

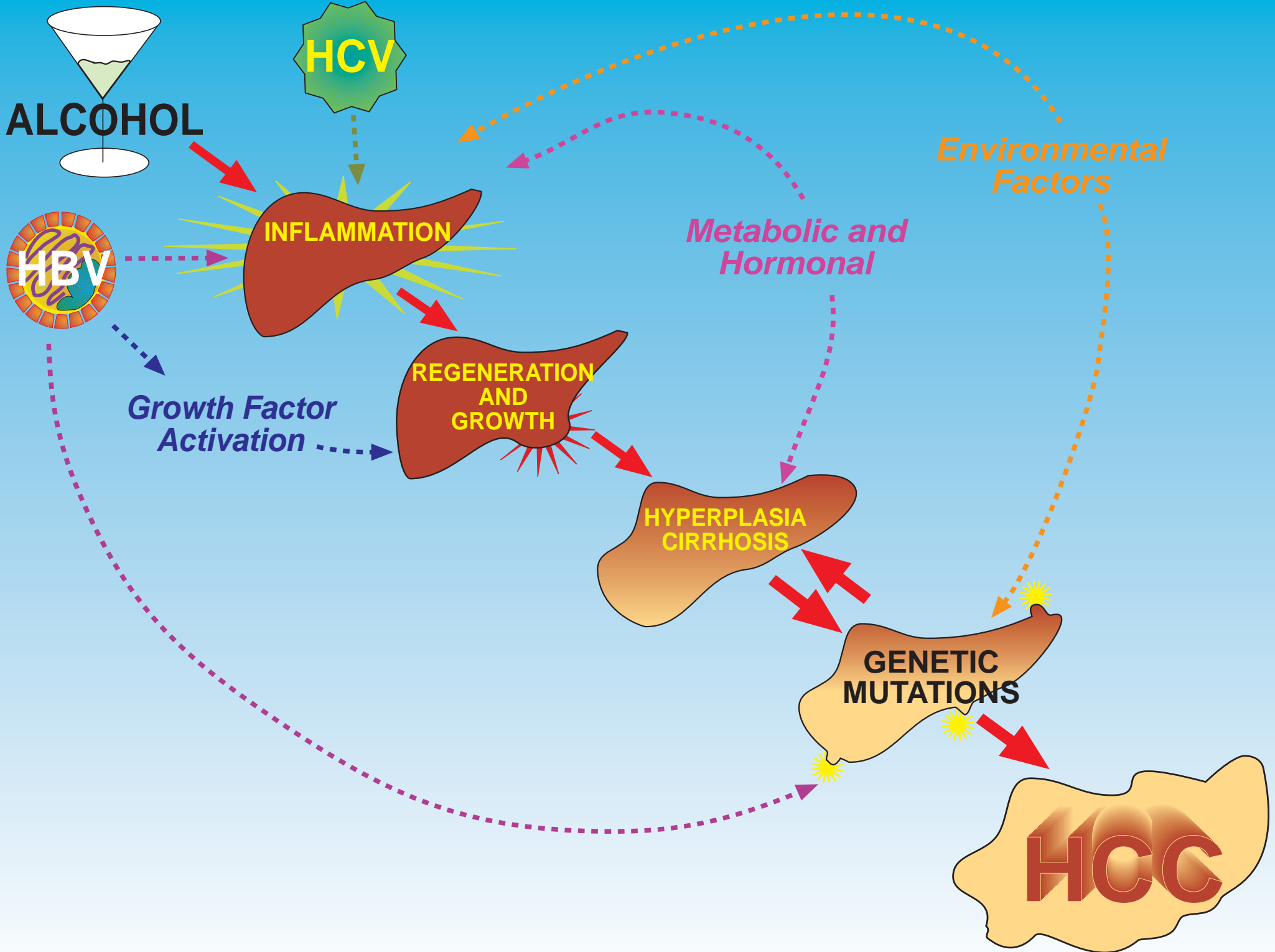
Harvard-MIT Division of Health Sciences and Technology
HST.121: Gastroenterology, Fall 2005
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Jeffrey and Kimberly Greenberg-
Artemis and Martha Joukowsky
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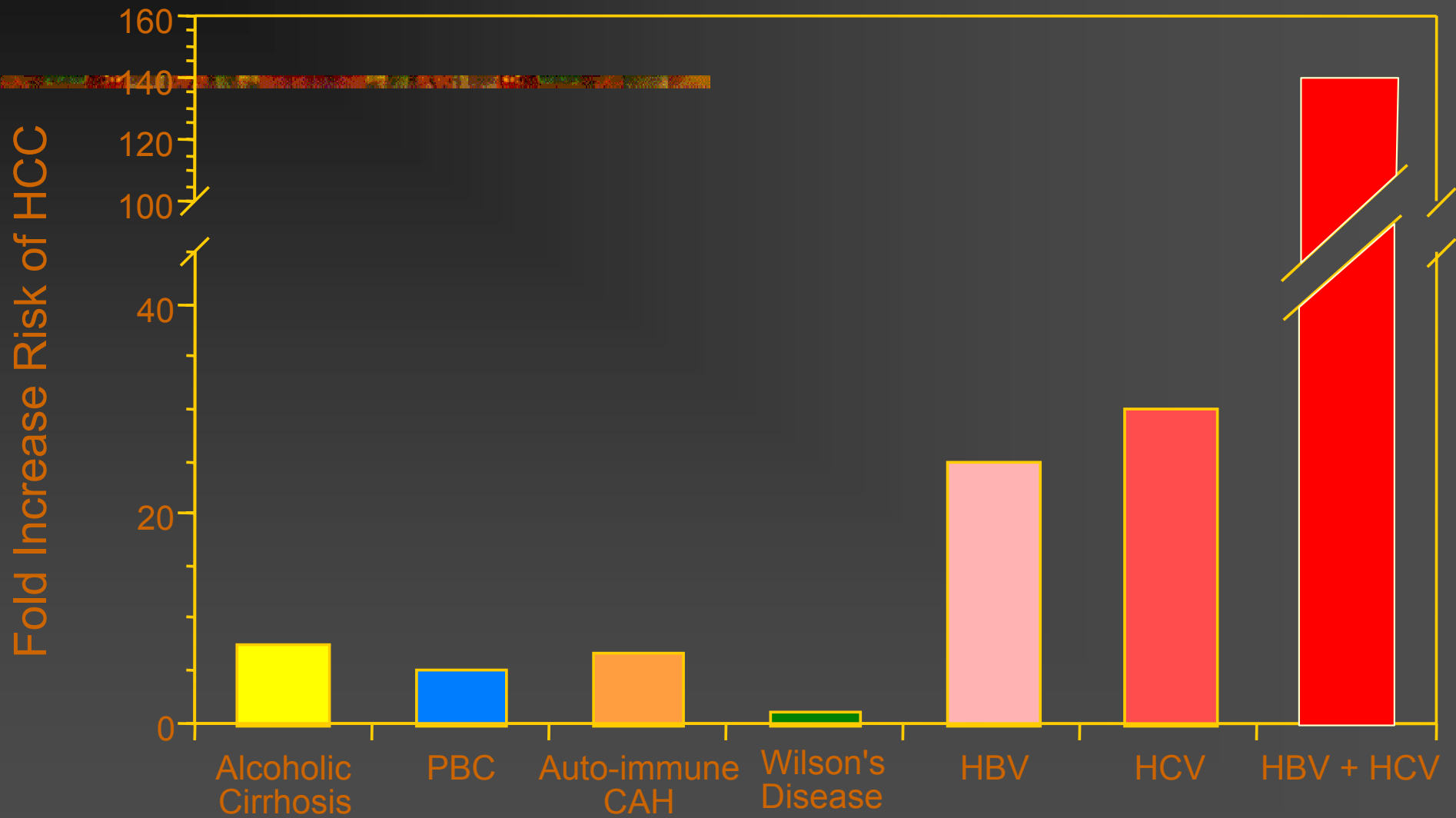
Director, Division of Gastroenterology and
The Liver Research Center



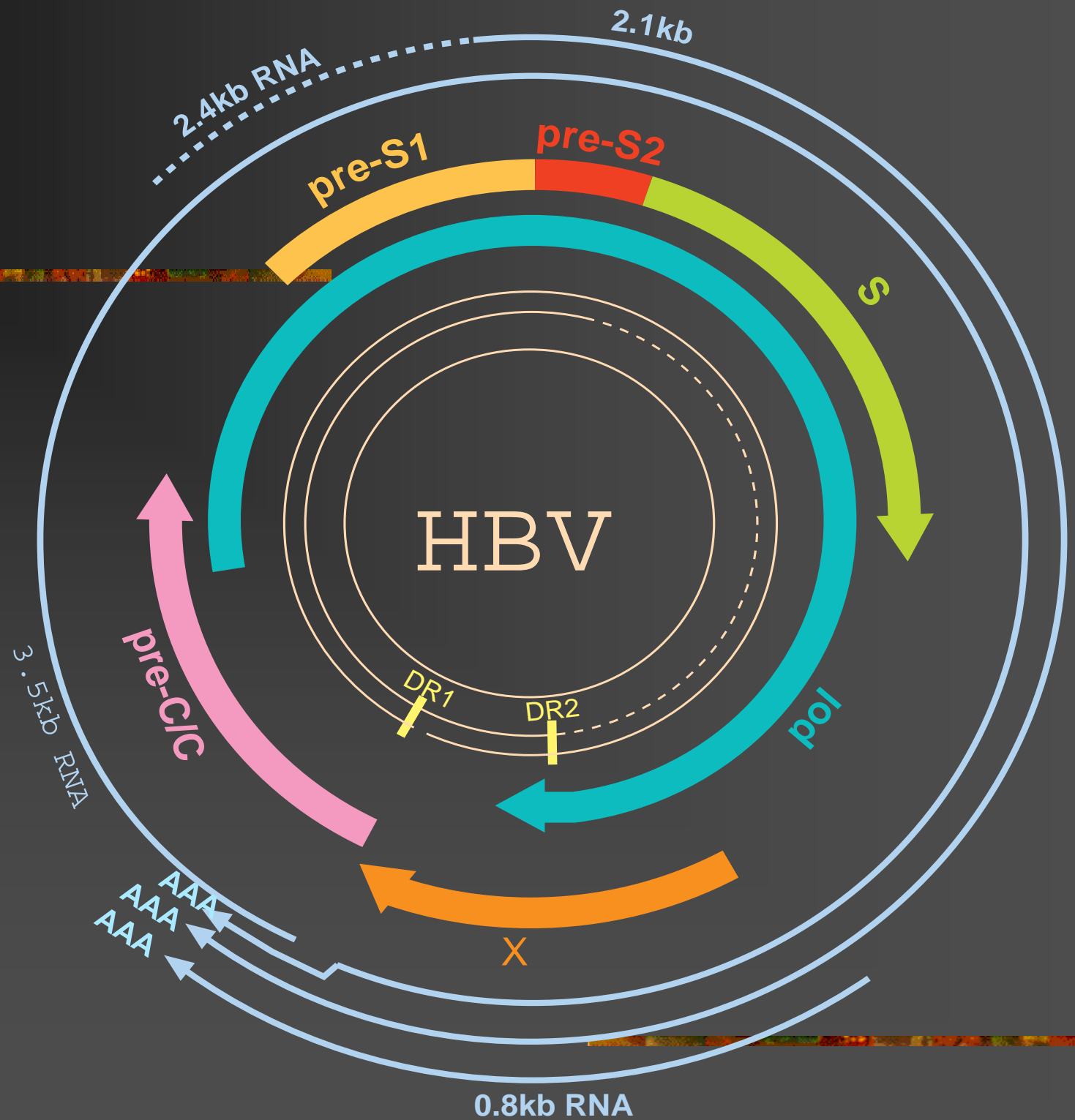




Risk of HCC Development



HBV Genome



Hepadnaviruses



Ducks

Woodchuck



Chimpanzee

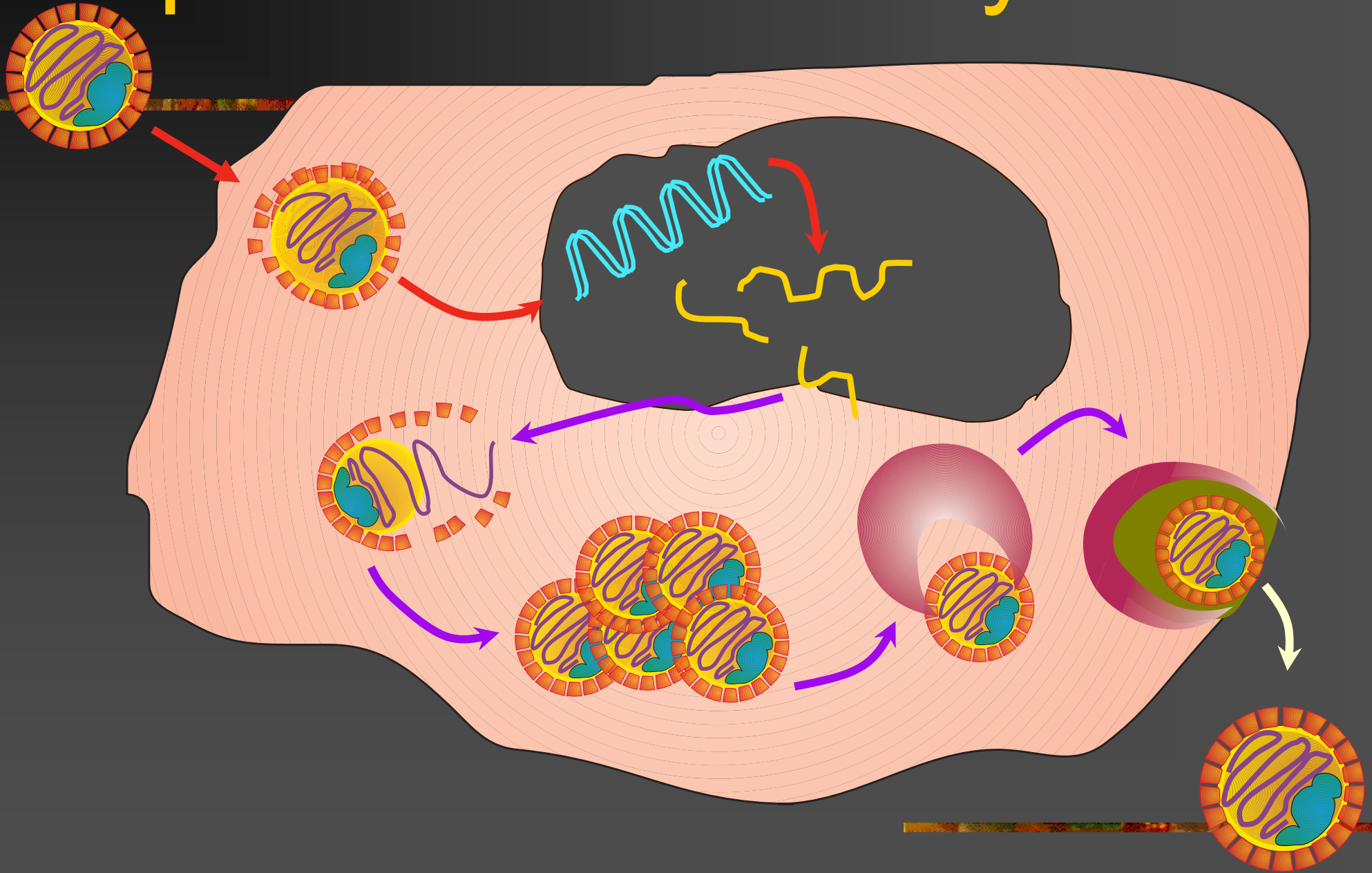


Humans



Ground Squirrel

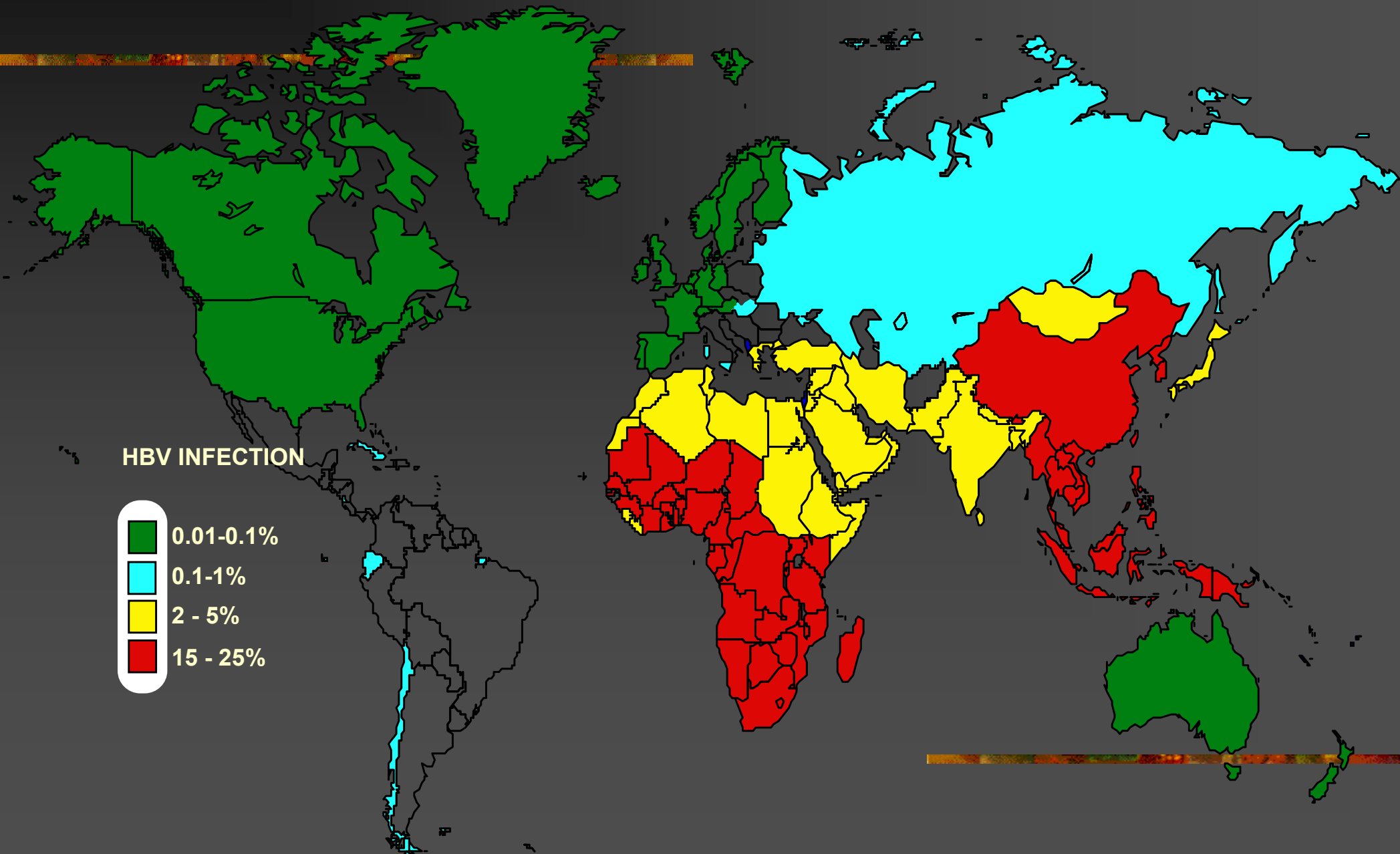
Hepadnaviral Life Cycle



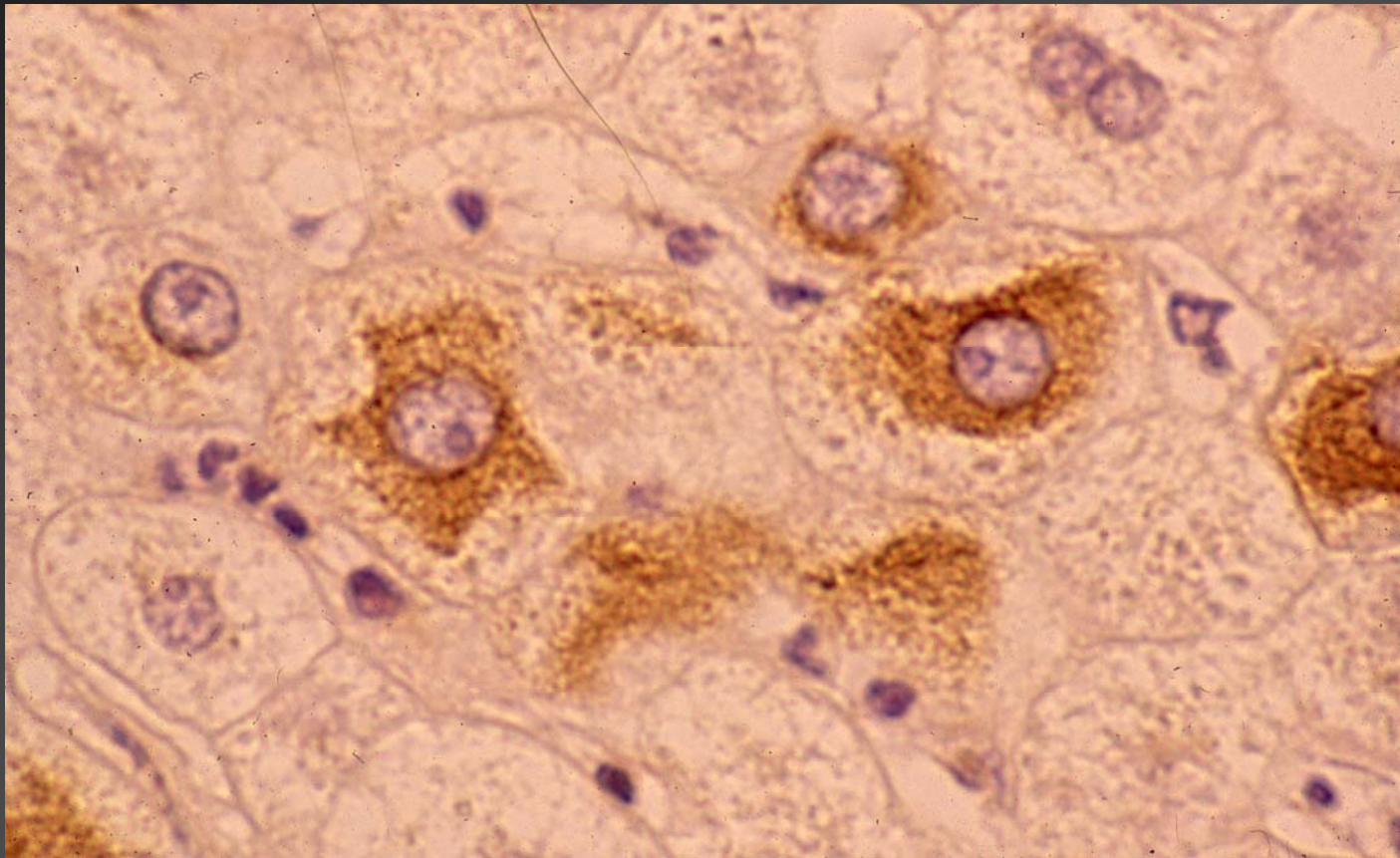
Burden of HBV Disease

- 350 to 400 million people worldwide have chronic HBV; 1.2 million in US
 - Up to 1 million deaths/year worldwide due to HBV-related complications of cirrhosis, liver cancer
-

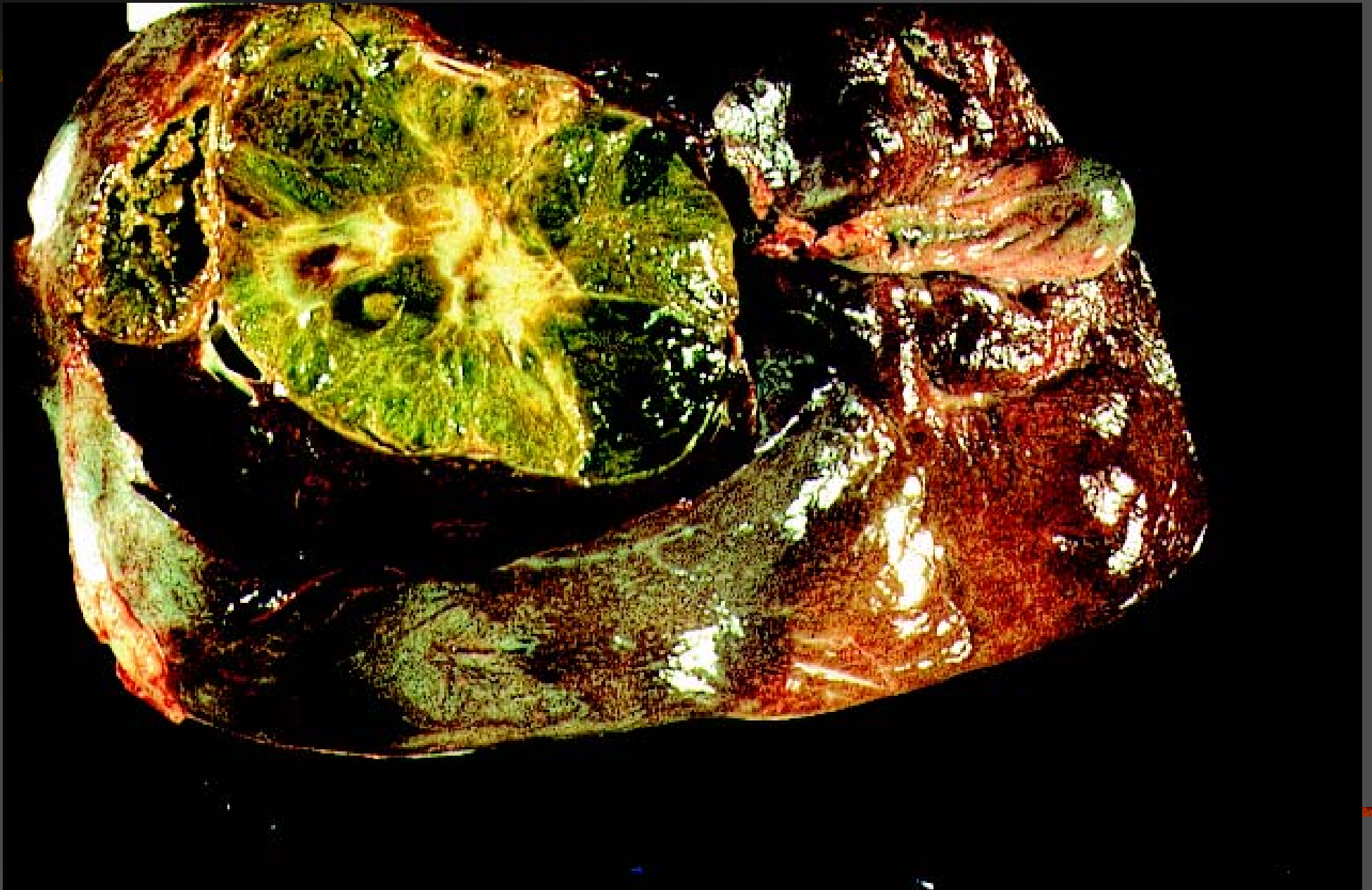
Chronic HBV Infection



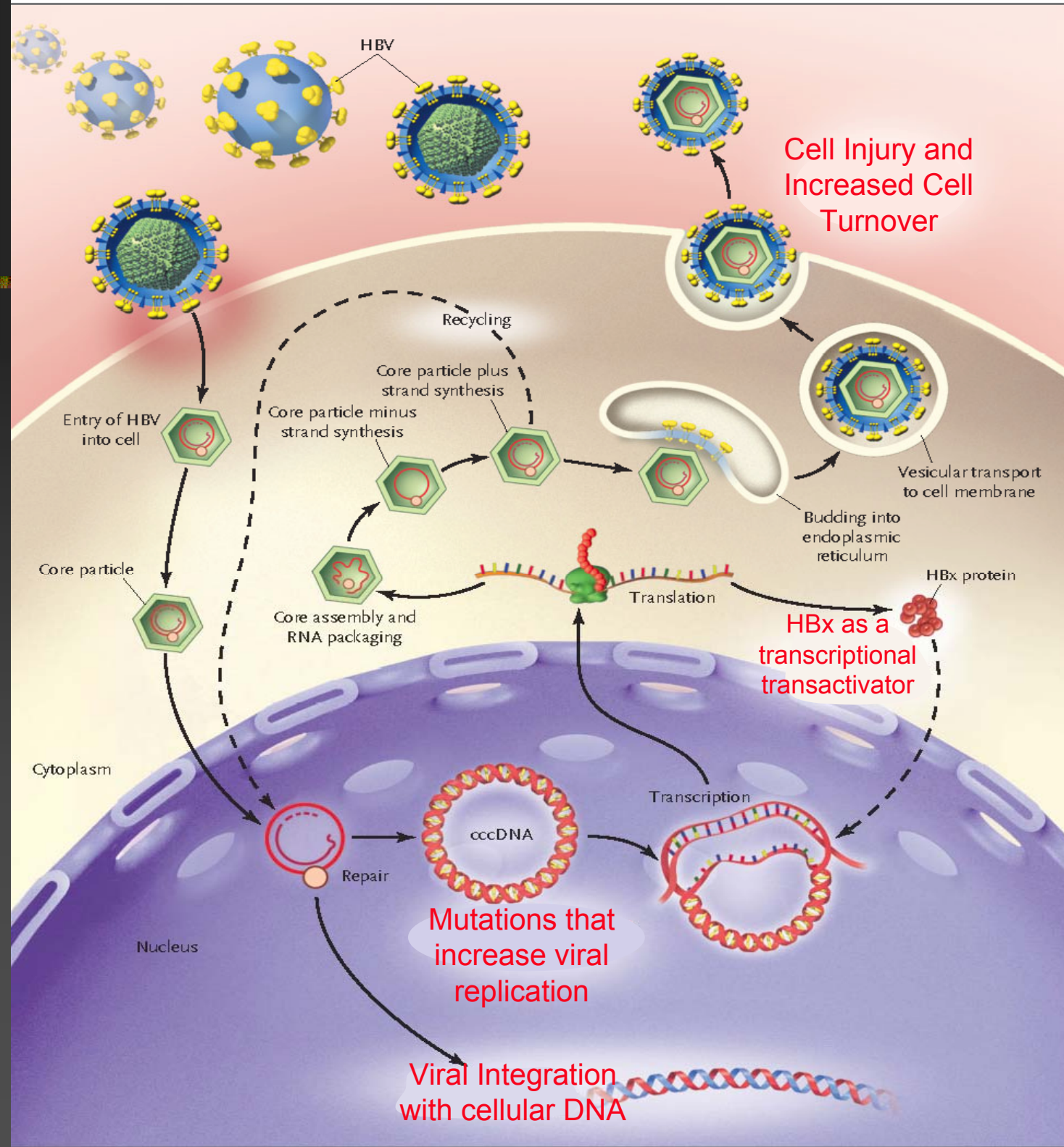
Chronic HBV Infection



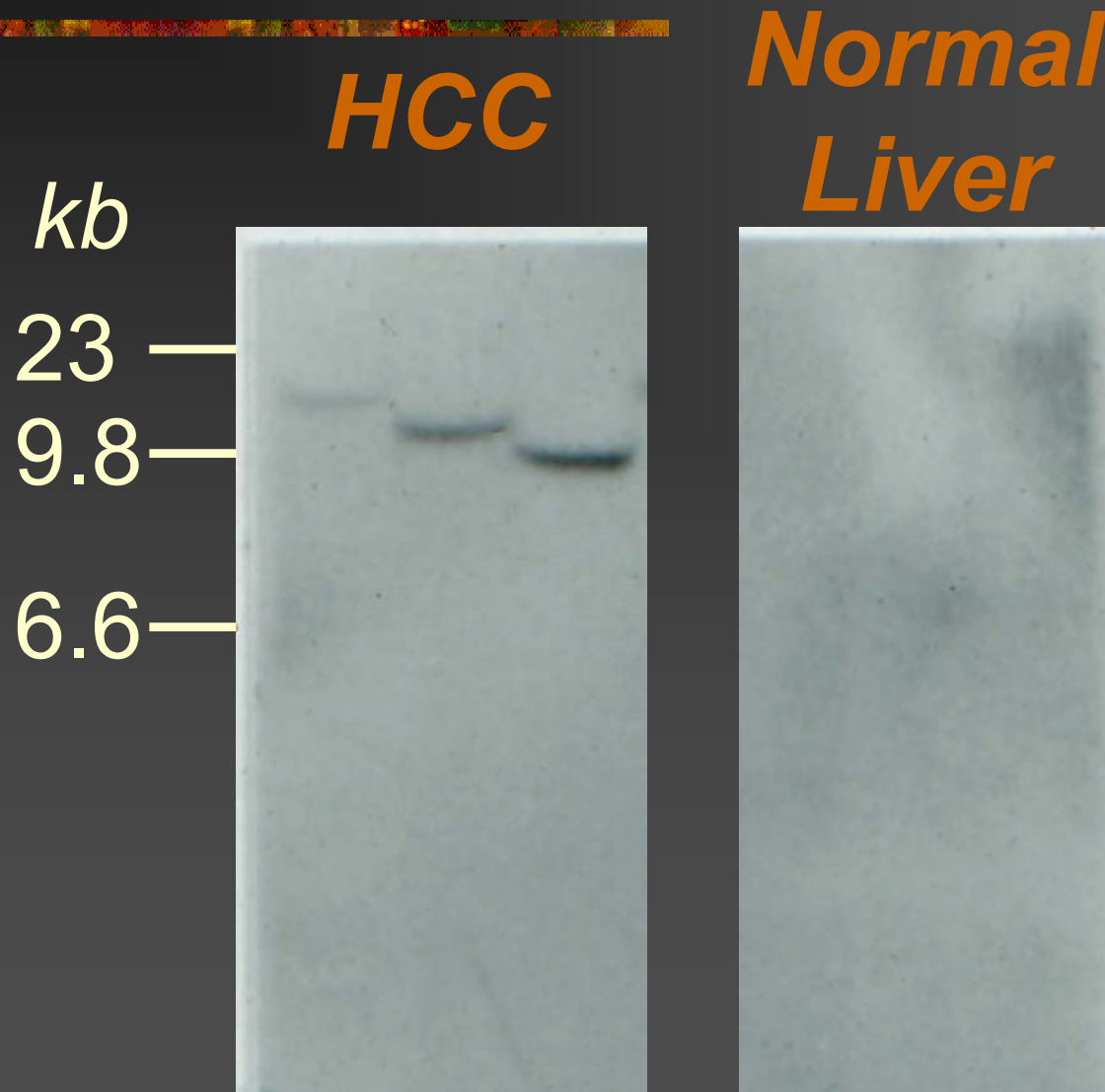
Liver Cancer



Pathogenesis of HCC



HBV Integration in HCC



Core promoter mutations cumulatively enhance HBV genome replication

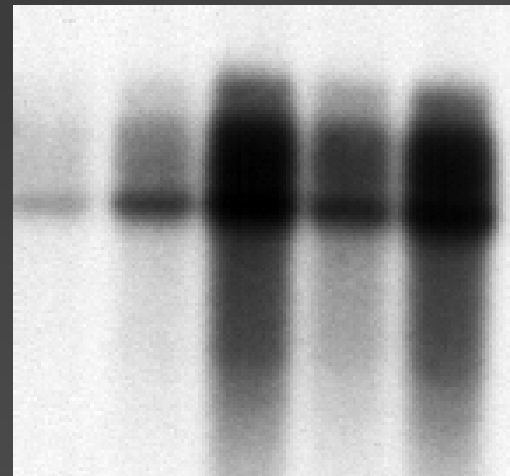
Core promoter mutations

1753C 1762T 1764A 1766T

| | | | | |
|---|---|---|---|---|
| 1 | - | - | - | - |
| 2 | - | + | + | - |
| 3 | - | + | + | + |
| 4 | + | + | + | - |
| 5 | + | + | + | + |

Hot-spot
mutations

1 2 3 4 5



Intracellular HBV replicative forms

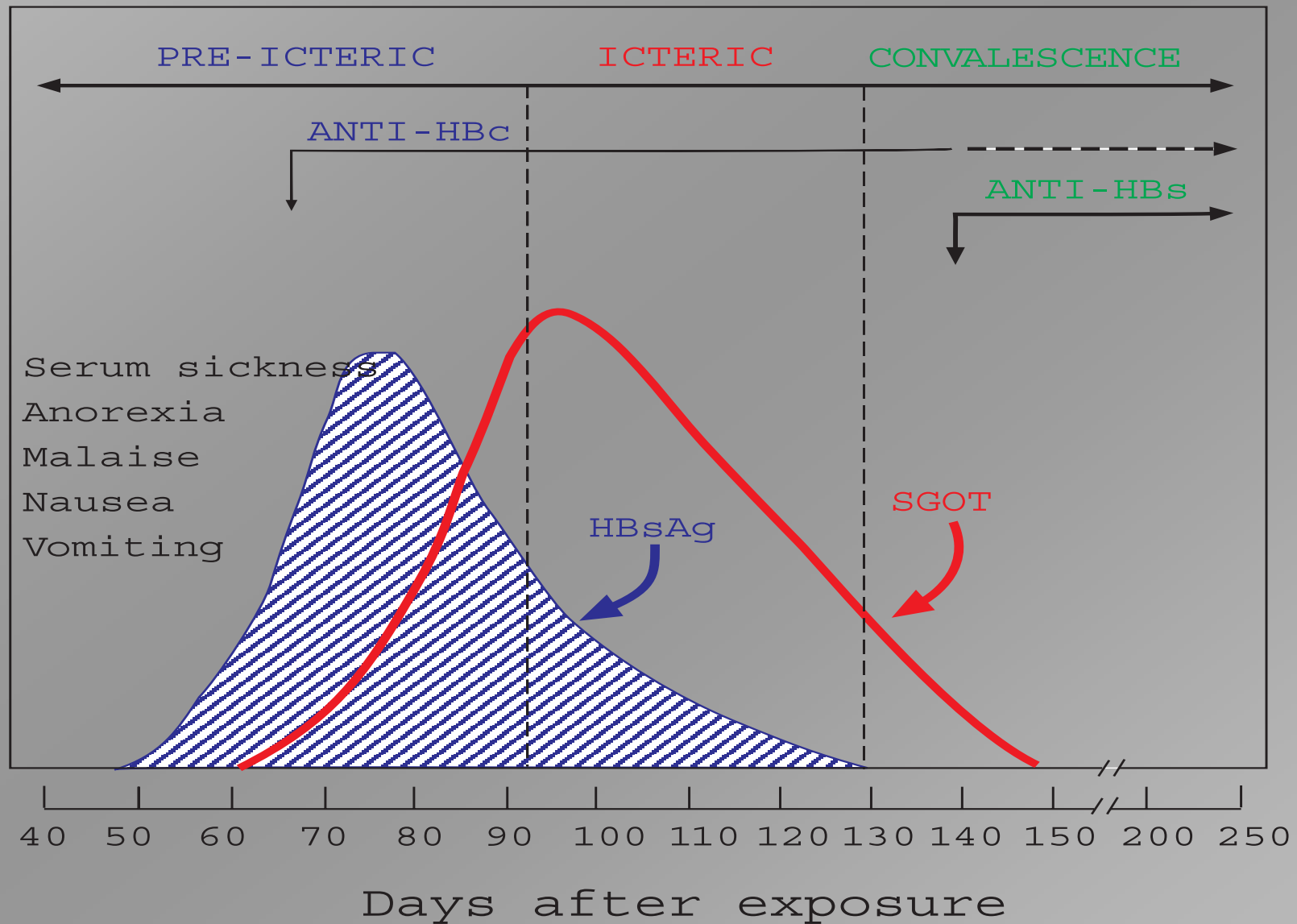
HYPOTHESIS

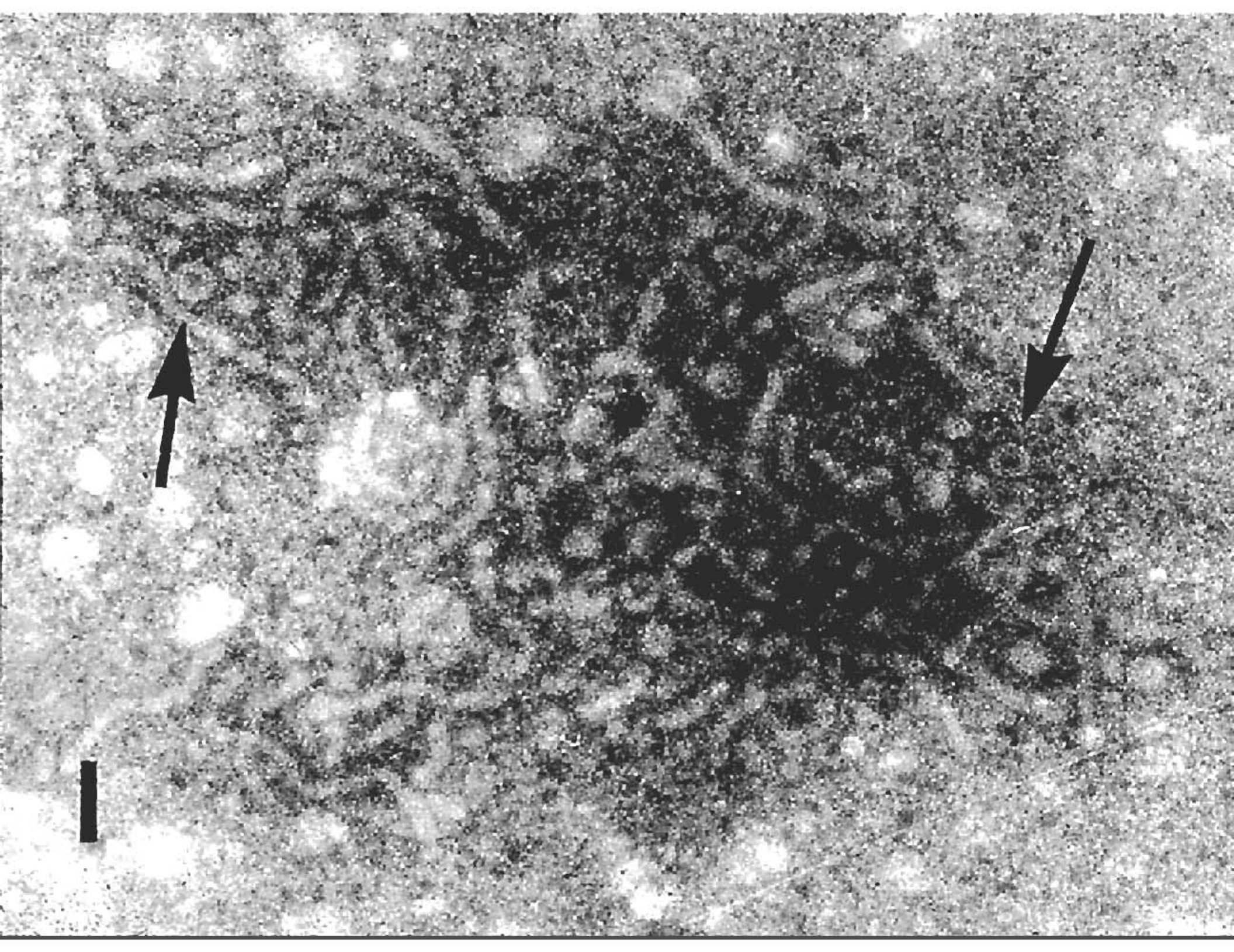
- **Natural occurring mutations in the precore region render the viral strain less responsive to agents that inhibit the viral polymerase**
 - **Sustained and complete inhibition of “wild type” HBV will reduce the frequency of break-through mutations and viral resistance**
 - **Complete inhibition of viral replication in the liver over time will substantially reduce the incidence of HCC**
-

Serologic Diagnosis of HBV Infection

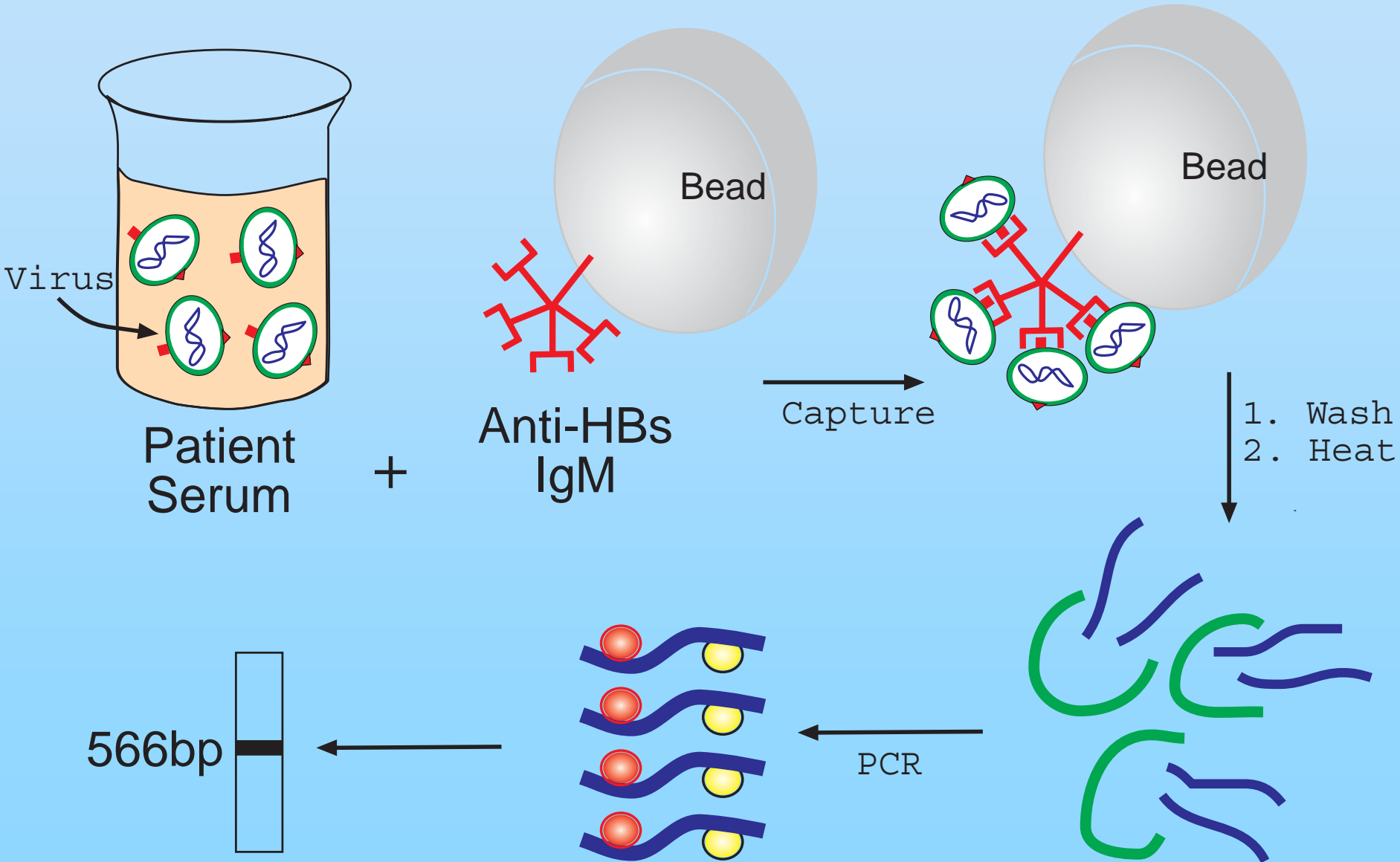
- HBsAg, HBeAg
 - HBV DNA
 - Anti-HBs, anti-HBc, anti-HBe
-

Serum Profile in HBV Infection





Detection of HBV and/or HBV Related Viral Genome in Serum



Clinical Relevance of Low Level HBV

- Etiology of chronic hepatitis and cirrhosis
 - Reactivation with immunosurppression - chemotherapy and transplantation
 - Viral persistence and infectivity
 - Often co-exits with HIV and HCV infection
 - Modulation of antiviral therapy?
-

Prevalence of HBV Infection in Patients with Idiopathic Liver Disease

| | | Serum HBV DNA | Liver HBV DNA |
|-------|----------|-----------------------------|-----------------------------|
| Group | Anti-HBs | No. positive/no. tested (%) | No. positive/no. tested (%) |
| 1 | - | 11/36 (31) | 16/22 (68) |
| 2 | + | 9/31 (29) | 13/20 (65) |
| 3 | - | 0/32 (0) | ND |
| 4 | + | 0/23 (0) | ND |

ND = Not done

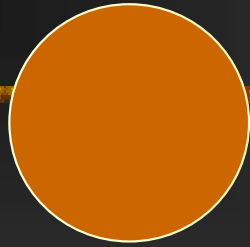
Clinical and Laboratory Characteristics and HBV DNA Detection in Individuals Convalescent Acute Hepatitis B

| Clinical Diagnosis | Time after disease onset (mo) | ALT (IU/L) | HBsAg* | Anti-HBS+ | Serum HBV DNA PCR-Southern |
|--------------------|-------------------------------|------------|--------|-----------|----------------------------|
| SL-AH | 0.5 | 2355 | + | - | + |
| | 3 | 42 | + | - | + |
| | 6 | 16 | - | - | + |
| | 9 | 32 | - | + | + |
| | 14 | 24 | - | + | + |
| | 28 | 15 | - | + | + |
| | 31 | 18 | - | + | + |
| | 46 | 10 | - | + | + |

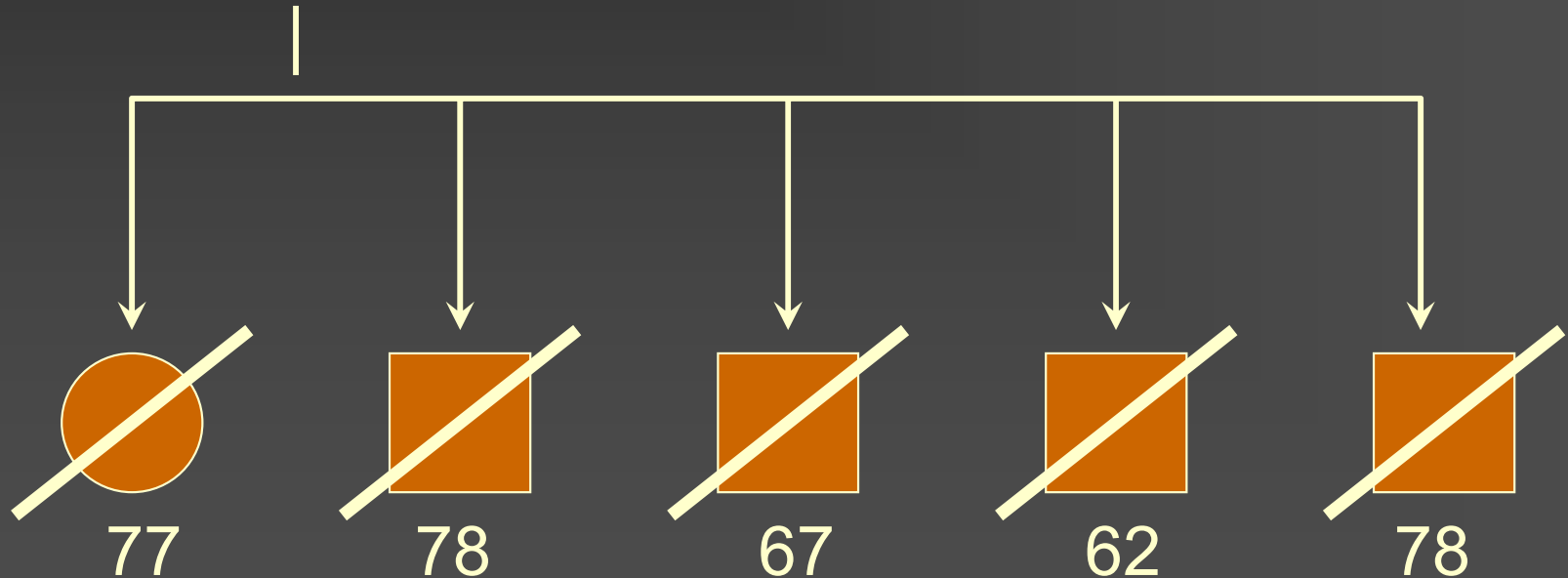
Clinical Relevance of HBV Mutations

- High level of replication and severe liver injury
 - Viral accumulation in the hepatocytes
 - Drug resistance
 - Vaccine escape
 - Promotes persistent viral infection
-

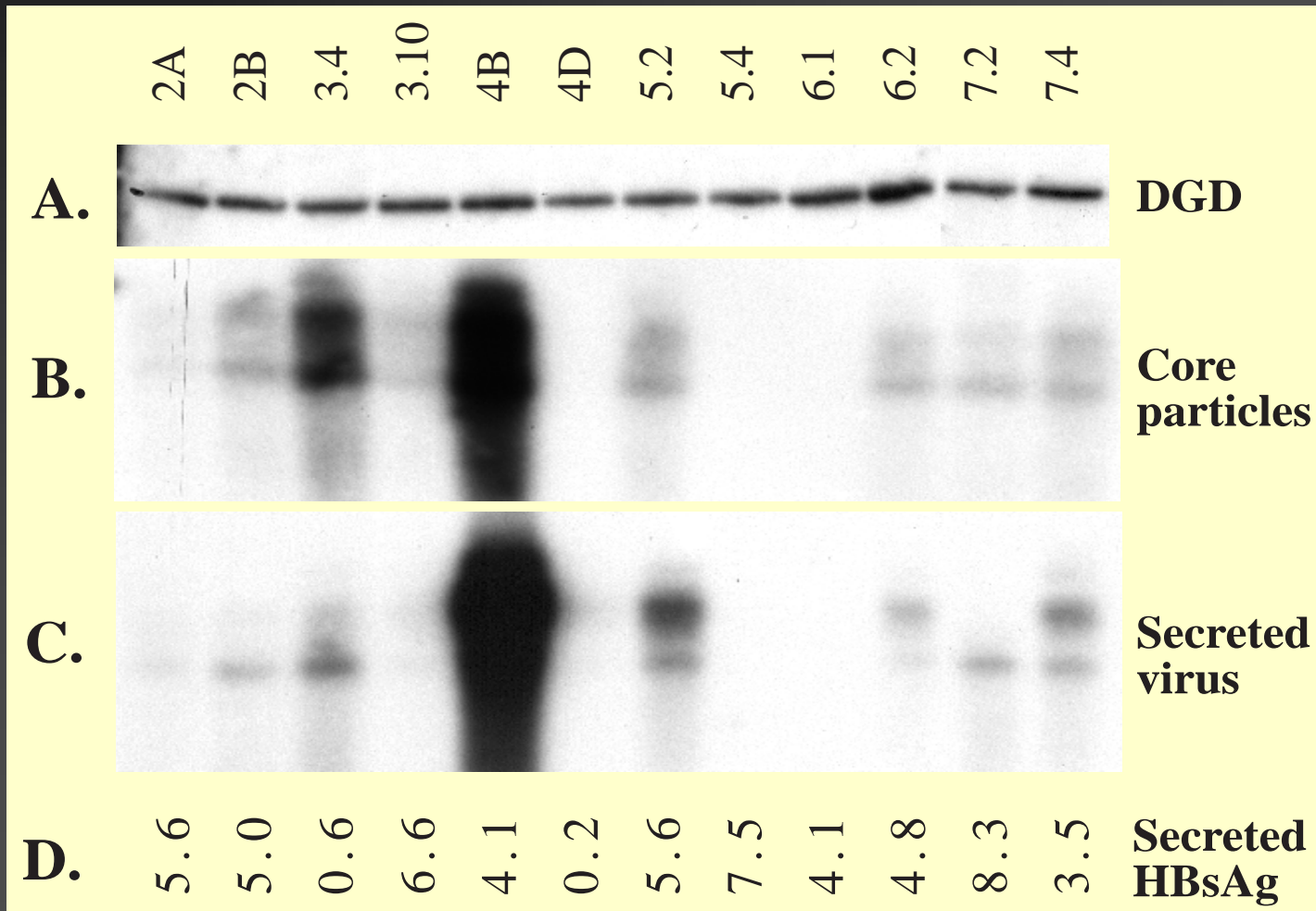
Outbreak of Fulminant Hepatitis B

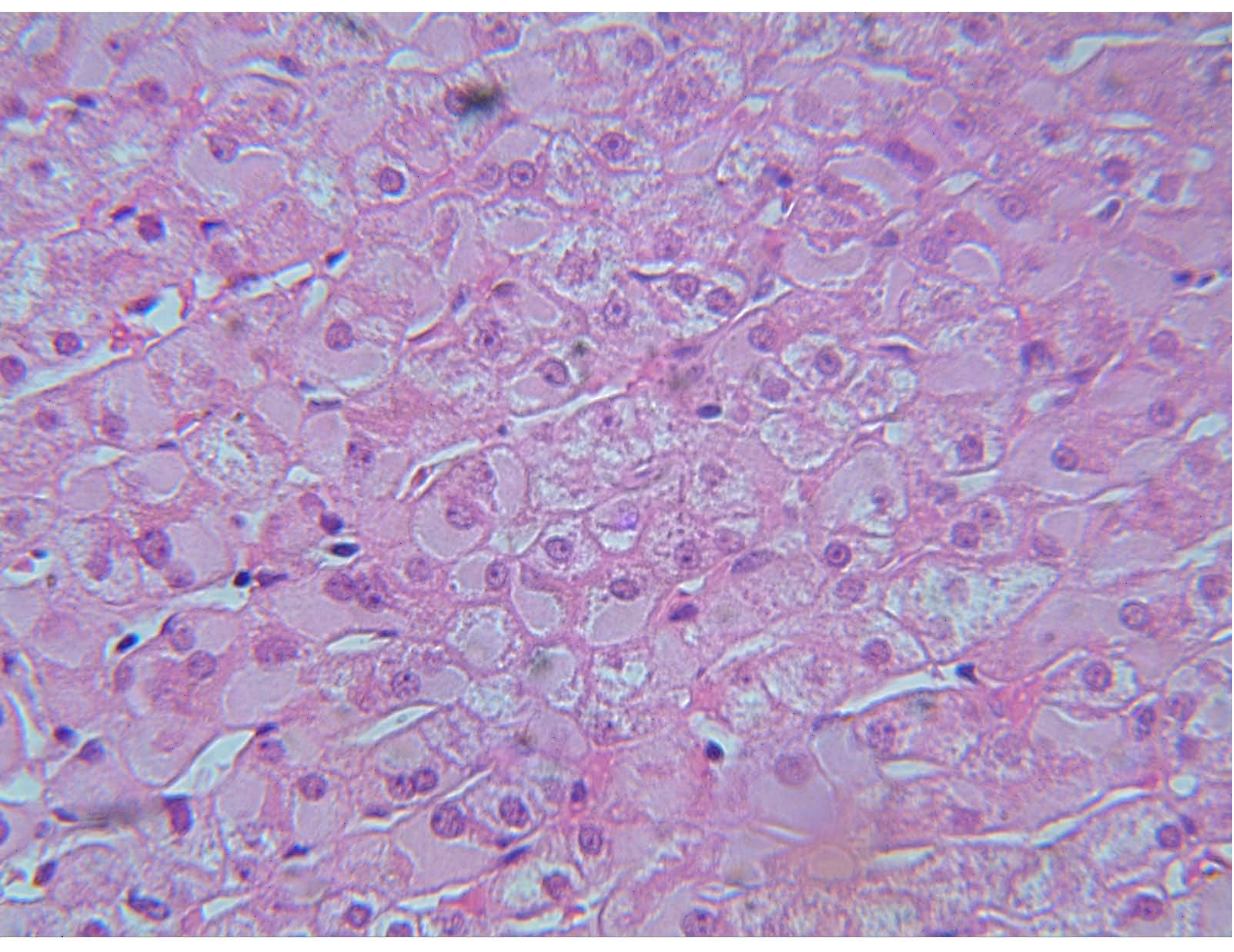


HBsAg Carrier
Chronic Hepatitis



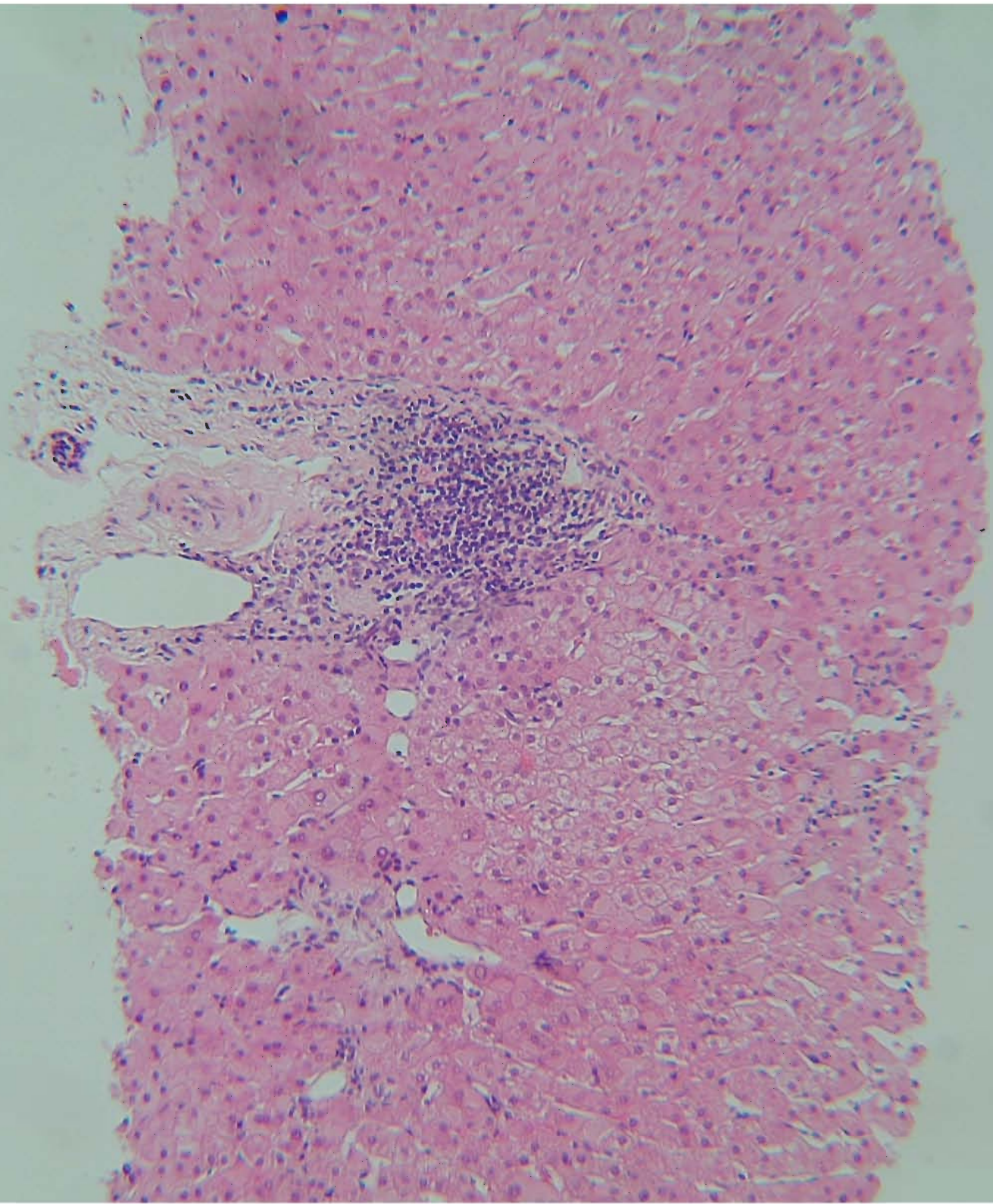
Viral replication and secretion from 12 naturally occurring HBV genomes

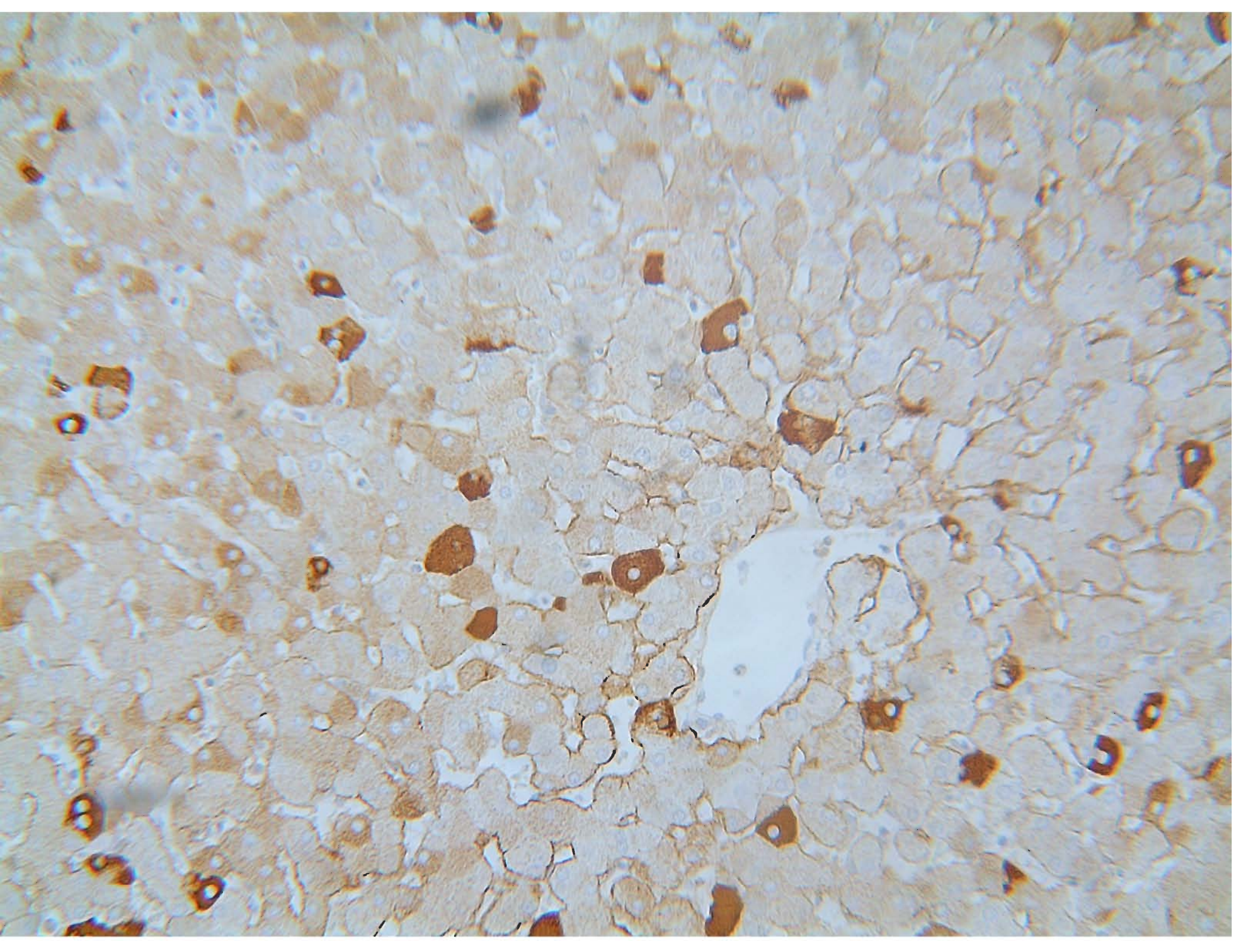


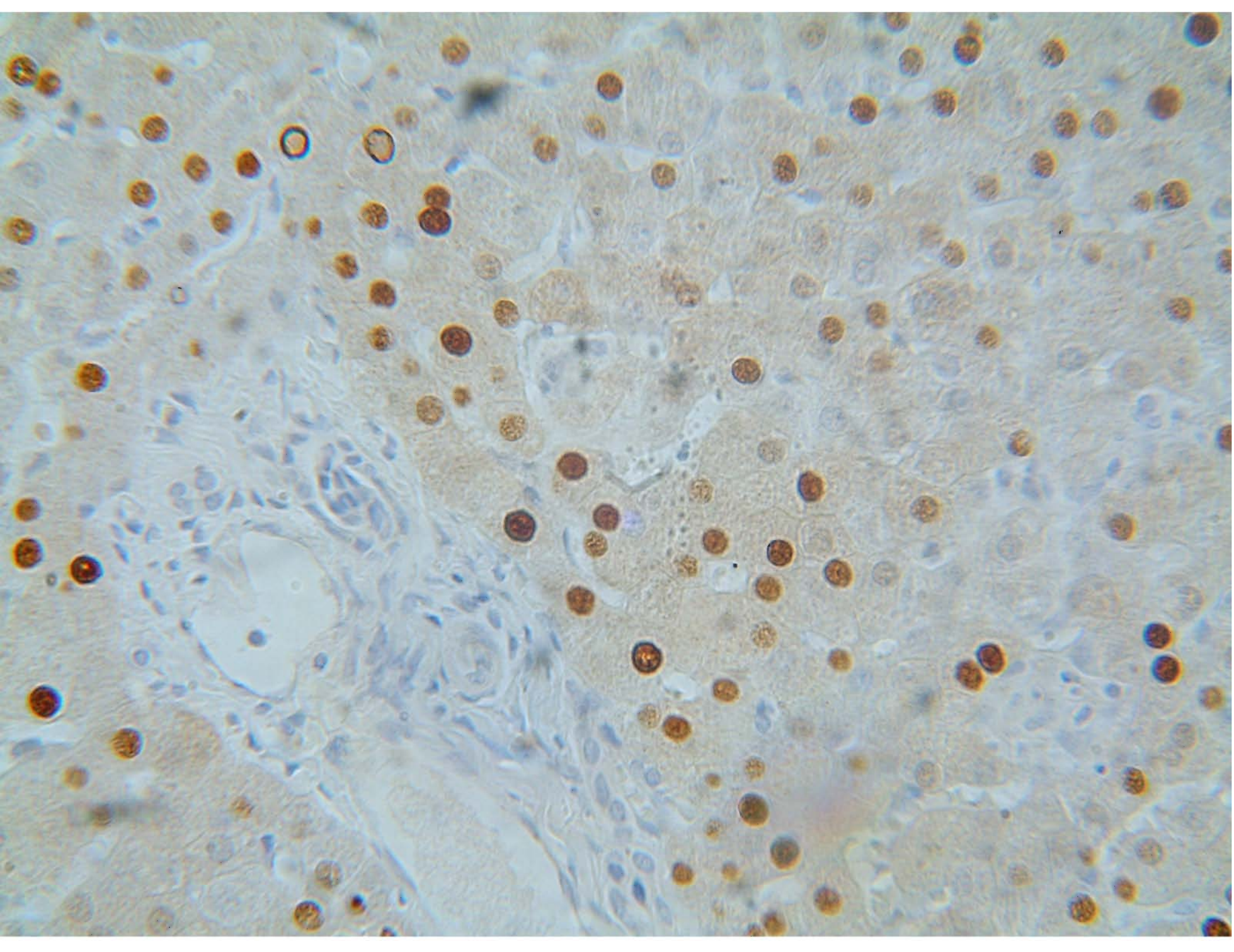


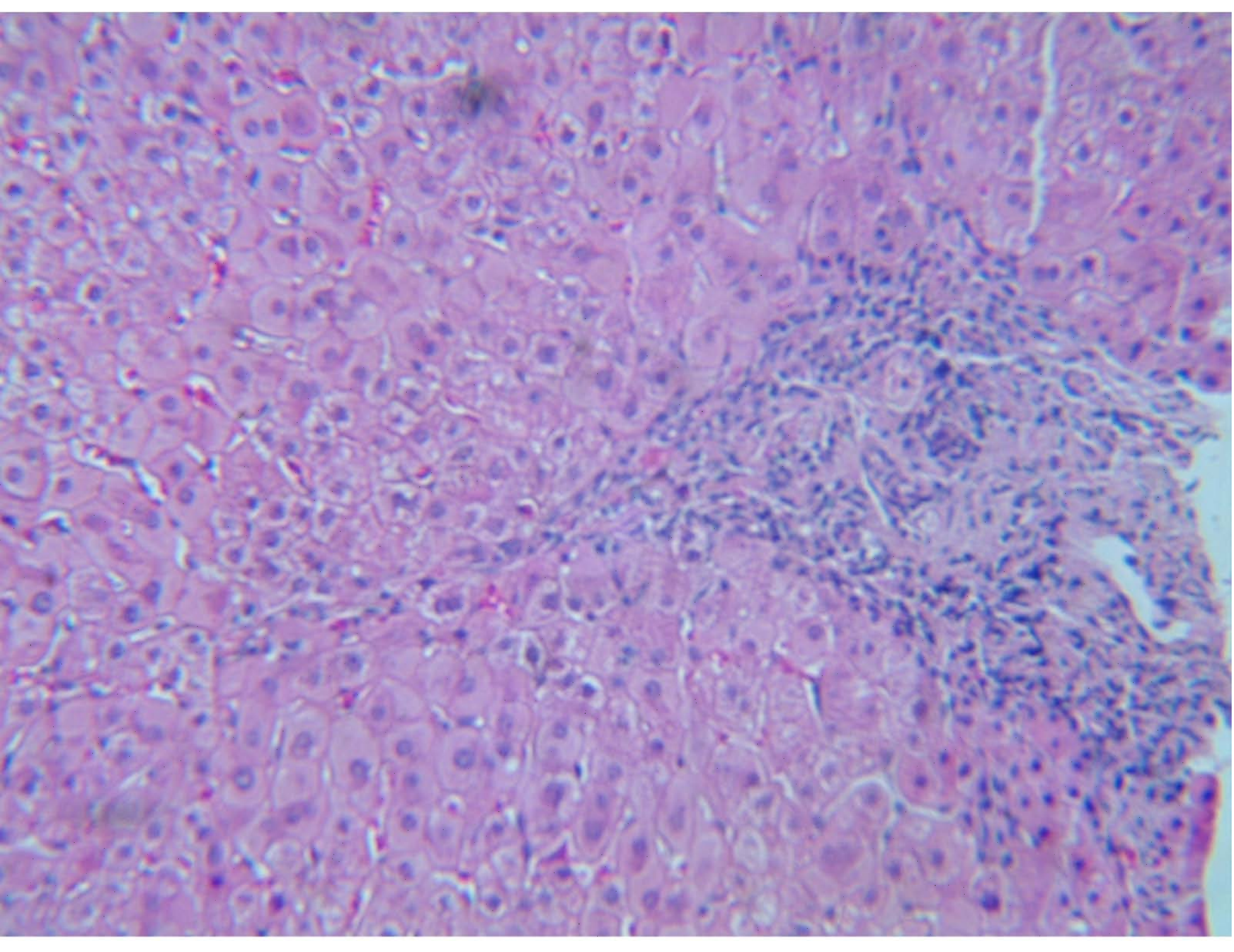
Indications for Treatment

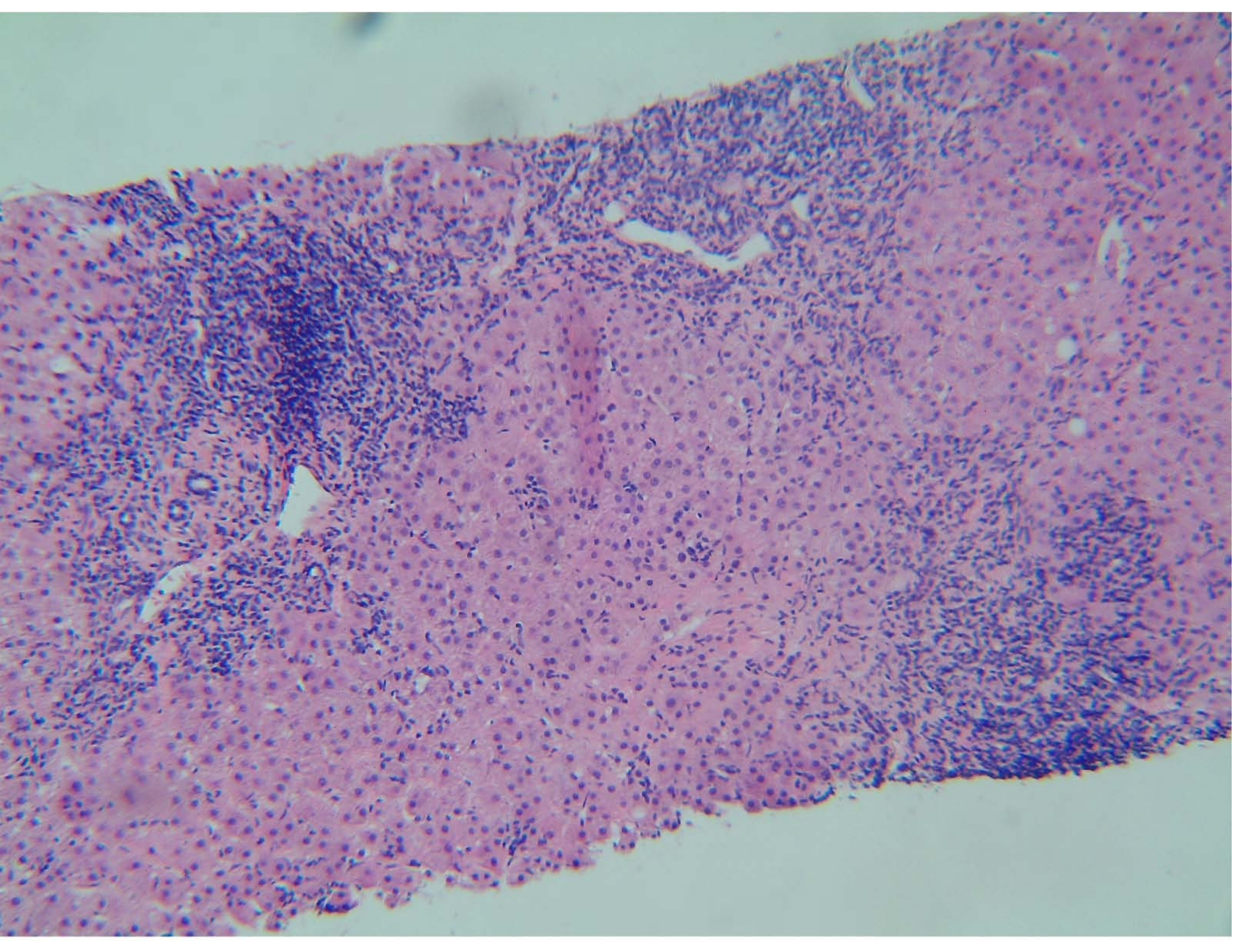
- Clinical symptoms
 - Biochemical activity
 - Histologic activity - ⊕ fibrosis and/or cirrhosis
-

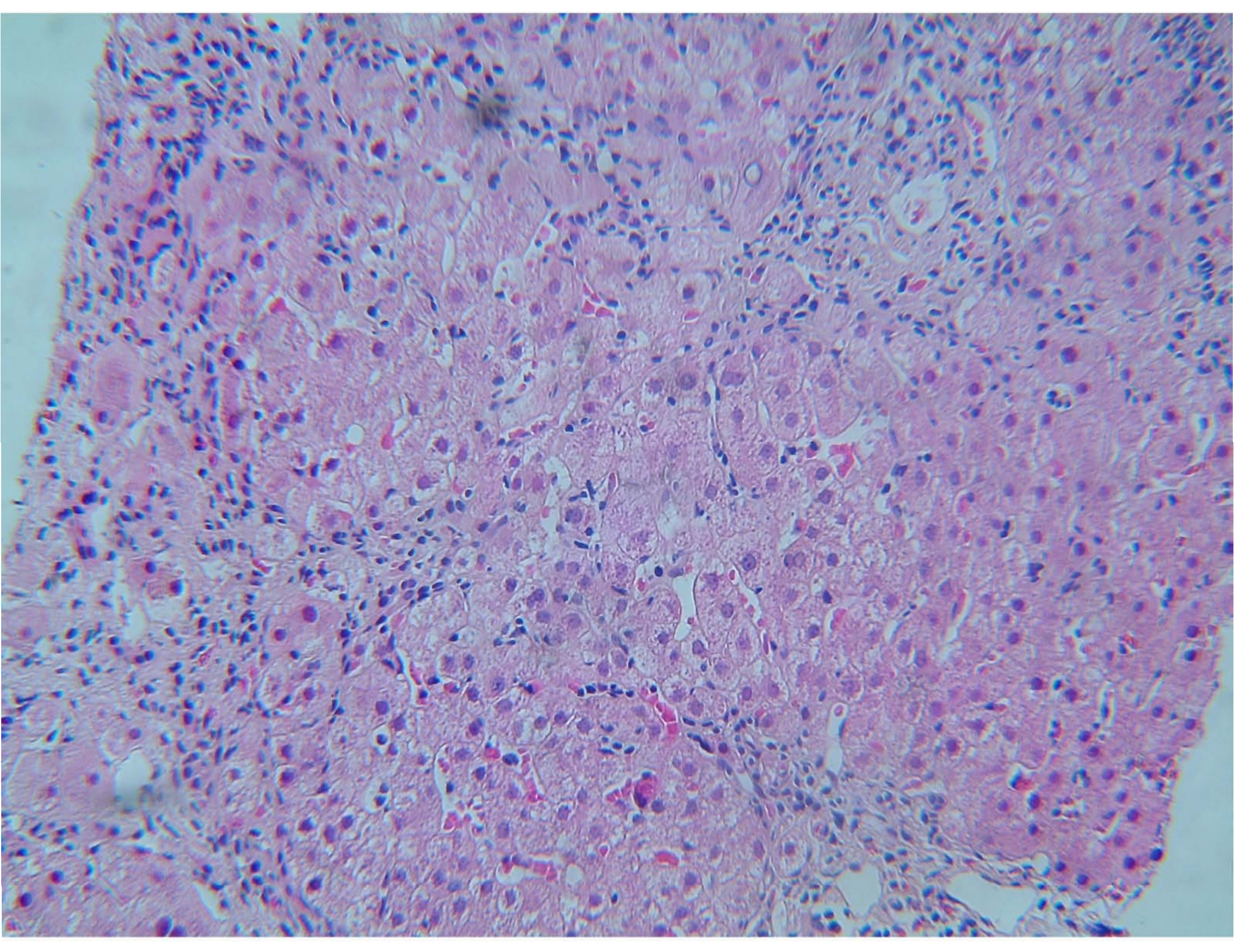


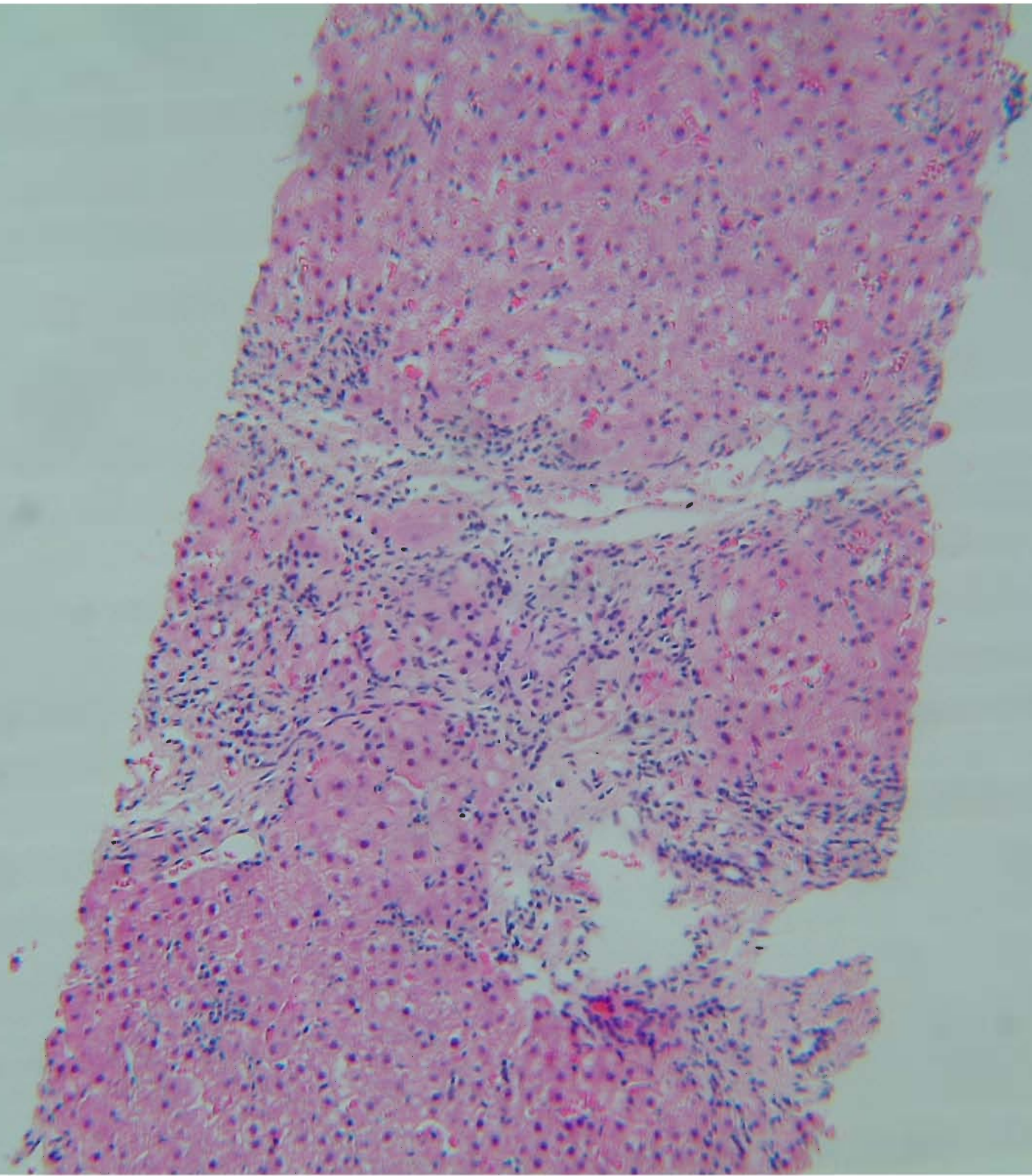














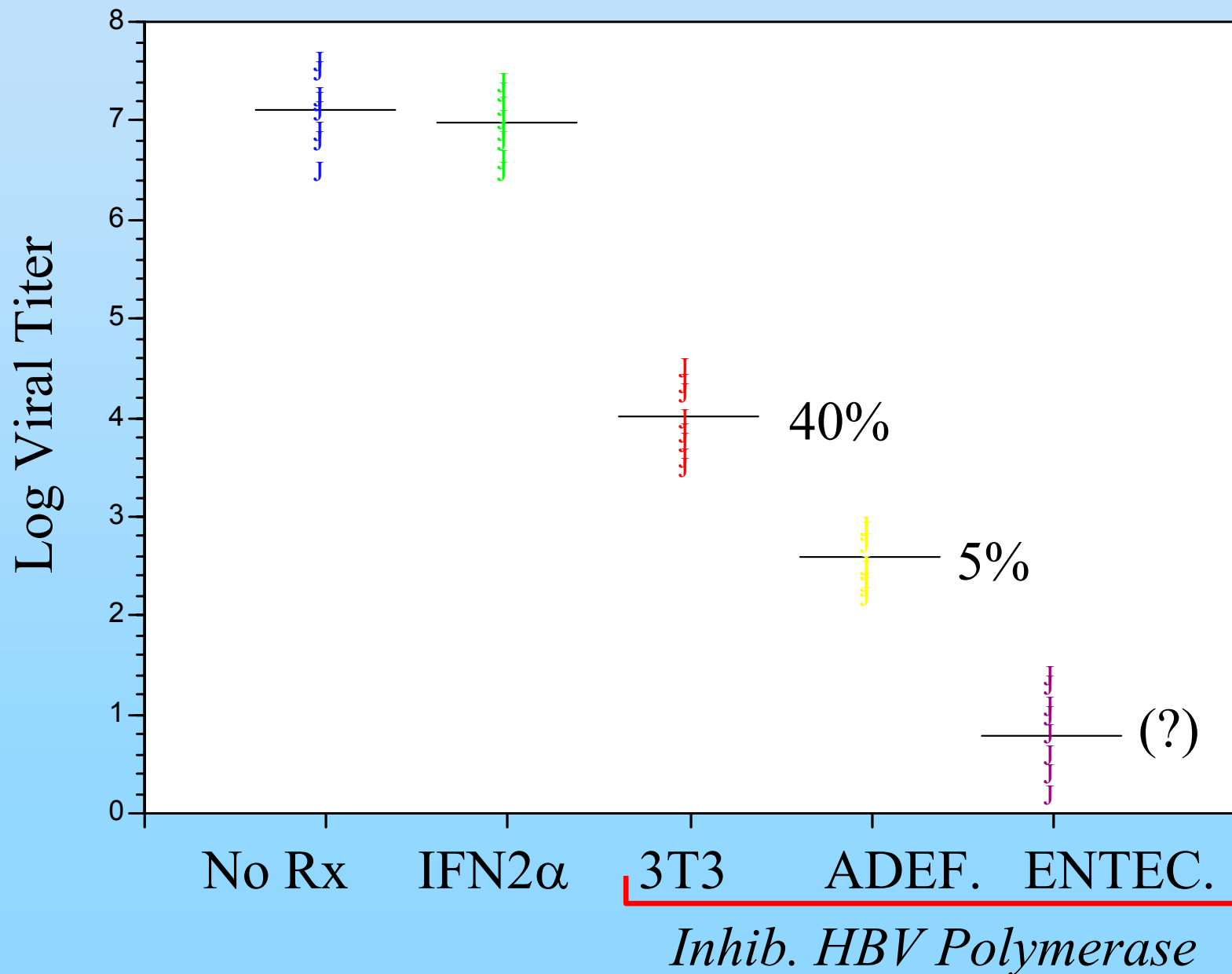
TREATMENT OF CHRONIC HBV



IFN- 2_{∞} , Lamivudine, Adefovir, Entecovir

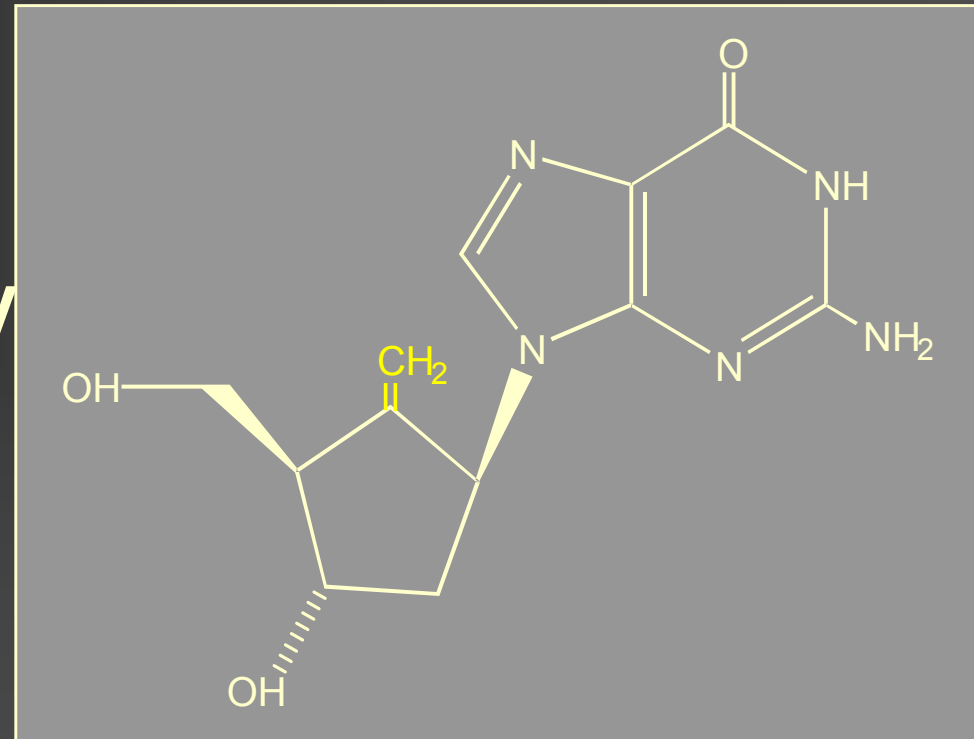
- Low response rates (<30%)
- Side effects
- Viral resistance (Lamivudine)
- Lack of a sustained response
- HBeAg- patients are difficult to treat

Importance of Drug Resistance Due to Mutation



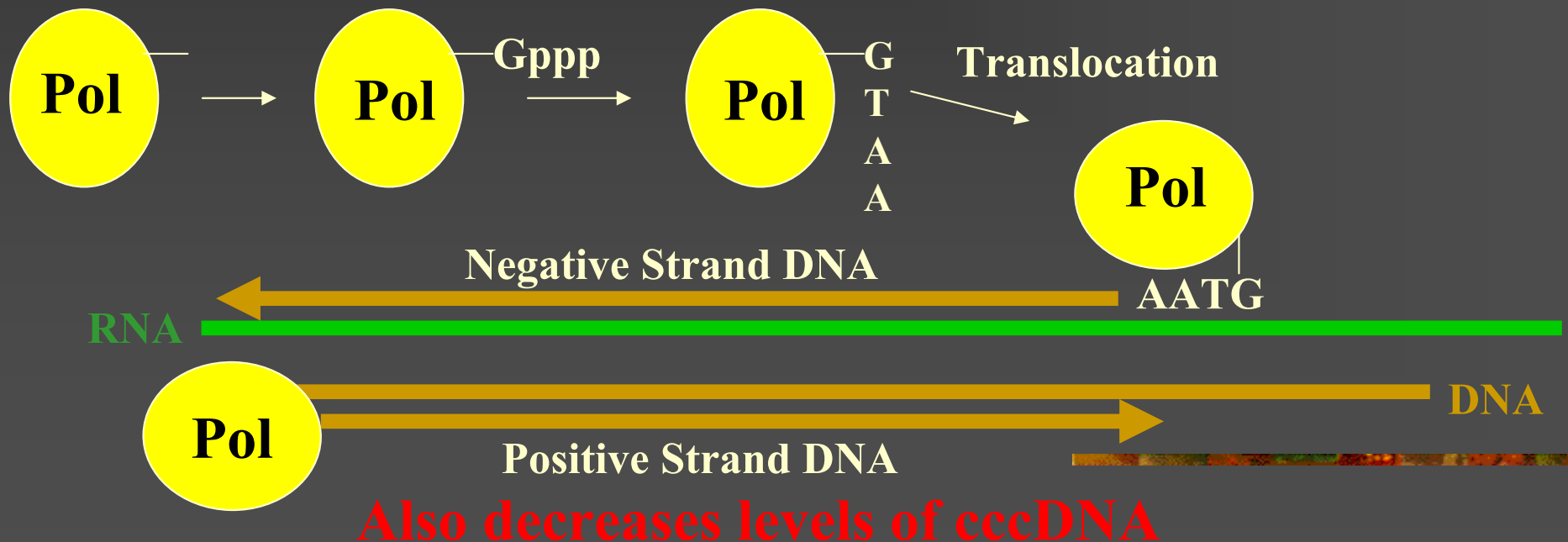
Entecavir

- Cyclopentyl guanine analog with exo C-C double bond
- Potent ($EC_{50}=4$ nM, $K_i=1$ nM) and selective inhibitor of HBV DNA polymerase
- Inhibits all 3 polymerase functions:
 - Priming
 - Negative strand formation
 - Positive strand synthesis

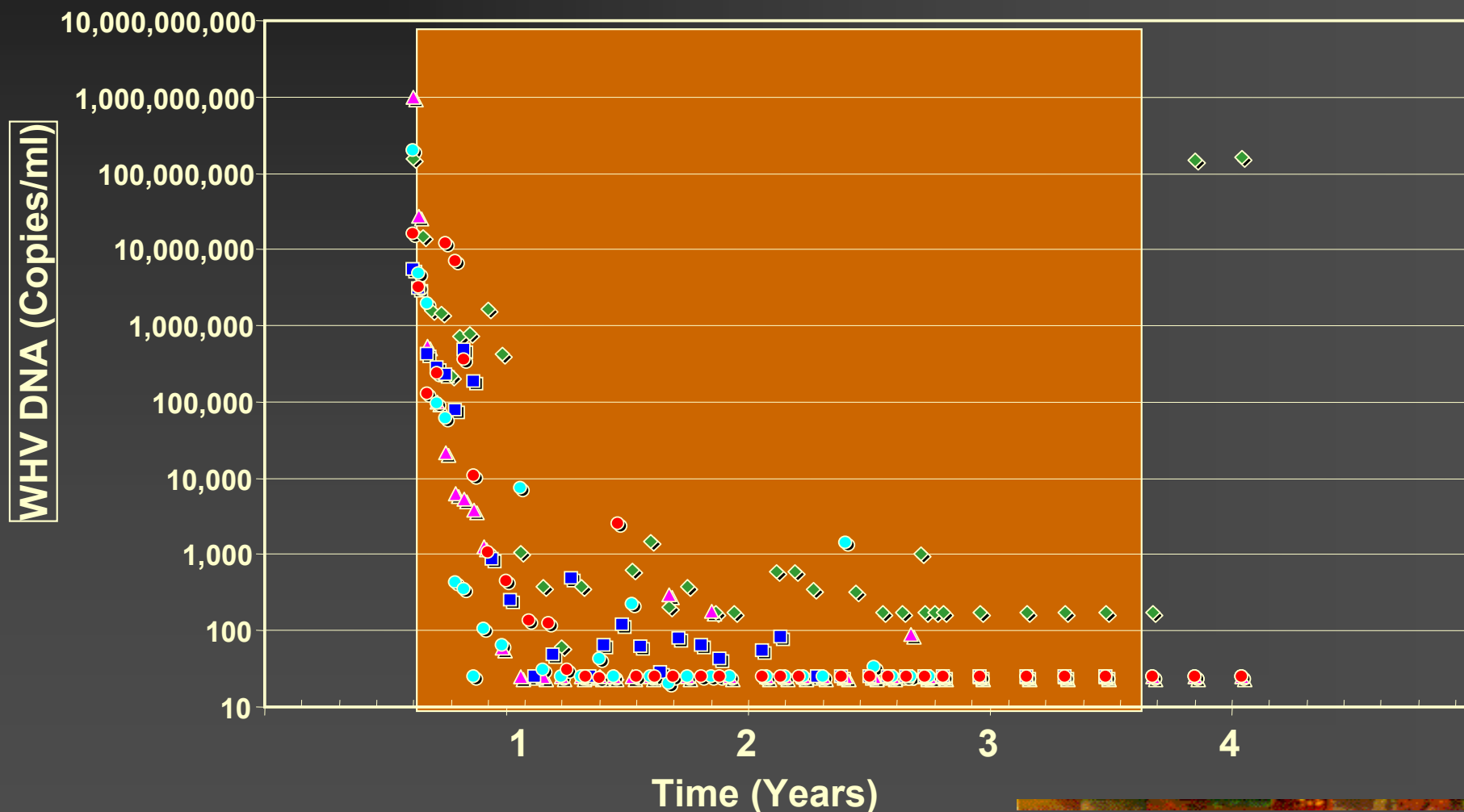


Mechanism of Inhibition

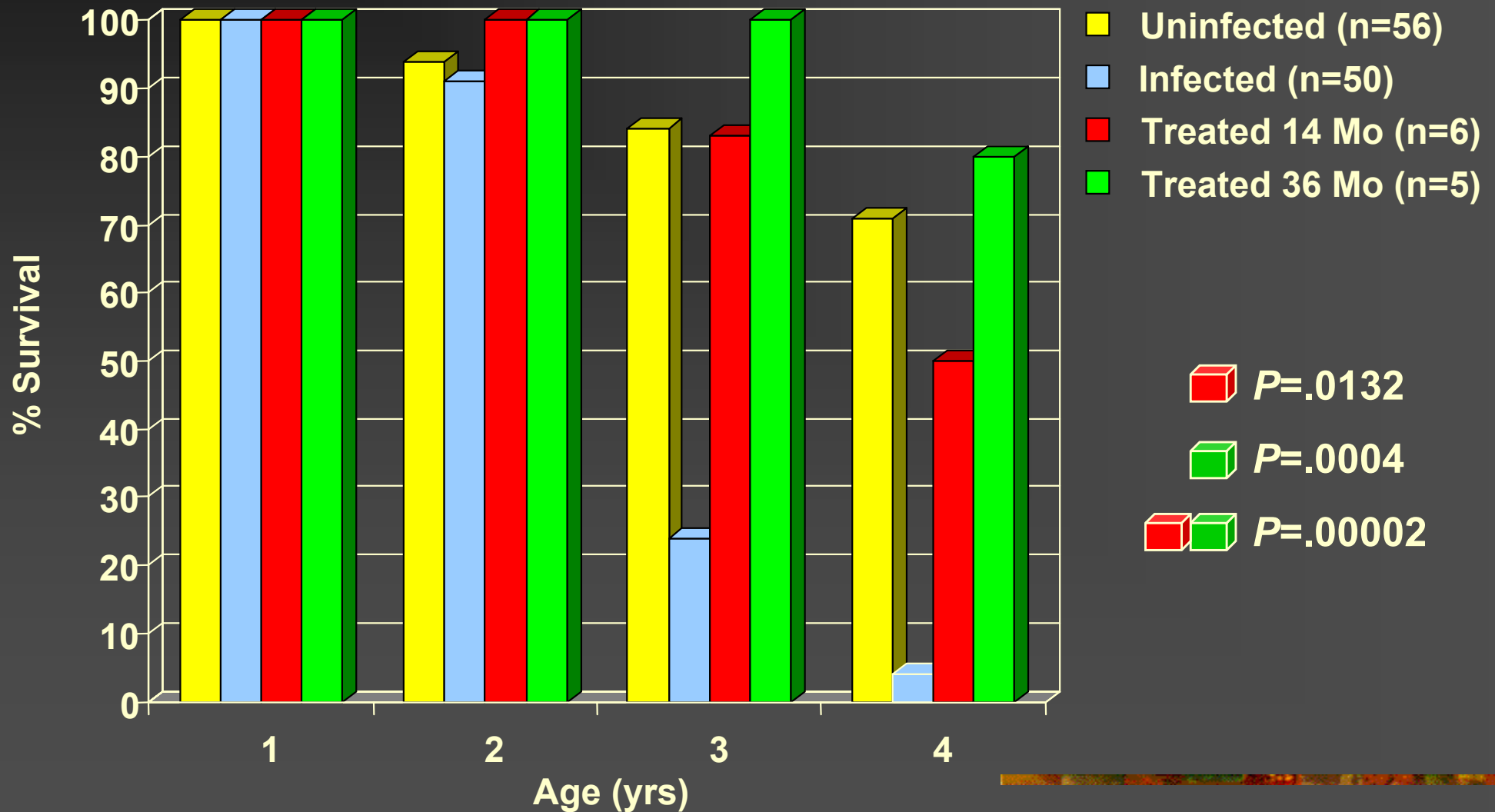
| IC50([Analog-TP]/[dNTP]) | | | |
|--------------------------|-------------|-----------------------|---------------|
| Analog | Priming | Reverse Transcription | DNA Synthesis |
| 3TC-TP | >400 | 1.44 | 3.94 |
| ETV-TP | 0.30 | 0.32 | 0.18 |



Entecavir Dramatically Reduces Viral Load in Woodchuck Hepatitis Model



Entecavir Increases Survival Rates in Woodchuck Hepatitis Model



Future Directions in HBV Therapy

- Determine whether monotherapy with more potent agents like entecavir can achieve higher cure rates
 - Combination therapy
 - Nucleoside/nucleotide + pegylated interferon
 - Two nucleosides/nucleotides (e.g., entecavir + adefovir)
-

Response to Therapy

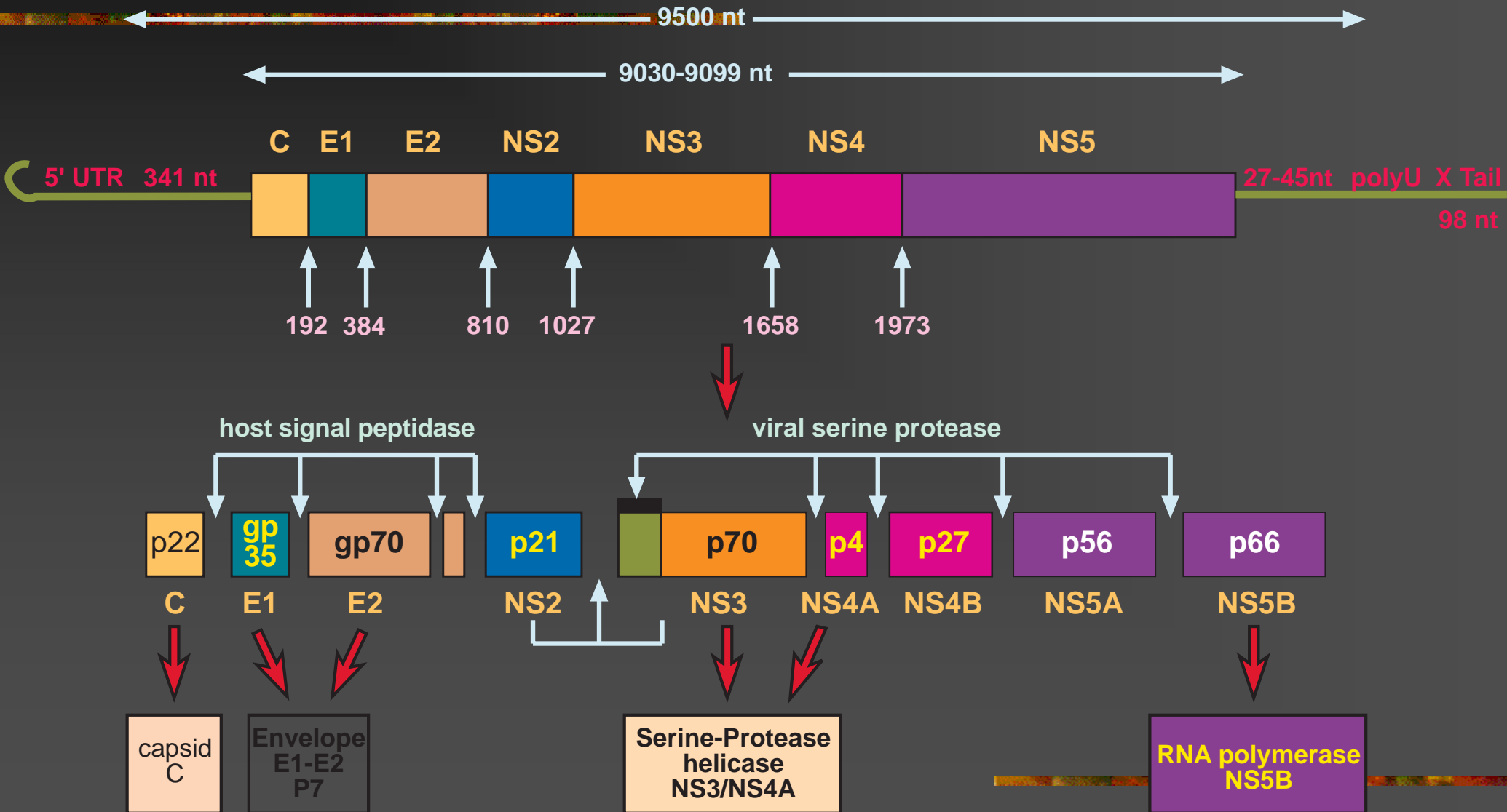
- Reduce viral replication - ↓ liver injury
 - Prevent progression to cirrhosis
 - Reduce the risk of Hepatocellular Carcinoma?
-

Incidence of Liver Cancer

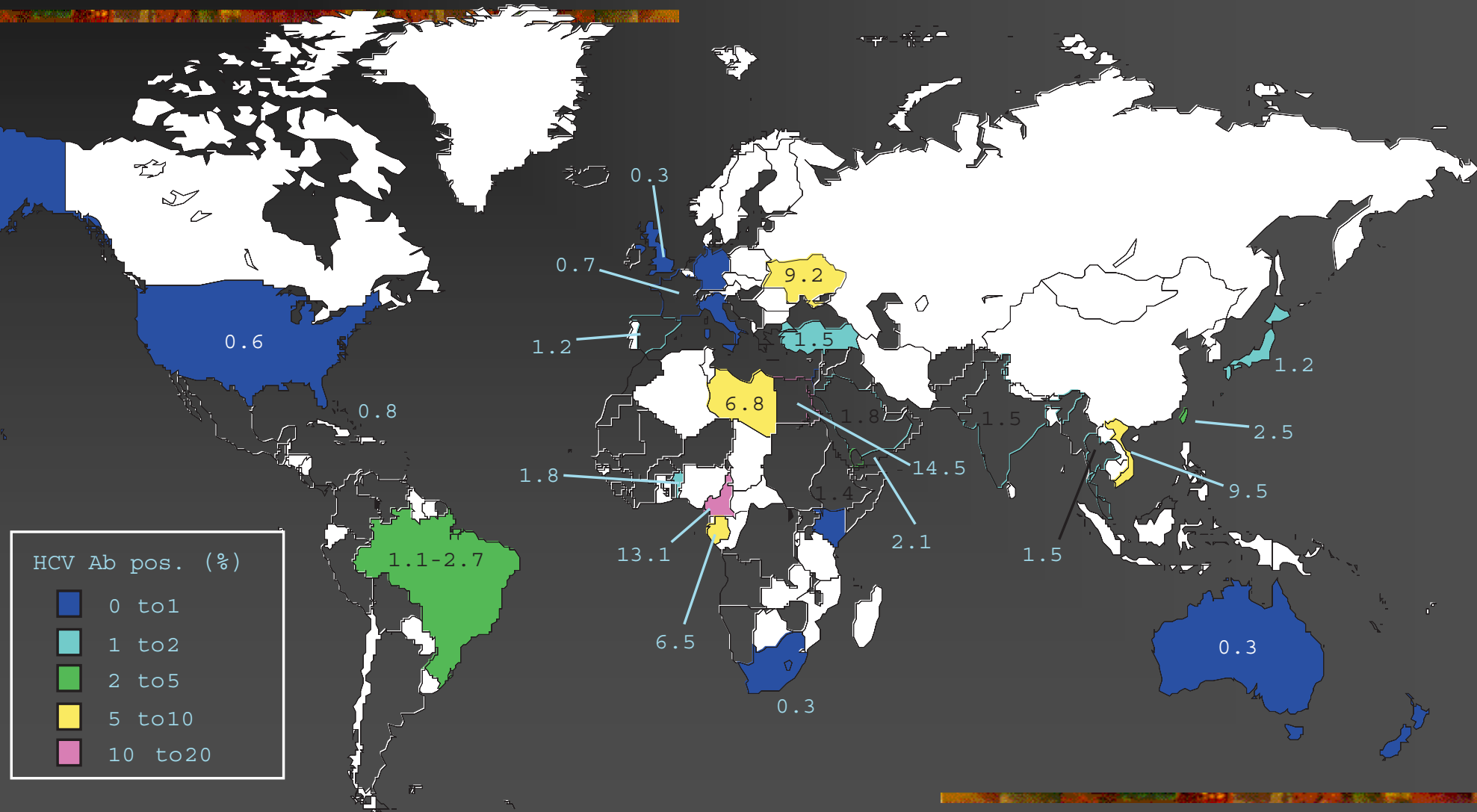
| Age at Daignosis | Before Program Cohort | | After Program Cohort | |
|------------------|-----------------------|----------------------------|----------------------|----------------------------|
| | Population | No. of Cancers (Incidence) | Population | No. of Cancers (Incidence) |
| 6 | 3,940,747 | 18 (0.46) | 648,642 | 0 (0.00) |
| 7 | 3,398,119 | 21 (0.53) | 347,051 | 1 (0.15) |
| 8 | 3,931,983 | 19 (0.48) | 644,982 | 2 (0.31) |
| 9 | 3,928,721 | 24 (0.61) | 340,521* | 0 (0.00) |
| Total | 15,739,570 | 82 (0.52) | 2,281,106 | 3 (0.13) |

* This value is based on data for the cohort born from July 1984 to June 1985. $P < 0.001$ for the comparison between birth cohorts

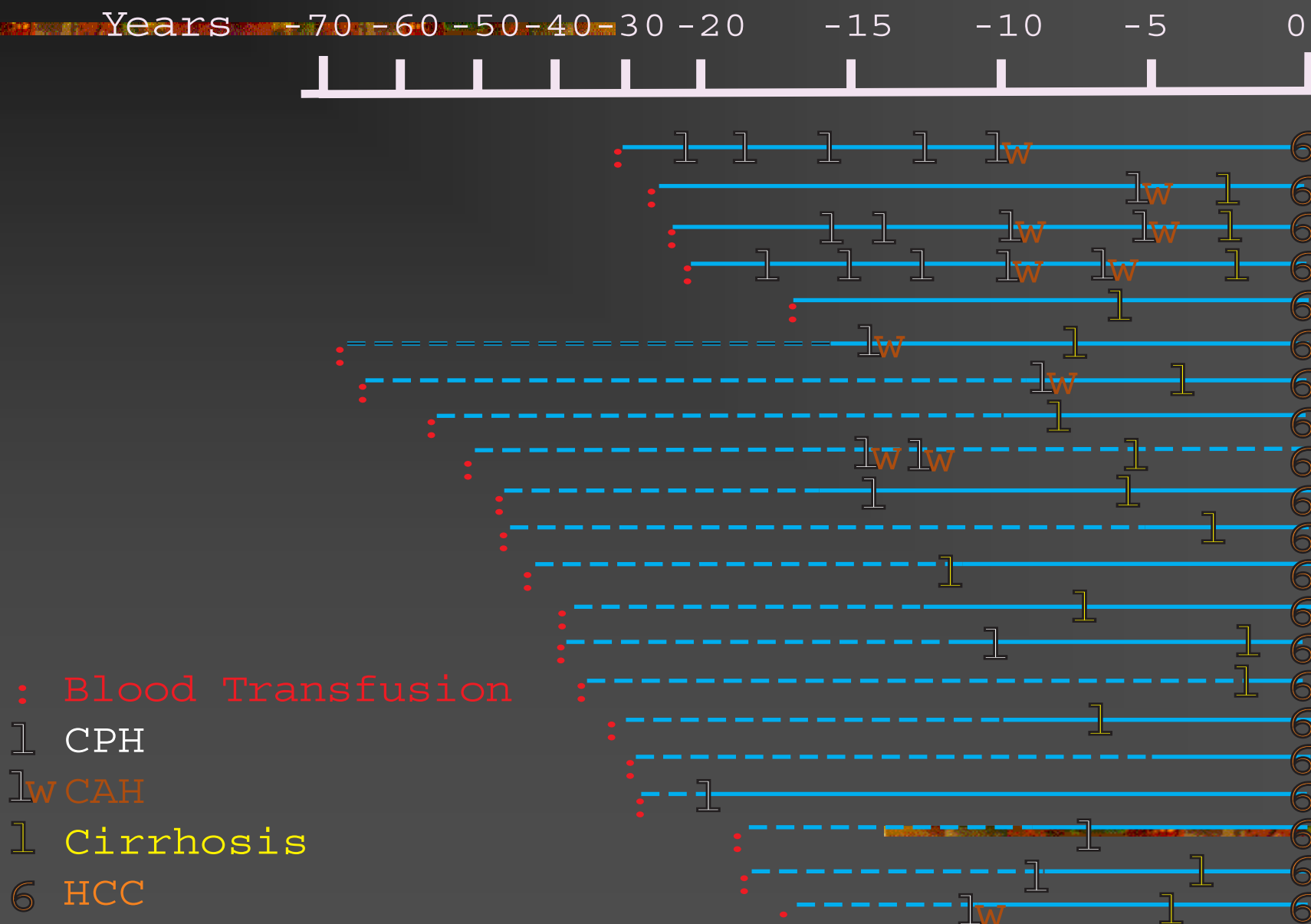
HCV Genome



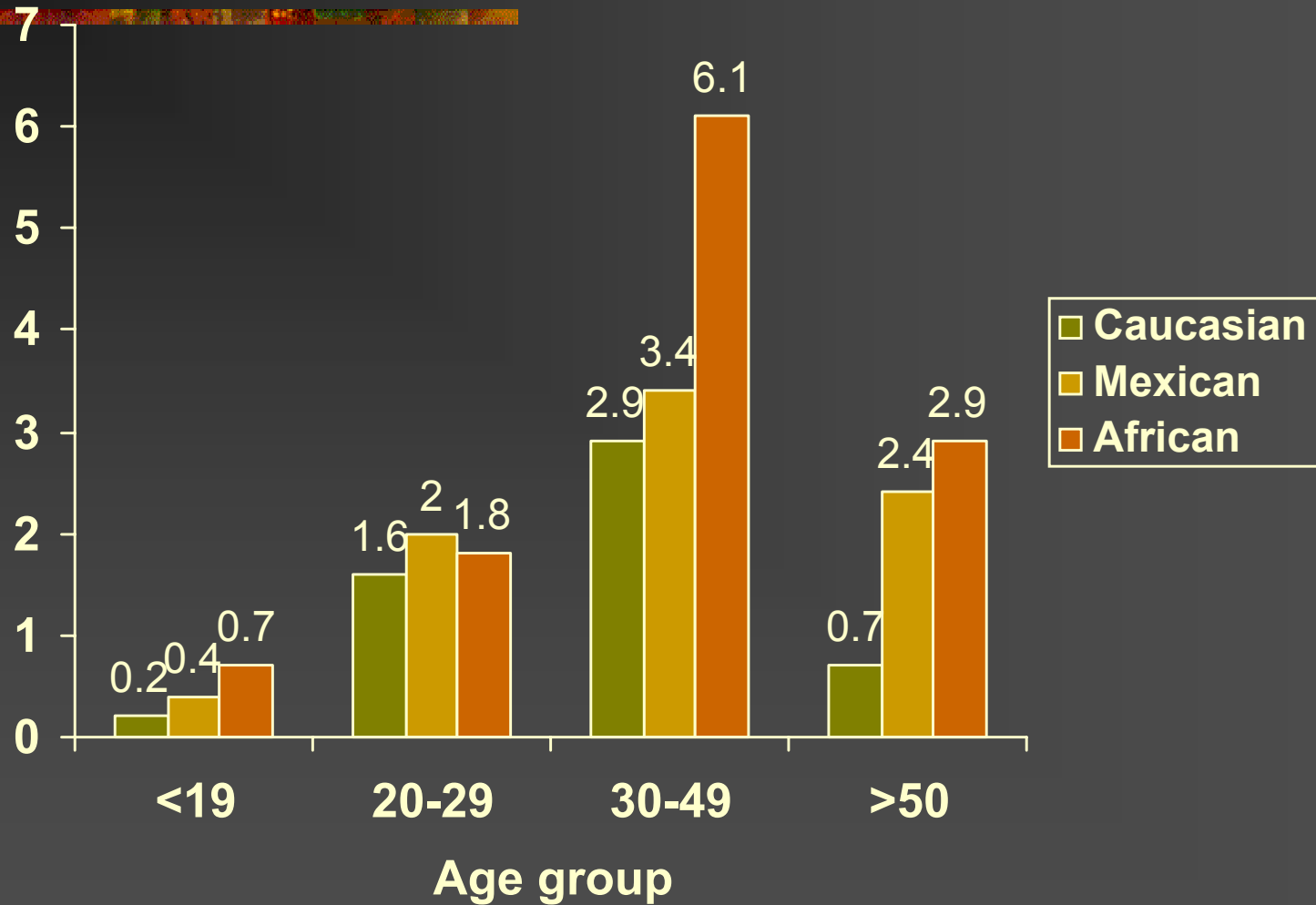
World Map Illustrating the Prevalence of HCV Antibodies in Blood Donors



Natural Course of Chronic HCV Infection



Prevalence of antibody to HCV in the US

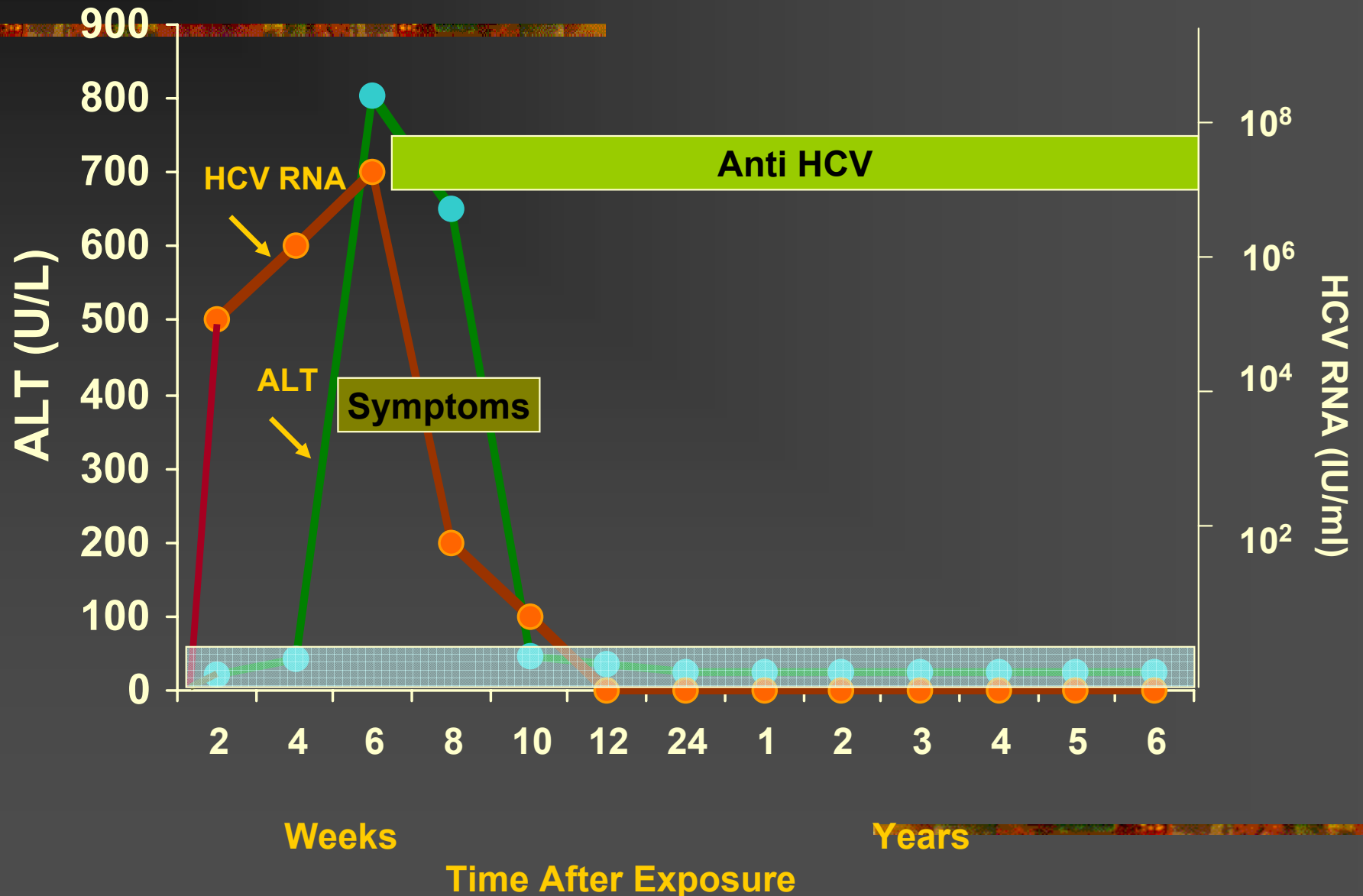


Anti HCV+ = 1.8% = 3.9 millions
HCV RNA + = 1.5% = 2.7 millions

Alter MJ, NEJM 1999;341:556-562

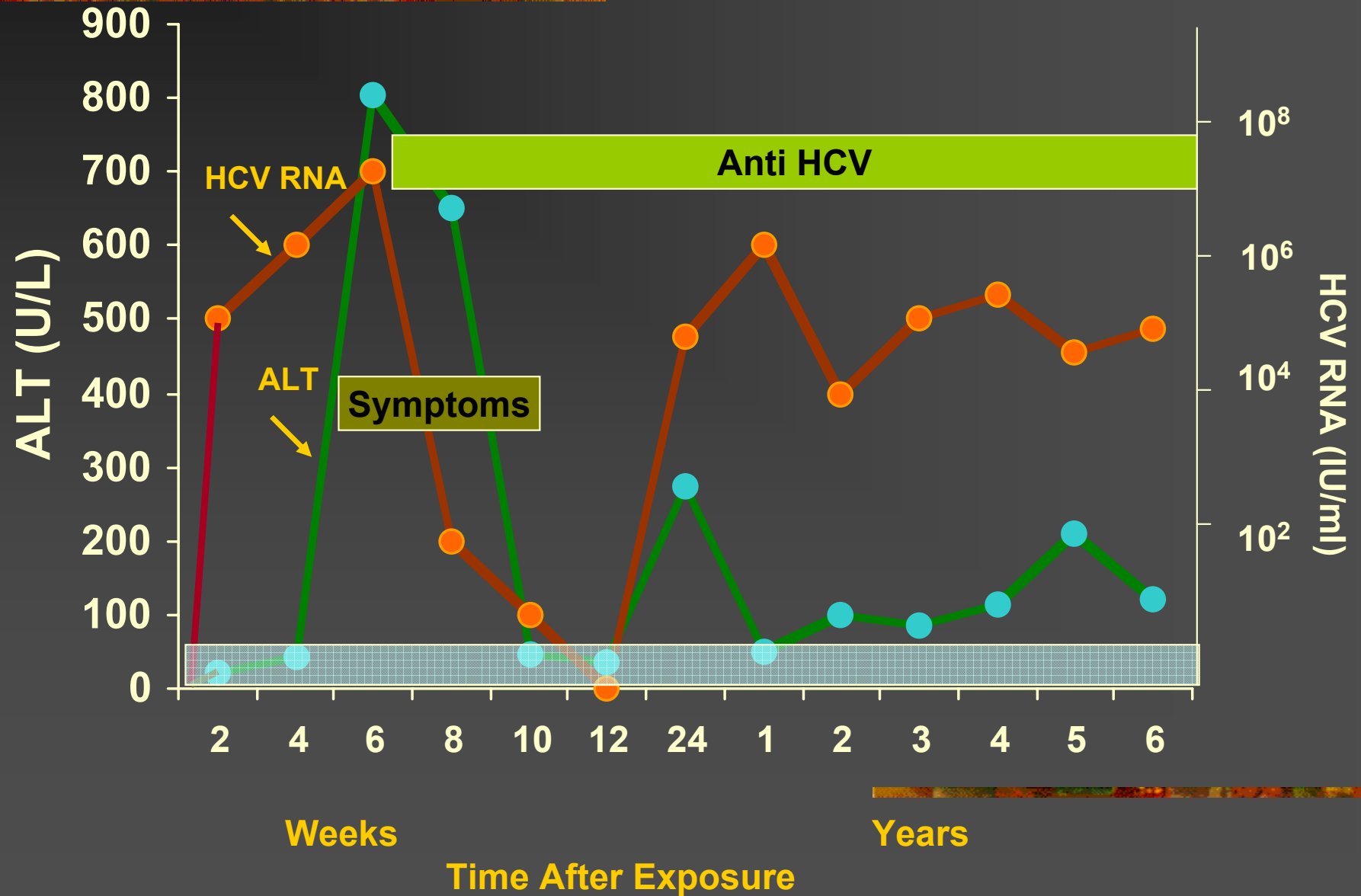
Acute Resolving Hepatitis C

HCV RNA - + + + + + + + + - - - - -

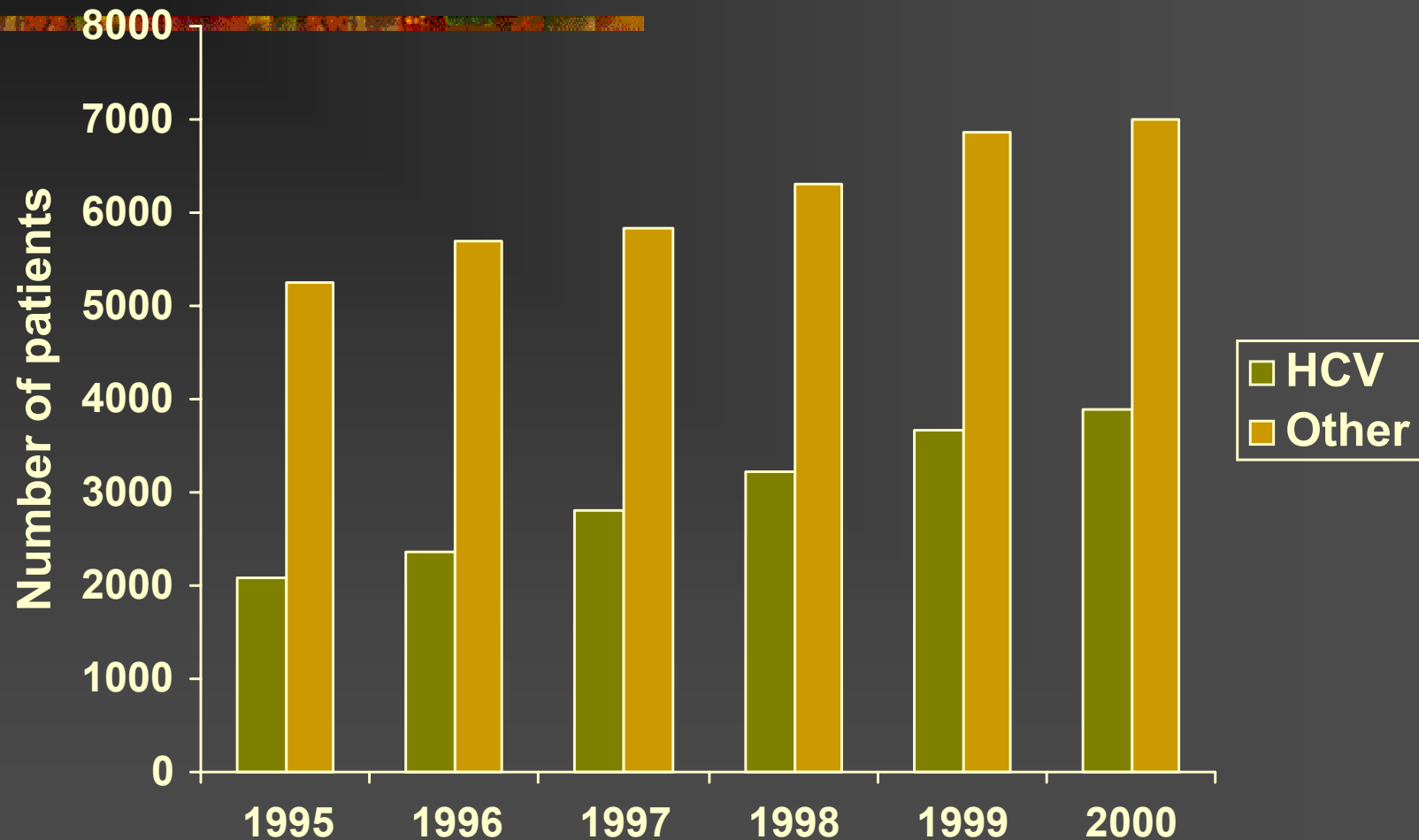


Acute Hepatitis C Evolves into Chronic Infection

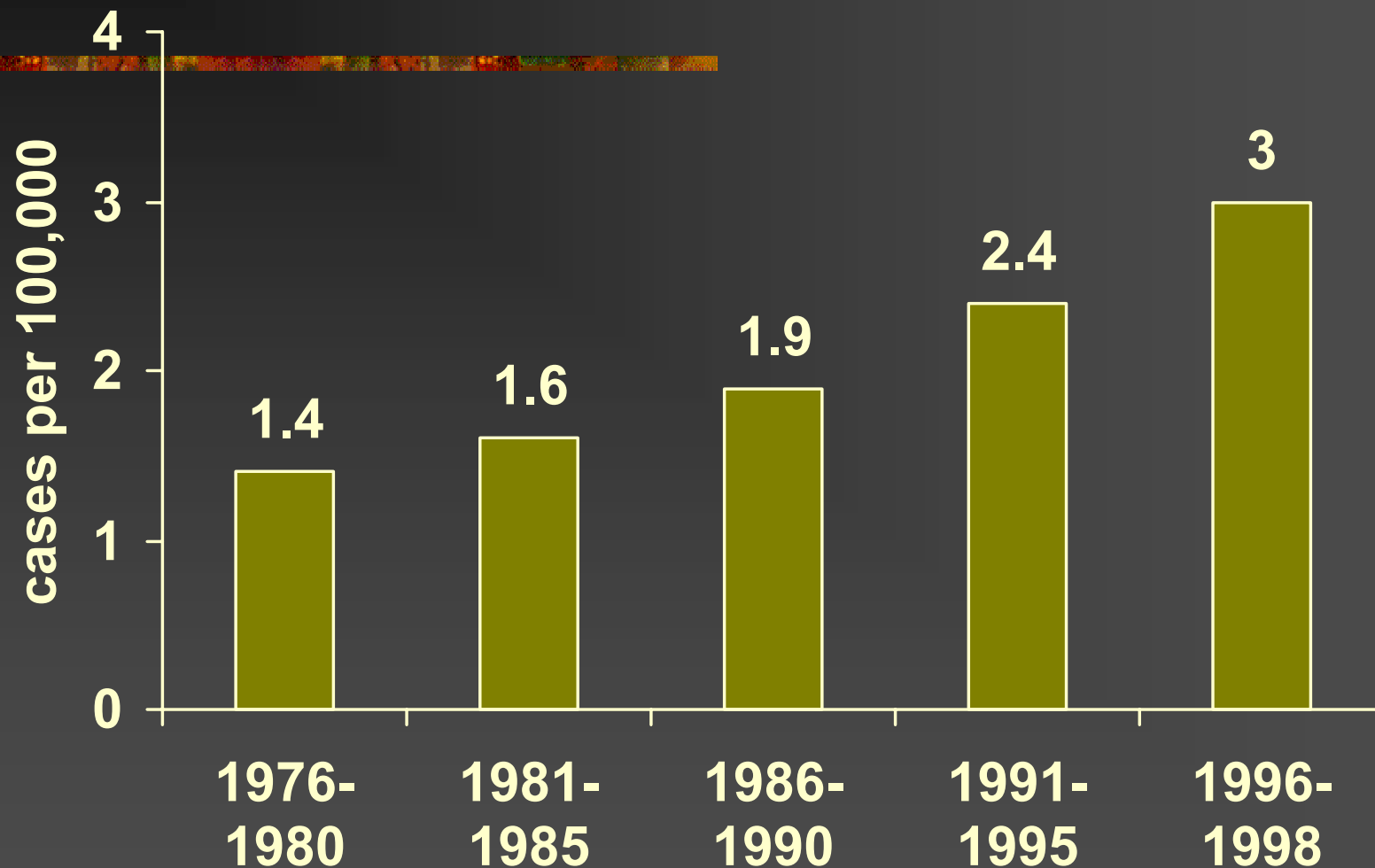
HCV RNA - + + + + + + + + - + + + + + + + + + + + + + +



Liver Transplant Waiting List in the U.S.



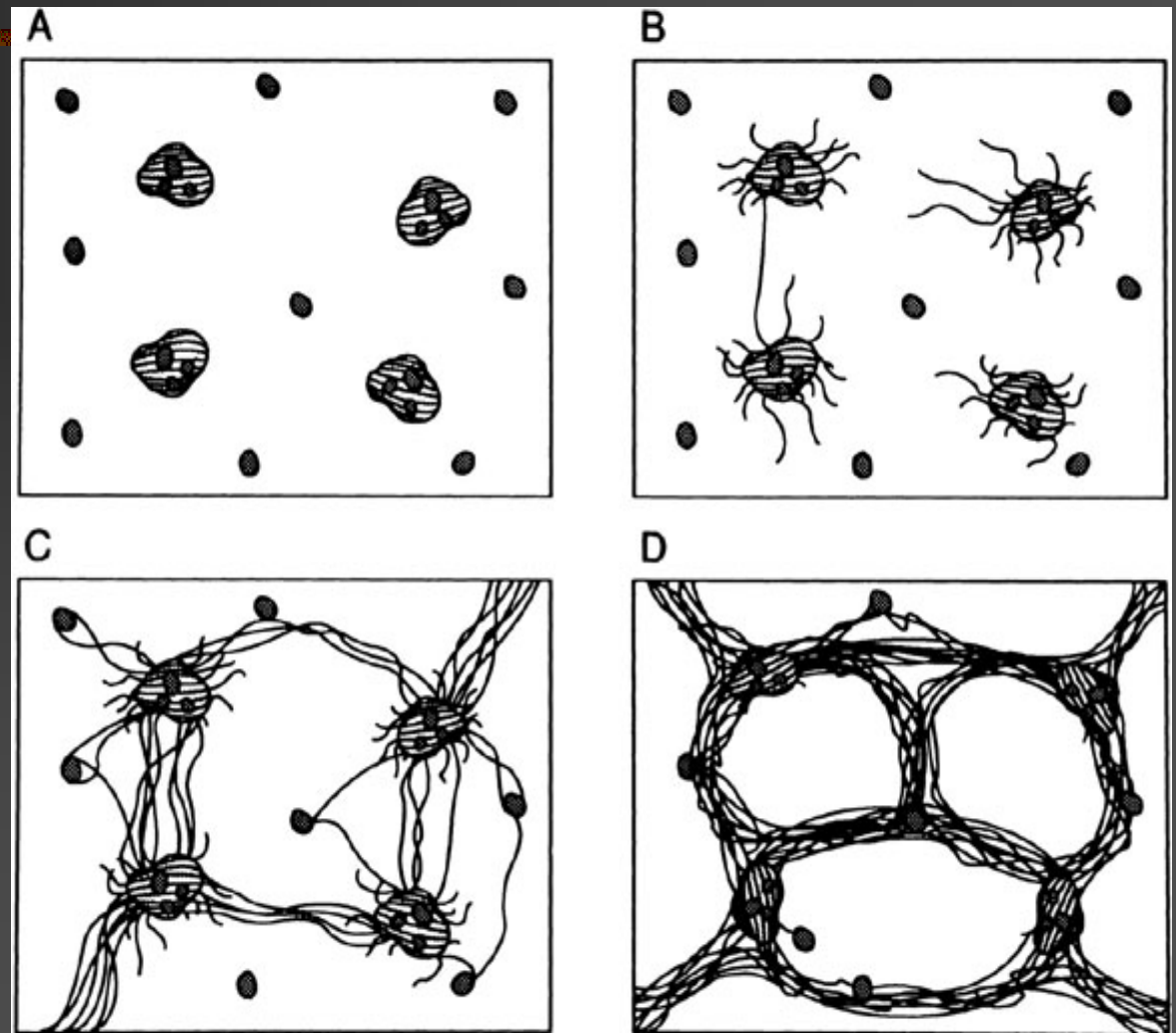
Incidence of Hepatocellular Carcinoma in the U.S.



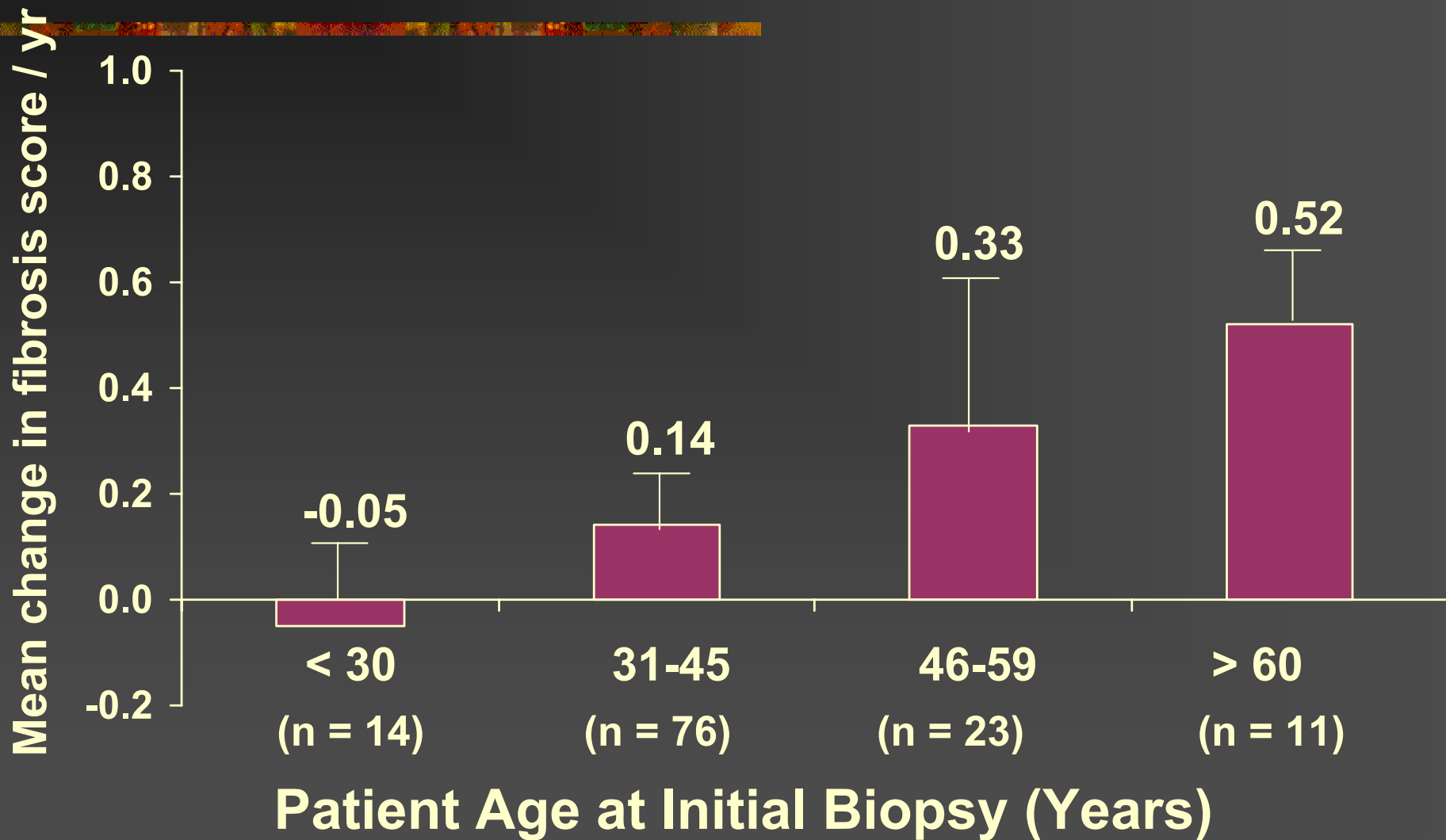
Modified from El-Serag & Mason, NEJM 1999

Progression of Fibrosis in Chronic hepatitis C

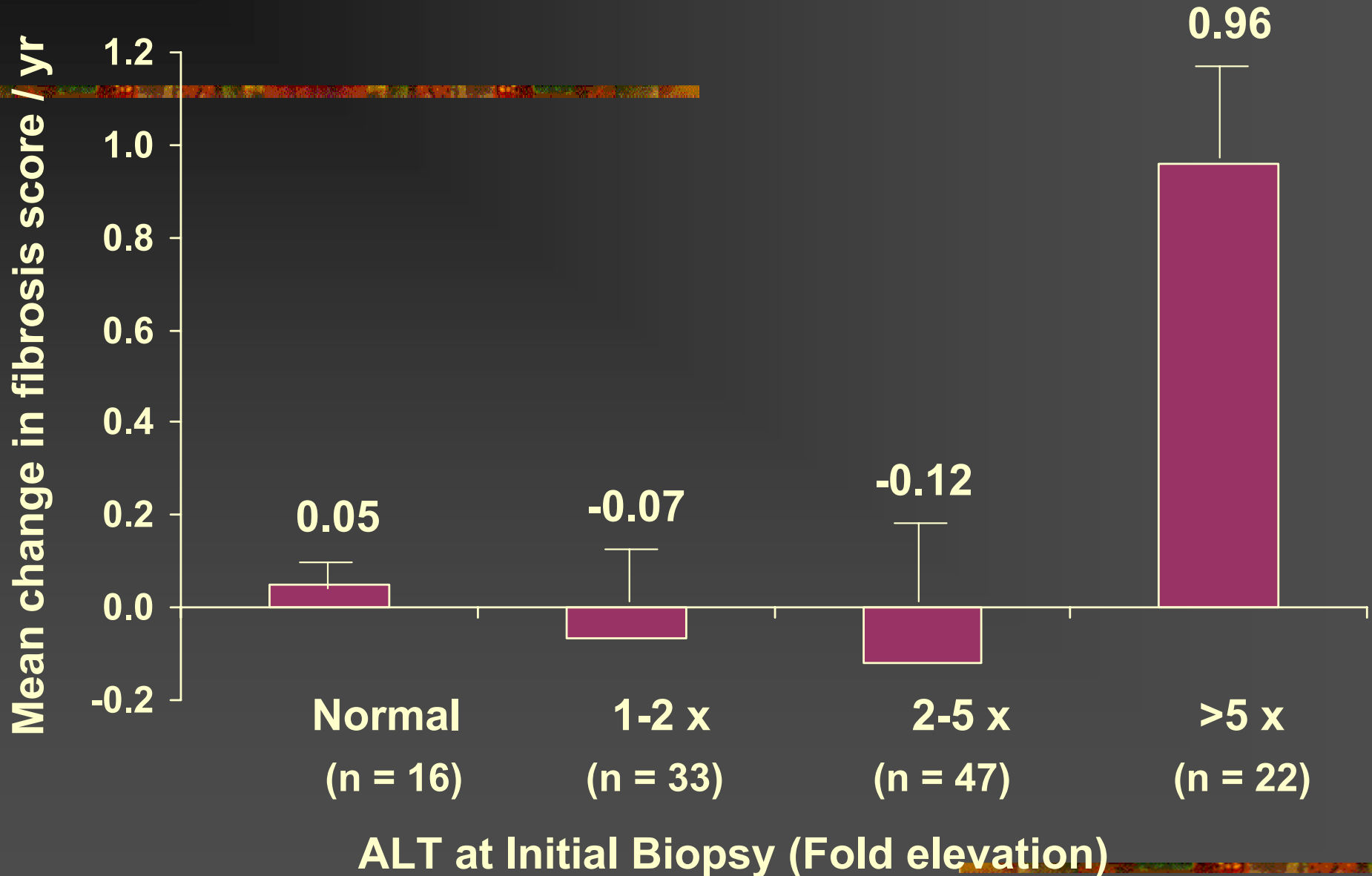
- 123 patients with chronic hepatitis C
- 2 liver biopsies without therapy
- Mean 44 months
- To better define natural progression of fibrosis in HCV



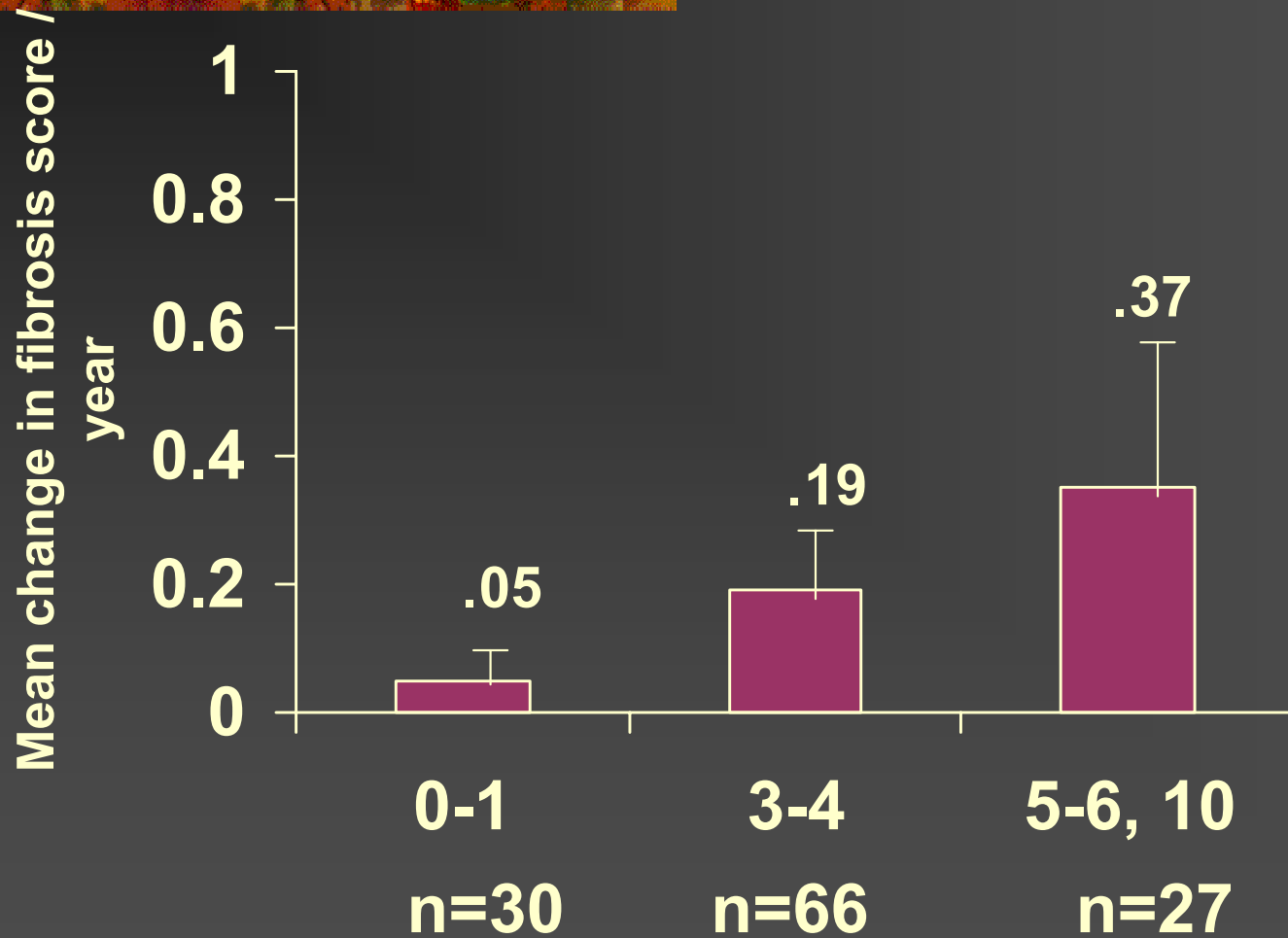
Age at Initial Biopsy and Progression of Fibrosis



ALT and Progression of Fibrosis



Periportal Inflammation and Progression of Fibrosis

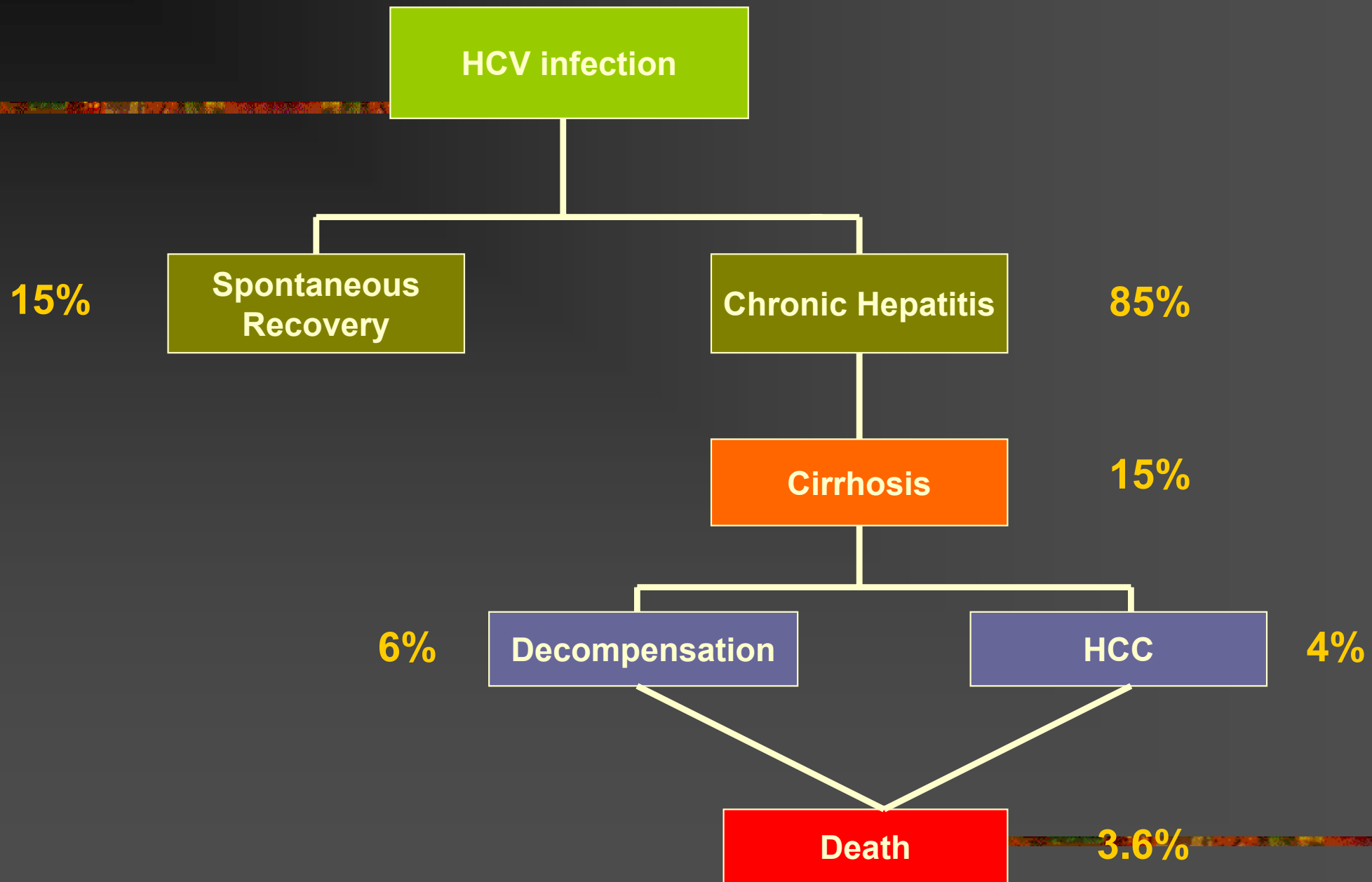


Composite periportal inflammation and necrosis score (0-10)

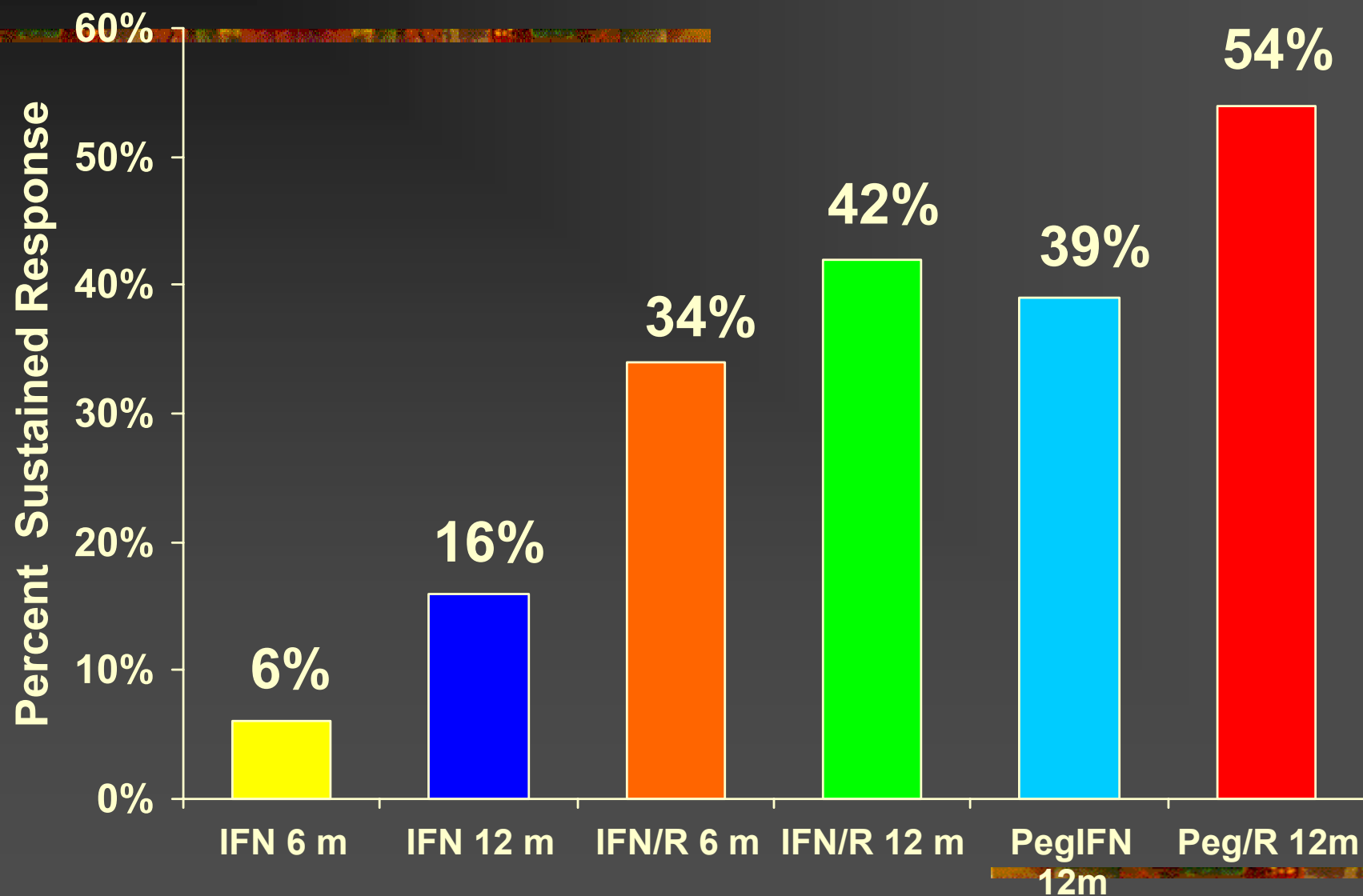
Factors Associated With Fibrosis Progression

- Age (at onset of infection).
 - Gender: M>F.
 - Alcohol: ?Low level consumption.
 - Immune status: HIV, post OLT.
 - Viral factors (-).
 - Others: racial, genetic, heterozygous HFE, overweight/steatosis.
-

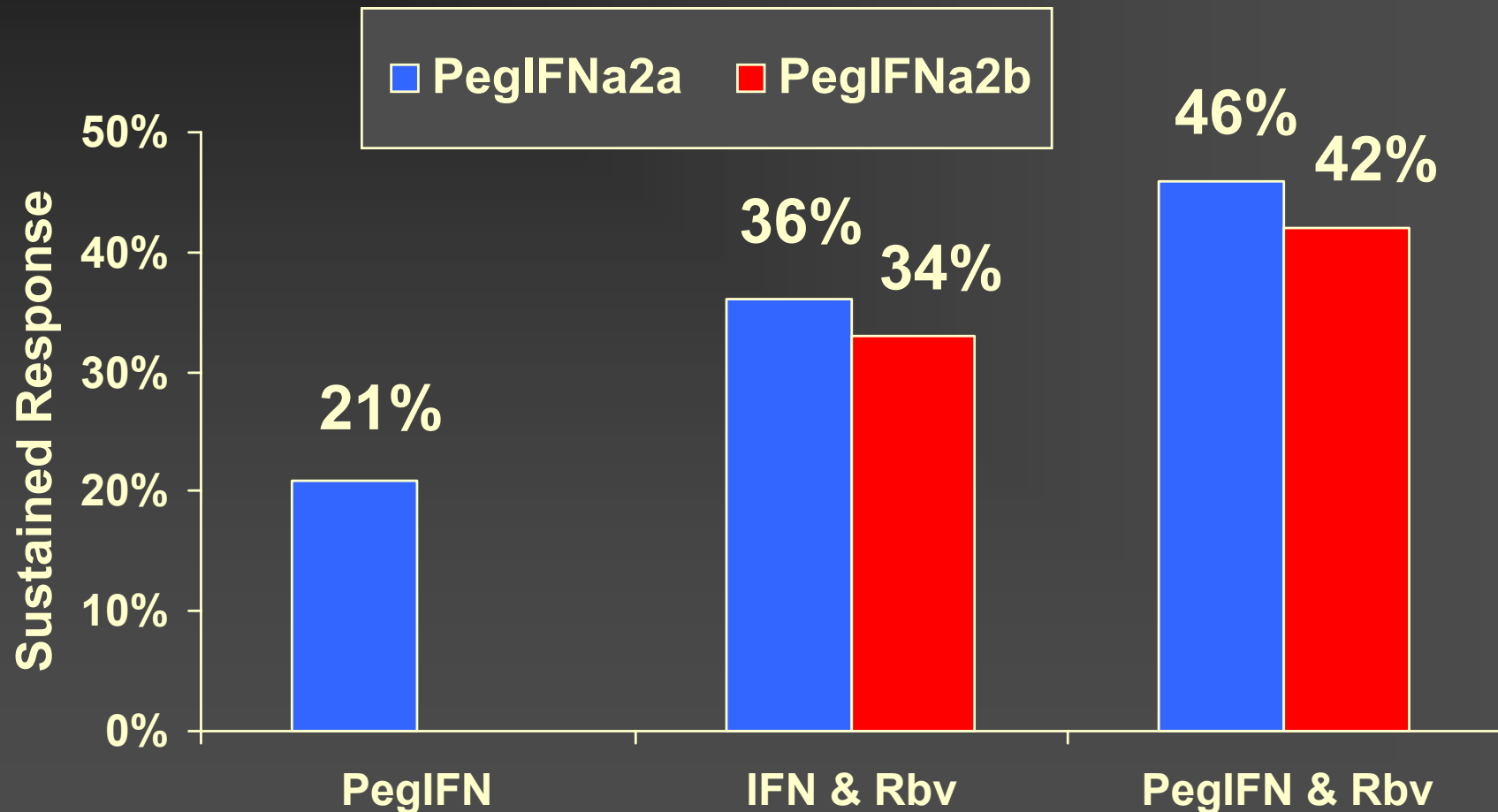
Summary: Outcomes of HCV Infection



Progress in Therapy of Hepatitis C



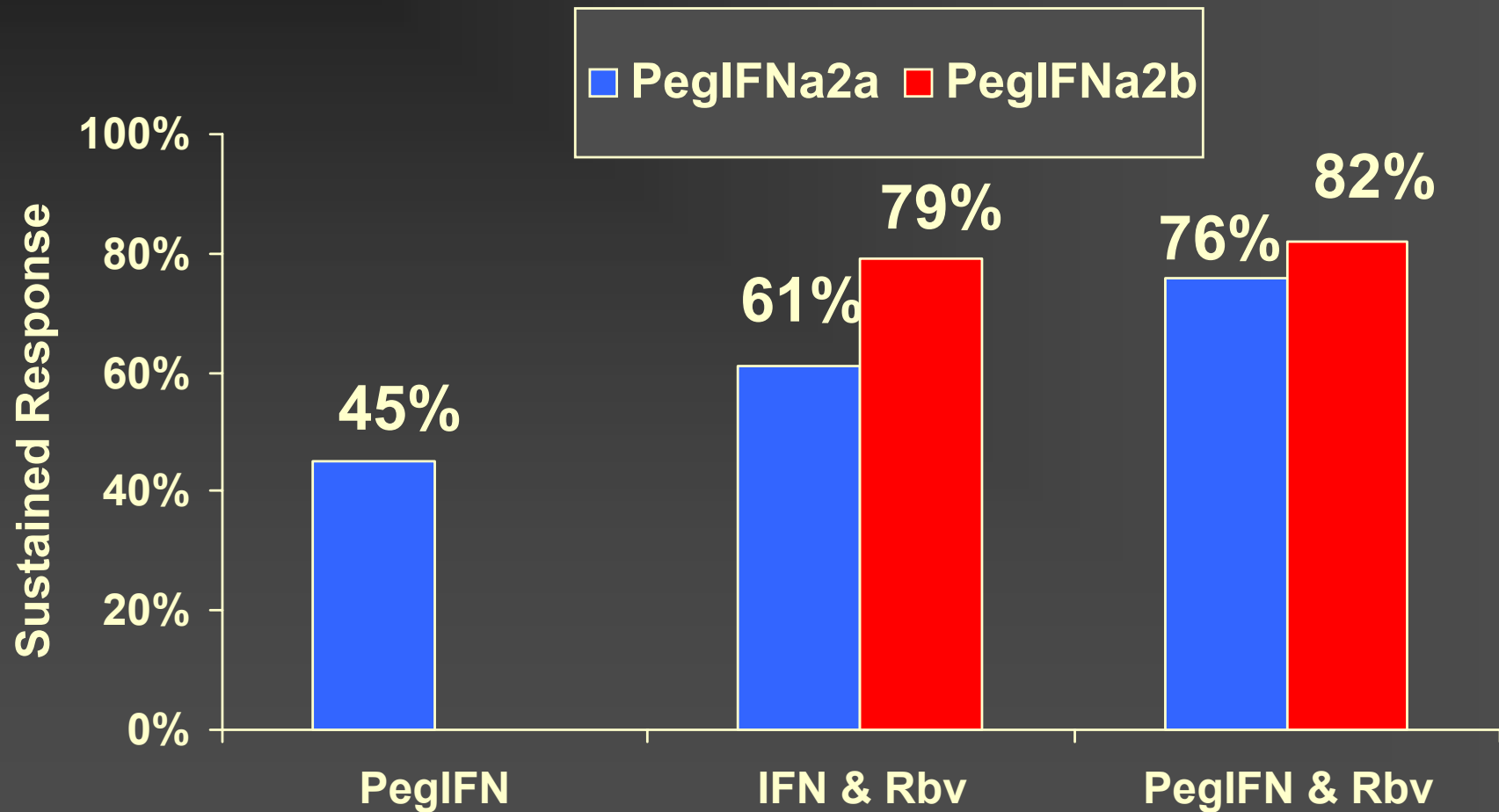
Pegylated Interferon and Ribavirin Chronic Hepatitis C: Genotype 1



Fried et al: NEJM 2002;347:975-982

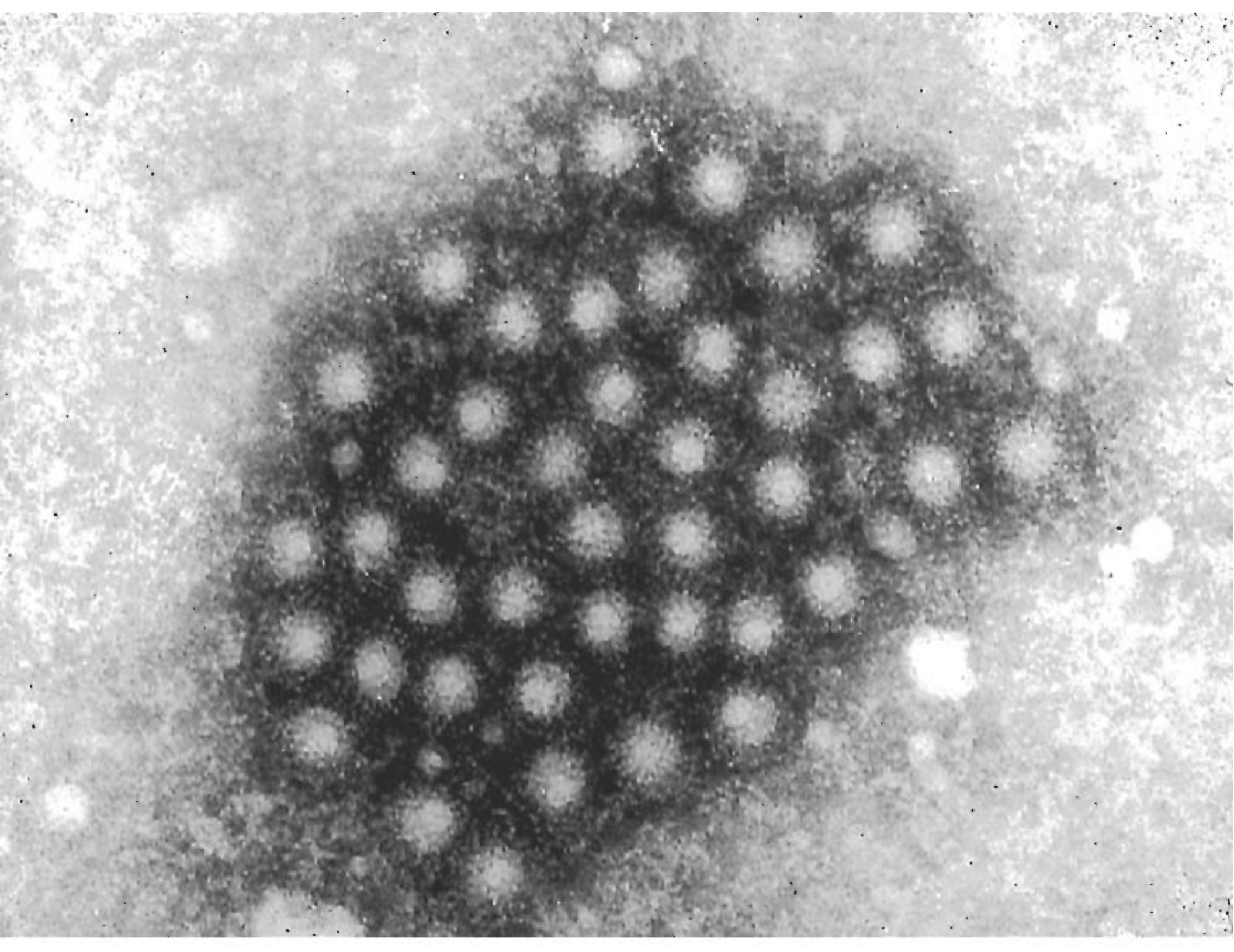
Manns et al: Lancet, 2001;358:958-965

Pegylated Interferon and Ribavirin Chronic Hepatitis C: Genotype 2 & 3



Fried et al: NEJM 2002;347:975-982

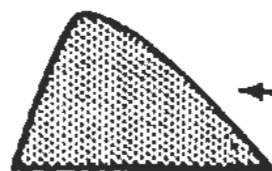
Manns et al: Lancet, 2001;358:958-965



EXPOSURE



Jaundice

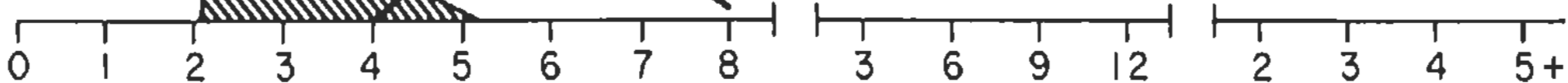


SGPT

anti-HAV in serum (IgM+IgG)

HAV in stool

anti-HAV (IgM)



WEEKS

MONTHS

YEARS

