

Hepatitis C

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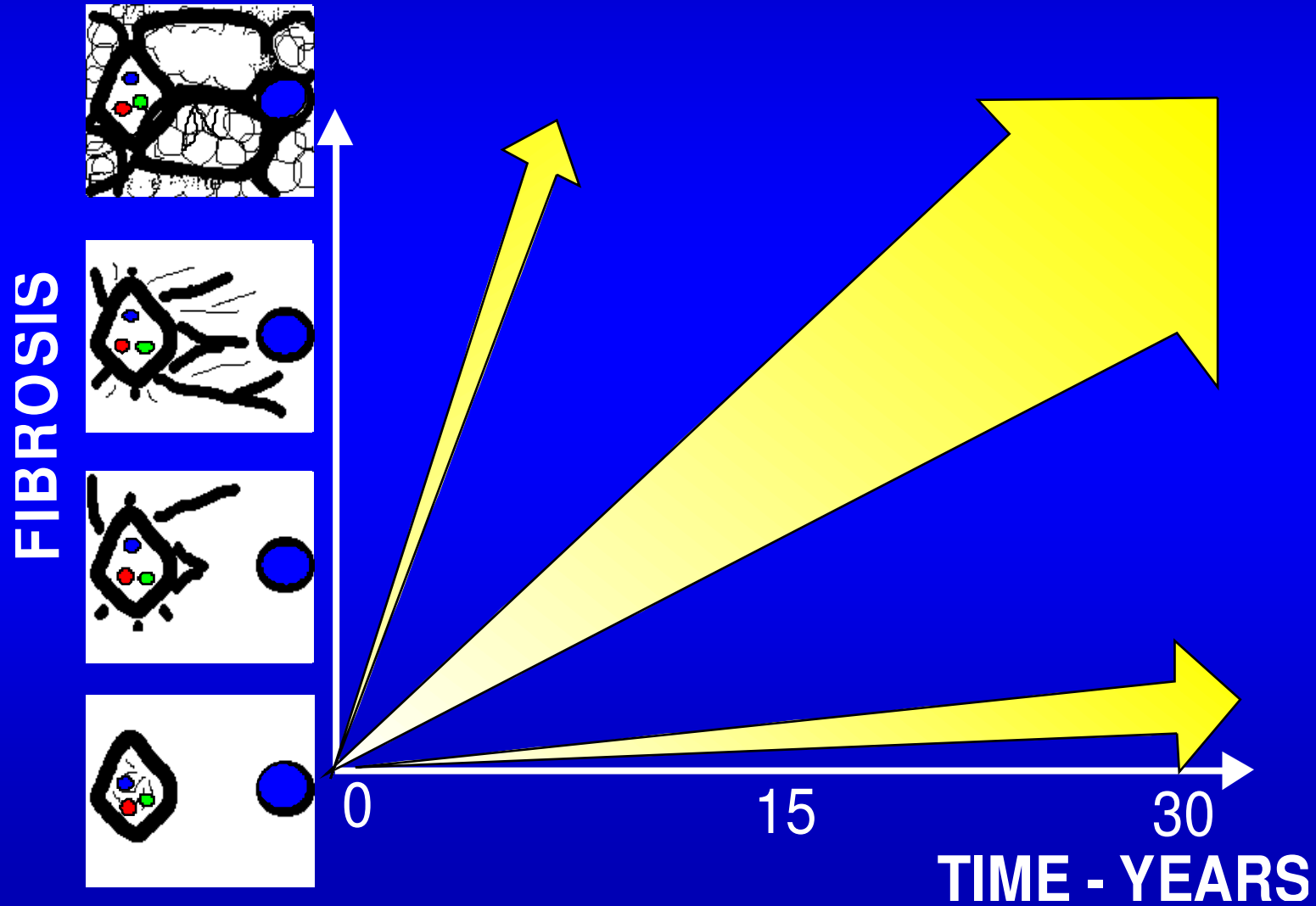
London

Hepatitis C

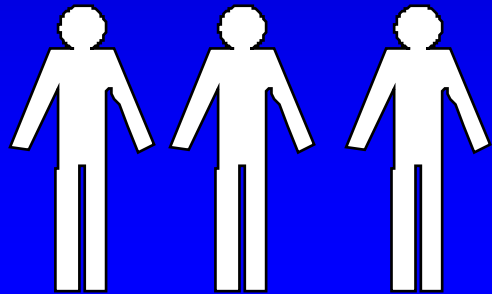
Recent progress

- Advances in natural history
- Advances in patient selection
- Advances in treatment

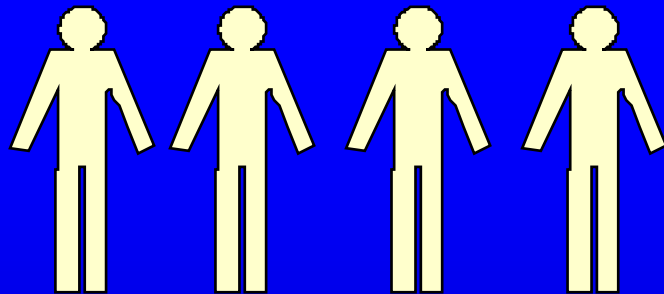
Natural History of HCV



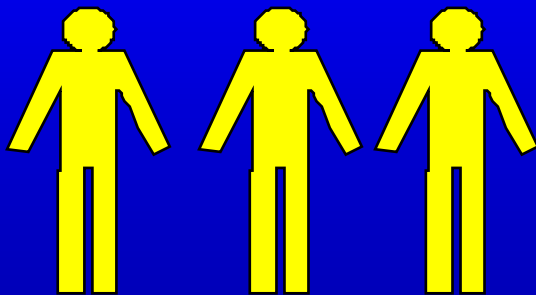
Outcome of Chronic HCV After 30 Years



30 % No liver disease



40% Liver fibrosis



30% Cirrhosis

HCV – 40 years on

The disease accelerates in the fourth decade

Hepatitis C

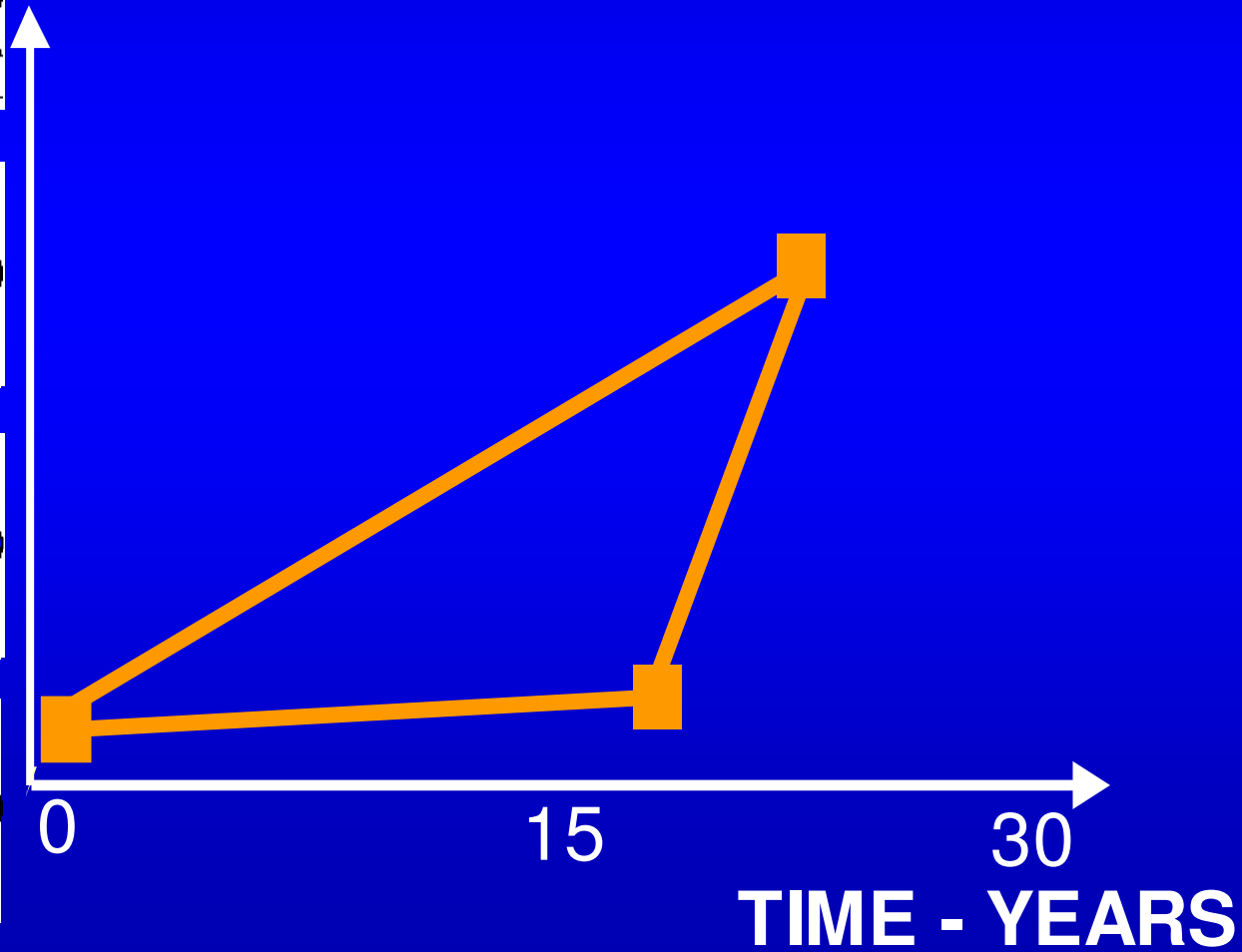
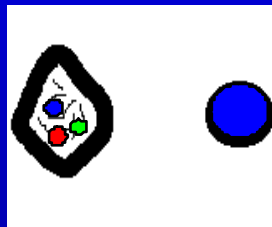
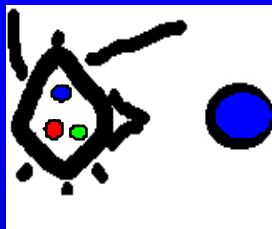
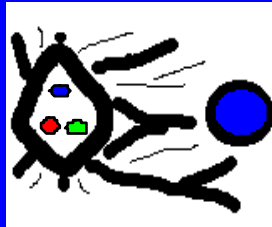
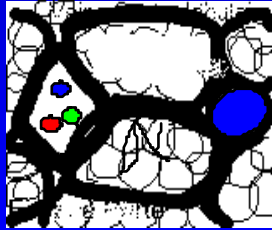
The patients tale

HCV Case Study

- Ms EH – Infected by contaminated antiD in 1977
- Liver biopsy 1994 (17 yrs) – Mild
- Liver biopsy 1997 (20 yrs) – Fibrosis 4/6
- Liver biopsy 2001 (24 yrs) - Cirrhosis

Natural History of HCV

FIBROSIS



How to get bad HCV

- Be male
- Catch it when you are old
- Drink a lot

NB

- You should pick the right parents

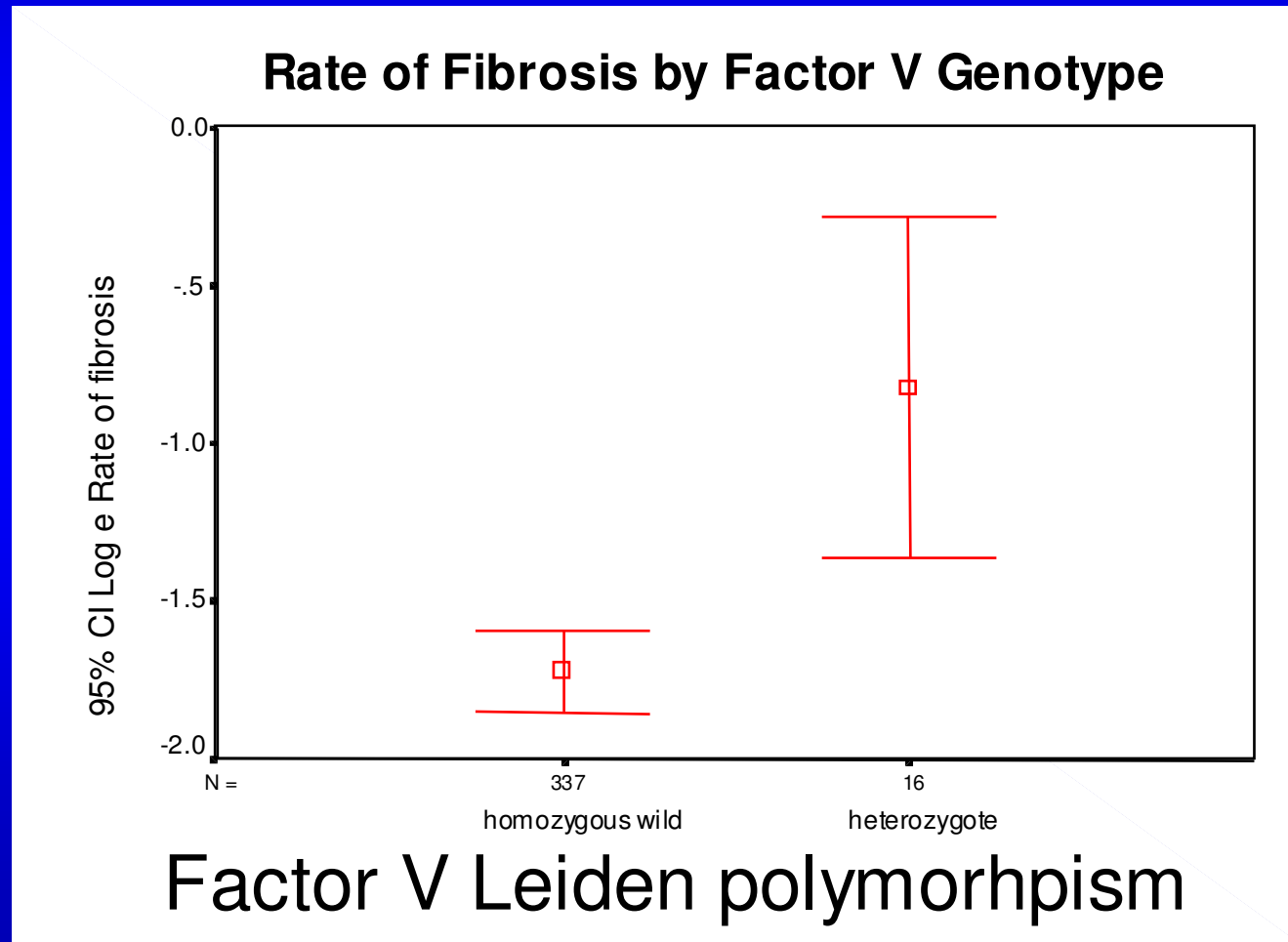
How to get bad HCV - Parental choice

- Some patients get progressive HCV despite minimal alcohol use
- Some patients get non-progressive HCV despite years of alcohol abuse

Your genes influence disease progression

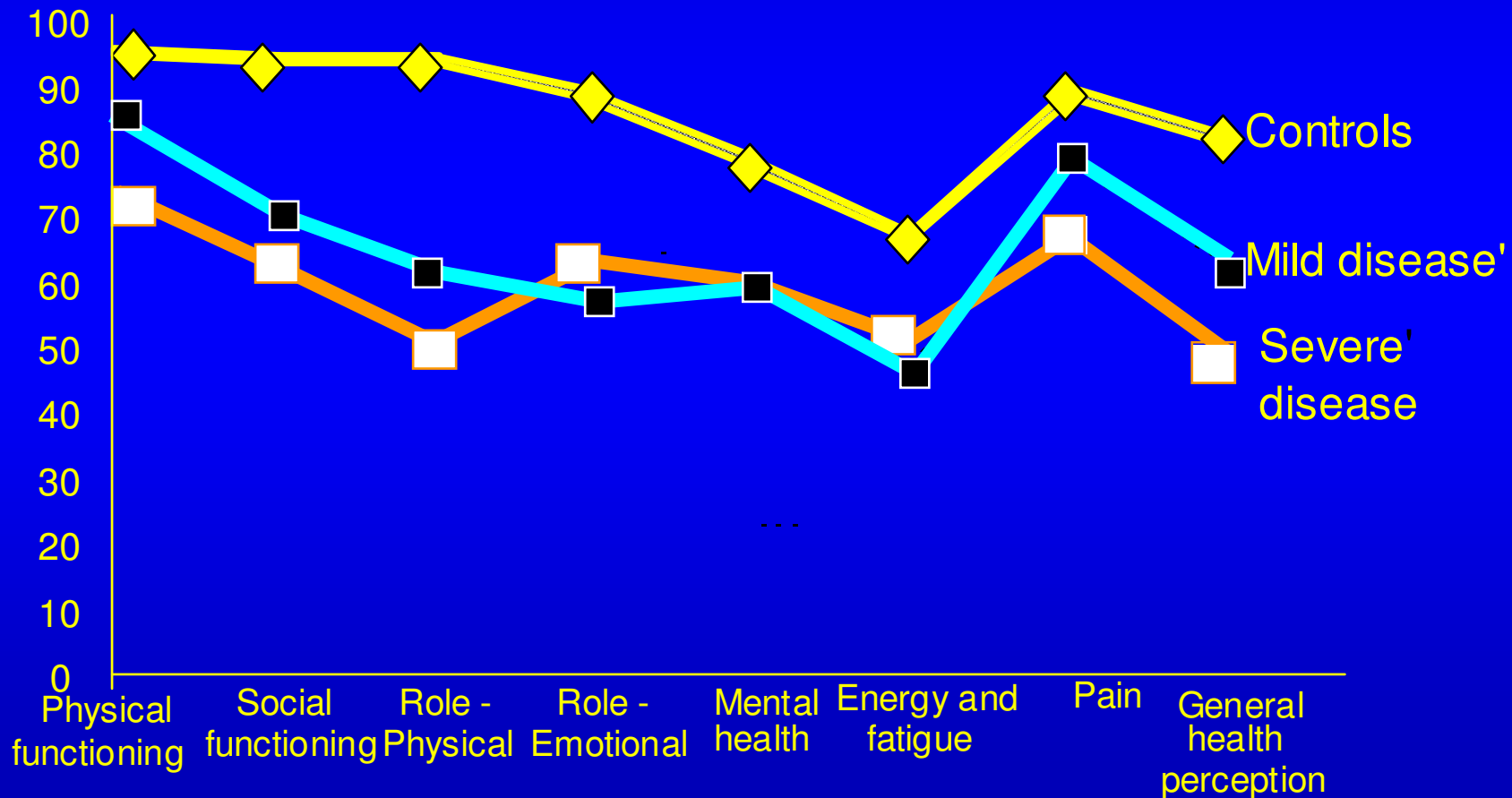
How to get bad HCV

Parental choice



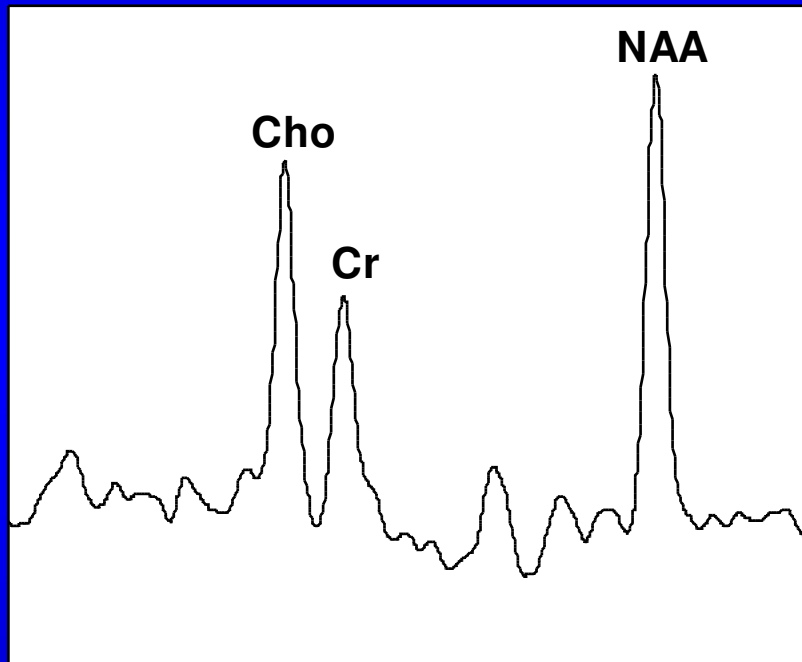
Thursz,
Wright
et al

Changes in QOL with HCV



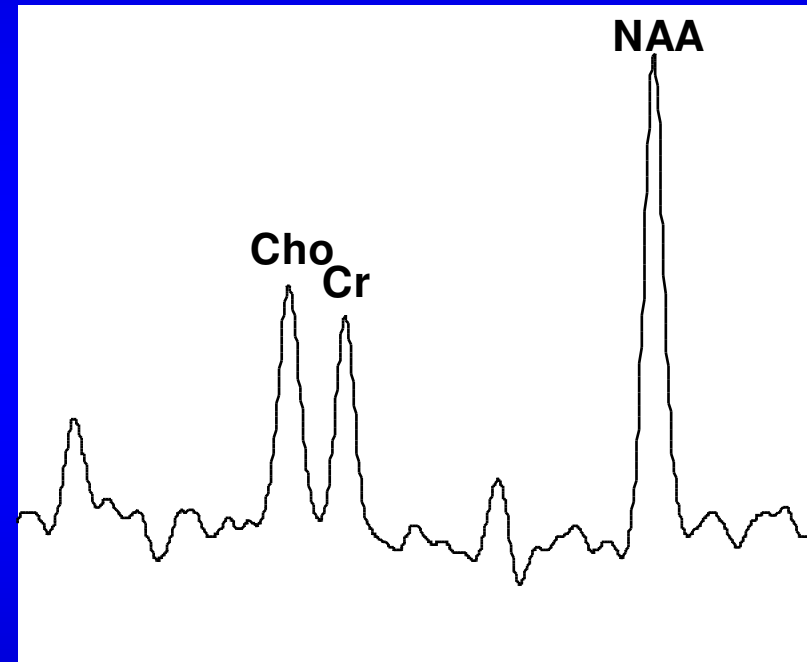
Hepatitis C and the brain

^1H - MRS results - white matter



Patient

Mean Cho/Cr 1.35



Volunteer

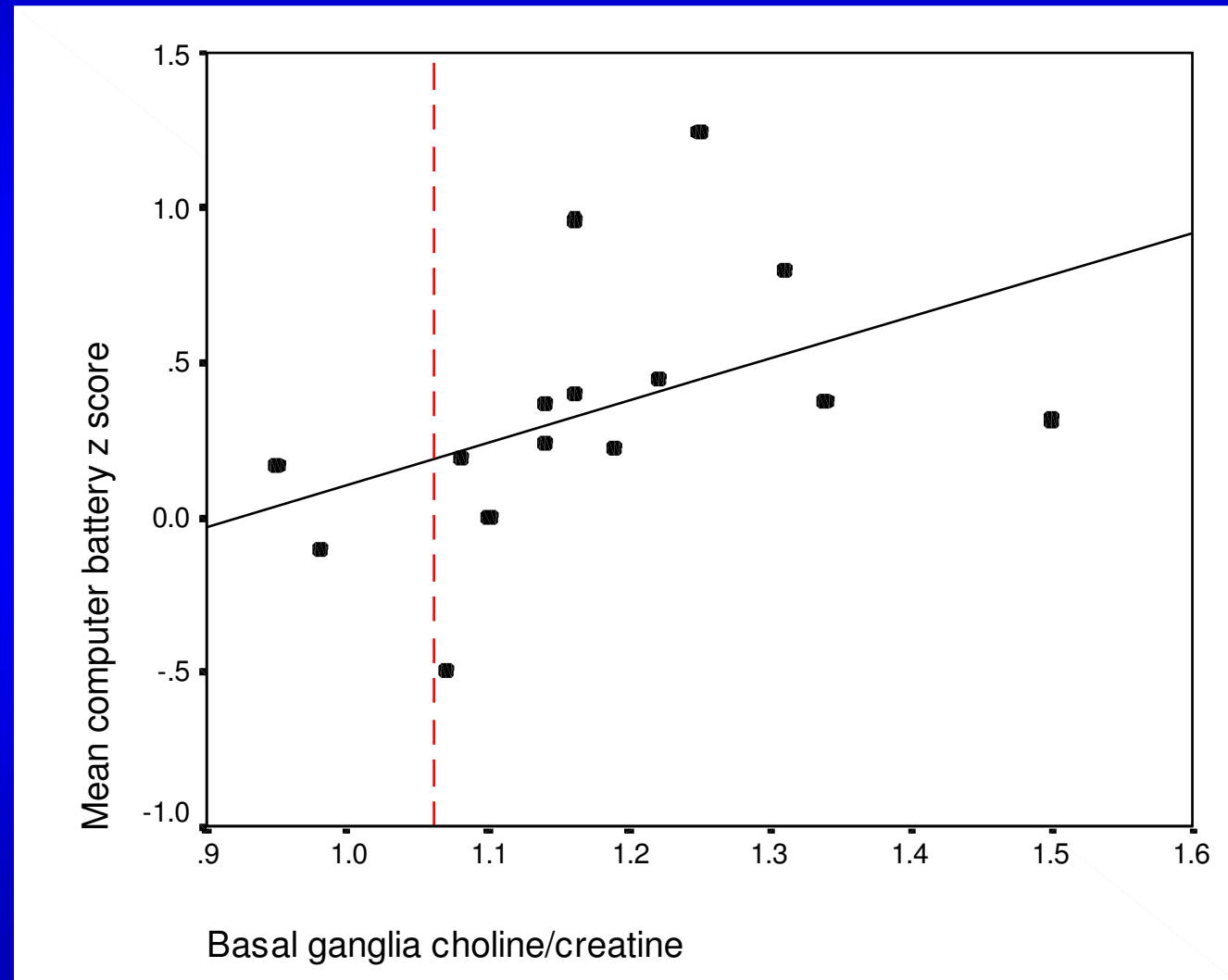
Mean Cho/Cr 1.18*

Fortan et al

* $p=0.001$

Hepatitis C and the brain

$r=0.71$
 $p=0.003$



Hepatitis C and the brain

- Hepatitis C infects the brain
- This may explain some of the symptoms associated with chronic infection

HCV – Who should we treat? (Opinion based medicine)

We should NOT treat active drug users

They will not comply
They will get reinfected

(They are not worth it)

NICE and IVDUs

‘Treatment of people who continue to use drugs is often not indicated due to the high probability of re-infection, presumed likelihood of relatively high levels of non-compliance and the possibility of drug interactions. Cessation of IVDU before starting antiviral treatment is therefore important’

HCV in drug users - evidence

Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up.

Dalgard O, Bjoro K, Hellum K, Myrvang B, Skaug K, Gutigard B, Bell H; The Construct Group.

Eur Addict Res 2002 Jan;8(1):45-9

Treatment of hepatitis C infection in injection drug users

Markus Backmund, Kirsten Meyer, Michael Von Zielonka, Dieter Eichenlaub

Hepatology July 2001 • Volume 34 • p188 to p193

HCV in drug users

Evidence based medicine

- Active IVDUs do benefit from therapy
- Active IVDUs do comply with treatment
- Active IVDUs do not get reinfected

HCV in drug users

- The fact that we CAN treat drug users does not mean that we MUST treat active users

Therapy for chronic HCV

Therapy for chronic HCV

Interferon plus ribavirin

(Cures 40%)

Treatment of HCV: Current Guidelines

- Perform a liver biopsy
- Assess severity
- Monitor mild disease
- Treat severe disease

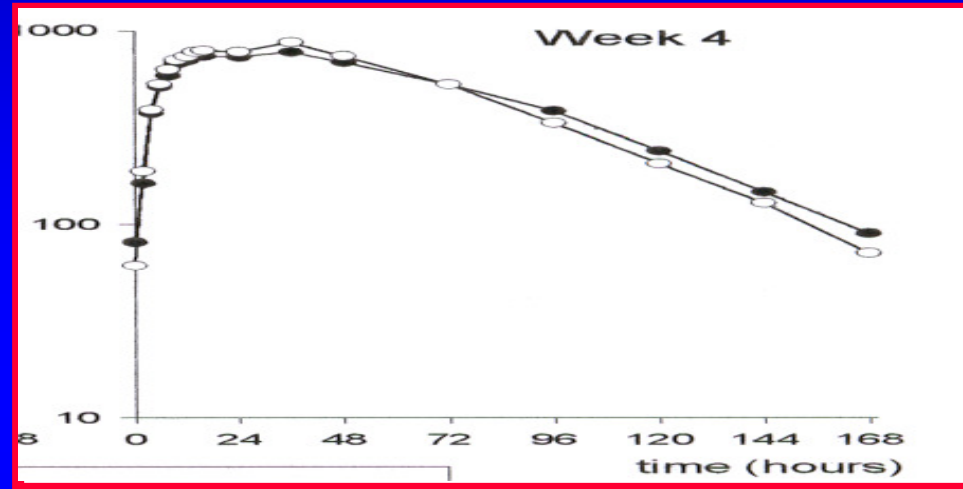
Treatment of HCV: The third millenium

Add Poly Ethylene Glycol (PEG) to IFN

- Increase half life
 - Increase efficacy
 - Decrease side effects
-
- 12 kD PEG IFN α 2b/40kD PEG α 2a

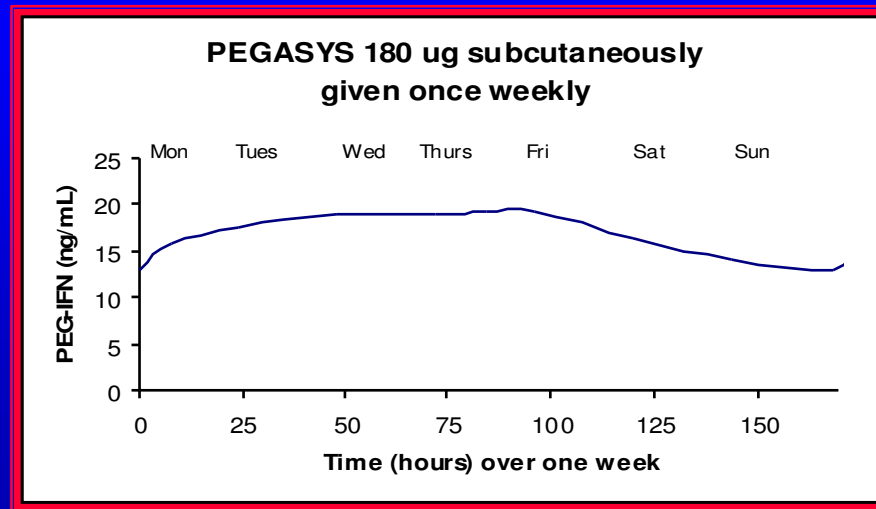
Half life of Pegylated IFNs

12 kD PEG
IFN α 2b



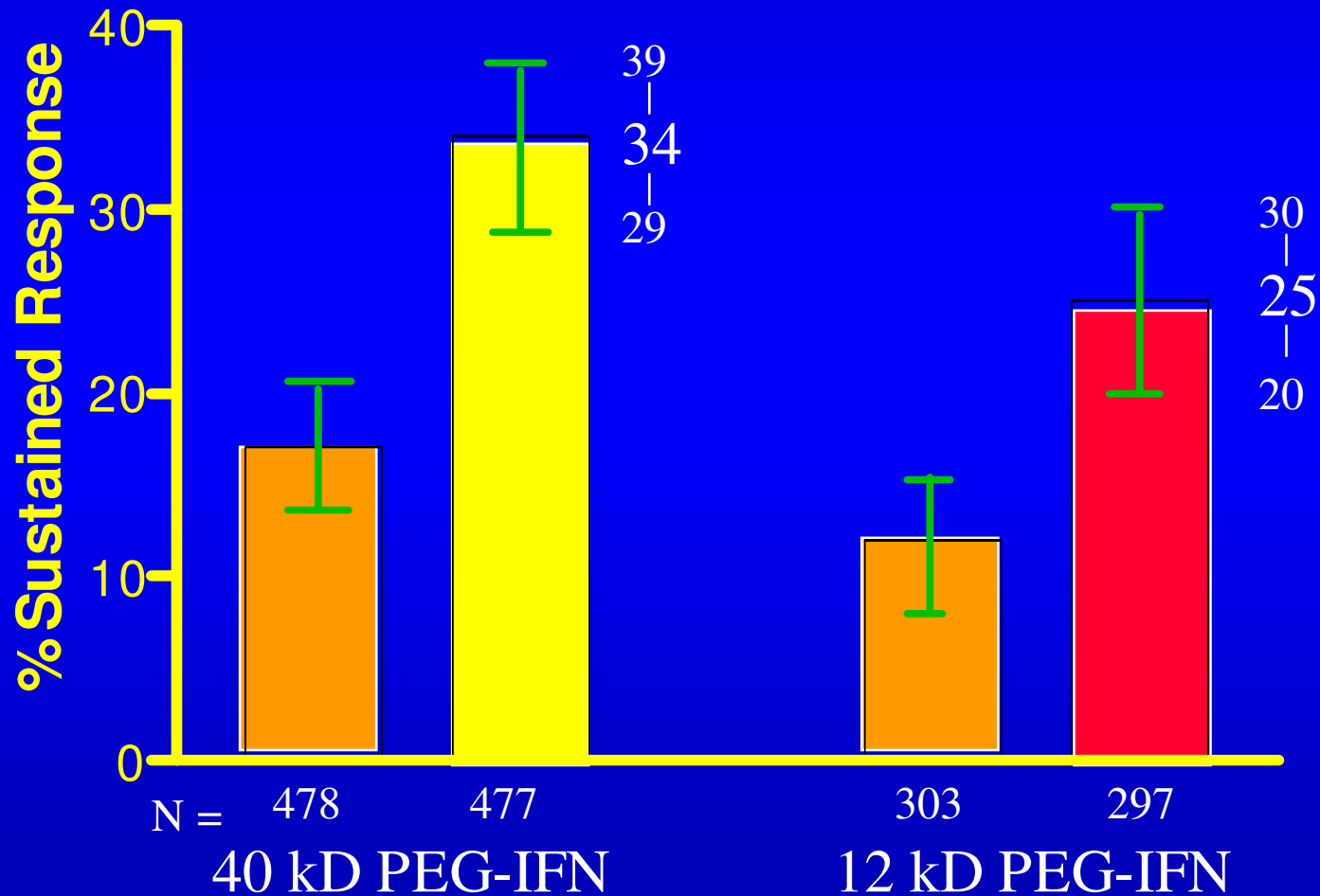
Powder
Dose by wt

40 kD PEG
IFN α 2a

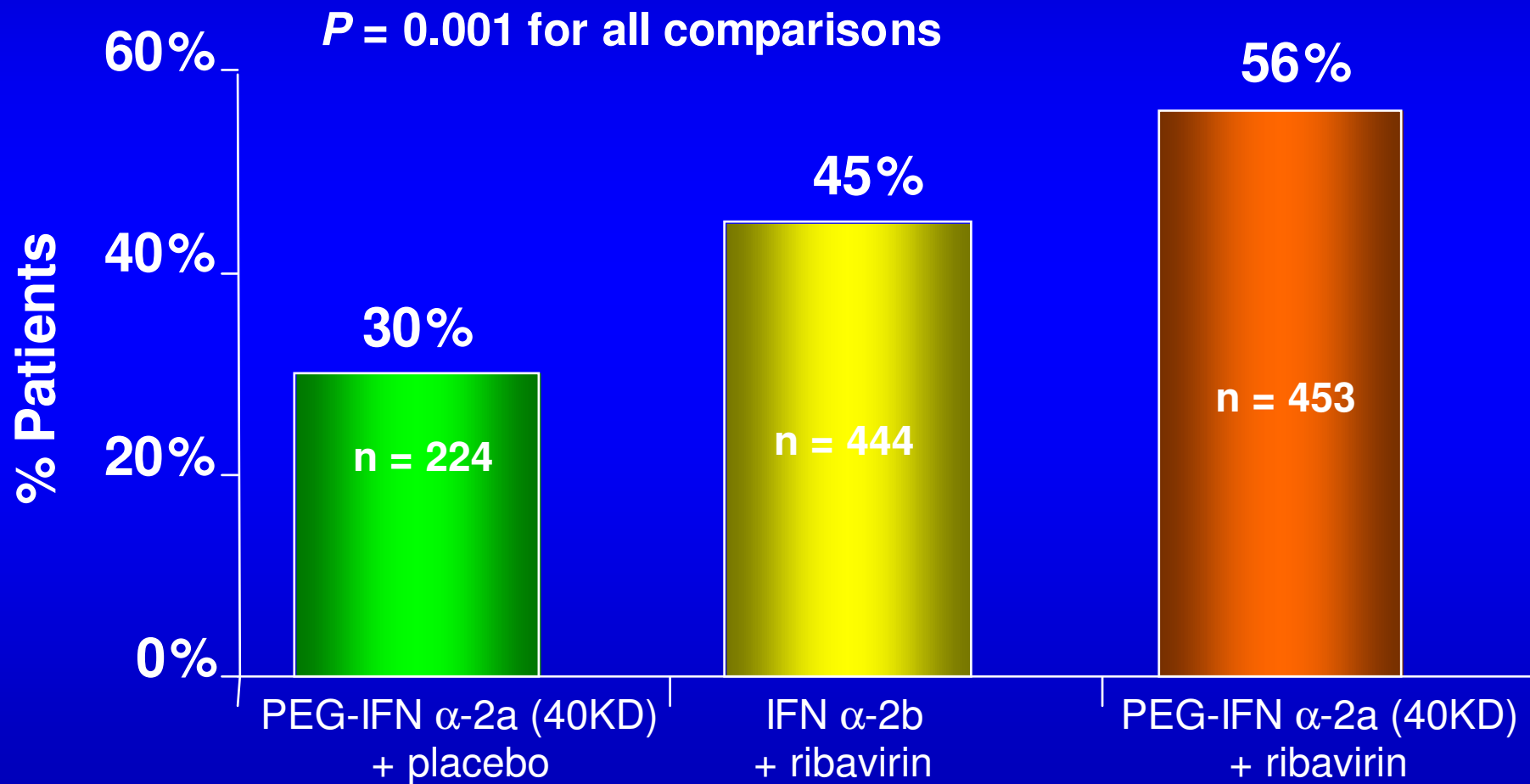


Solution
Fixed
dose

PEG-IFN Trials to-date

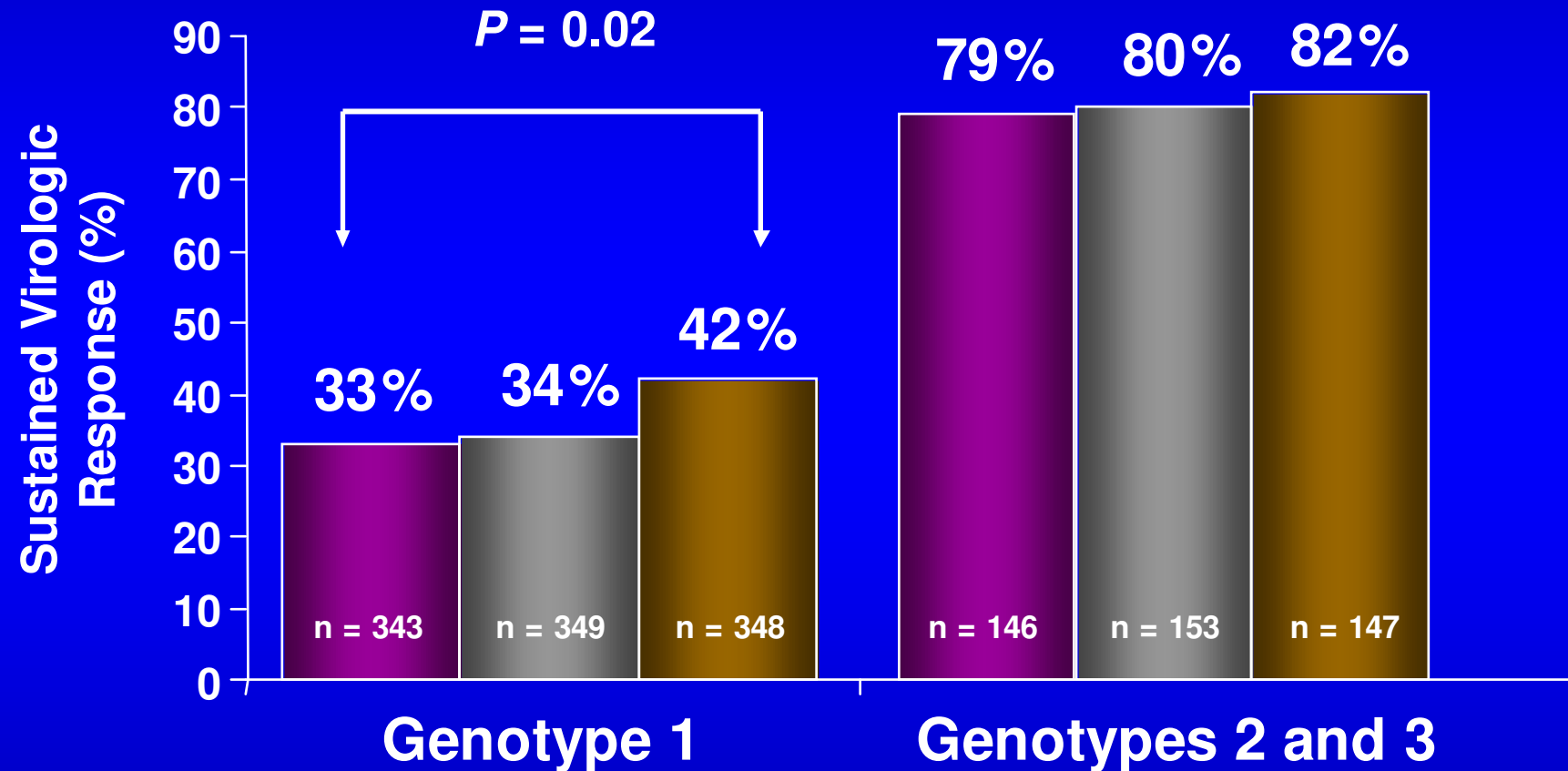


PEG-IFN α -2a (40KD) + Ribavirin Sustained Virologic Response (SVR)



Fried MW et al. *DDW*. 2001.

PEG-IFN α -2b (12KD) + Ribavirin SVR by Genotype



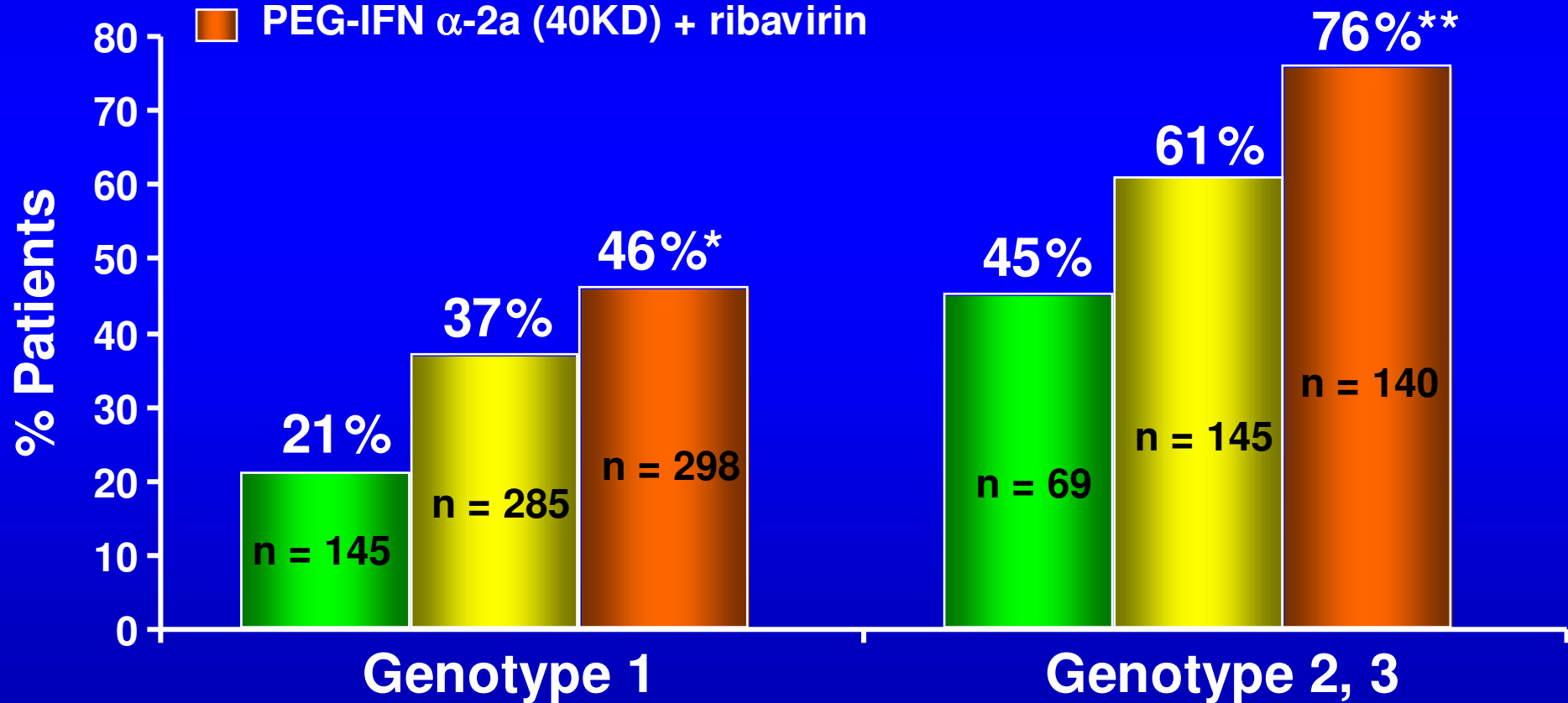
- IFN α -2b + ribavirin
- PEG-IFN α -2b 1.5 / 0.5 μ g/kg + ribavirin
- PEG IFN α -2b 1.5 μ g/kg + ribavirin

Manns MP, et al. *Lancet*. 2001;358:958-965.

PEG-IFN α -2a (40KD) + Ribavirin SVR by Genotype

- PEG-IFN α -2a (40KD) + placebo
- IFN α -2b + ribavirin
- PEG-IFN α -2a (40KD) + ribavirin

* $P = 0.016$ vs IFN α -2b + RBV
** $P = 0.008$ vs IFN α -2b + RBV



Fried MW et al. *DDW*. 2001.

Early Discontinuation PEG(40kDa)IFN+RBV Combination

All PEG (40kDa) Patients + RBV Patients



New Guidelines for HCV ?

- Assess genotype
- For genotypes 2/3 – six months therapy with pegylated IFN + Ribavirin
- For genotype 1 – biopsy and treat severe disease

New Drugs for HCV

- Better ribavirins
- Protease inhibitors
- Polymerase inhibitors

Better Ribavirins

- Several ribavirin analogues are now being studied

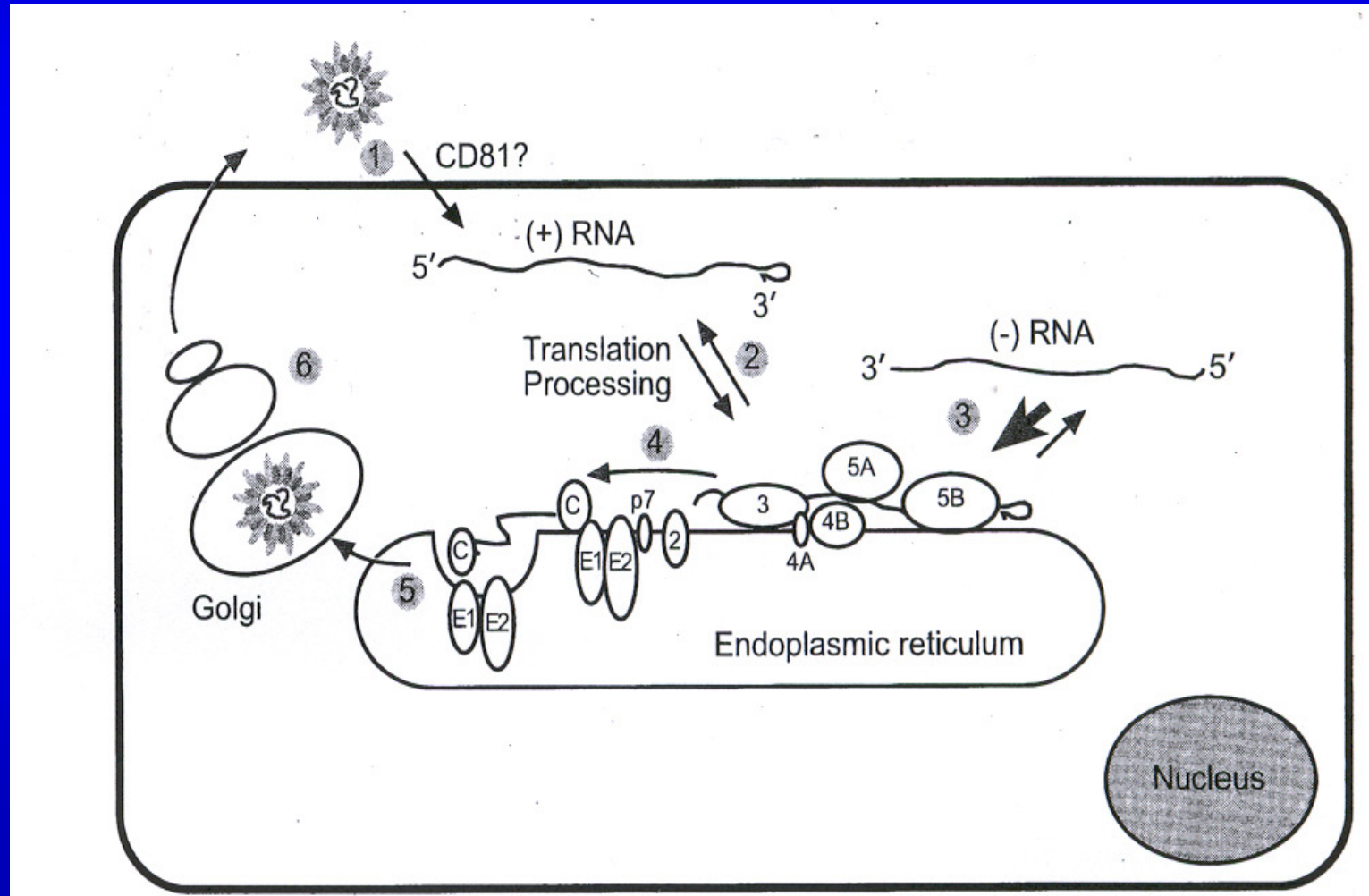
? Fewer side effects

Unlikely to have greater efficacy

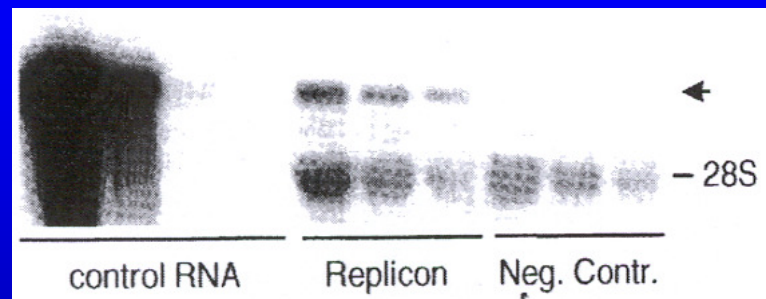
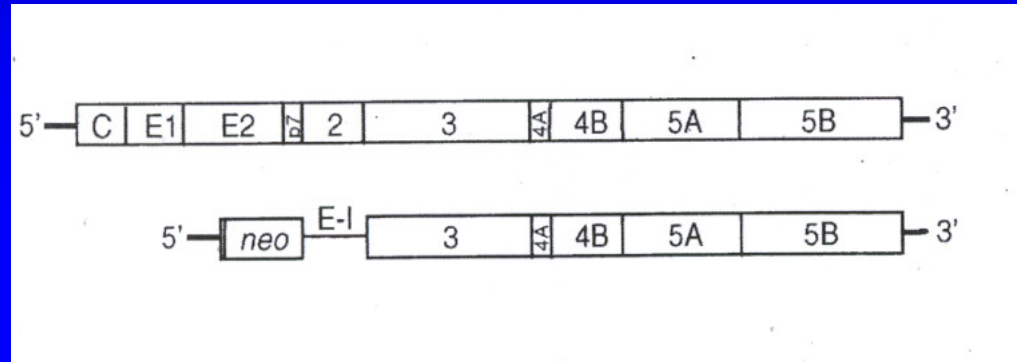
Protease Inhibitors

- The first protease inhibitor is now going into patients

Replication of HCV



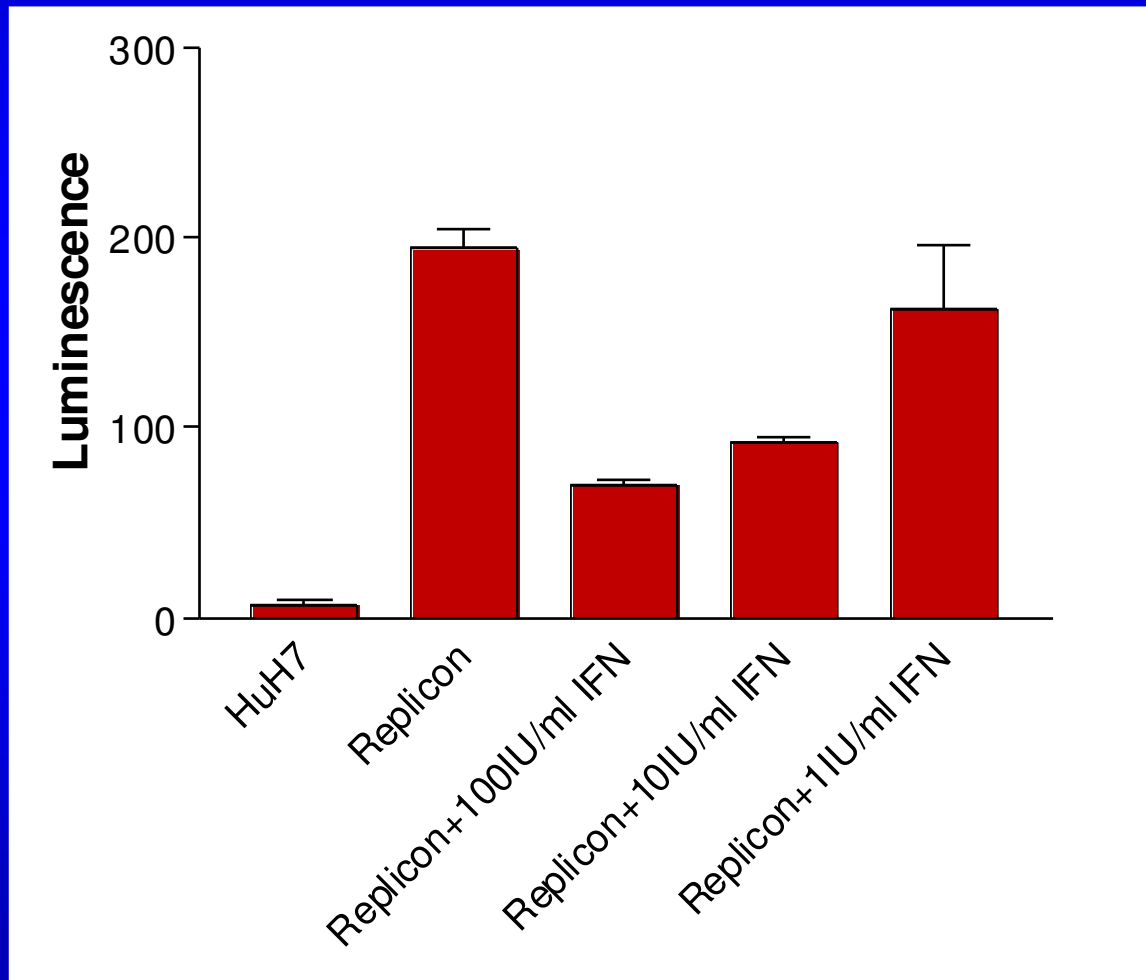
HCV: The 'Replicon'



The HCV 'Replicon'

- By incorporating a marker gene in the replicon we can develop screening assays for new drugs

Luciferase containing Replicon



The HCV Replicon

- Studies with the HCV replicon will lead to the development of new drugs in the near future

HCV – the future

- HCV is not as benign as we once thought
- HCV can be treated in most patients
- Therapy for HCV is now good and likely to get even better