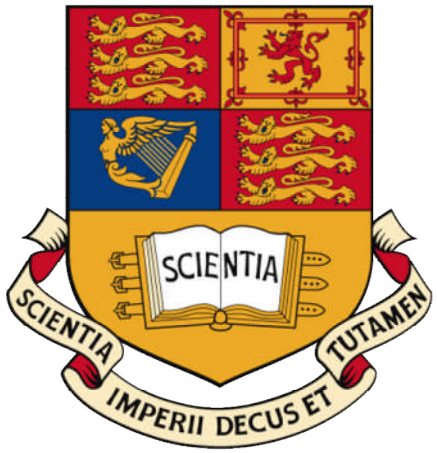
Imperial College
London

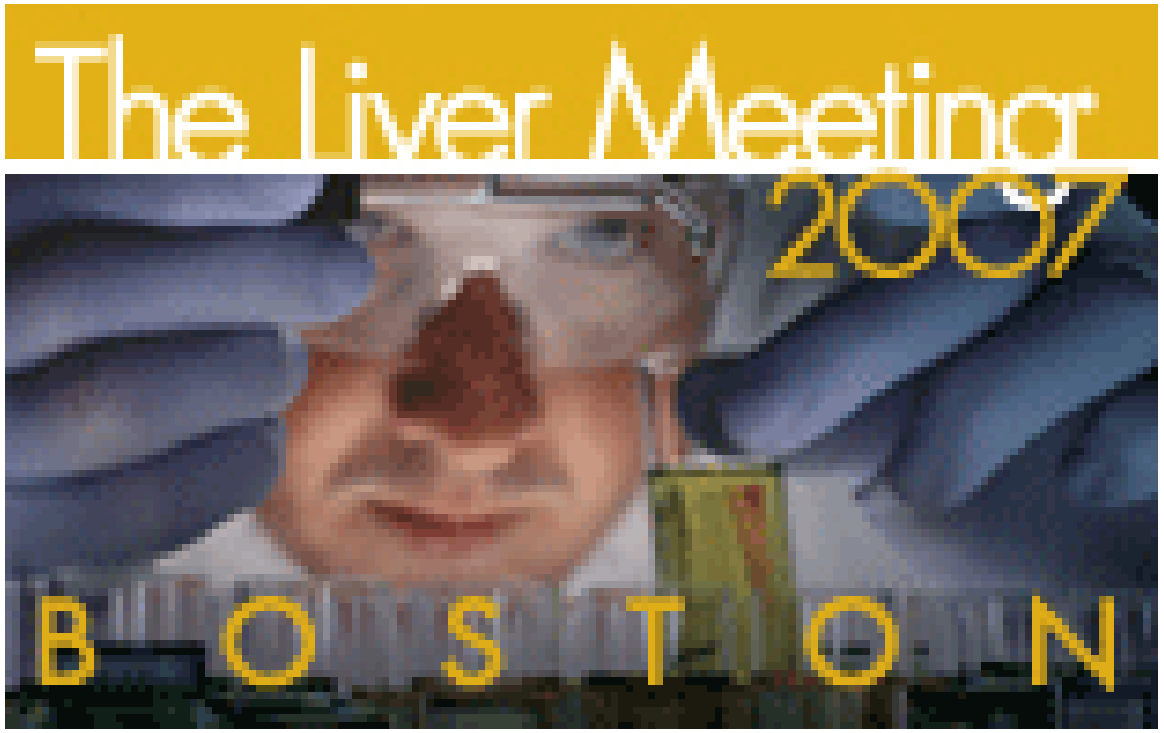
Highlights from this year's AASLD meeting

Rob Goldin

Update in Liver Histopathology

Lancaster 2007





https://www.aasld.org/

Postgraduate Course:
Pathophysiologic Basis for the Therapy of Liver Disease

1. Pathology of genetic liver disease (**Clouston**)
2. Histopathology of nonalcoholic (metabolic) fatty liver disease (**Brunt**)
3. Assessment of fibrosis liver biopsy in HCV (**Goodman**)
4. Vascular mechanisms in liver disease (**Wanless**)
5. Dysplasia and neoplasia in the liver (**Roskams**)

Biliary tract disease

69

Natural history of small duct primary sclerosing cholangitis

69

- Said to have a more favourable diagnosis than large duct PSC

83 patients, median follow-up 13 years:

- Significantly better long-term survival than large duct disease
- ¼ of patients progressed to large duct PSC
- No cases of cholangiocarcinoma

704

Progression in PBC: New insights from follow-up liver biopsies after diagnosis

704

- 56 paired liver biopsies
- 93% female, average age 46 years, 80% AMA positive
- Treated with UDCA

- **Fibrosis progression was greater in patients:**

1. Who did not response to treatment
2. With higher baseline ALT levels
3. With higher titres of anti-glycoprotein-210 antibodies
   (Hepatology 45 (1): 118)

- **Non response to treatment was associated, in the initial biopsy, with:**

1. Interface hepatitis
2. Ductopaenia

1036

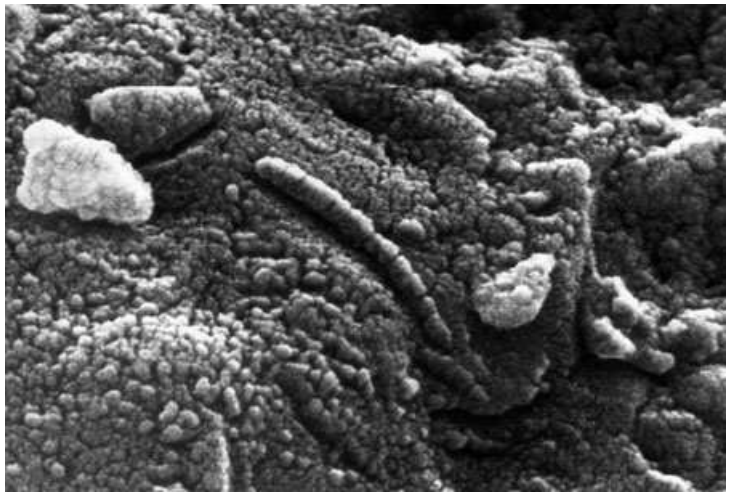
The role of nanobacteria in cholecystitis and cholelithiasis

1036

- Nanobacteria are submicroscopic blood particles (less than 200nm in diameter)
- May contain RNA
- They form calcium phosphate shells

- **Have been found in:**

1. blood
2. atheromatous plaques (*Am J Physiol Heart Circ Physiol* 2004; 287 (3): H1115)
3. kidney stones (Urol Res. 2006;34(1):53)
4. placenta (J Biosci. 2007;32(6):1163)
5. breast (Breast J. 2006;12(3):287)



1036

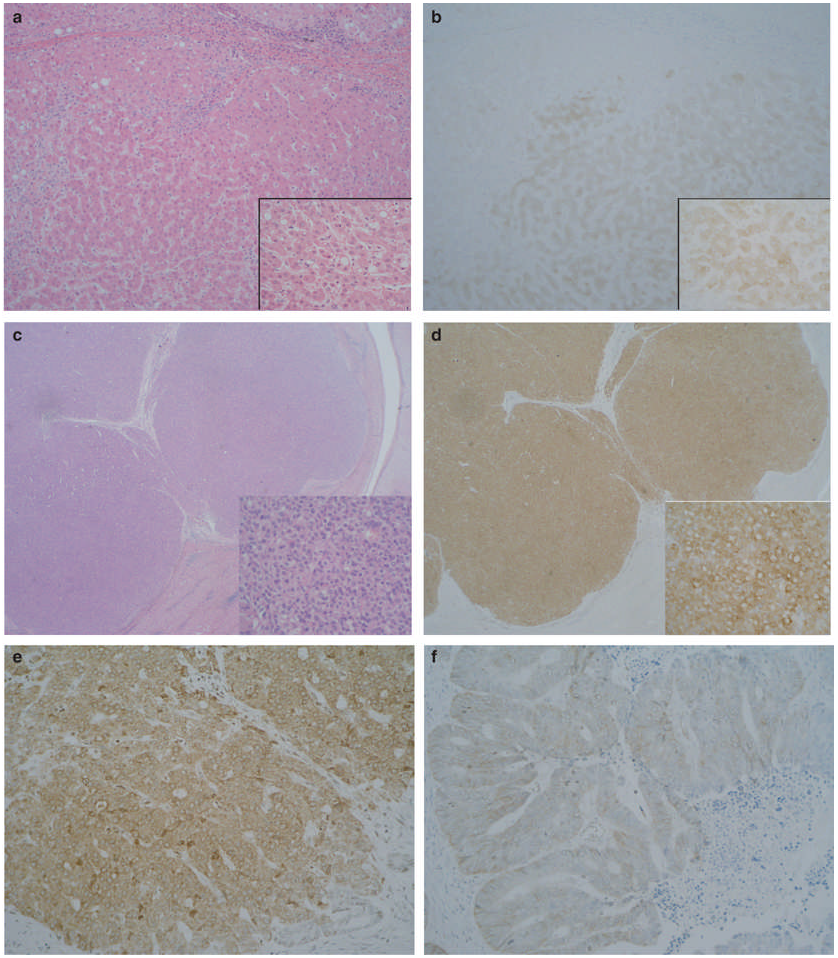
- Nanobacteria were identified, immunohistochemically, in 25/26 cases of cholecystitis
- They were found in the epithelium, inflammatory sludge and stones

Liver Tumours

357

Validation study of the prognostic immunohistochemical marker glypican-3 in HCC

Modern Pathology 2005:18;1591



a and **b**: GPC3 immunohistochemistry of hepatic dysplastic nodule (low grade)

c and **d**: GPC3 immunoreactivity of hepatocellular carcinoma.

e: GPC3 immunohistochemistry of hepatoblastoma

f: GPC3 immunohistochemistry of hepatic metastasis of colorectal carcinoma.

357

	sensitivity	specificity
Leuven 2003	0.77	0.96
Leuven 2007	0.84	0.96
Milan 2007	0.79	0.87

357

For the diagnosis of small focal lesions in cirrhosis, glypican–3 staining is:

1. Easily interpretable
2. Reproducible

360

Hepatocyte differentiation in cholangiocarcinoma, suggesting hepatic progenitor cell origin

360

- Cholangiocarcinoma has a poor prognosis
- Hepatic progenitor cells (HPC) play a role in the development of HCC
- HCCs with HPC features have a worse prognosis

360

- 93 cases
- **Hepatocellular differentiation markers:**
  Hepar, pCEA, CD10
- **Biliary / progenitor markers:**
  CK7, CK19, NCAM

360

- 40% of CC showed hepatocyte differentiation (CCH)
- **CCHs showed 2 patterns:**

1. Thick trabecula and cells with abundant eosinophilic cytoplasm *and/or*
2. Cords with small uniform cells

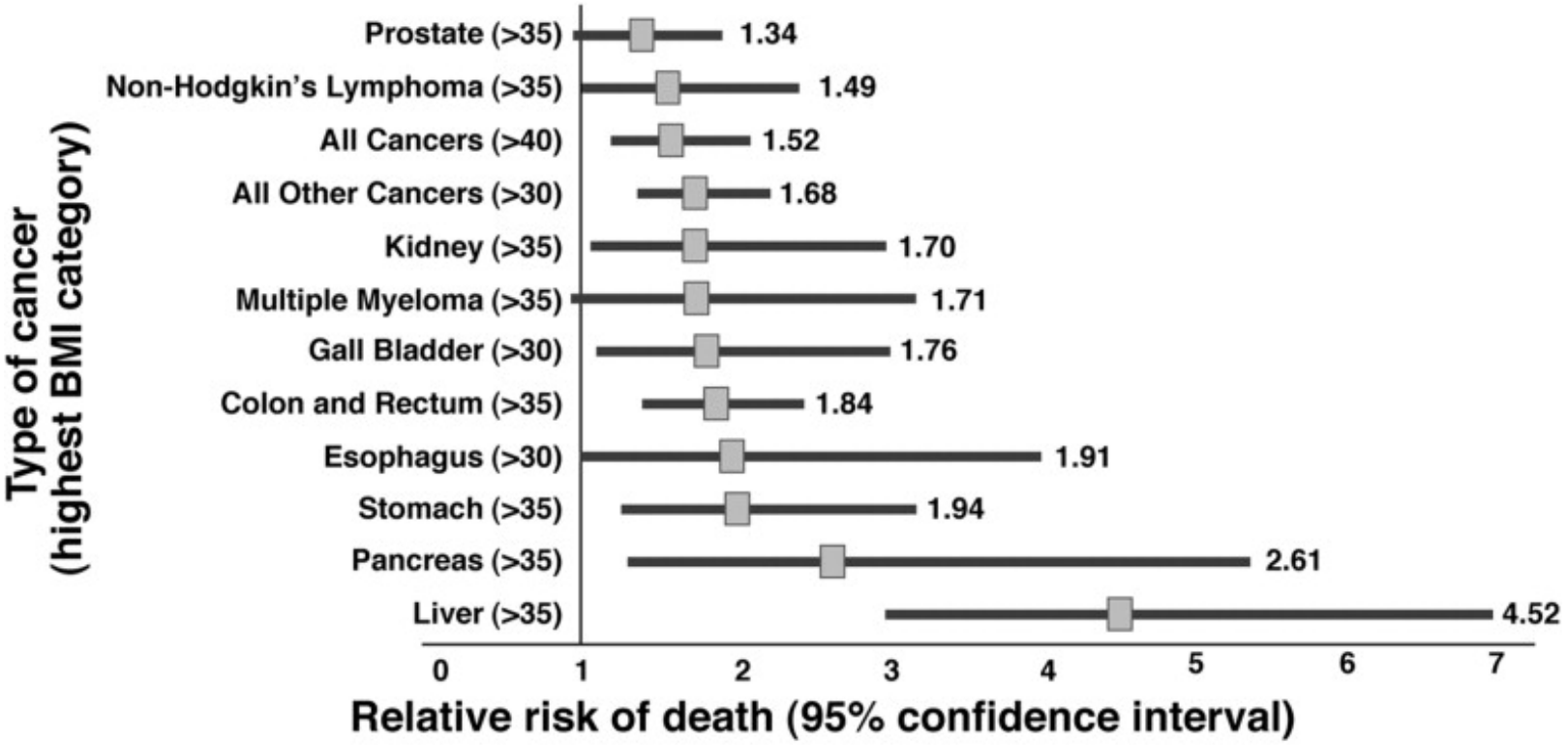
- **Immunohistochemical findings in each pattern:**

1. Intermediate CK 7 positive cells (with a submembranous pattern of staining) with canalicular staining in most cases
2. HPC-like small, round oval cells with cytoplasmic CK7 +/ CK19+ (most also NCAM positive)

370

HCC in patients with the metabolic syndrome

Obesity and HCC



N Engl J Med 2003 ;348:1625

Liver tumours associated with the metabolic syndrome

1. Liver cell (telangiectatic) adenomas

   Hepatology 2007;46:140

2. Focal nodular hyperplasia
3. Hepatic adenomatosis

   Nature Clinical Practice Gastroenterology & Hepatology 2006;3: 526

4. Hepatocellular carcinoma

370

- 28 patients with the metabolic syndrome, all elderly Caucasian males, had a resection for HCC
- **Results:**

1. Significant fibrosis in 35% (24.5% with cirrhosis)
2. In HCCs arising in normal liver 5/18 arose from pre-existing adenomas (3/5 telangiectatic)

- **Conclusion**

  Telangiectatic adenomas are a significant pathway for the development of HCCs in the metabolic syndrome

377

Grading of microscopic vascular invasion for resected hepatocellular carcinoma

Vascular invasion in HCC

9.1.2 Vascular invasion

Microscopic vascular invasion is an important prognostic factor;[10-12] tumours with microscopic vascular invasion are stage pT2.

It is often difficult to determine whether nodules of hepatocellular carcinoma surrounded by fibrous tissue, adjacent to the main tumour represent vascular invasion, unless a part of the endothelialised lumen is apparent. Vascular invasion may be suspected where the nodule is within a portal area, at the site appropriate to a portal vein, or by the presence of satellite nodules; these should prompt a thorough search for vascular invasion. However, for proper classification for TNM purposes, where the tumor nodule is within a portal area at the site appropriate to a portal vein, vascular invasion is only confirmed if one can clearly identify the lumen and endothelium of a portal vein (personal communication: Professor LH Sobin, TNM Helpdesk).

http://www.rcpath.org/resources/pdf/G050DatasetLiverSept07-AR.pdf

377

- In 384 cases in which gross macrovascular invasion had been excluded, microscopic invasion was seen in 131

- **In multivariate analysis, decreased survival was associated with:**

1. Invasion of a vessel with a muscular wall
2. Invasion more than 1cm from the tumour

419

Mass forming type of intrahepatic cholangiocarcinoma: favouring features and histological changes in the non-tumorous liver

Known risk factors for the development of cholangiocarcinoma

1. primary sclerosing cholangitis (7-42% of these patients)
2. infection by liver flukes
3. HCV
4. Thorotrast
5. anabolic steroids
6. intrahepatic lithiasis
7. fibro-polycystic liver disease

- The incidence of mass forming cholangiocarcinomas is increasing

419

- 48 cases
- Excluded all cases of cirrhosis and biliary tract disease

- **Underlying causes:**

1.	None	18
2.	Metabolic syndrome	18
3.	Iron overload	2
4.	Porphyria cutanea tarda	2

- **Adjacent liver**

• Fatty change	32
• Fatty liver hepatitis	10
• Parenchymal iron	31

419

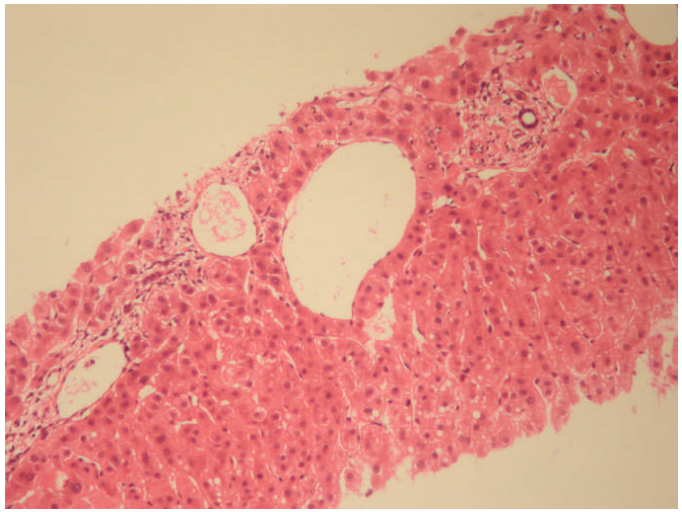
- Fatty liver disease
- Iron overload

Are important risk factors for the development of cholangiocarcinoma

Vascular Disease

764

HIV-associated nodular regenerative hyperplasia is linked to portal obstructive venopathy and autoimmune protein S deficiency



764

- A known association
- Linked to antiviral exposure, especially didanosine

- 13 patients – 2 of which underwent liver transplantation
- Case control study

- **In patients with HIV associated NRH:**

1. Active protein S levels lower
2. All had higher titres of anti-PS IgG
3. The 2 explants – showed typical portal obstructive venopathy

767

Nodular regenerative hyperplasia: A clinico-pathological evaluation

767

- Studied patients with chronic granulomatous disease, sickle cell disease, systemic mastocytosis and common variable immuno-deficiency
- 129 biopsies evaluated
- Approximately 15% had NRH

767

- **NRH was associated with:**

1. Sinusoidal fibrosis
2. Ductular proliferation
3. Central CK7 expression

- **Veno-occlusive changes were associated with:**

1. Haemorrhage
2. Central CK7 expression

- **Conclusion:**

  NRH is associated with vascular damage and evidence of regeneration

Fatty liver disease

1109

Daily cannabis use, a novel risk factor of steatosis severity with chronic hepatitis c

1109

Cannabis Sativa binds 2 receptors: CB1 and CB2

- The CB1 receptor has a profibrinogenic effect
  (Nat Med 2006;12:671)
- Both the CB1 and CB2 receptors promote fatty change

315 liver biopsies from patients with chronic HCV

Severe steatosis was defined as ≥30%

Non users: 16%, occasional users: 8%, daily users: 33%

In logistic regression analysis, daily cannabis use was an independent predictor of severe steatosis.

Miscellaneous Lifestyle (NAFLD) Papers

- **1114 Modest wine drinking is associated with a decreased prevalence of suspected nonalcoholic fatty liver disease**

  Prevalence of NAFLD, based on serum ALT:

  3.2% of non drinkers, 0.4% of modest wine drinkers
- **1128 Advanced fibrosis in NAFLD is associated with lifetime alcohol use, diabetes, and age but not with lifetime cigarette smoking**

  No link between smoking and liver fibrosis in NAFLD
- **1341 Higher caffeine consumption is associated with milder fibrosis in chronic liver disease**

  Associated with milder fibrosis in patients with chronic liver disease, especially HCV infection
- **1170 Daily exercise increases hepatic fatty oxidation and prevents steatosis in Long-Evans Fatty Rats`**

  “Access to voluntary running wheels” lead to “attenuated weight gain”

1129

Non-alcoholic fatty liver disease can induce portal hypertension, demonstrated by hepatic venous gradient measurement related to the severity of steatosis but not fibrosis in overweighed (*sic*) and obese patients

1129

- Hepatic venous pressure gradient (HPVG) was measured in 30 patients undergoing transjugular liver biopsy for NALD

- **In patients with increased HPVG (≥6mm Hg):**

1. 6/9 had no fibrosis
2. Significantly more steatosis and higher NASH activity score (but not inflammation or ballooning)
3. BMI was significantly higher

An increased HPVG is related primarily to the severity of the steatosis

1134

Ultrastructural evaluation of hepatocytes with type 2 Mallory-Denk bodies: clues to ballooning in nonalcoholic steatohepatitis (NASH)

1134

- Mallory-Denk bodies (Mallory's hyaline) is associated with hepatocyte ballooning

  (J Pathol 2006; 208: 653)

- A prospective study of 40 biopsies of patients with NASH were studied by transmission electron microscopy and 40 grids per patient examined
- Type 2 Mallory's hyaline was defined as: irregular cytoplasmic aggregates of randomly orientated filaments of varying diameter)
- Identified on 6 patients

1134

- **Hepatocytes >30um** 3/6
- **Cytoplasm containing small droplets of fat** 5/6
- **Dilated endoplasmic reticulum** 5/6
- **Crystal containing mitochondria** 2/6

- **Ballooning of cells is due to:**

1. Small droplet fat
2. Dilated endoplasmic reticulum

Hypothesised oxidative injury in the rim of the endoplasmic reticulum – derived small fat droplets disrupts trafficking of these droplets and impedes endoplasmic reticulum function

1138

Histological characteristics of patients with ‘cryptogenic’ cirrhosis and prior biopsy showing NASH

1138

- **Background:**

  Serial biopsy studies in patients with NASH show that in late disease steatosis may no longer be seen

- **Aim**

  to characterise late stage histology in patients with a previous biopsy showing non-cirrhotic NASH

- **Methods**

  4 patients: 11 biopsies

  Time between first and last biopsy: 4-14 years

1138

- **In the late biopsy:**
  3 / 4 had no fatty change
  4 / 4 had ballooning and lobular inflammation
  3 / 4 had Mallory bodies
  2 / 4 had glycogenated nuclei
  - in one case, which transplanted, the cycle was repeated

Conclusions:

1. Fatty change is lost in late stage NASH
2. Supports previously published descriptions of late stage NASH that have been used in classification schemes of cryptogenic cirrhosis:

Contos Liver Transplantation 2001; 7: 363

Ayata Human Pathology 2002; 33: 1098

Viral hepatitis

970

Liver biopsy: still essential in the management of chronic hepatitis B

970

- NICE recommendations are unique in that they consider cost-effectiveness as well as clinical efficacy
- 783 HBsAg+ patients were assessed over a 12 year period
- 212 patients underwent liver biopsy

Group 1: 76 HBeAg+ - 9 repeat biopsies

Group 2: 136 anti-HBe+ - 31 repeat biopsies

treated patients were followed longitudinally and six month 'on-treatment' virologic response was evaluated to determine the validity of this strategy in predicting the early emergence of resistance

970

Fibrosis	HBeAg+	anti-HBe+
mild	57%	52%
moderate/ severe	43%	48%

- in the HBeAg+ group: 4/14 (29%) with cirrhosis had HBV DNA > 10^7 copies/ml and ALT values within normal limits
- in the anti-HB+ goup: 27/65 (42%) with moderate to severe fibrosis had HBV DNA > 107 copies/ml and ALT values within normal limits
- these patients were labelled ‘immunotolerant’ and as such would be excluded from treatment
- liver biopsy confirms advanced liver disease highlighting the importance of histology in managing these patients

970

Fibrosis	HBeAg+	anti-HBe+
mild	57%	52%
moderate/ severe	43%	48%

- age and ALT (and grade) correlated with fibrosis (but HBV DNA did not)
  age> 43 years was a predictor of cirrhosis in both groups
- 81% of HBeAg+ and 65% of anti-HBe+ CHB patients who required adefovir add-on therapy were identifiable after six months lamivudine monotherapy, by continuing HBV DNA positivity
- rate of progression did not correlate with eAg status, HBV DNA and ALT levels but correlated with a BMI > 25

970

- **Conclusions**

1. the importance of liver histology in formulating management plans
2. the potential of pre-treatment levels of viraemia in identifying those needing combination therapy *ab initio* and
3. the value of the early detection of sub-optimal viral load suppression, enabling the timely introduction of an additional therapy.

925

Tracing hepatitis B virus DNA back to the 16th century in a Korean mummy

925

- C-14 dating of cloths and coffin
- Laparoscopy identified a parenchymatous organ in the right upper quadrant
- HBV DNA (genotype C) identified
- No hepatocytes identified but normal architecture on Masson’s trichrome
- Tuberculosis confirmed

1340

Histological outcomes after 30 years in untreated Irish women with chronic HCV genotype 1B, do genetic factors influence?

1340

- 56 women
- infected in 1977
- 3 biopsies per patient

Change in grade 2 points
Change in stage 1 point

	Grade	Stage
worse	29%	18%
the same	52%	55%
better	20%	!8%

Genetic factors studied

1. HLA Class 1
2. HLA Class 2
3. TNF-alpha
4. TGF-beta
5. IL-10
6. IL-6
7. IFN-gamma

None of these account of the “favourable” histological outcome

1353

Natural history of hepatitis C virus infection in HIV-infected patients in the era of heart

1353

- Systematic review and meta-analysis
- 16/65 studies suitable for study

- **Annual transition rates:**

F0-F1 = 0.1

F1-F2 = 0.1

F2-F3 = 0.2

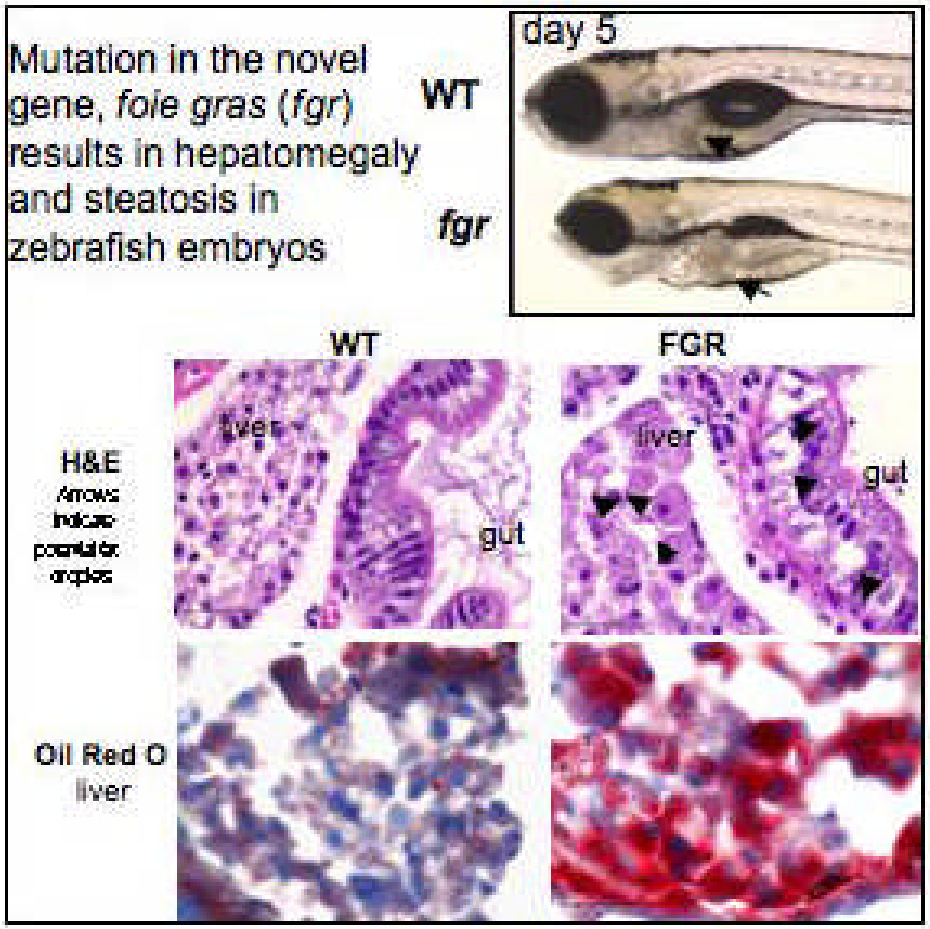
F3-F4 = 0.1

- Probability of cirrhosis after 20 years = 25%, after 40 years 77%

- **Rate ratio of cirrhosis:**
  HIV/HCV coinfected : HCV monoinfected = 2.1

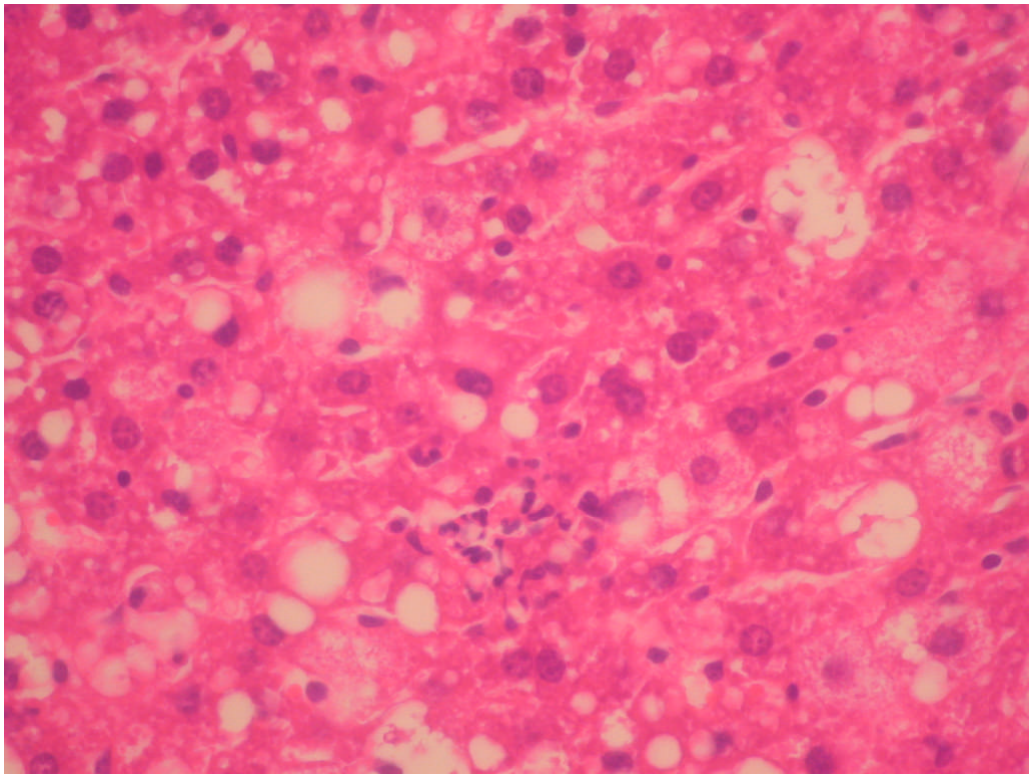
Animal models of fatty liver

Green and Maher



Sadler-Edepli KC, Amsterdam A, Soroka C, Boyer J, Hopkins N.
A genetic screen in zebrafish identifies the mutants vps18, nf2 and foie gras as models of liver disease.
Development 2005 Aug; 132(15):3561-72.

Ballooning in mouse models of fatty liver disease?



Working Party:

The development of a histopathological classification system for gall bladder cancer and precancer

The Liver Meeting

Oct 31-Nov 4, 2008 San Francisco, CA