Hepatitis C

with Judy Wyatt

Hepatitis C and the histopathologist

- Pre-2006 biopsy based treatment of moderate-severe chronic hepatitis
- Now biopsy for:
  - Watchful waiting, to confirm mild disease
  - ? Cirrhosis – patient follow-up
  - Post transplant, protocol biopsies
- Mainly want to know fibrosis stage

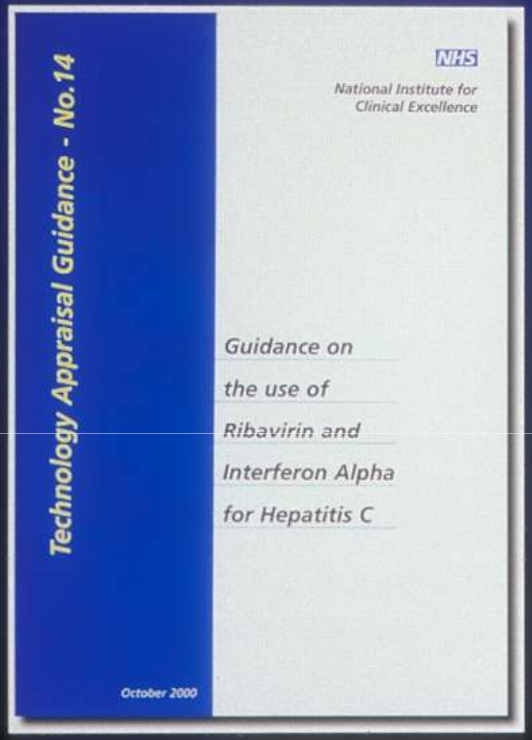
What do we mean by “liver fibrosis”?

Differences between morphological appearance, description, stage scoring and liver fibrosis measurement

Appearance	Ishak stage: Categorical description	Ishak stage: Categorical assignment	Fibrosis measurement*
	No fibrosis (normal)	0	1.9%
	Fibrous expansion of some portal areas ± short fibrous septa	1	3.0%
	Fibrous expansion of most portal areas ± short fibrous septa	2	3.6%
	Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3	6.5%
	Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C))	4	13.7%
	Marked bridging (P-P and/or P-C), with occasional nodules (incomplete cirrhosis)	5	24.3%
	Cirrhosis, probable or definite	6	27.8%

Standish R et al. An appraisal of the histopathological assessment of liver fibrosis. Gut 55;569;2006

NICE Guidance on the use of ribavirin and interferon alpha for hepatitis C



Biopsy based treatment

Moderate to severe hepatitis C

defined as histological evidence of

significant scarring (fibrosis) and/or significant necrotic inflammation.

First NICE guidance October 2000

Reviewed January 2004 – retain biopsy based treatment; may revise when results of mild hepatitis C studies are available

August 2006 – treatment of mild chronic hepatitis C

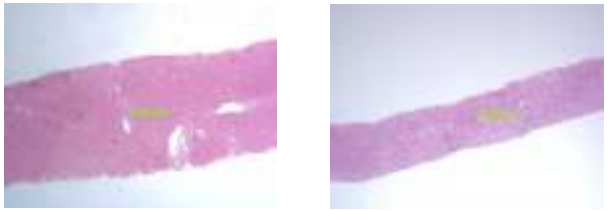
Biopsy to determine severity of disease
not an exact science

What will the biopsy result depend on?

- Time of biopsy – LFTs fluctuate
- Biopsy site *variation between biopsies*
- Biopsy length *>25mm**
- Biopsy width *>1mm***

Smaller biopsies underestimate severity
Need >10 portal tracts**

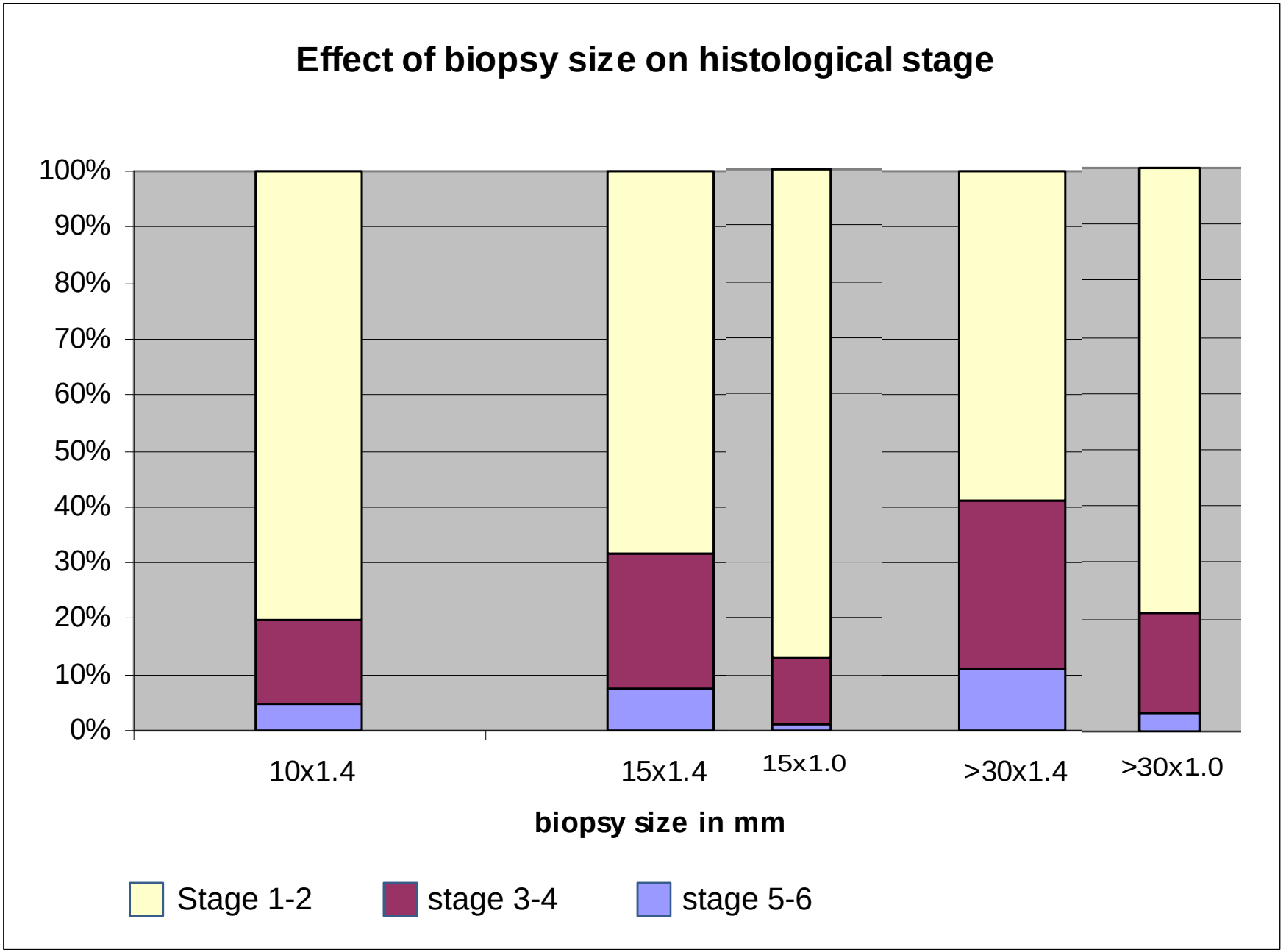
1998
1.3mm
wide



2005
0.56mm
wide

Which Pathologist? *Inter-observer variation*

** Bedossa et al Hepatology 2003;38;1449-1457*
*** Colloredo et al J Hepatol 2003;39;239-244*



*** Colloredo et al J Hepatol 2003;39;239-244*

Histopathological features of chronic hepatitis C

Non-specific – any chronic hepatitis

- Inflammation – portal, interface, parenchymal
- Fibrosis, architectural distortion

Characteristic of hepatitis C

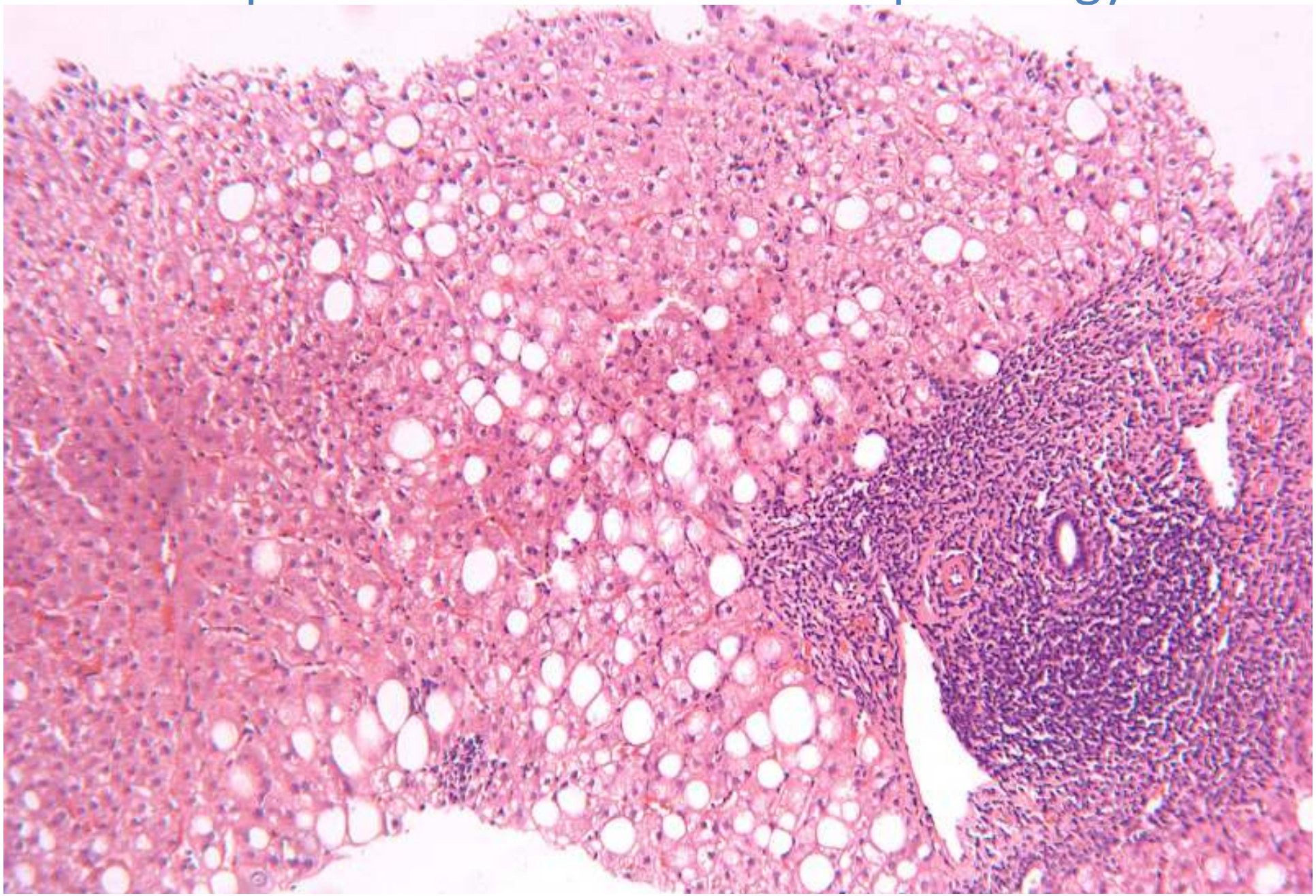
- Steatosis
- Portal lymphoid aggregates/follicles
- Bile duct lesions
- Fibrosis progression despite little inflammation

And also

different disease post transplant

high frequency of HCC in cirrhosis – RNA virus

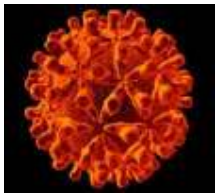
Hepatitis C characteristic histopathology



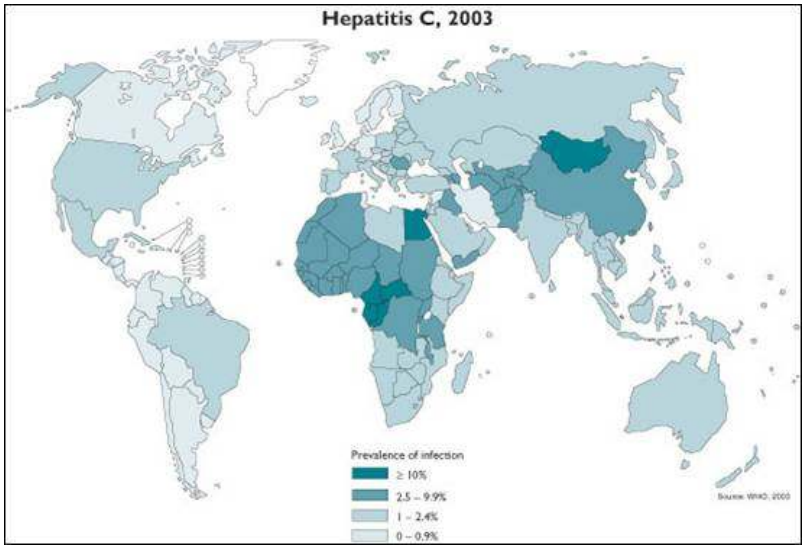
Introduction:

Hepatitis C:
20th anniversary of discovery

The 1989 discovery of the hepatitis C virus by George Kuo, Qui-Lim Choo and Michael Houghton was a triumph of new techniques and good old human perseverance.



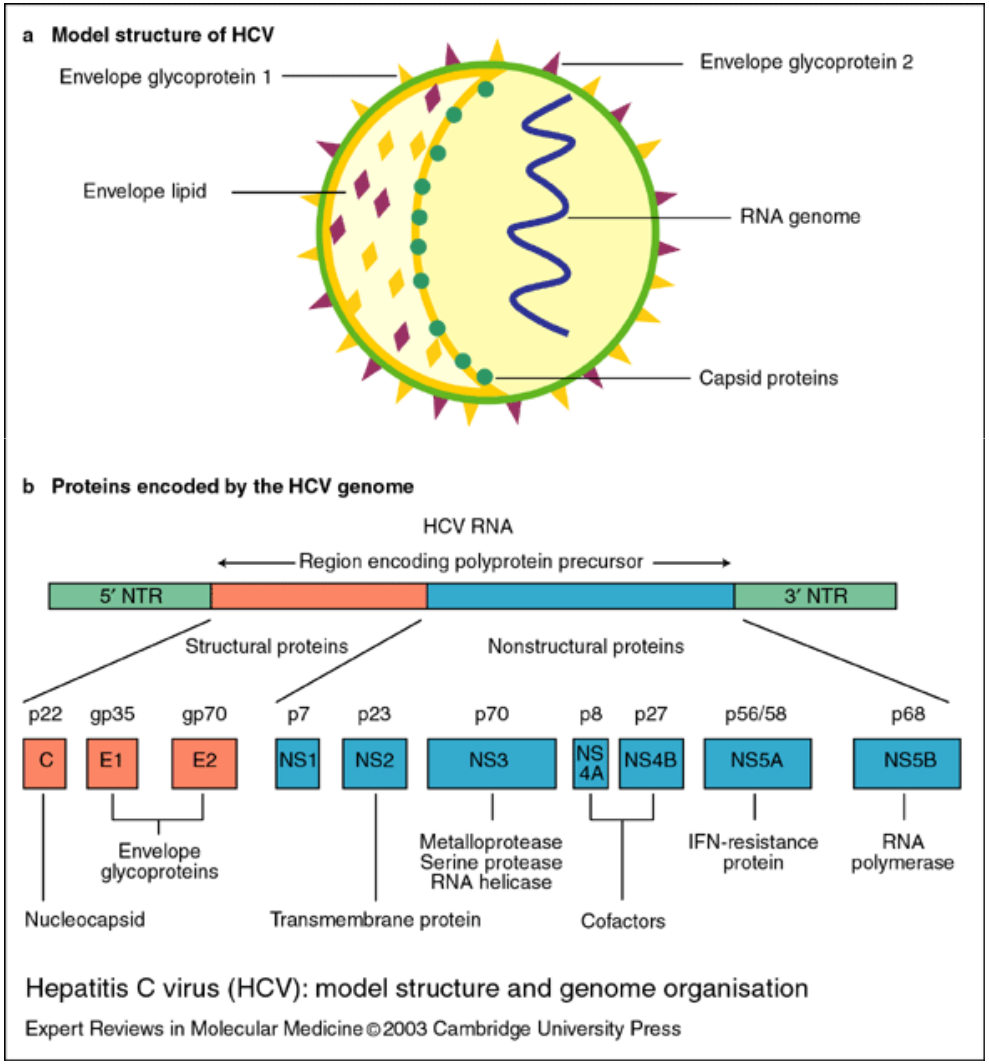
Who are you and where did you come from?



- Hepacivirus, member of genus flavivirus, identified in 1989
- can establish stable chronic infection in 80% people
- Been around for centuries, but spreading in developed world due to travel and IVDU
- RNA positive strand virus, error-prone replication, 6 genotypes, many subtypes, and 1000's of quasispecies
- Very difficult to identify in cells and grow in culture

Tell me about you life

- Outside – variable envelope protein and host lipoprotein
- Inside – single strand RNA with ribosomal entry site, and core protein
- Non-structural proteins for replication, and disturb host cell homeostasis



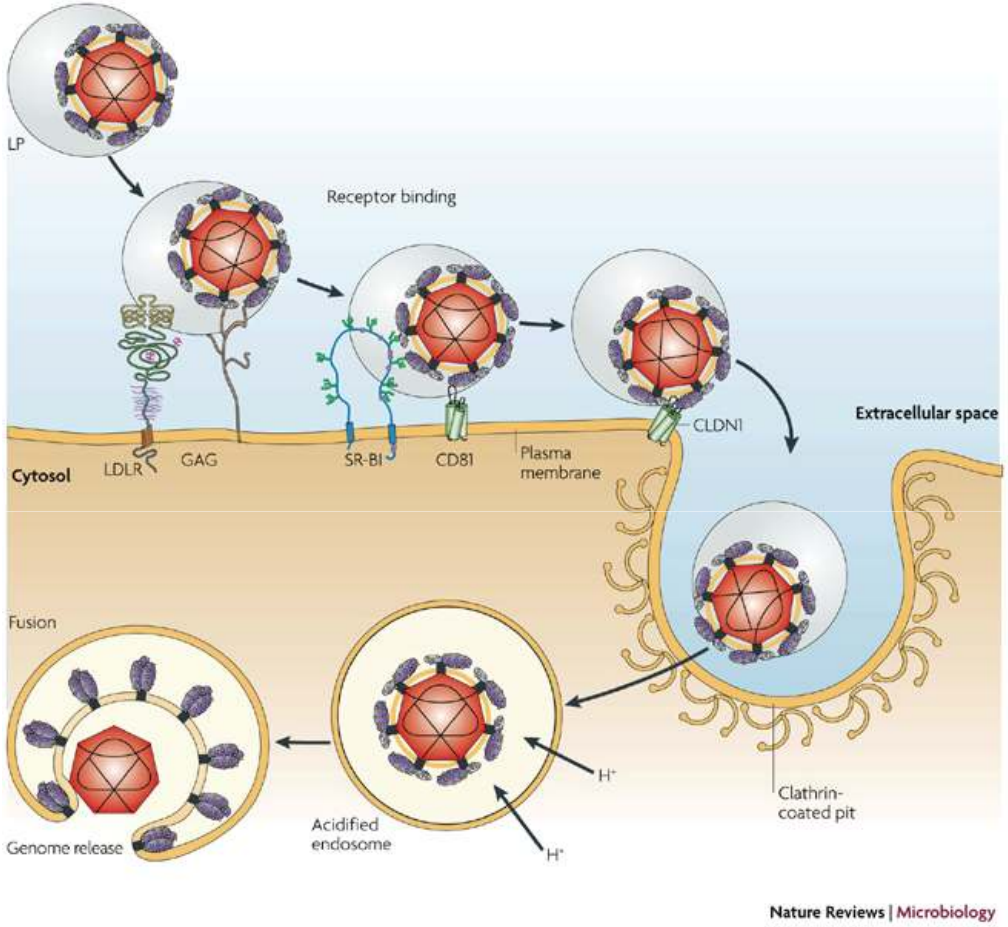
Hepatitis C virus (HCV): model structure and genome organisation

How do you get in?

Four receptors on hepatocyte

? Also other cell types,

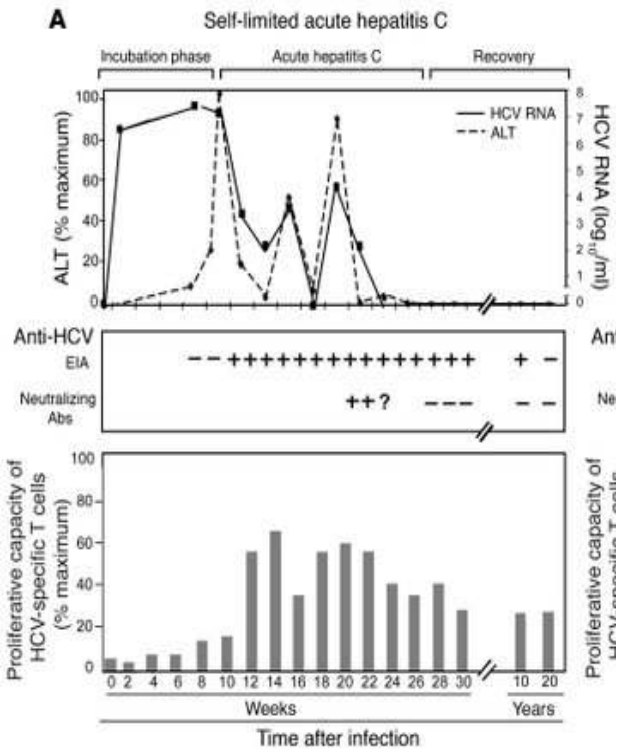
Dendritic cell – suppresses T cell responses



Moradpour D, Penin F, Rice CM
Nature Reviews Microbiology **5**, 453–463

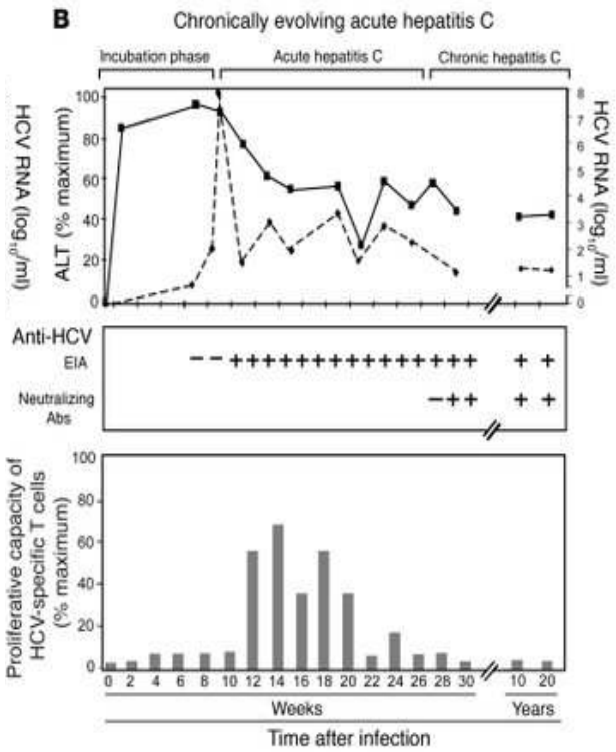
Chronic hepatitis C

About 20% infections are cleared by host immune response – good array of strong T cell antigen responses



Other viruses – chronic in immuno-compromised host

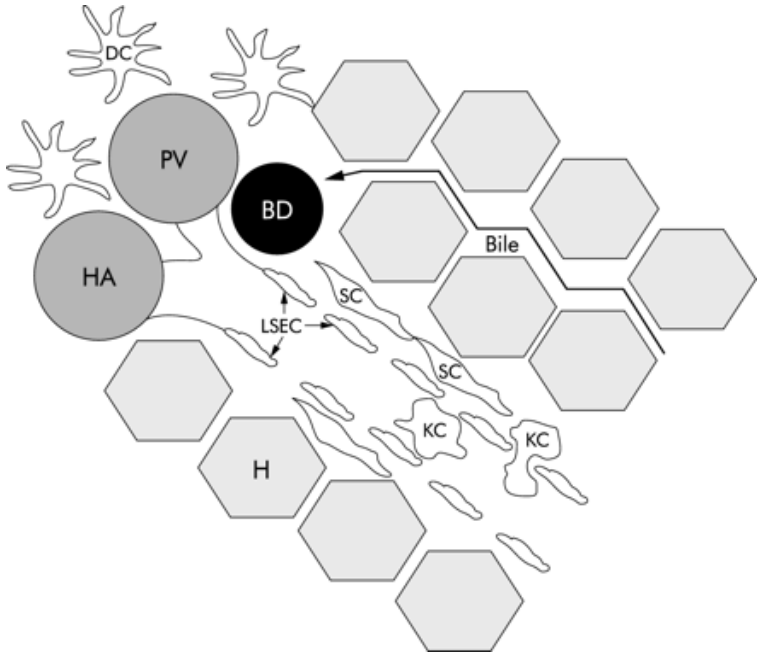
Remaining 80% never cleared – more and more quasispecies evolve, escape immune response

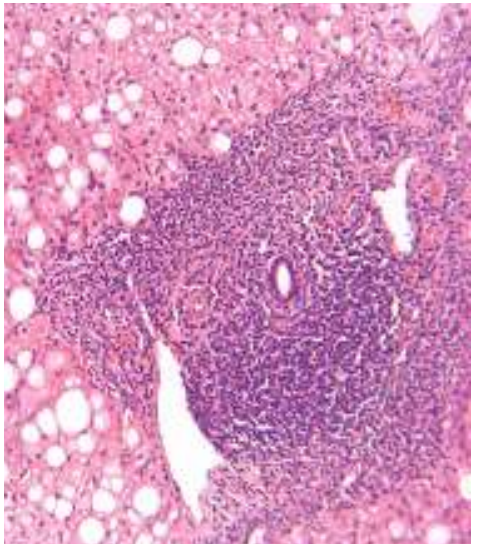


Hepatitis C – causes immune compromise specific for itself, reversible when virus is eradicated by antiviral treatment

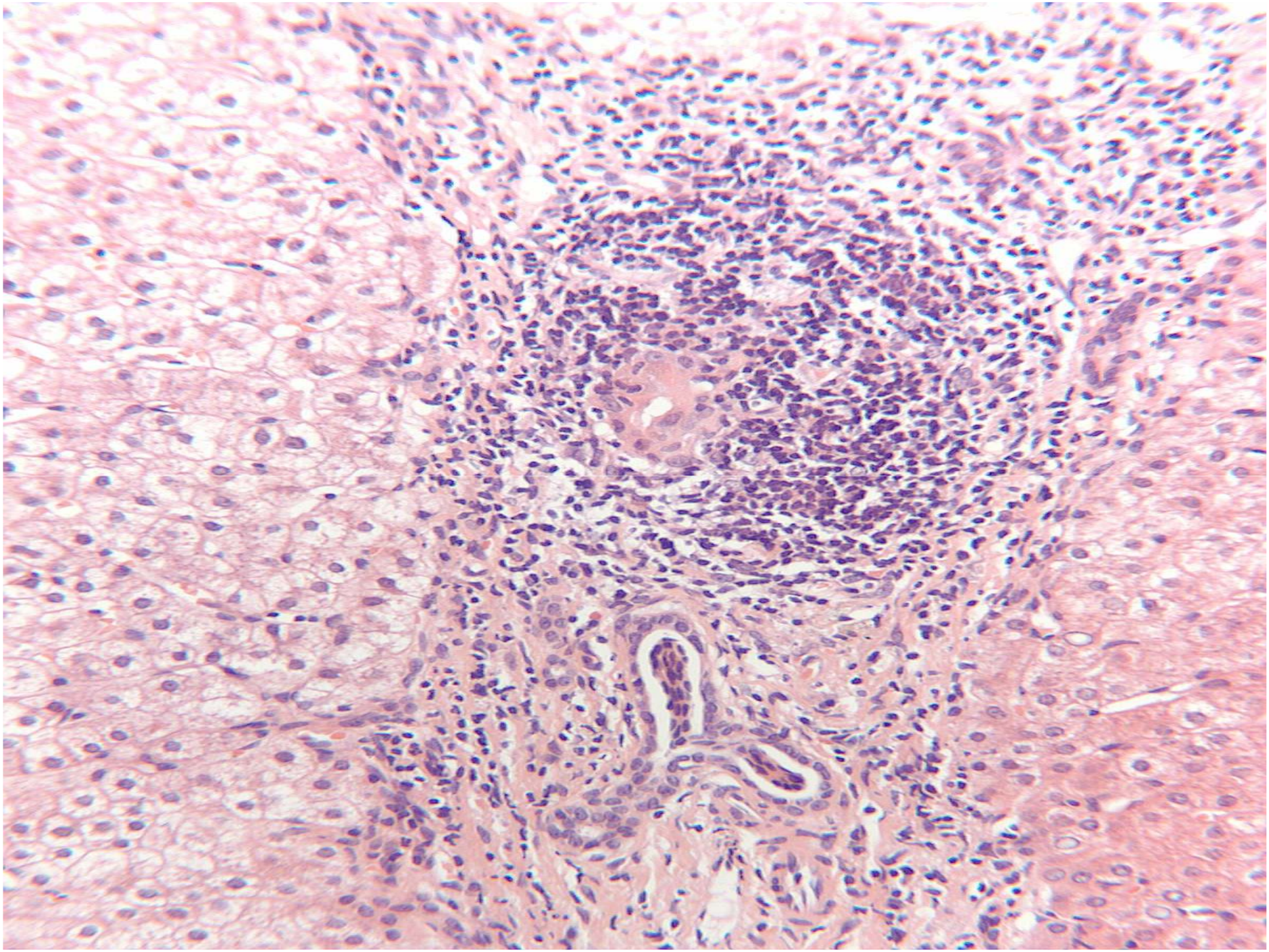
Your host is not immunocompromised, how do you survive without being eliminated?

- In hepatocyte – virus reduces responsiveness to IFN
- In Dendritic cell – inhibit helper T cell response



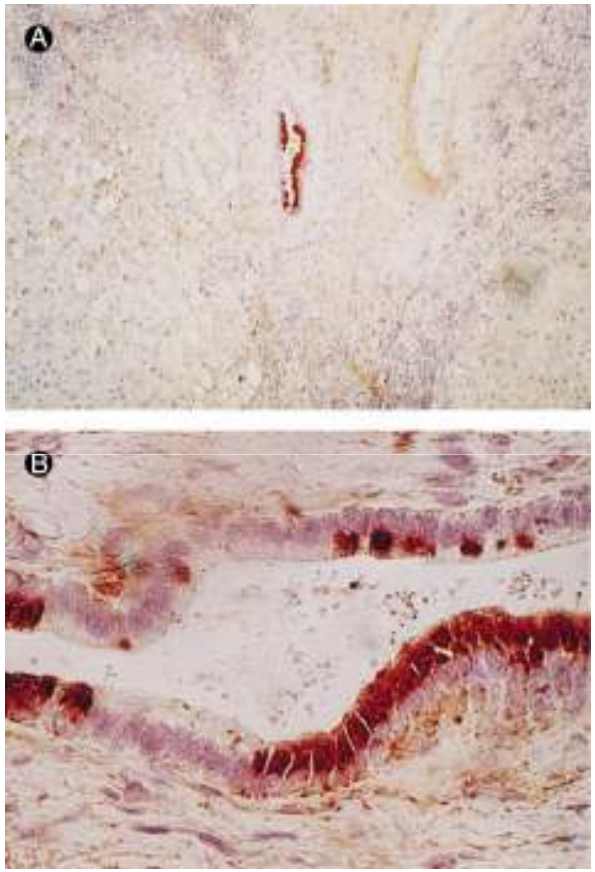


PALT description



What about those bile duct lesions?

- HCV +ve bile duct epithelium
- HCV excreted in bile
- HLA DR +ve bile ducts - ? Target for immune-mediated injury
- Similarity with transplant rejection



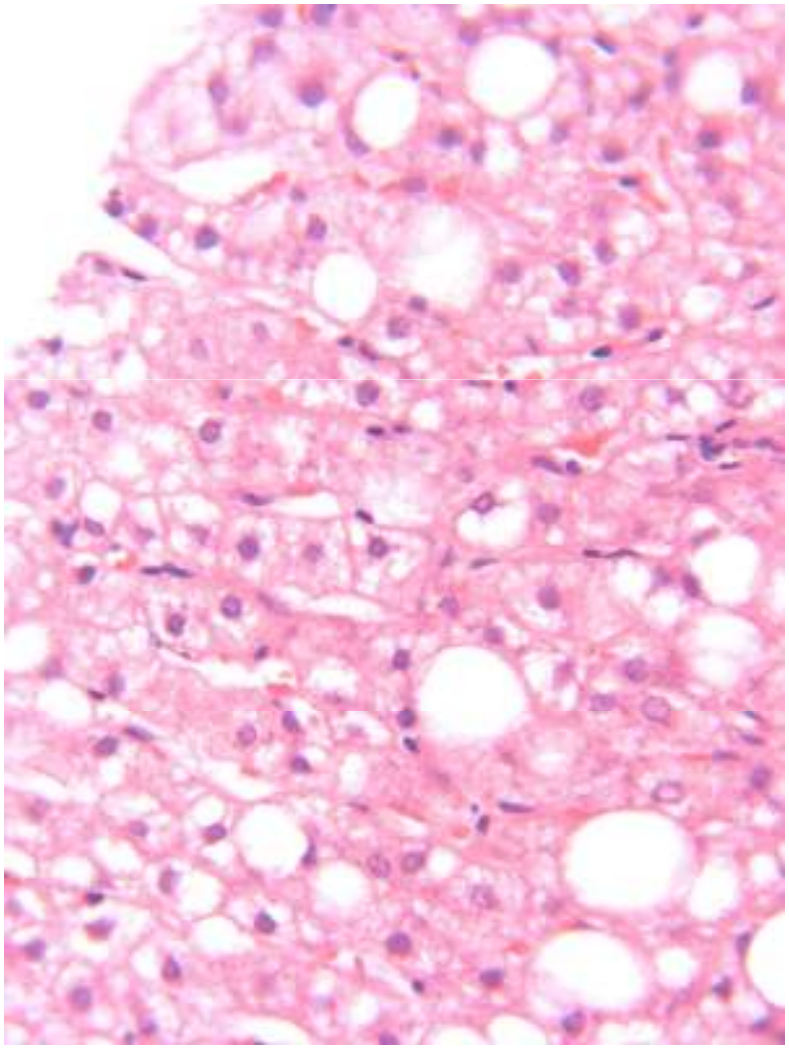
? Of any significance?

No association with disease progression, and do not result in ductopaenia,

Haruna et al.
Hepatology 2001;33;977-980

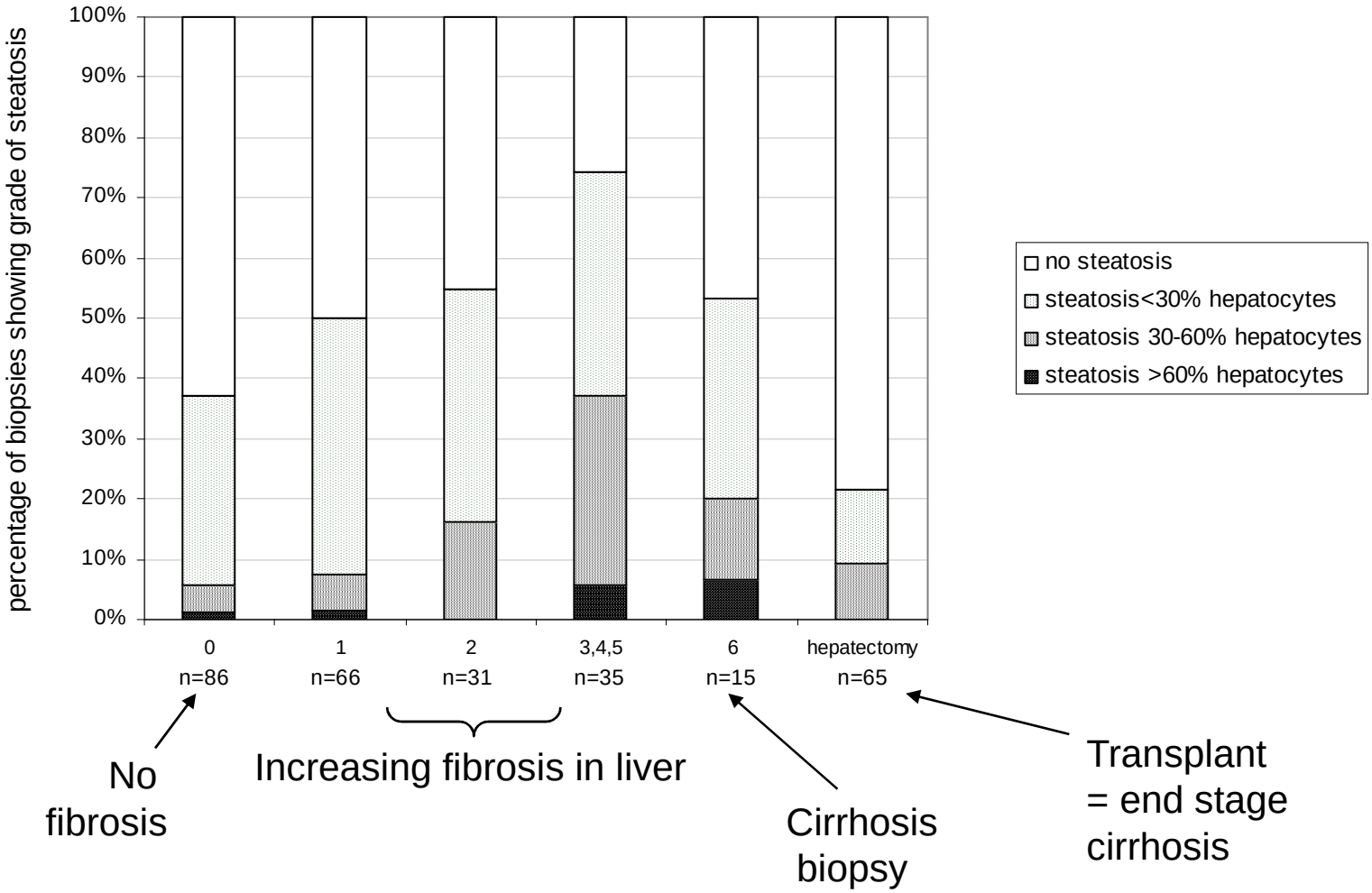
Well let's get to something that really is important – tell us about your relationship with fat...

- Increases with stage of disease
- Type 3 – effect of virus, other types synergy with risk factors for metabolic syndrome
- Predicts progression
- Associated with impaired response to treatment



Steatosis v stage of fibrosis in hepatitis C

235 patients with liver biopsy and 65 transplanted for hepatitis C



Wyatt J et al J Clin Pathol 2004

How do you do it?

Two ways of causing steatosis:

1. Viral steatosis, type 3a, direct cytopathic effect

2. Metabolic steatosis, increases susceptibility to steatosis from metabolic causes

   ? Also from alcohol

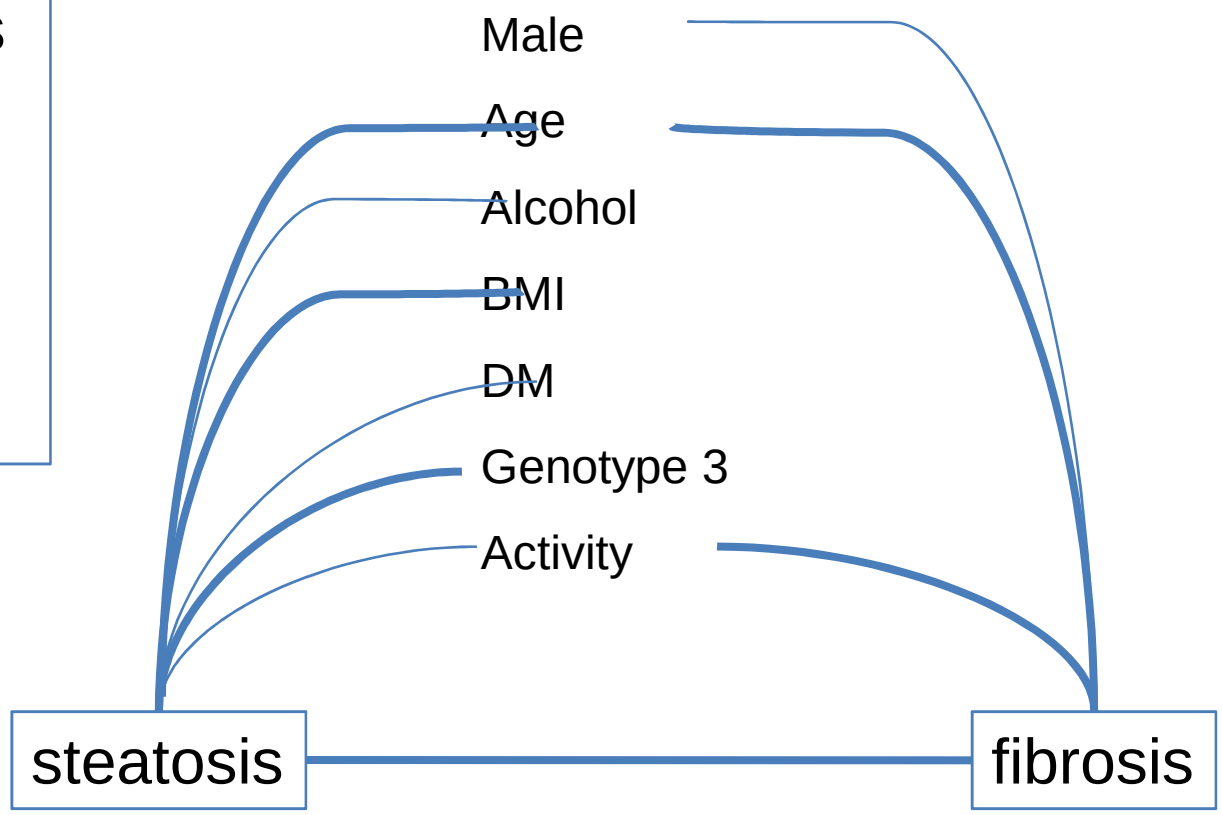
Associated with

- increased fibrosis progression
- lower response to treatment

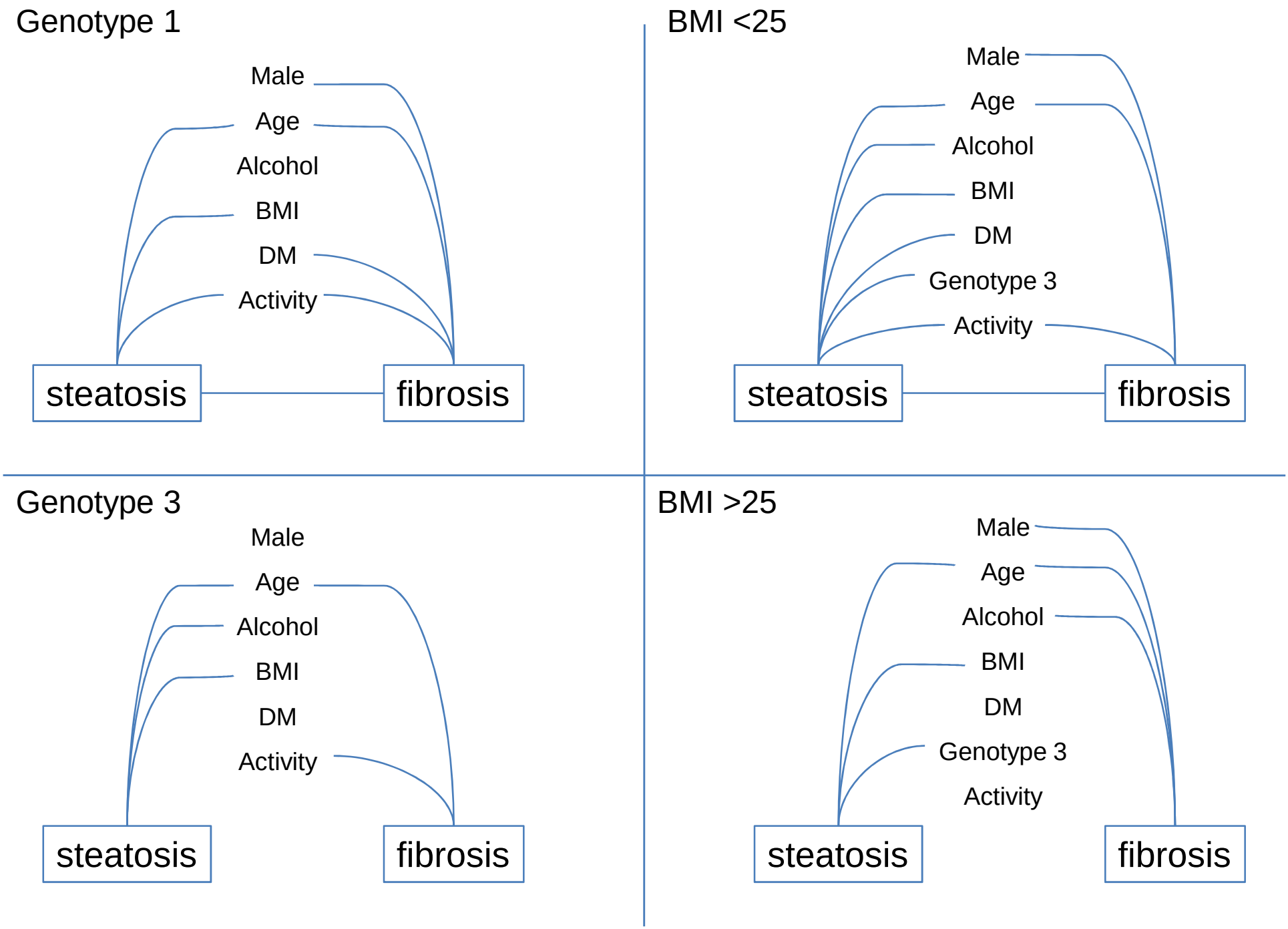
What has steatosis got to do with fibrosis?

Meta-analysis,
3068 patients
10 studies:

Significant on
Multivariate
analysis



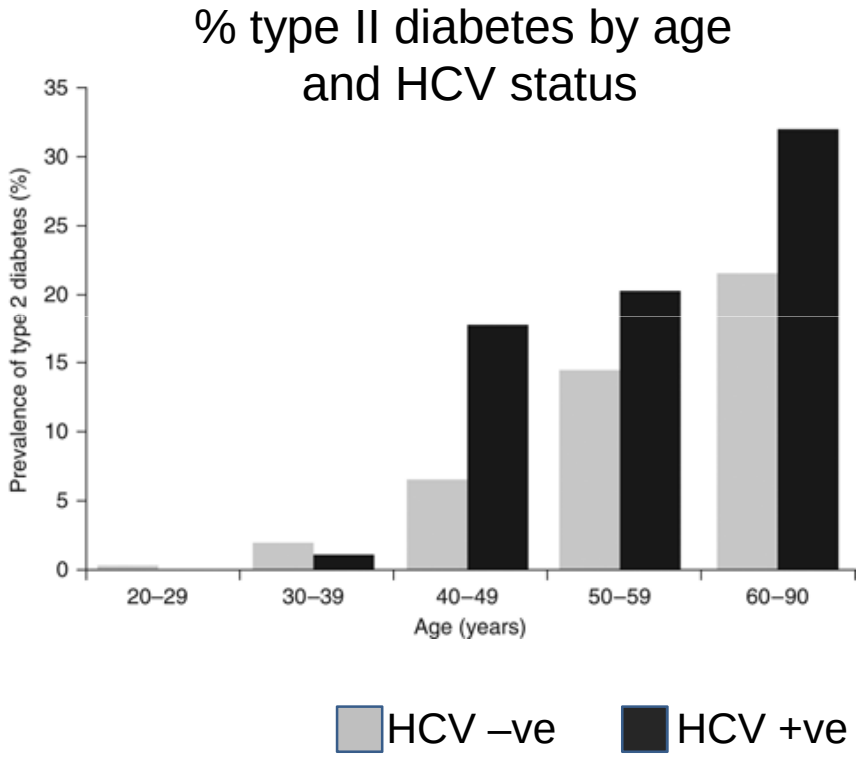
Leandro et al. Gastroenterology 2006;130;1636-1642


Genotype 1
Male
Age
Alcohol
BMI
DM
Activity
steatosis
fibrosis
BMI <25
Male
Age
Alcohol
BMI
DM
Genotype 3
Activity
steatosis
fibrosis
Genotype 3
Male
Age
Alcohol
BMI
DM
Activity
steatosis
fibrosis
BMI >25
Male
Age
Alcohol
BMI
DM
Genotype 3
Activity
steatosis
fibrosis

Metabolic steatosis: Hepatitis C and insulin resistance

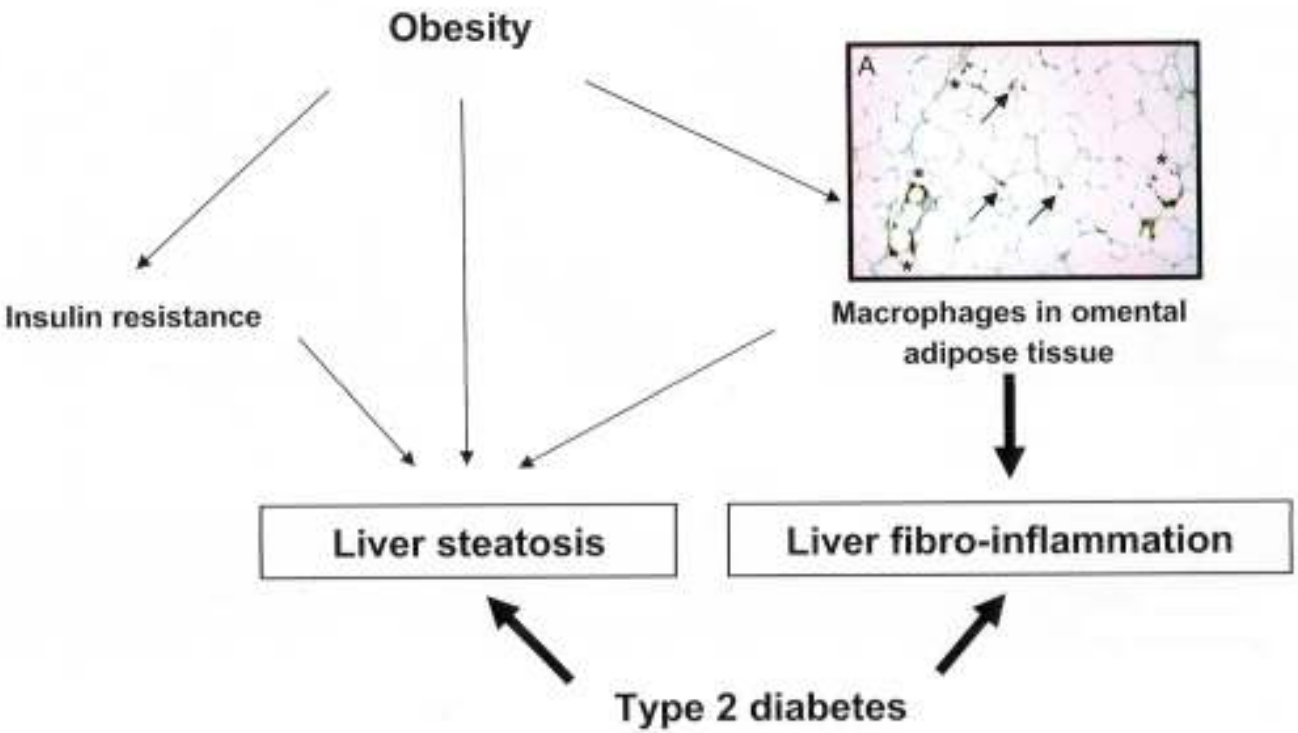
- HCV core protein associates with lipid droplet membrane and causes increased SOCS-3*
- SOCS-3 does two things:
  - Promotes insulin resistance
  - Reduces response to IFN
- Insulin is growth factor for fibroblasts, so more fibrosis

* suppressor of cytokine signalling



Mehta SH et al.
Ann Intern Med 2000; 133:592–9.

Association between **omental adipose tissue macrophages** and **liver histopathology** in morbid obesity:



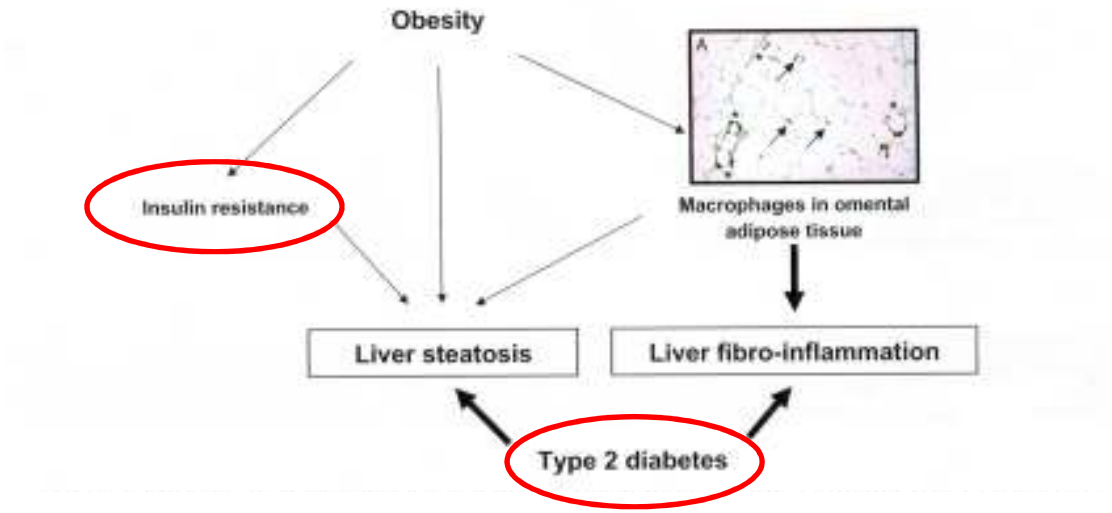
The severity of fibro-inflammation in the liver is related to macrophage accumulation in the omental adipose tissue, independently of insulin resistance.

Tordjman J et al. J Hepatol. 2009 Aug;51(2):354-62.

Why it's bad to be overweight and have hepatitis C synergistic in liver disease:

- Central obesity - NASH is the effect of adipocytokines from abdominal fat on steatotic hepatocytes

- Hepatitis C sensitises liver to the effects of metabolic syndrome Greater insulin resistance relative to the degree of obesity

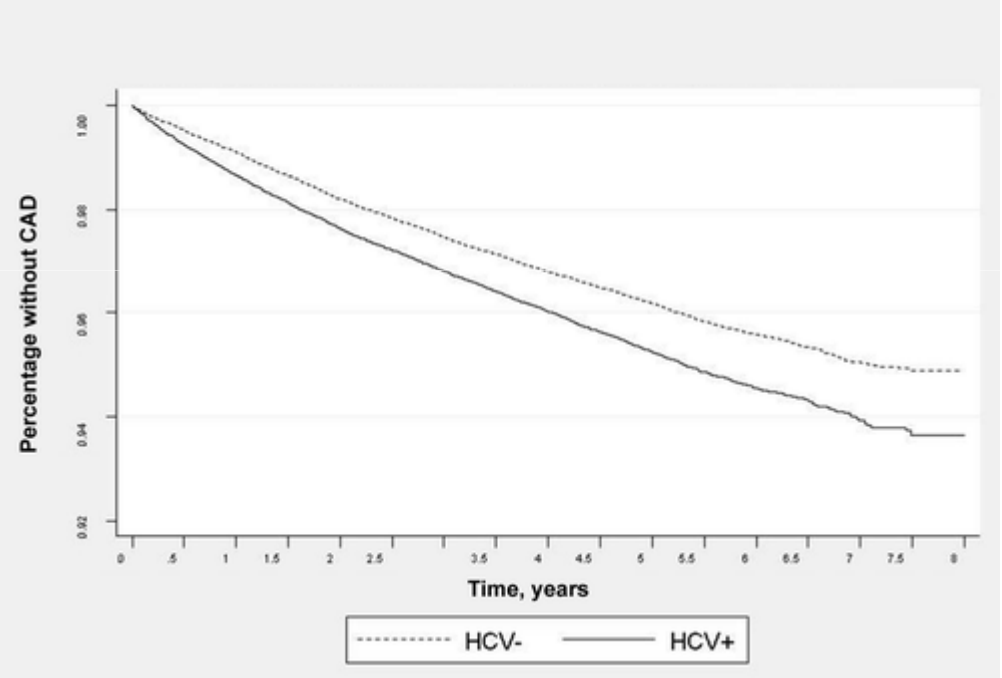


HCV and coronary artery disease

82,000 HCV +ve
89,500 HCV –ve

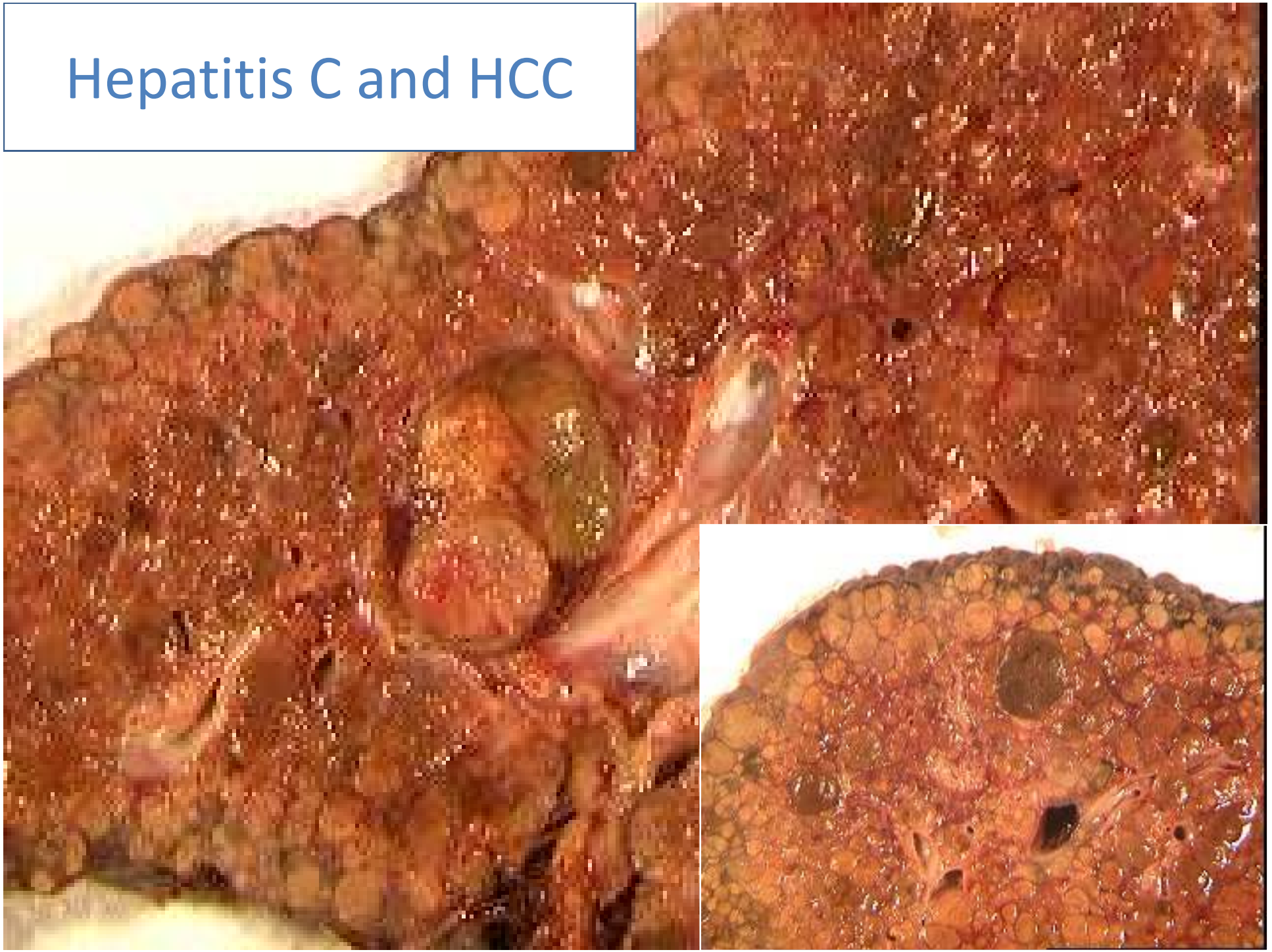
HCV +ve were:
Younger,
Lower lipids
Less hypertension

But still they had 1.25 relative risk of coronary artery disease after adjusting for other variables



Butt et al. *Clin Infect Dis 2009:49:225-232*

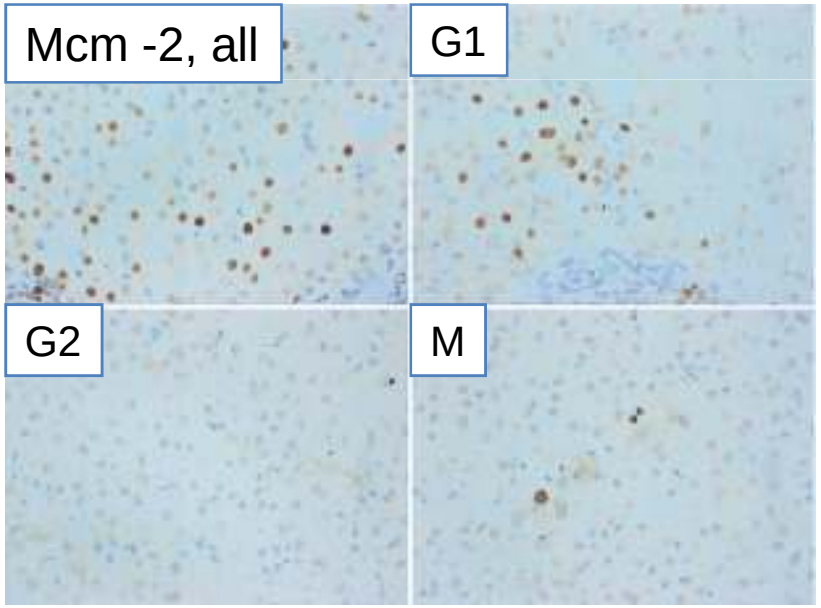
Hepatitis C and HCC



RNA virus, so how can it cause cancer?

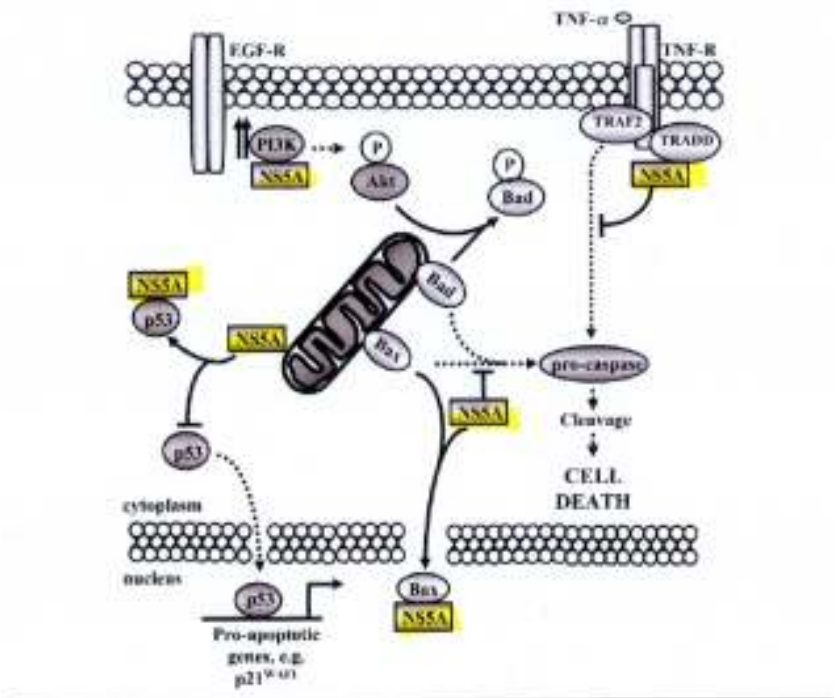
Interferes with cell cycle:

Cell cycle arrest – cells stuck in G1,
Normal <0.01% hepatocytes,
HCV 13% mcm-2+ve,
Correlates with fibrosis and activity



Marshall Gastroenterol 128;2005;p37

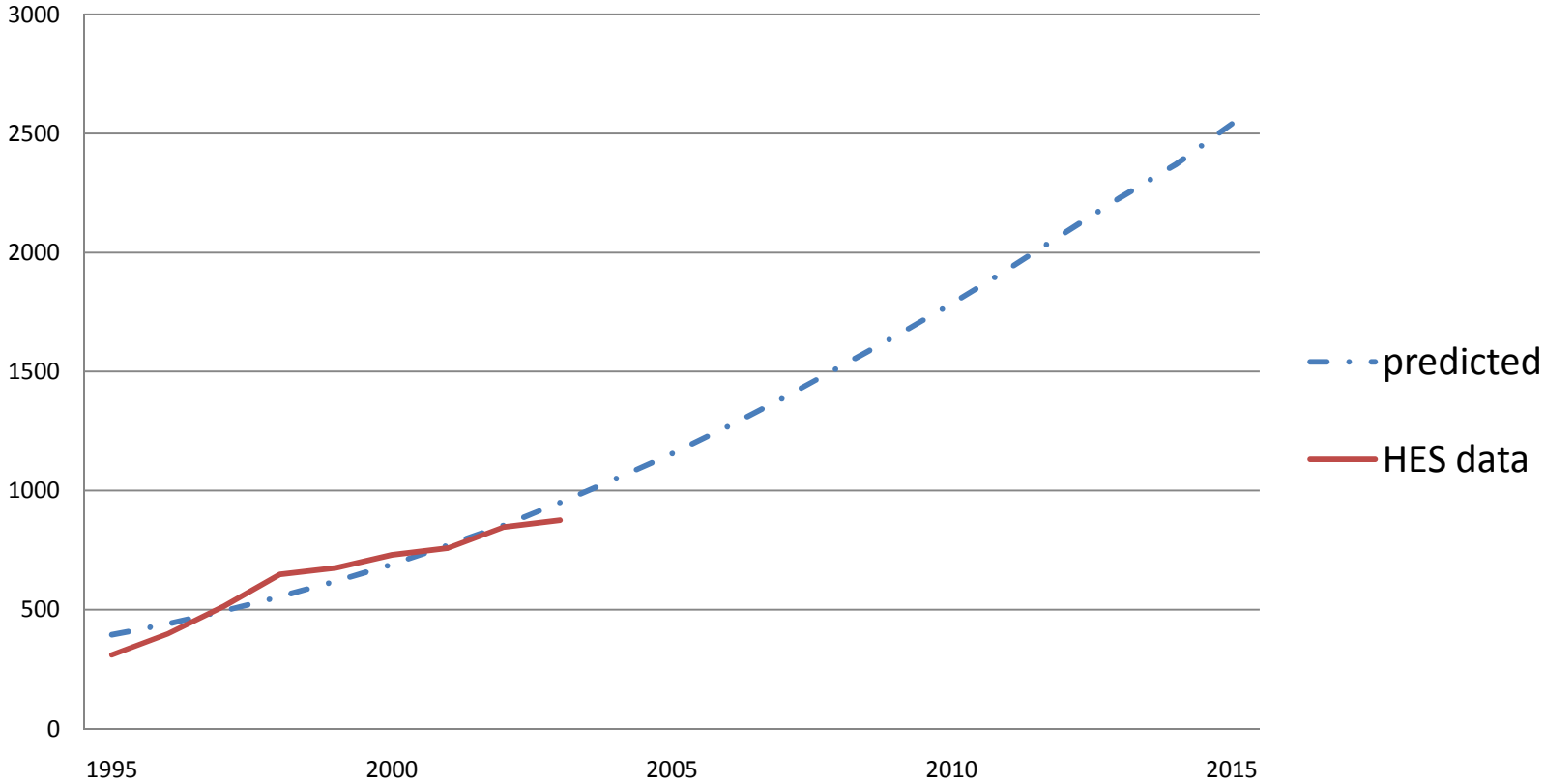
Inibits apoptosis
NS5a interferes with apoptotic Pathways in 6 ways



J Gen Virol 2004; 85;p2495

What are your plans for the future?

Estimated burden of end stage liver disease in HCV infected population, if patients are left undiagnosed and treated (England)



Sweeting MJ et al. J Viral Hepatitis 2007;14;570-576

Summary – hepatitis C - virus of our time

Hepatitis C has been infecting people since antiquity

why is it suddenly so important?

Couldn't have known about it

Science:
discovery,
virology,
pharmaceutical
industry

Not in developed countries

Transmission:
worldwide travel,
blood transfusion,
IVDU

Lifestyle
age
obesity
alcohol
viral co-infection

Only clinically important late in stage disease