IEF and/or histology (PASD & IHC PiZ)
    - Cacciotolo, Eu J Gas &Hep, 2014

RESULTS

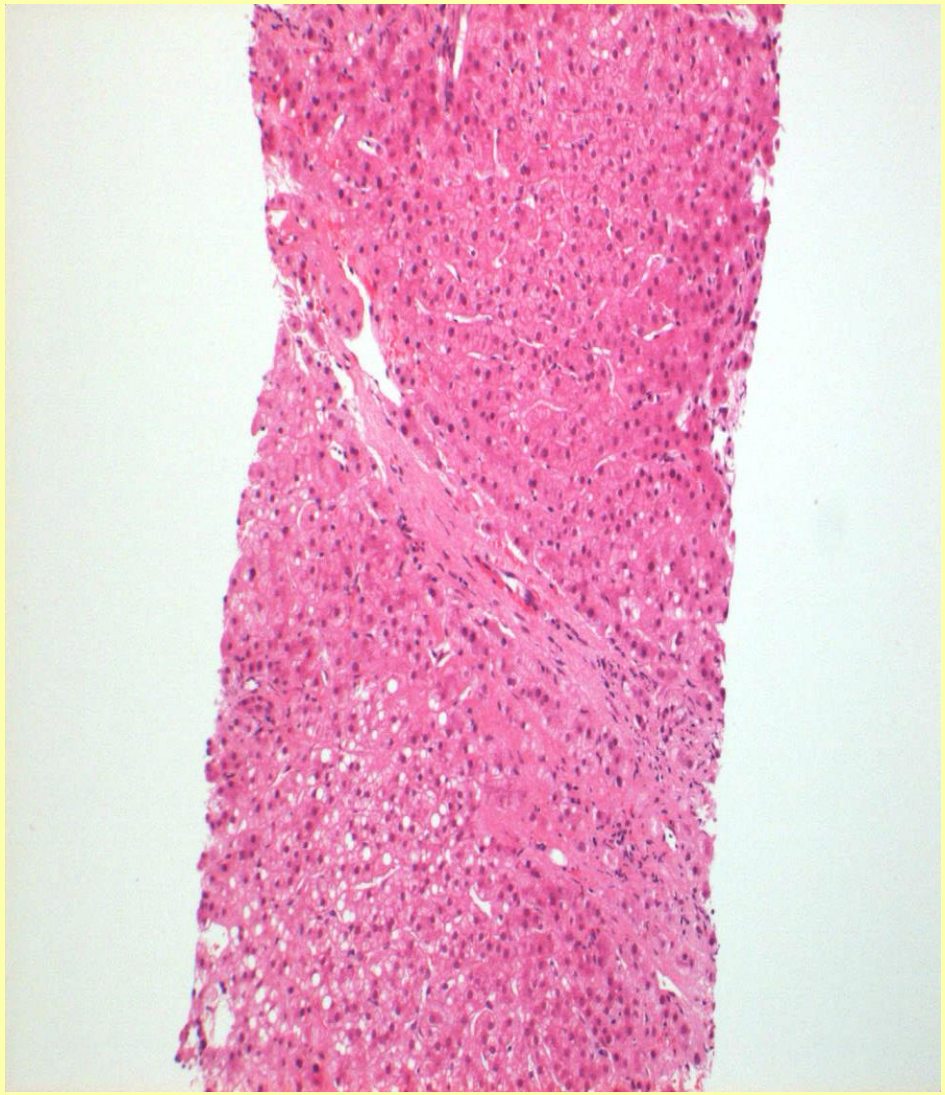


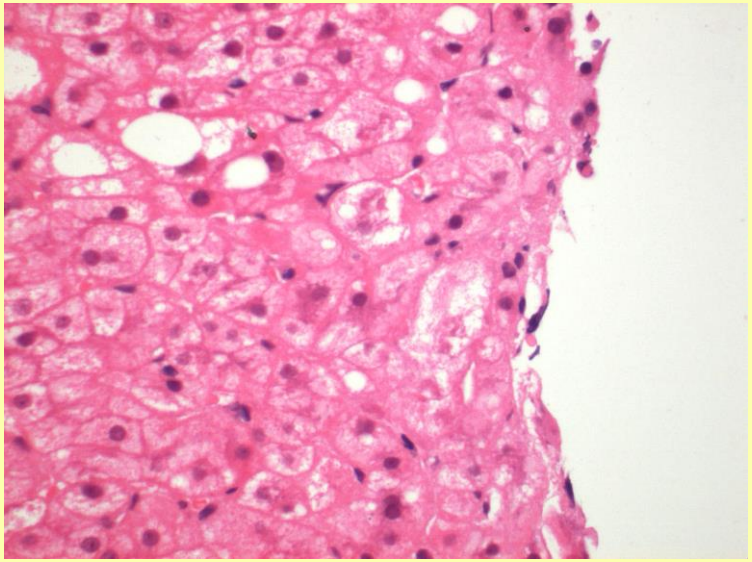
Mean Prevalence of Pi*Z Allele Carriers by disease group

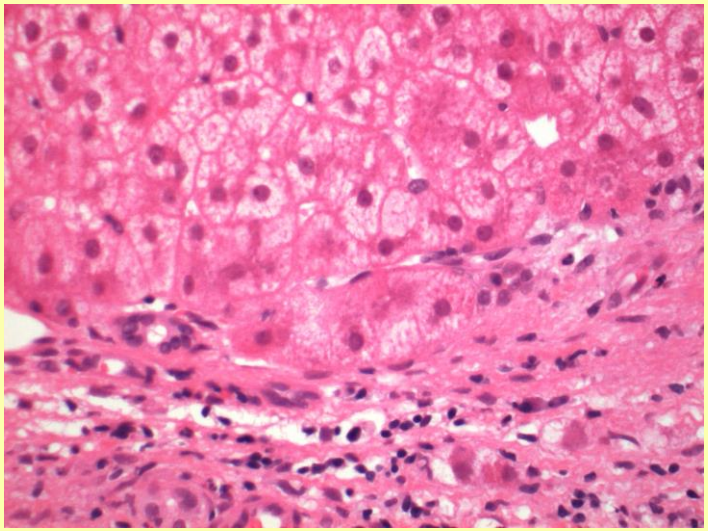
A1AT – is heterozygote a factor?

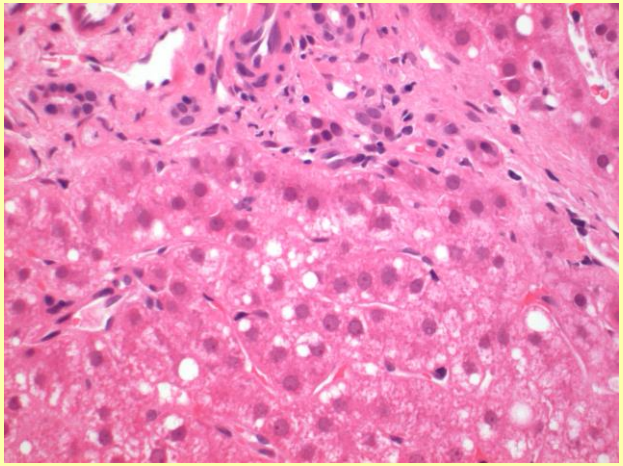
- 9.8% prevalence of heterozygote (underestimate of the MS type)
- 2.9% on histology only as IEF not done due to normal serum value
- PASD globules 95% positive predictive value
- IHC of PiZ 100% correlation with Z phenotype

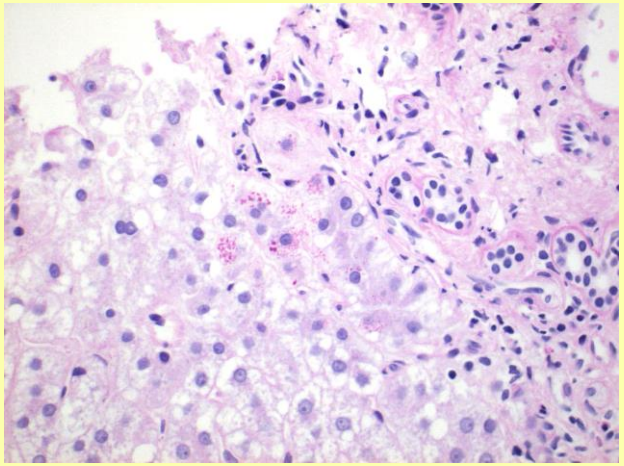
54yr F diabetic



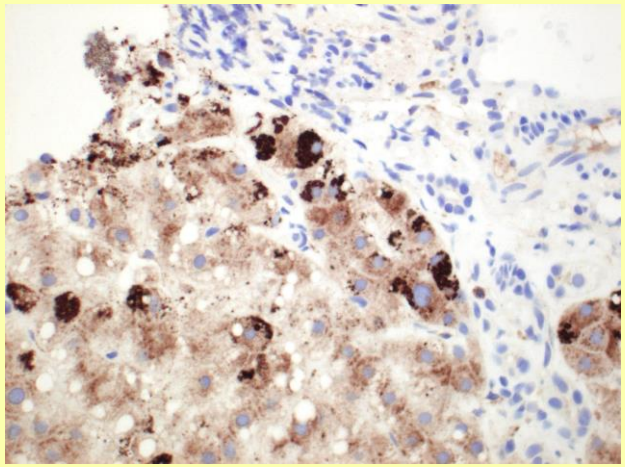




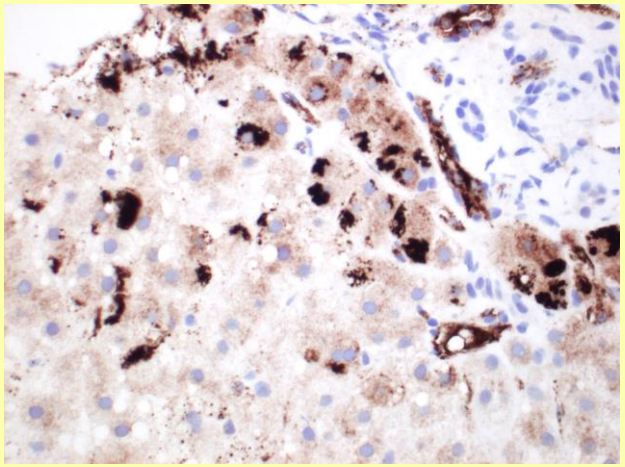




PASD



A1AT



PiZ

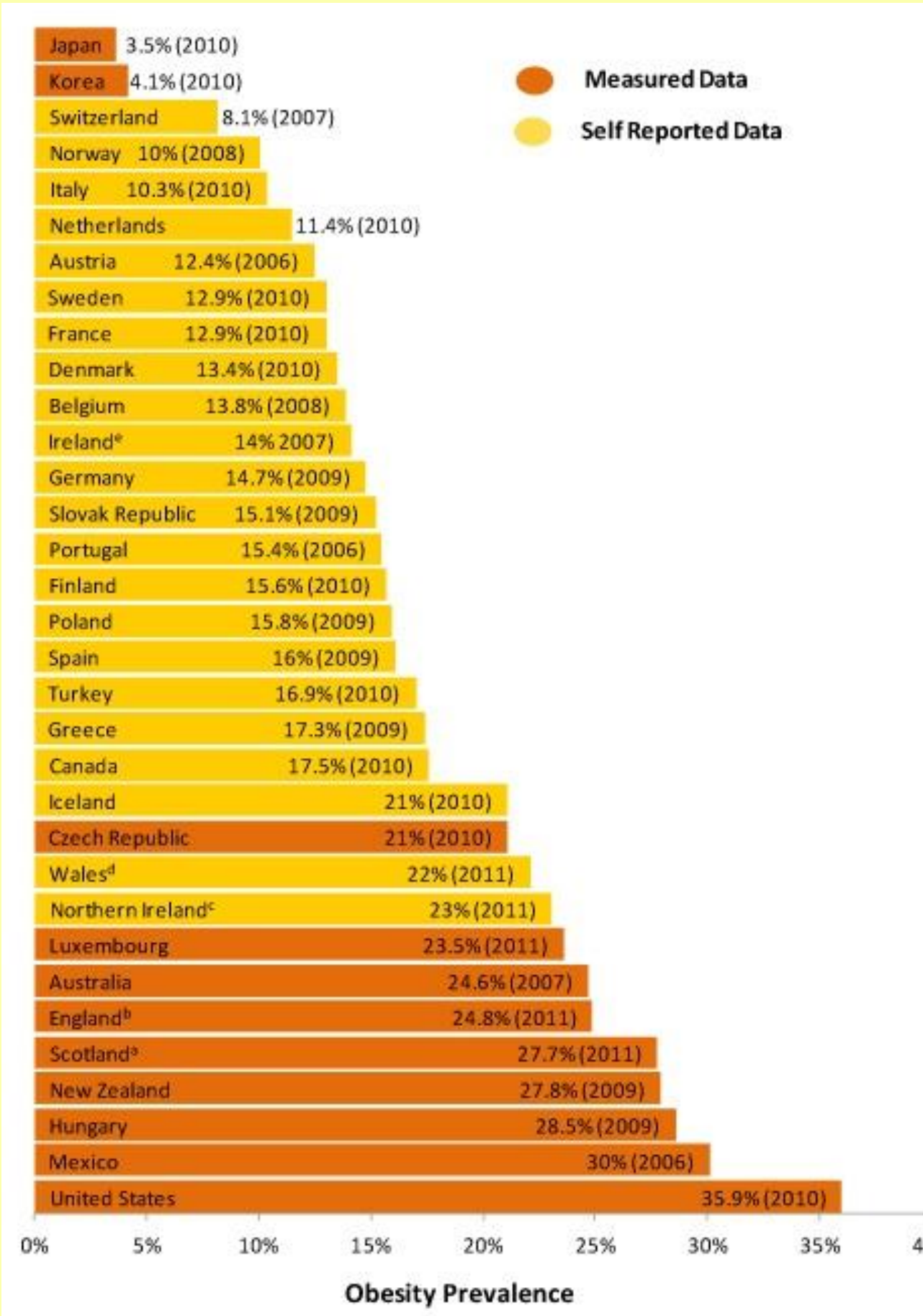
Iron

- Commonest genetic disorder
- HFE gene defects account 80-85% of HH, other genes of iron regulation now recognised
- Phenotypic expression is variable.
- Grade 2 or more would lead to investigation – or non-hepatocyte siderosis think of other genes or haematological causes
- Siderosis common in NAFLD - ?role of ferritin in insulin resistance. In HCV can impair treatment response.
- Caution – ferritin often raised in chronic liver disease

When could there be a 2nd pathology?

- Natural history or complication of the disease
- Common risk factors for other disease
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

NAFLD


Japan 3.5% (2010)
Korea 4.1% (2010)
Switzerland 8.1% (2007)
Norway 10% (2008)
Italy 10.3% (2010)
Netherlands 11.4% (2010)
Austria 12.4% (2006)
Sweden 12.9% (2010)
France 12.9% (2010)
Denmark 13.4% (2010)
Belgium 13.8% (2008)
Ireland* 14% 2007)
Germany 14.7% (2009)
Slovak Republic 15.1% (2009)
Portugal 15.4% (2006)
Finland 15.6% (2010)
Poland 15.8% (2009)
Spain 16% (2009)
Turkey 16.9% (2010)
Greece 17.3% (2009)
Canada 17.5% (2010)
Iceland 21% (2010)
Czech Republic 21% (2010)
Wales[d] 22% (2011)
Northern Ireland[c] 23% (2011)
Luxembourg 23.5% (2011)
Australia 24.6% (2007)
England[b] 24.8% (2011)
Scotland[a] 27.7% (2011)
New Zealand 27.8% (2009)
Hungary 28.5% (2009)
Mexico 30% (2006)
United States 35.9% (2010)
Measured Data
Self Reported Data
0%
5%
10%
15%
20%
25%
30%
35%
Obesity Prevalence

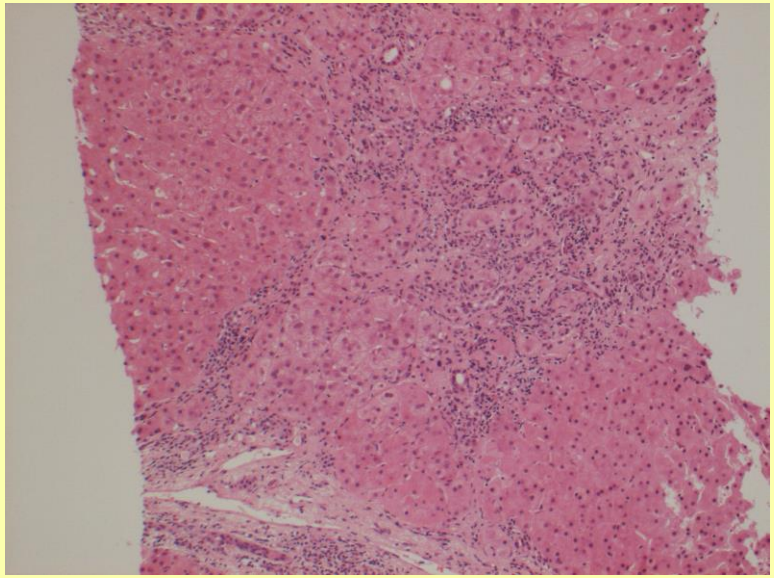
Alcohol

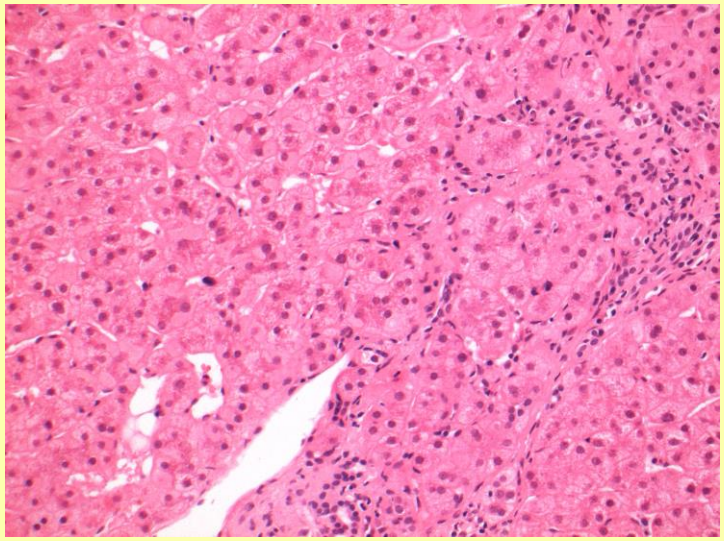
Difficult to separate from NAFLD often.

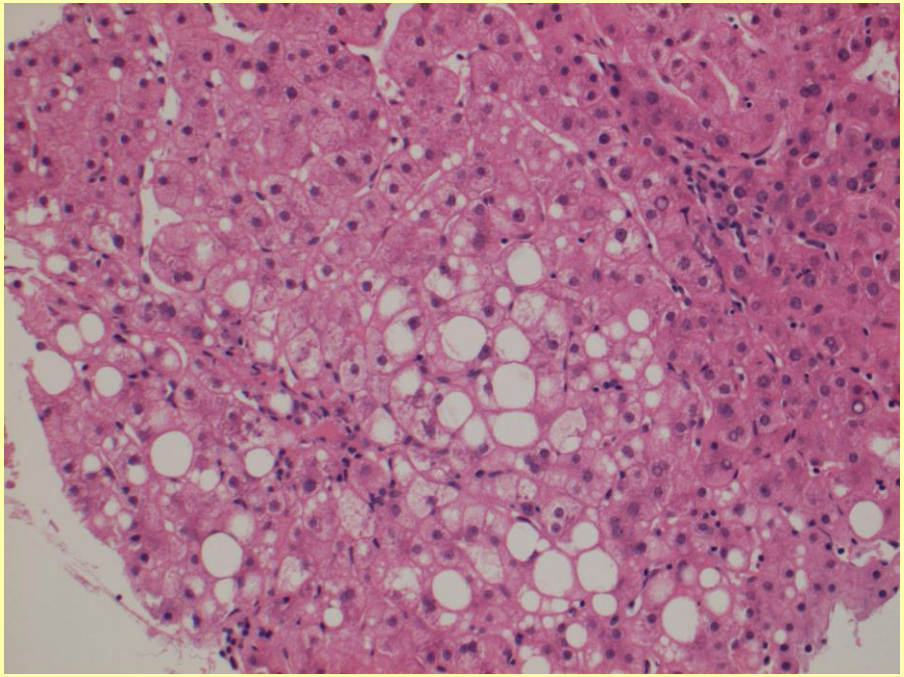
May be denied, so harder to establish clinically

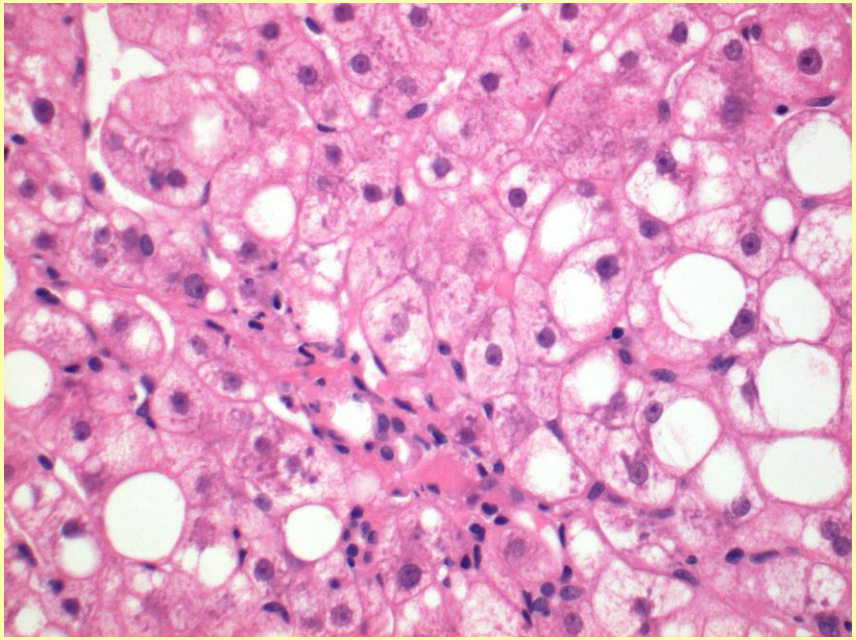
On increase in UK still

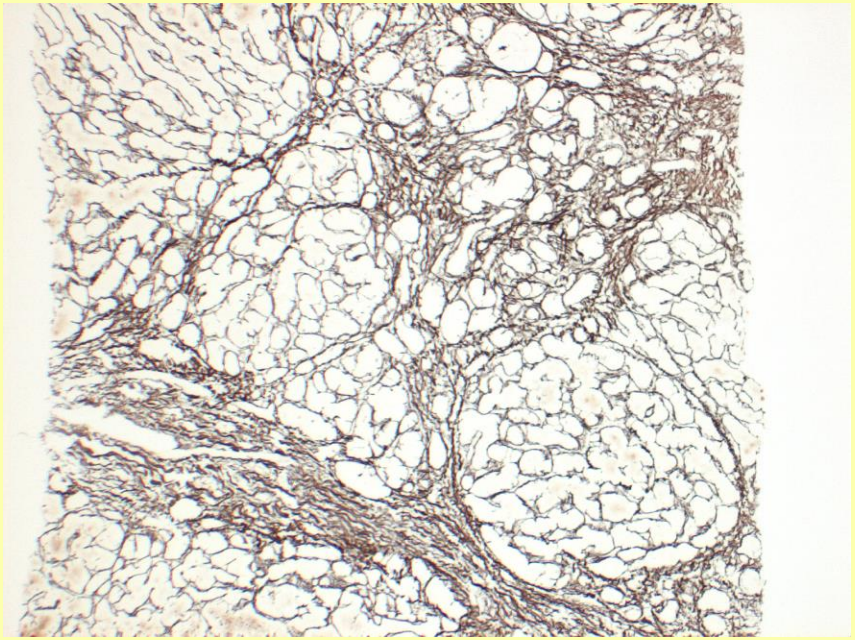
5yr M HBV pos









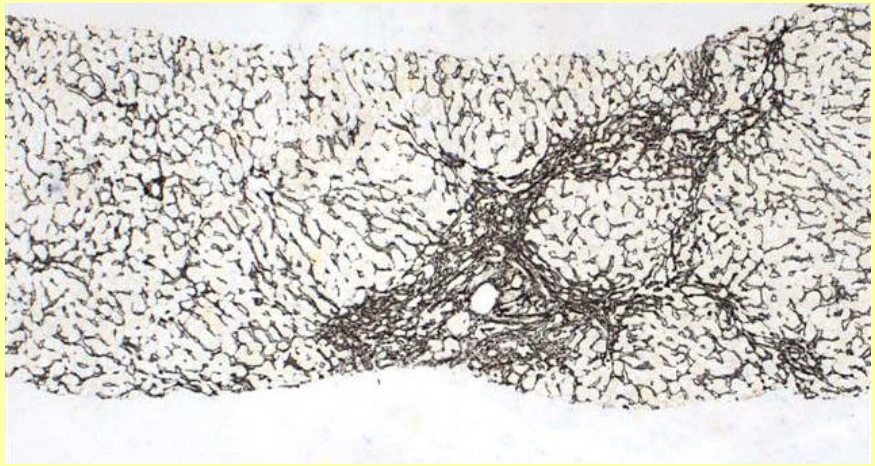


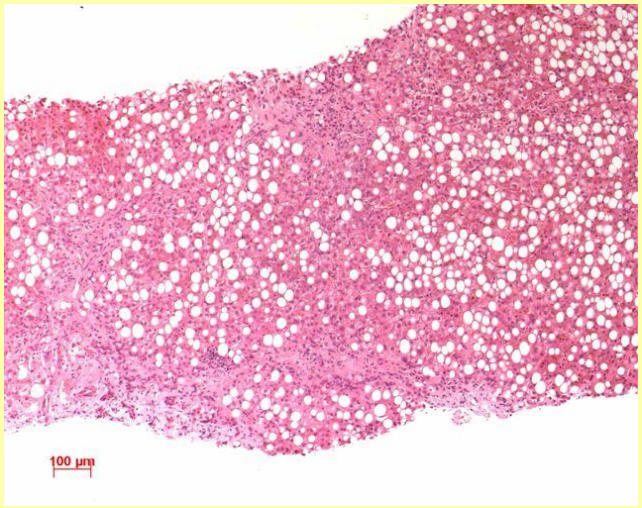
Drugs

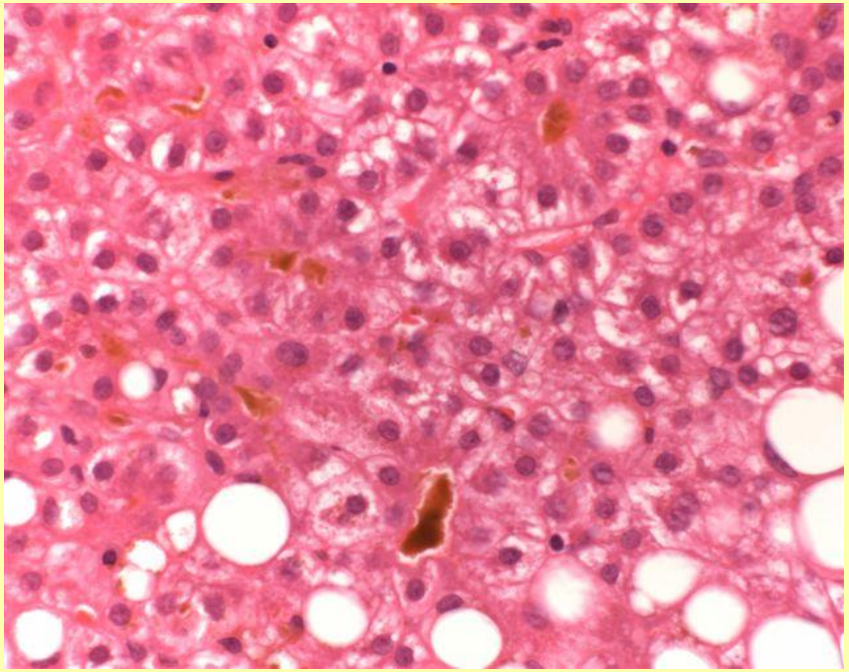
- Numbers consumed?

- Problem arises when pt with known disease or with risk factor gets a drug reaction

48yr old known alcoholic becomes jaundiced



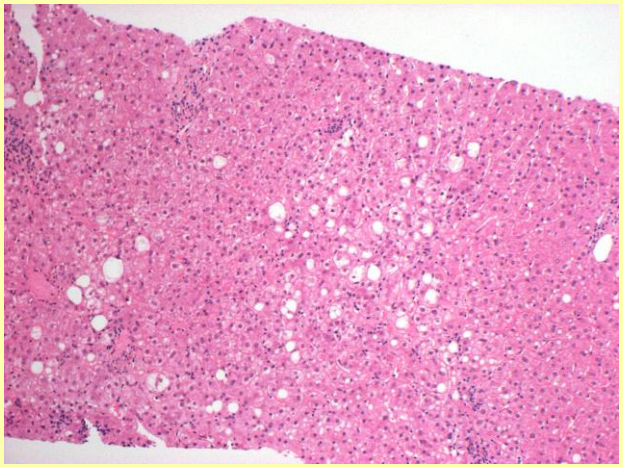


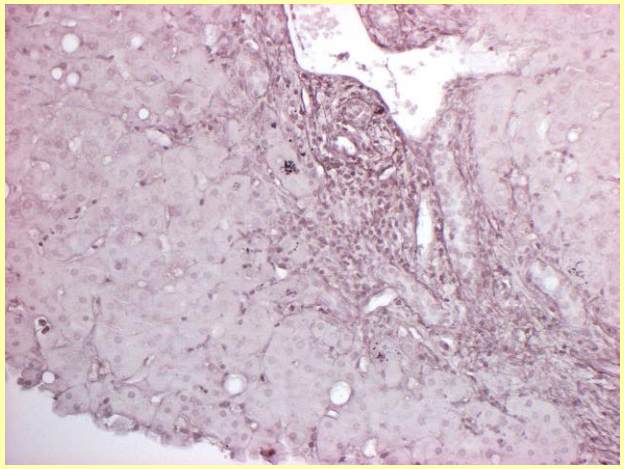


When could there be a 2nd pathology?

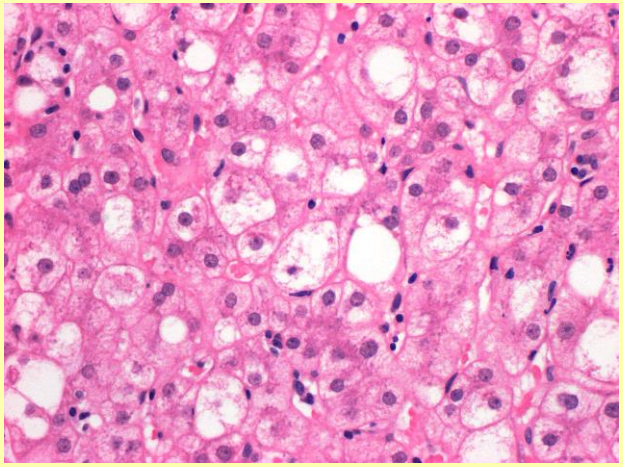
- Natural history or complication of the disease
- Common risk factors for other disease
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

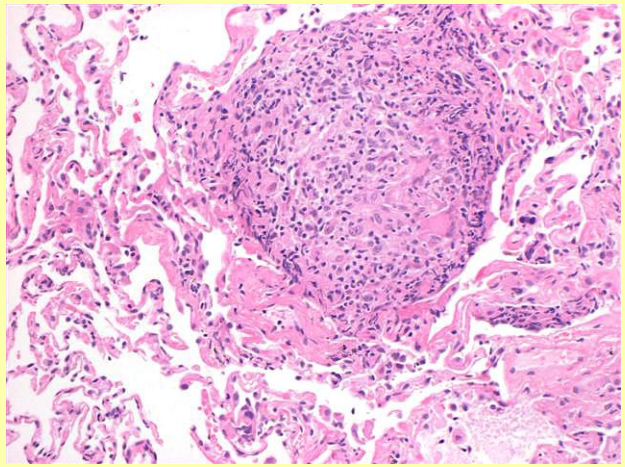
54yr M ? NAFLD





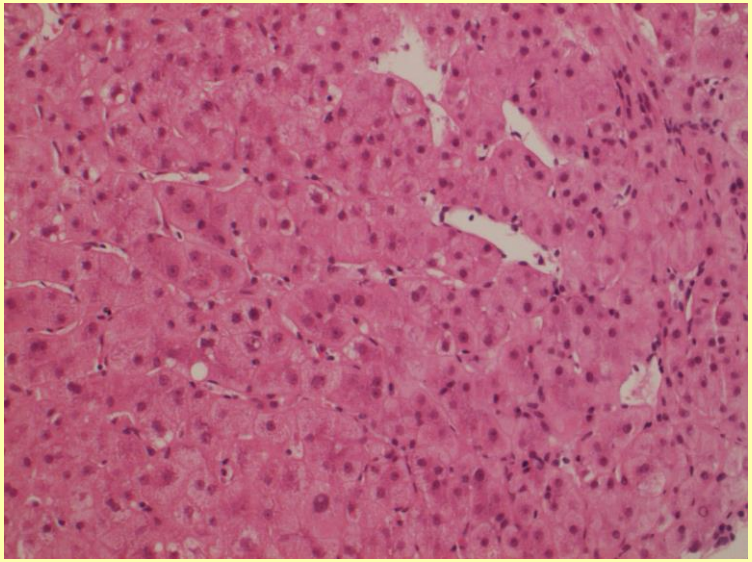
Too much CAP

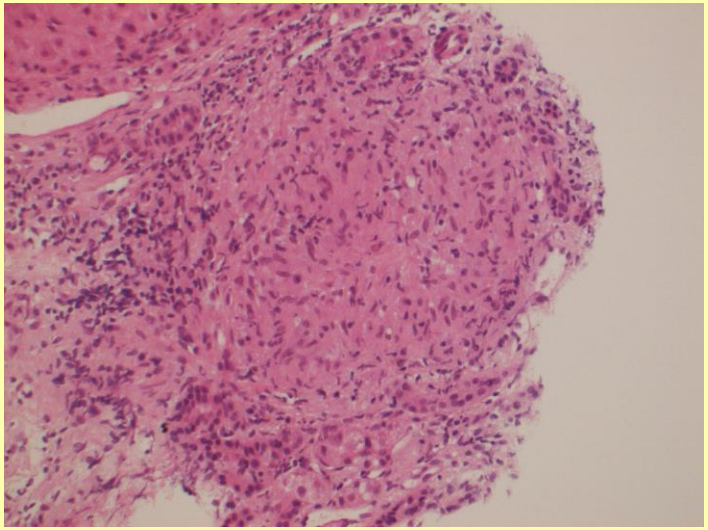


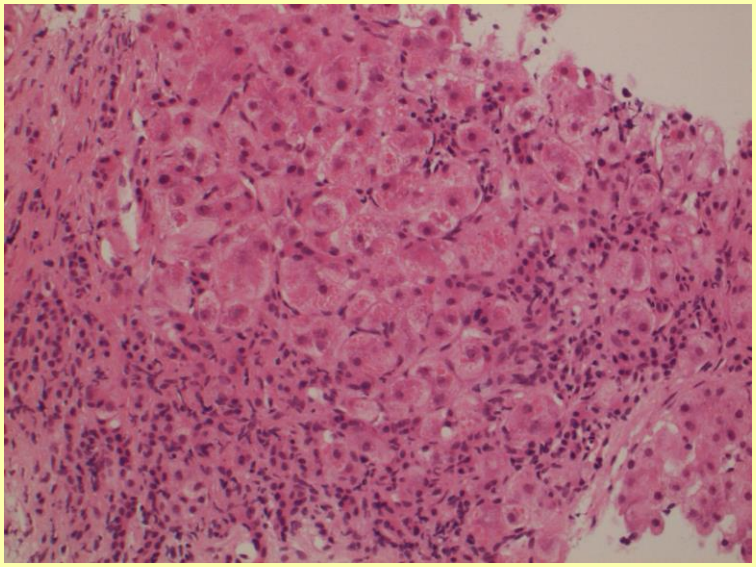


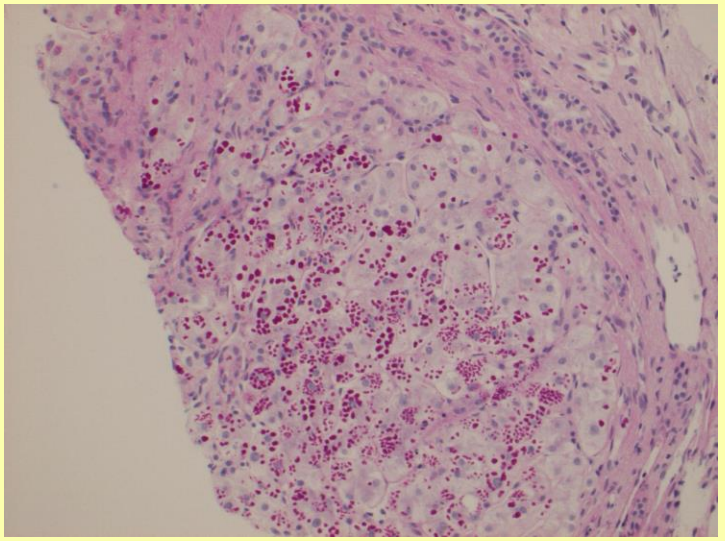
Subsequent lung biopsy

Abstinent alcoholic with abN LFTs



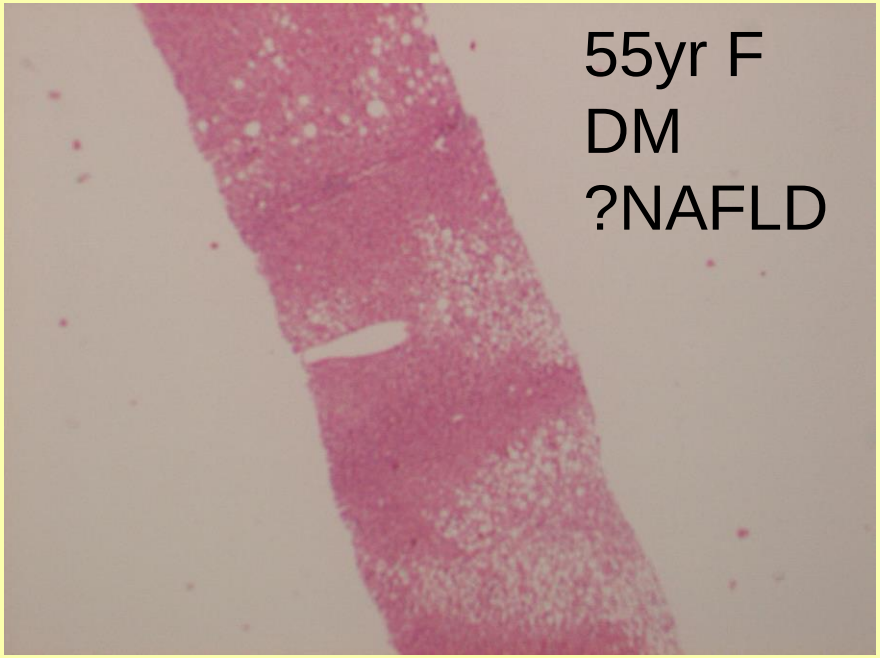


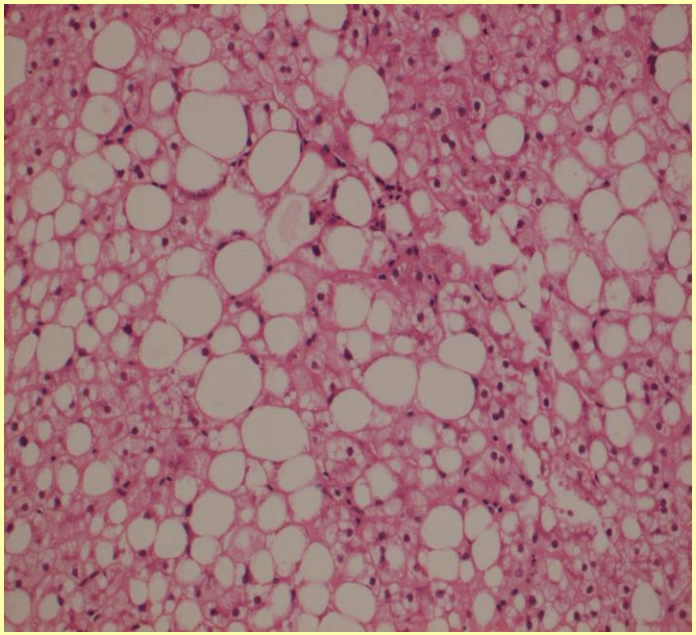


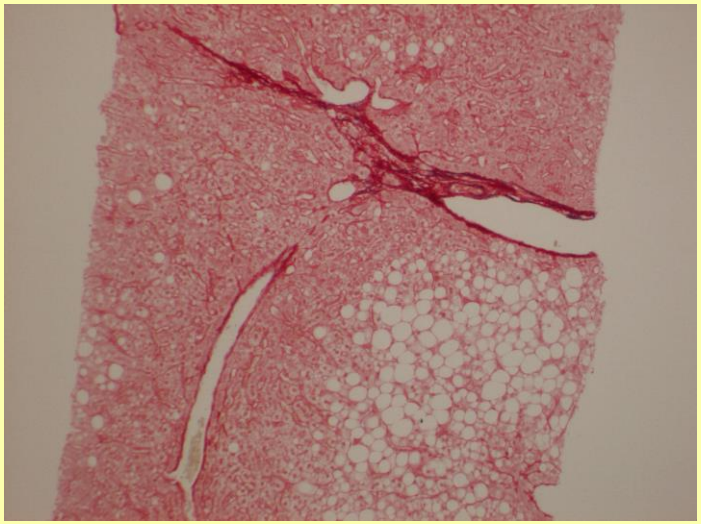


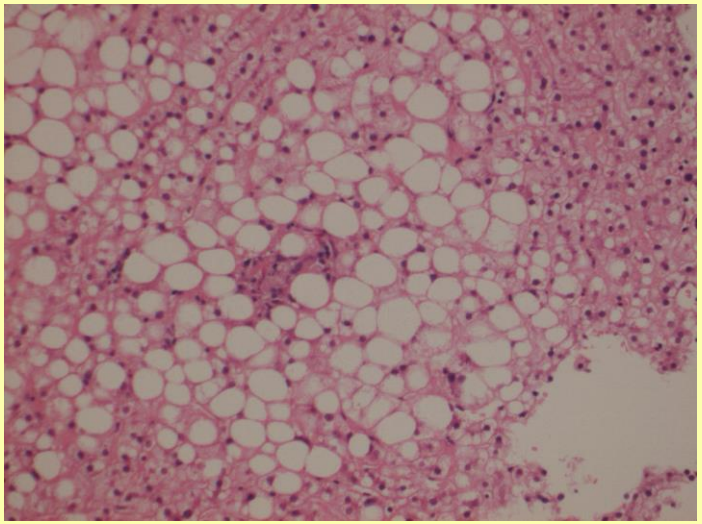
Granulomatous disease

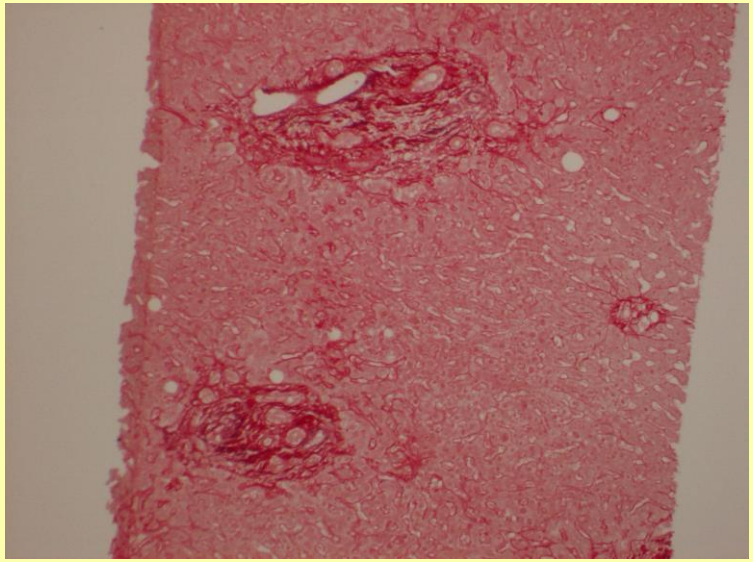
- Huge list of causal agents
- Huge list of drugs implicated

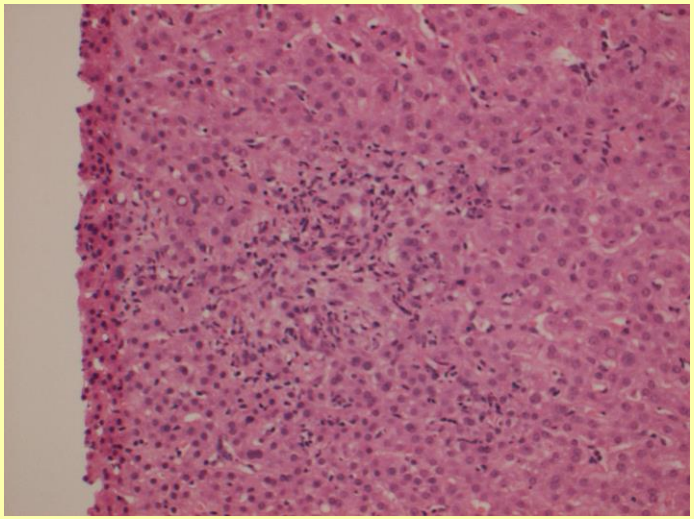

55yr F
DM
?NAFLD

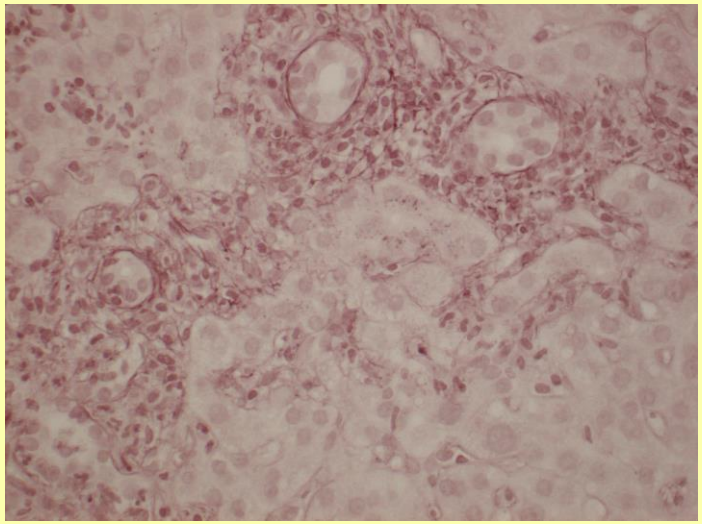


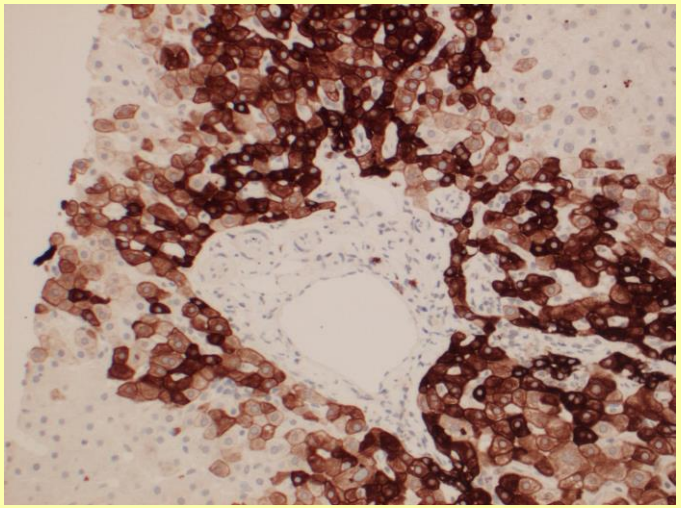












Is it a real issue? CUH study

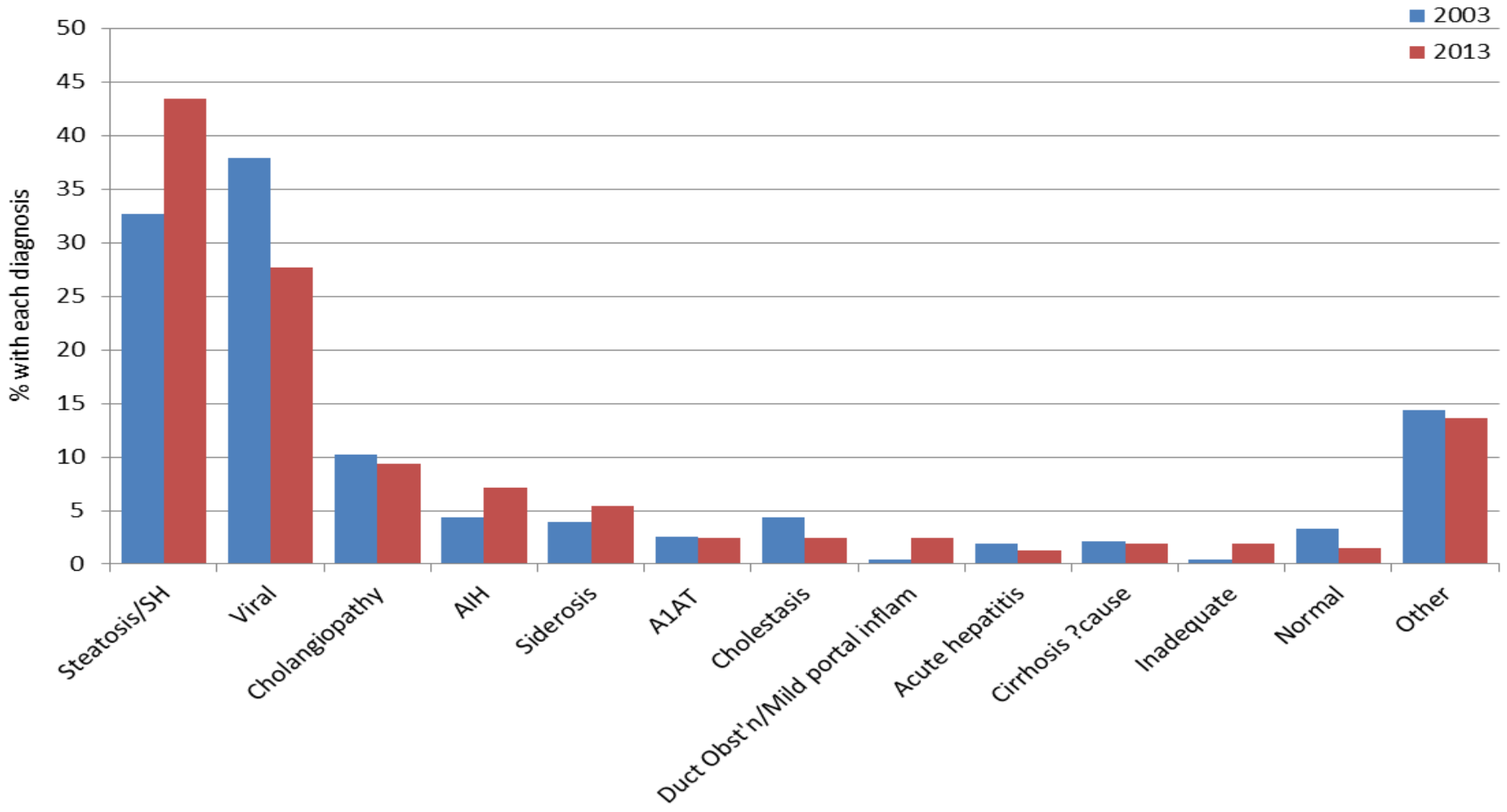
2003

- 85/480 (18%) >= two pathologies
- 4/480 (1%) three pathologies
- In 61/85 (72%) cases, based on the clinical details provided, the dual pathology was not expected

2013

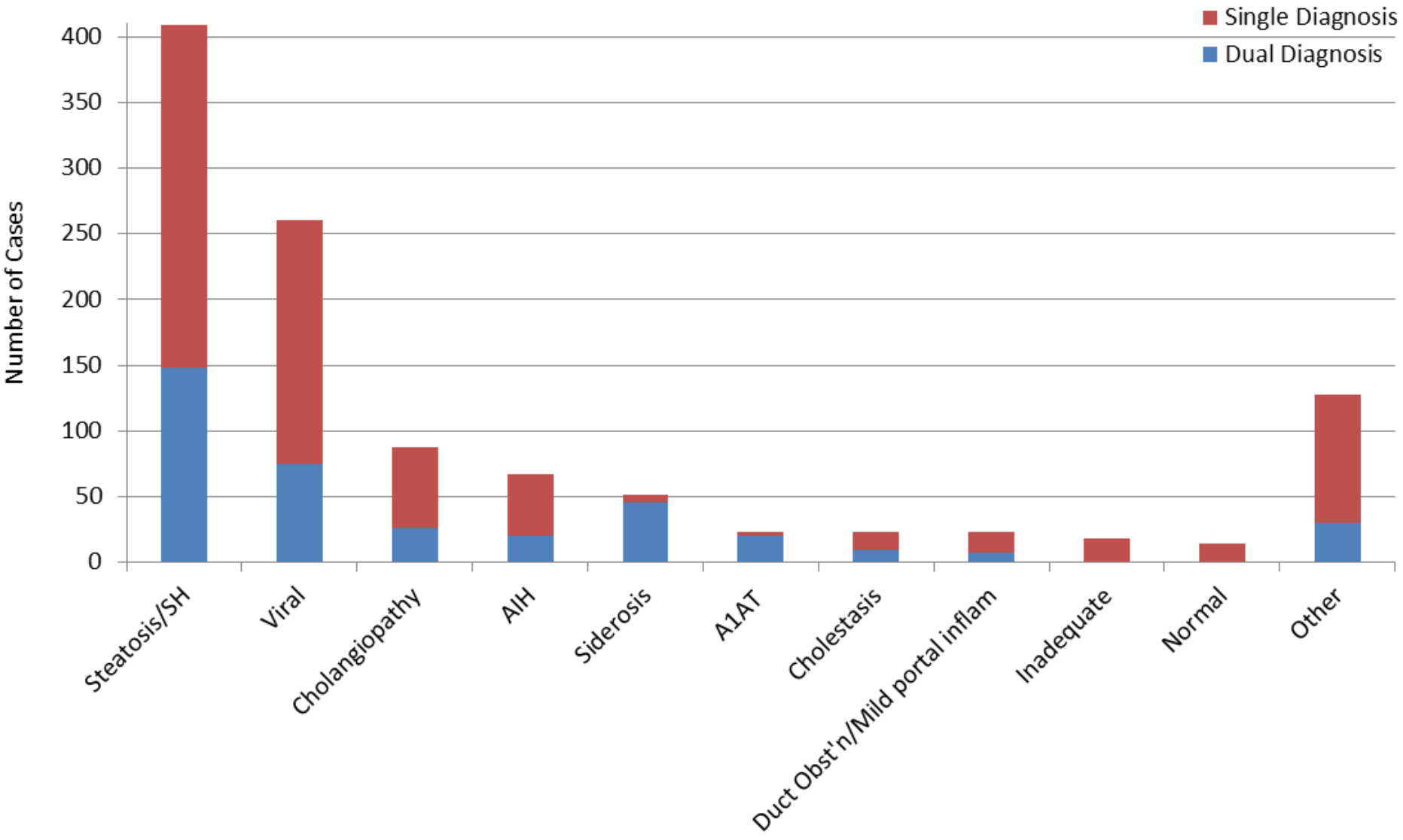
- 189/941 (21%) >= two pathologies
- 9/941 (1%) three pathologies
- In 152/189 (80%) cases, based on the clinical details provided, the dual pathology was not expected

Pathologies Present (2003 & 2013)



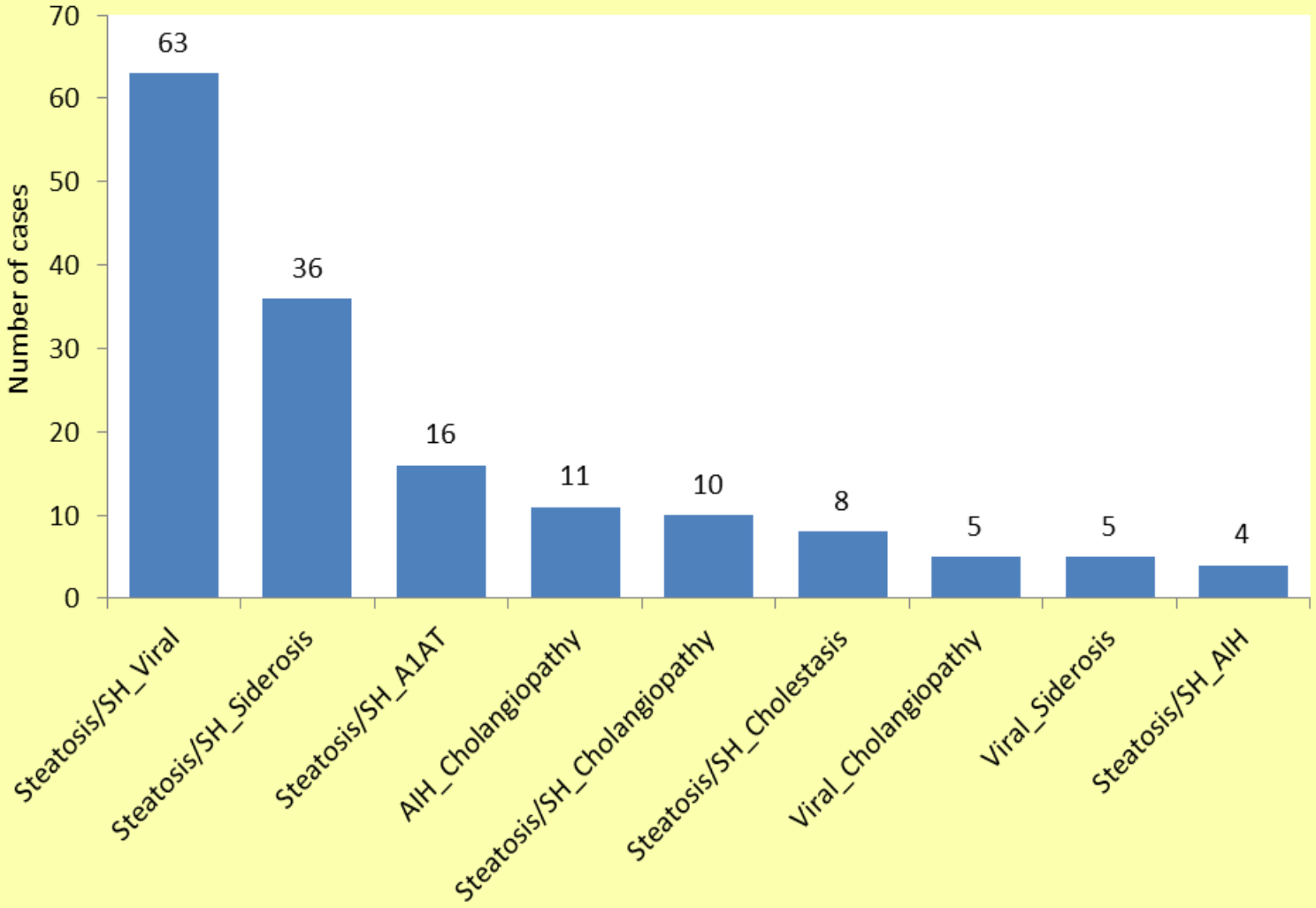
Dual Pathology (2013)

Number of cases with each pathology; including the number that are present as part of a dual pathology. Pathology present based on microscopy not the clinical impression.



Pathology Combinations (2013)

Number of cases with particular combinations of pathologies in 2013; 158 of 189 cases are shown. In the remainder cases the dual pathology occurs in <4 cases or one of the pathologies is classified as "other".



Conclusion I - on being faced with a liver biopsy

- Do all of the histological features fit the presumed clinical diagnosis?
  - Good histochemistry
- Common things are common
  - we consume shed-loads of food, alcohol and drugs! Could they be having an affect?
  - have these risk factors brought someone to medical attention – but there is another or additional aetiology at play?

Conclusion II

- Do the patterns of LFTs and serology fit fully with the presumed clinical diagnosis?
- In other words, why was the biopsy taken?
  - COMMUNICATION – clinico-pathological correlation.

- Identifying all of the disease processes is important, for treatment and management strategies and also prognostication.

Thanks

- Anna Paterson
- Rebecca Brais
- Liver Unit of CUH