PATHOLOGIE der LEBER II.

Andras Kiss
dr. med. habil., Ph.D., D.Sc.

Semmelweis Universität,
Budapest
II. Institut für Pathologie

den 15. Februar 2019

HEPATITIDEN:

- **kleine (20-200 nm) Infektionserreger ohne !!! eigenen Stoffwechsel benötigen Enzyme des Wirtes für Vermehrung**

♦ **DNA Viren (ein oder strängige) Herpesviren, Humane Papillomaviren, Molluscum-contagiosum-Virus, usw. HBV !!**

- **RNA Viren (reverse Trankriptase)**

z. B. Myxoviren, Togaviren

HEPATITIDEN

- **Hepatitis VIREN**

A	B	C	D	E
RNA	DNA	RNA	RNA	RNA
fäkal-oral	parent-sex.	parent-sex.	parent-sex.	fäkal-oral
Inkubation:				
2-5 W	4-25 W	2-28 W	12-16 W	4 W
Verlauf:				
4 W	4-9W	9 W	4-9 W	4- W
Chronizität:				
-	+	++ (80 %)	+	-

Hepatotrope Viren

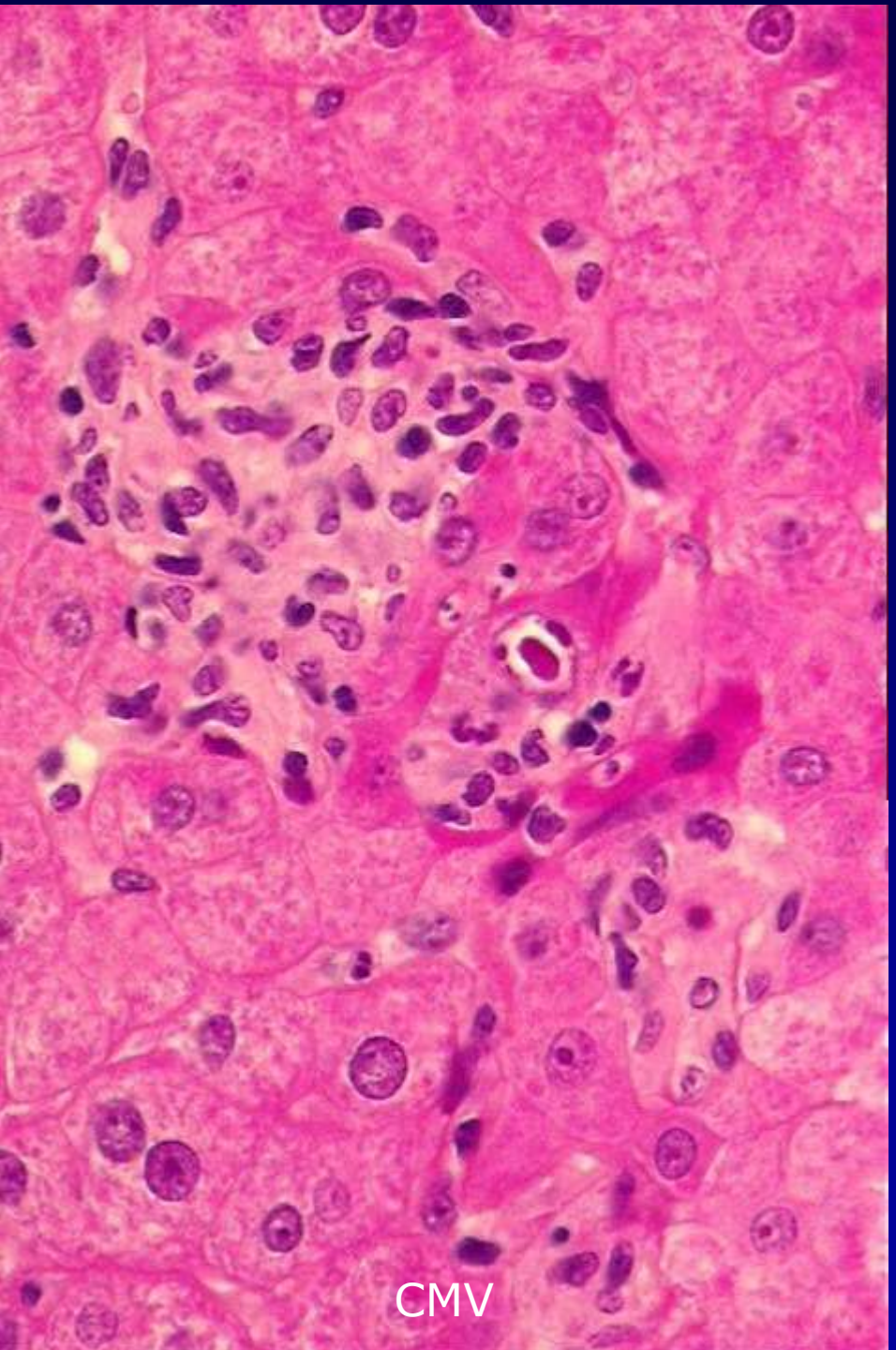
	HAV	HBV	HCV	HDV	HEV
Erreger Typ	RNA (Picornav.)	DNA (Hepadna)	RNA (Flaviv.)	Incomplet t RNA	RNA (Flaviv.)
Übertrag-ung	Fäkal-oral	Parente ral	Parenter al	Parente ral	Fäkal-oral
Chronizi-tät	-	+ (10%)	++ (50%)	(80%)	-
Träger-status	-	+	+	+	-

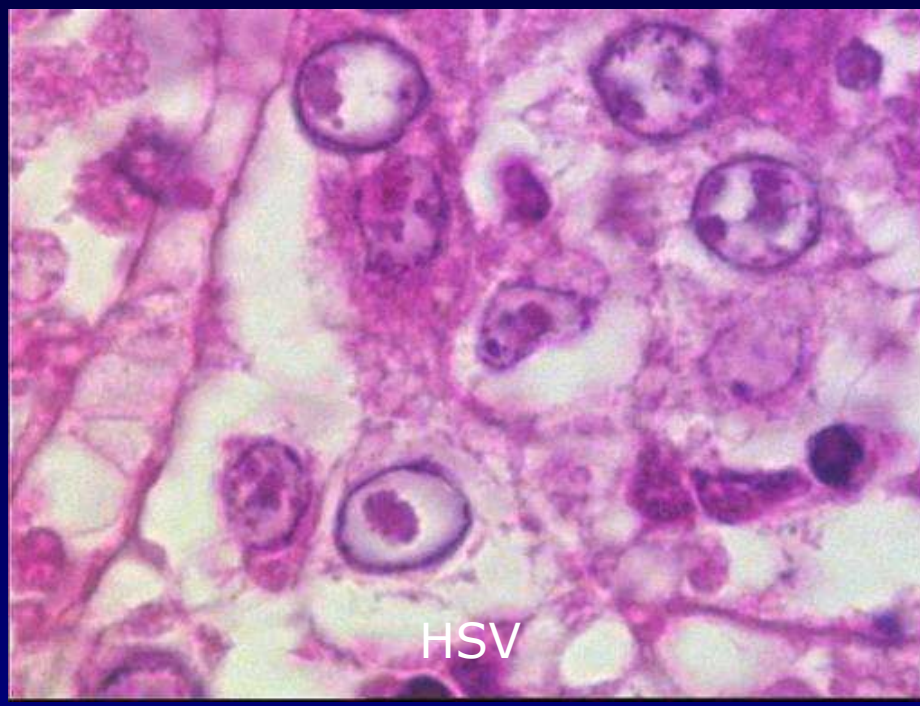
Hepatitiden

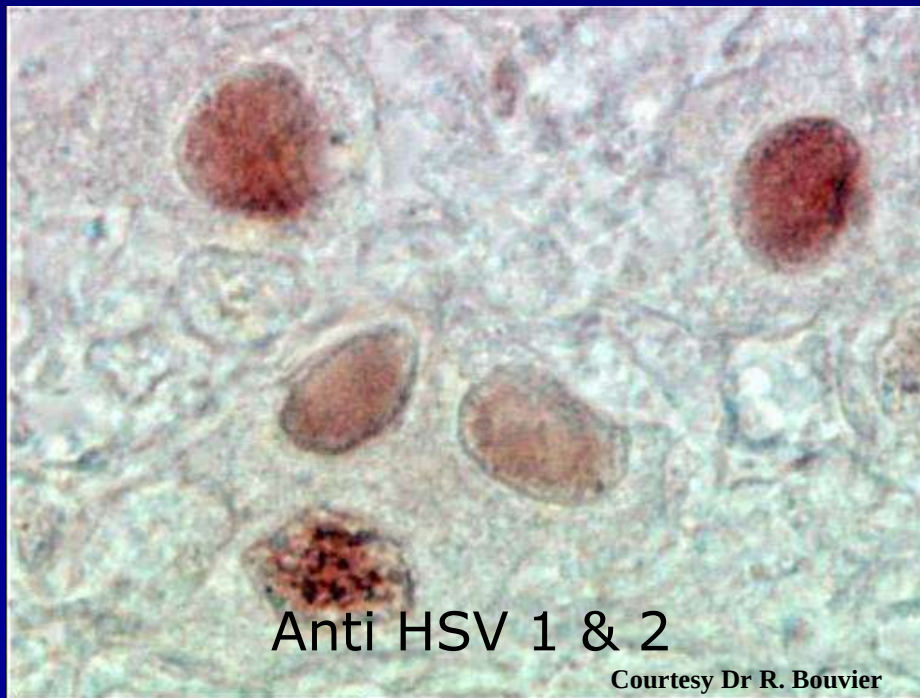
- **andere Viren: Herpes-simplex virus, Zytomegalie-virus, EBV, Coxsackie virus**

- **Makroskopie: Leber ist vergrössert, gelbgrün**

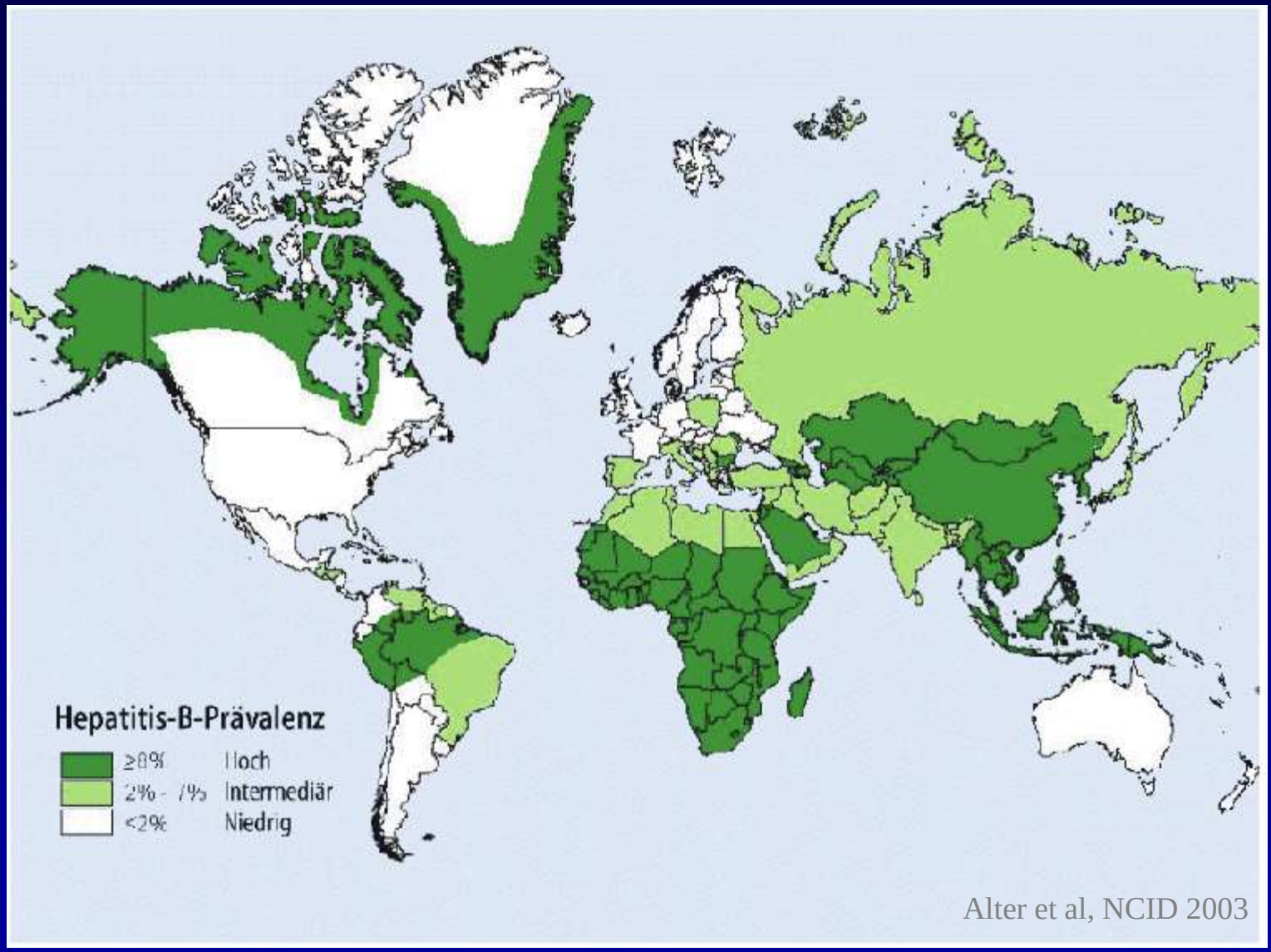
- **Mikroskopie: Einzellzellnekrosen mit Councilman Körperchen, ballonierte Leberzellen, proliferierende Kupffer Zellen. Lymphozytäre Infiltration.**


CMV


HSV


Anti HSV 1 & 2
Courtesy Dr R. Bouvier

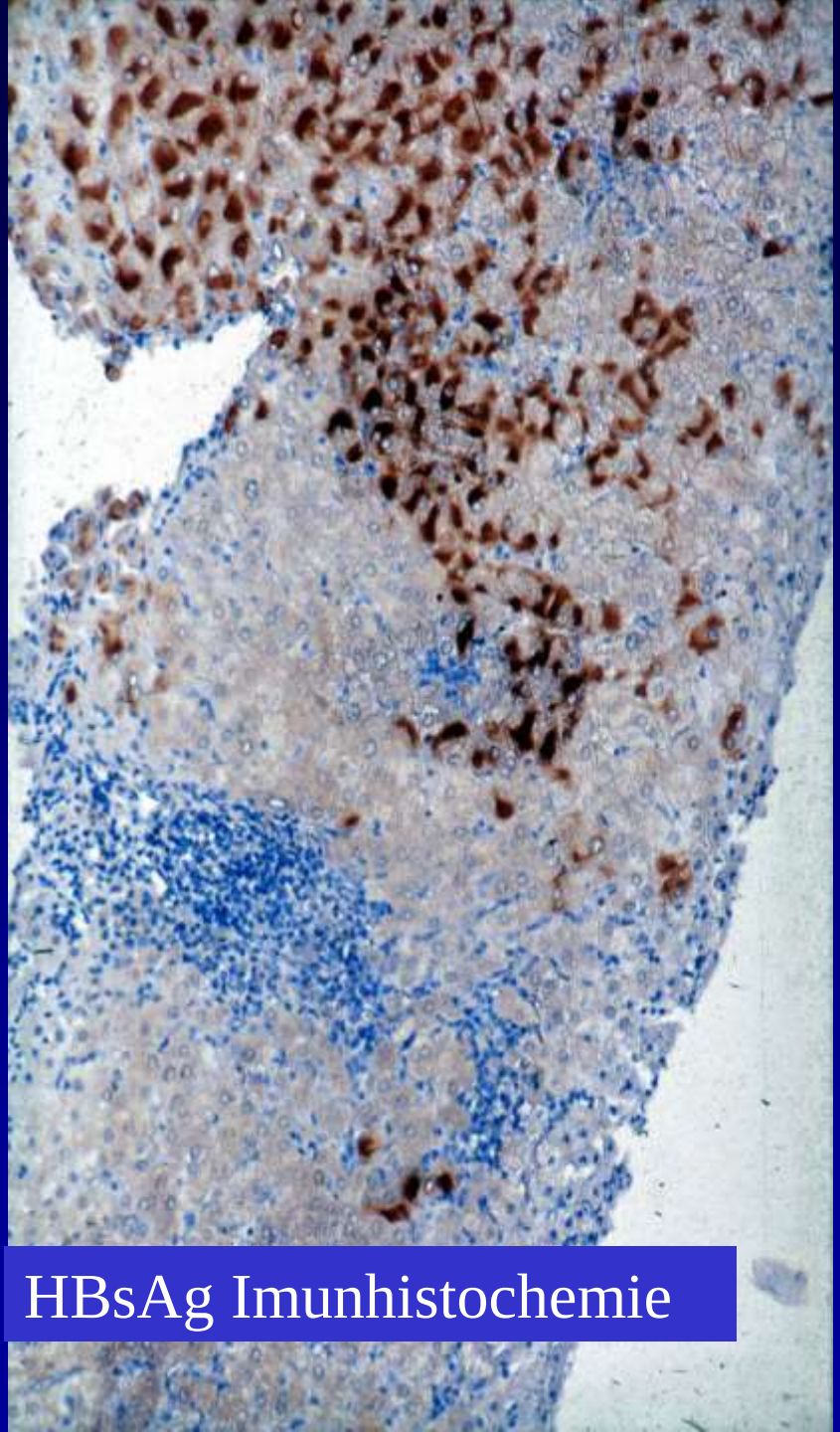
Hepatitis B



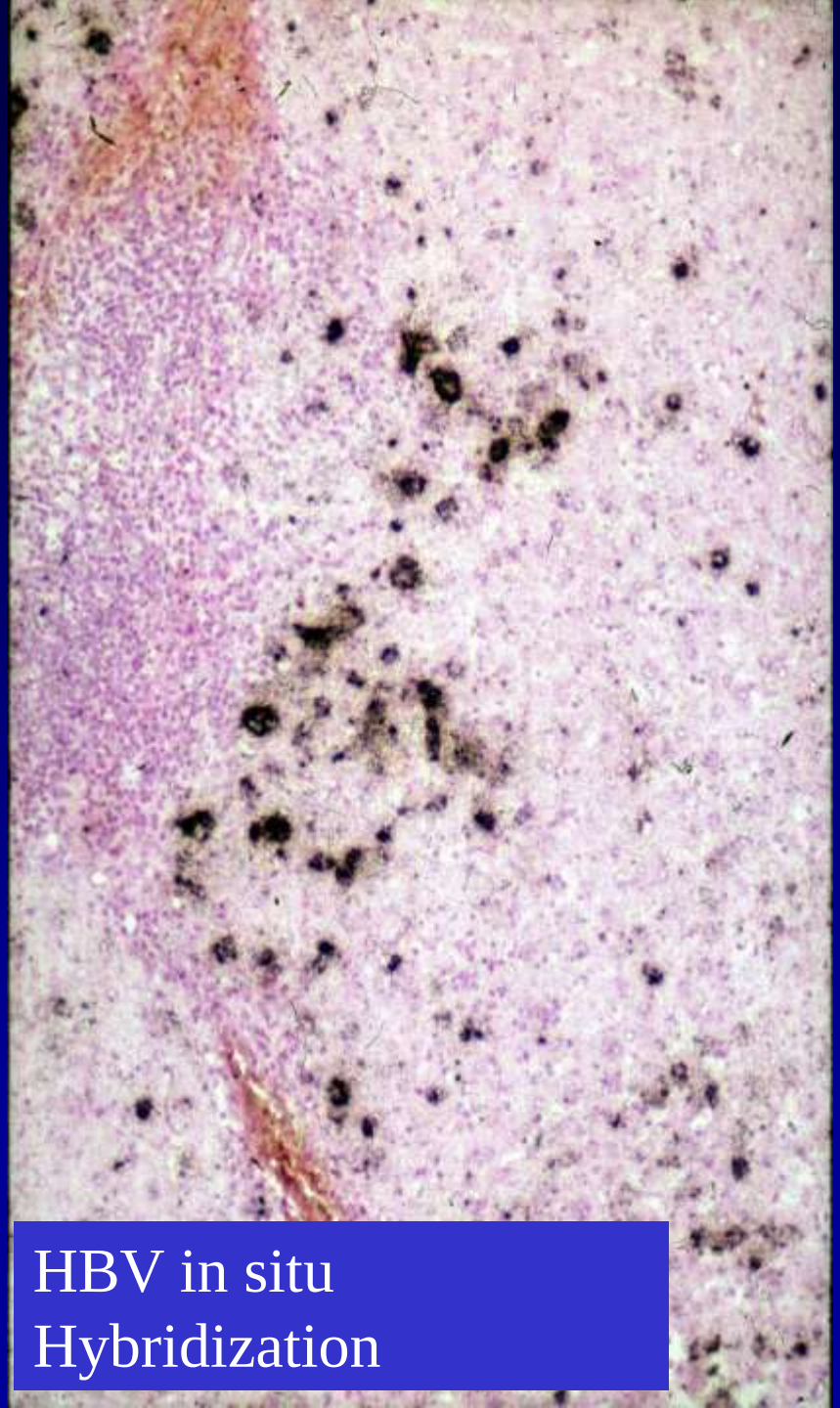
Alter et al, NCID 2003

Hepatitis B

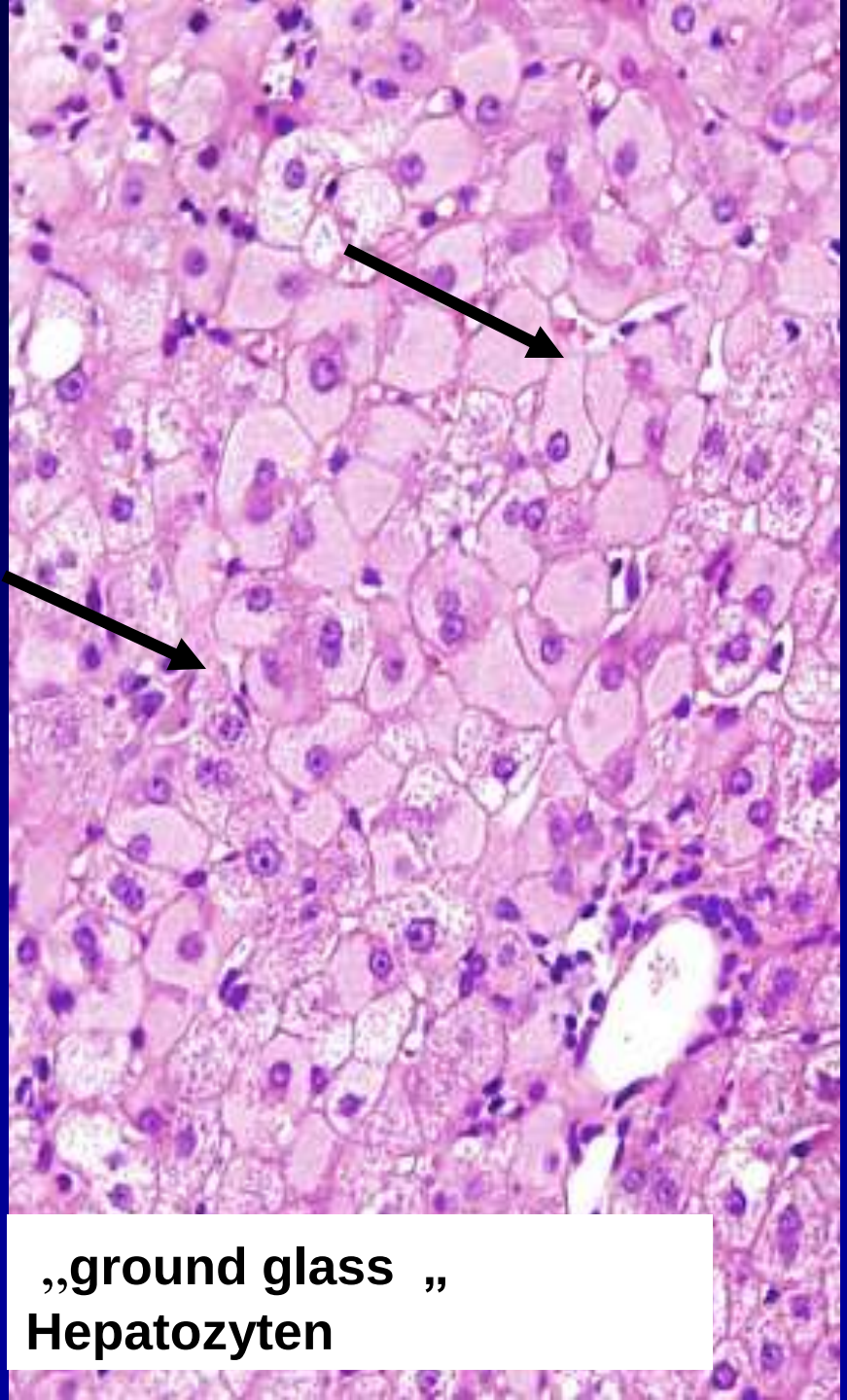
FIGURE 1. The worldwide geographic distribution of chronic hepatitis B virus infection (source: Centers for Disease Control, 2006).



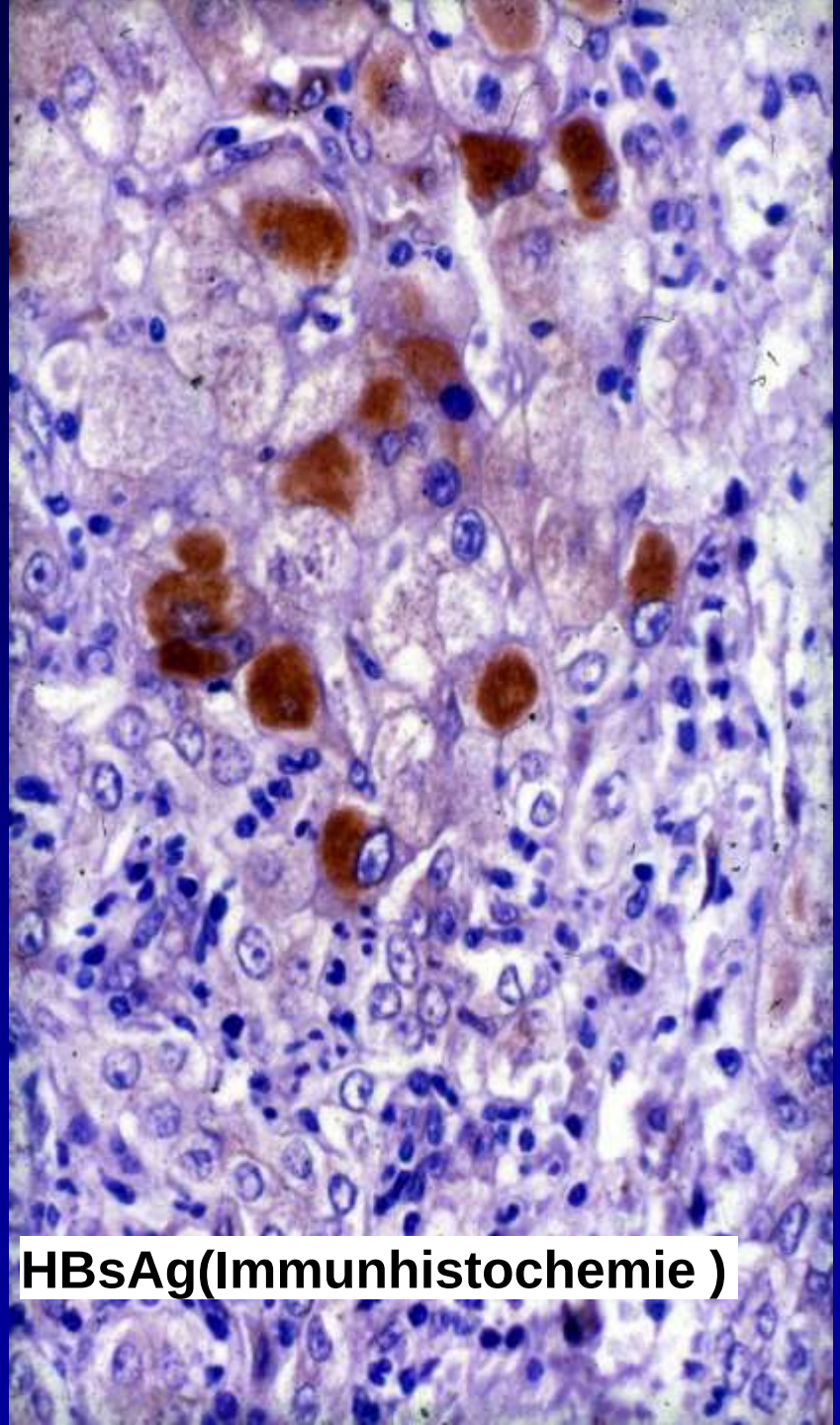
HBsAg Imunhistochemie



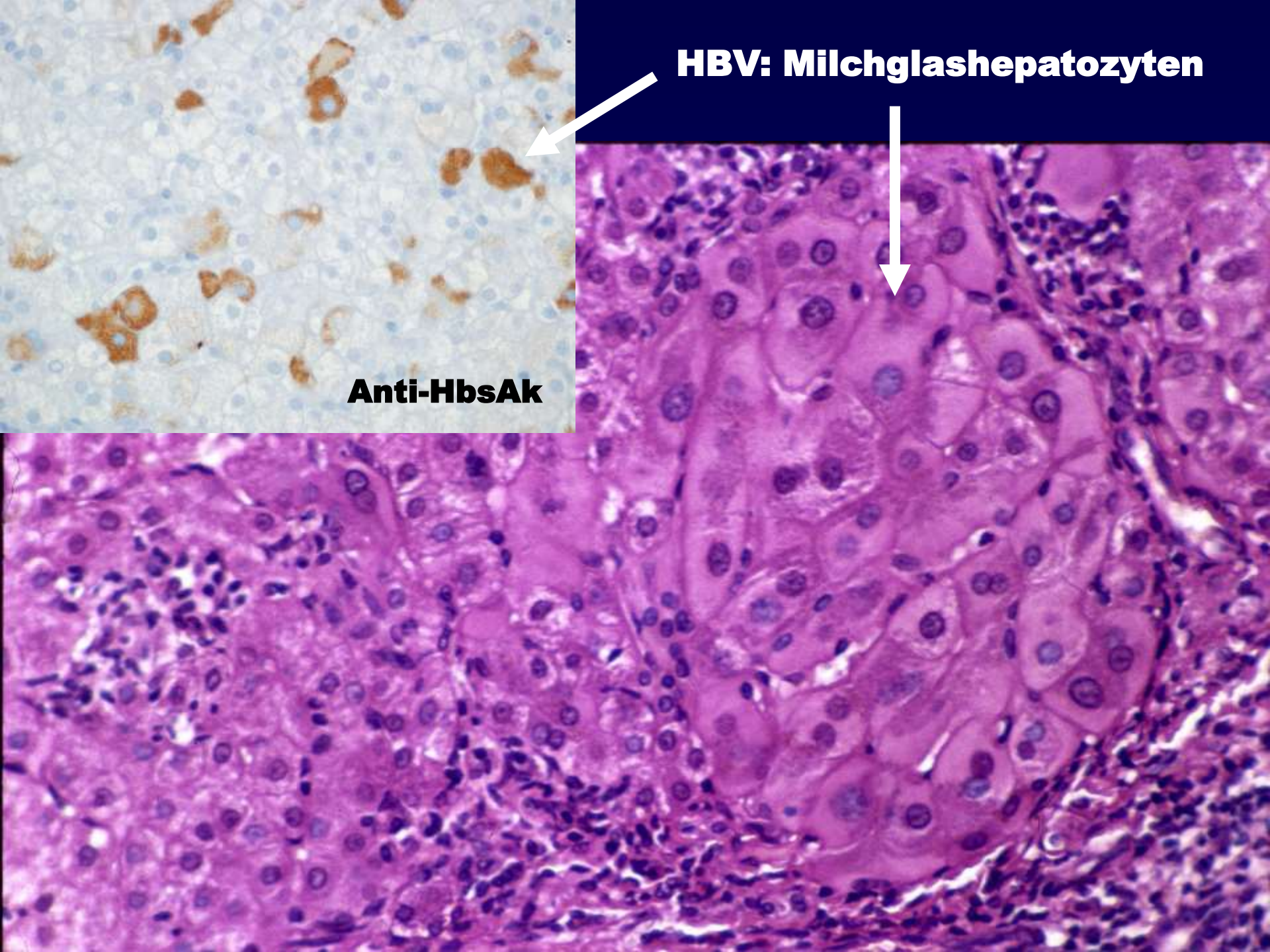
HBV in situ Hybridization



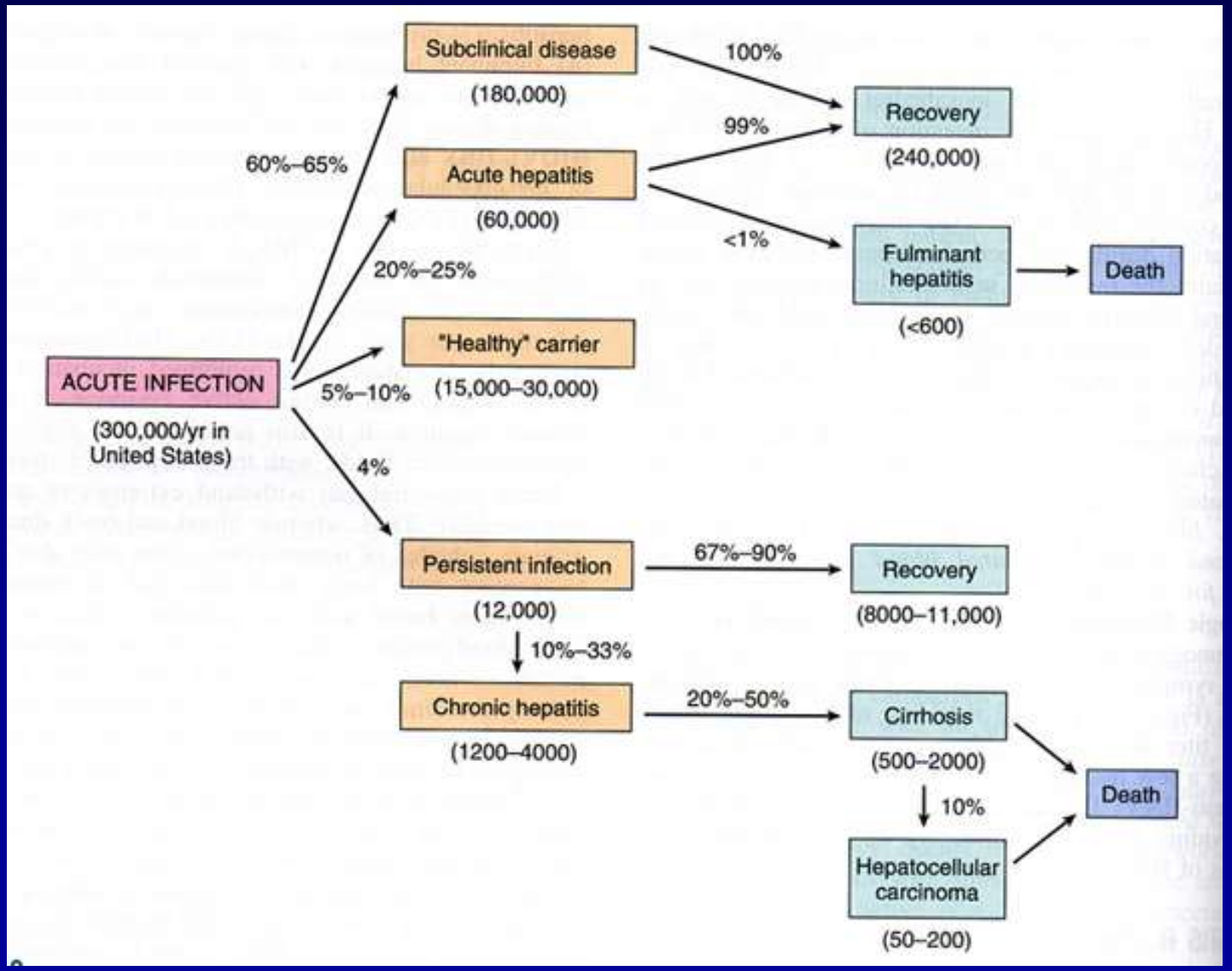
„ground glass „
Hepatozyten



HBsAg(Immunhistochemie)


HBV: Milchglashepatozyten
Anti-HbsAk

Verlauf der HBV Infektion



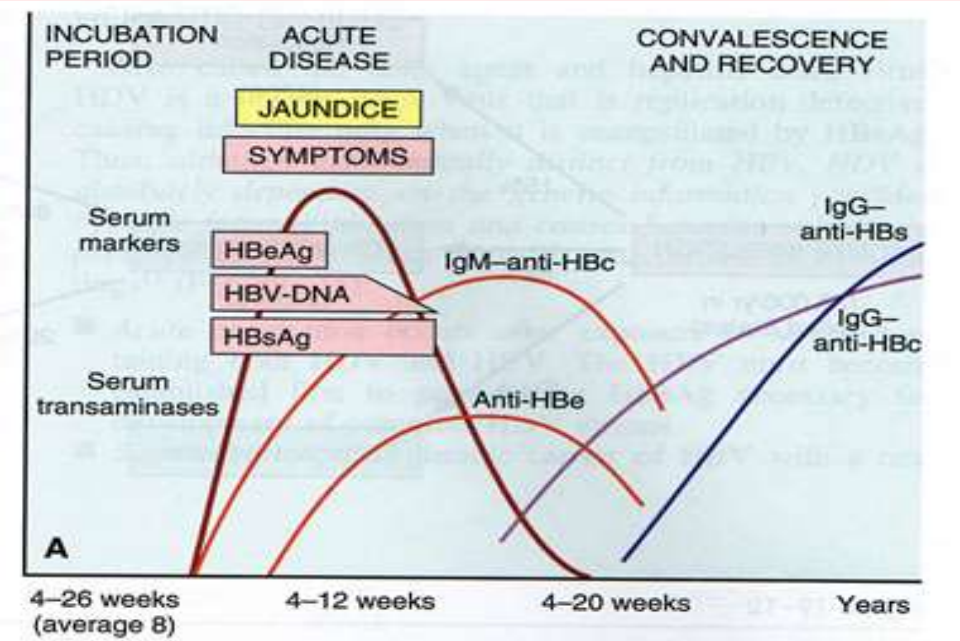
HBV

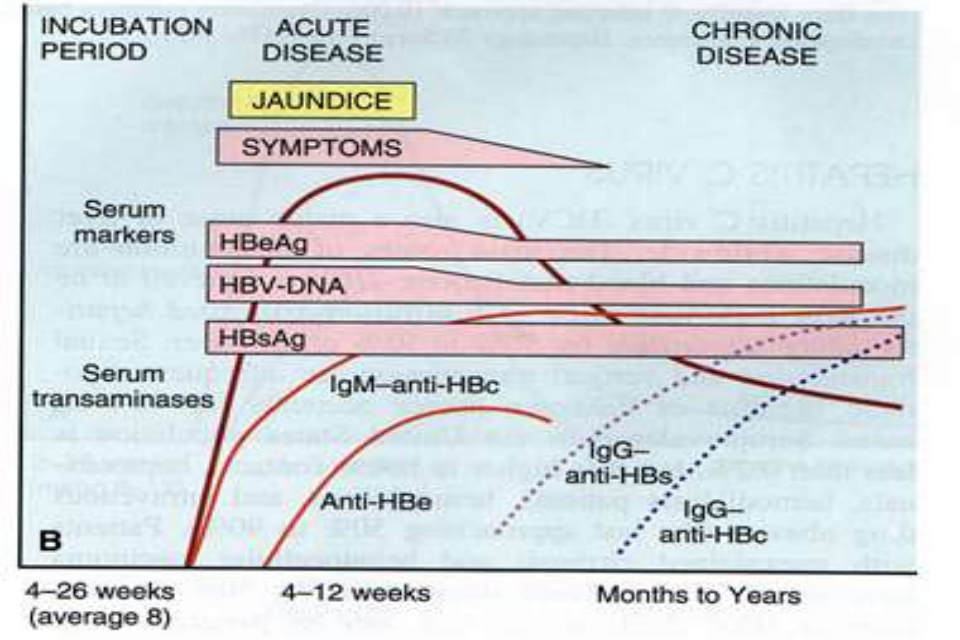
400 Millionen

Schutz / Prevention gegen HBV Infektion

Schutz / Prevention gegen HBV Infektion

Verlauf der HBV Infektion





Verlauf der HDV Infektion

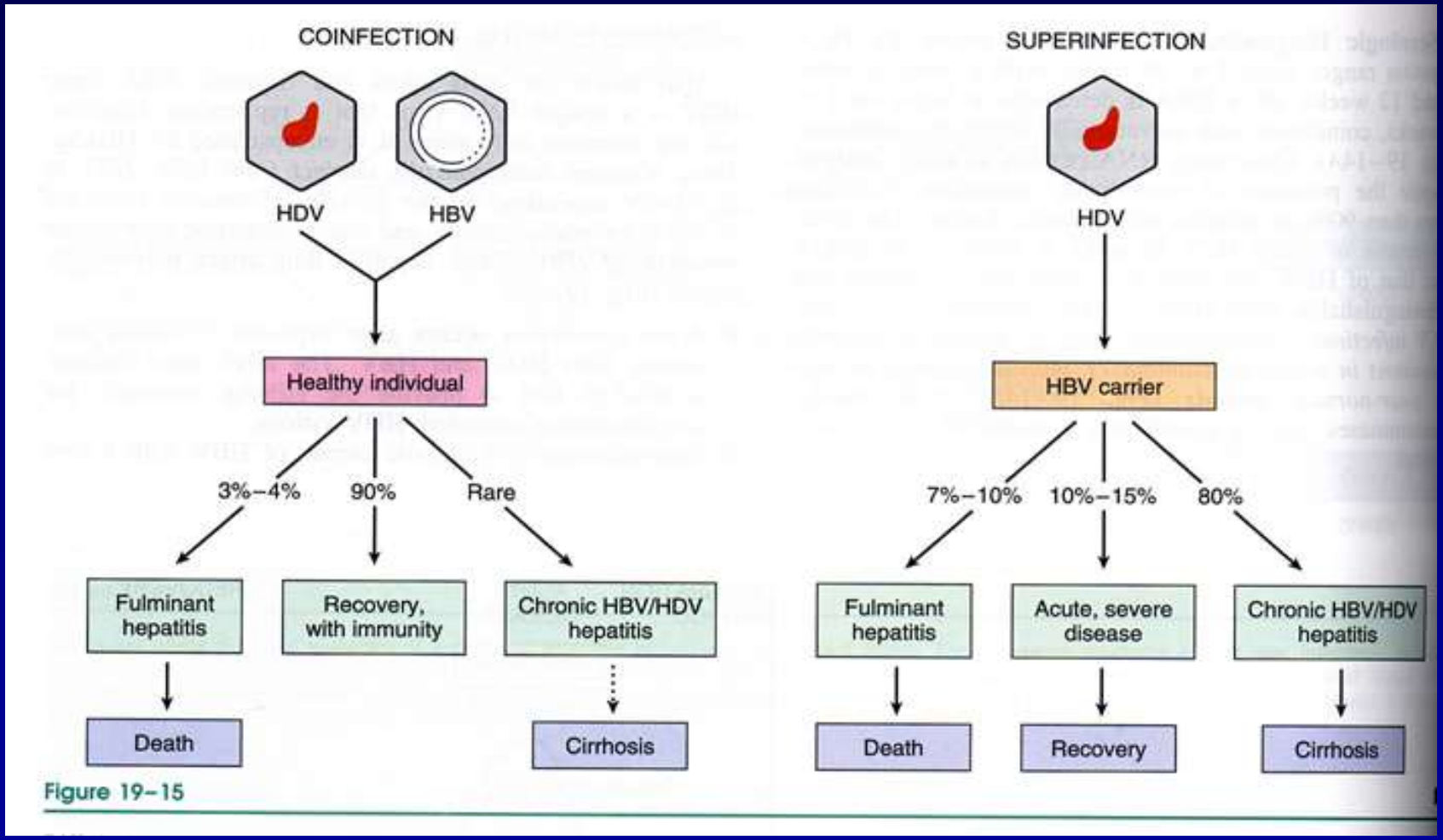
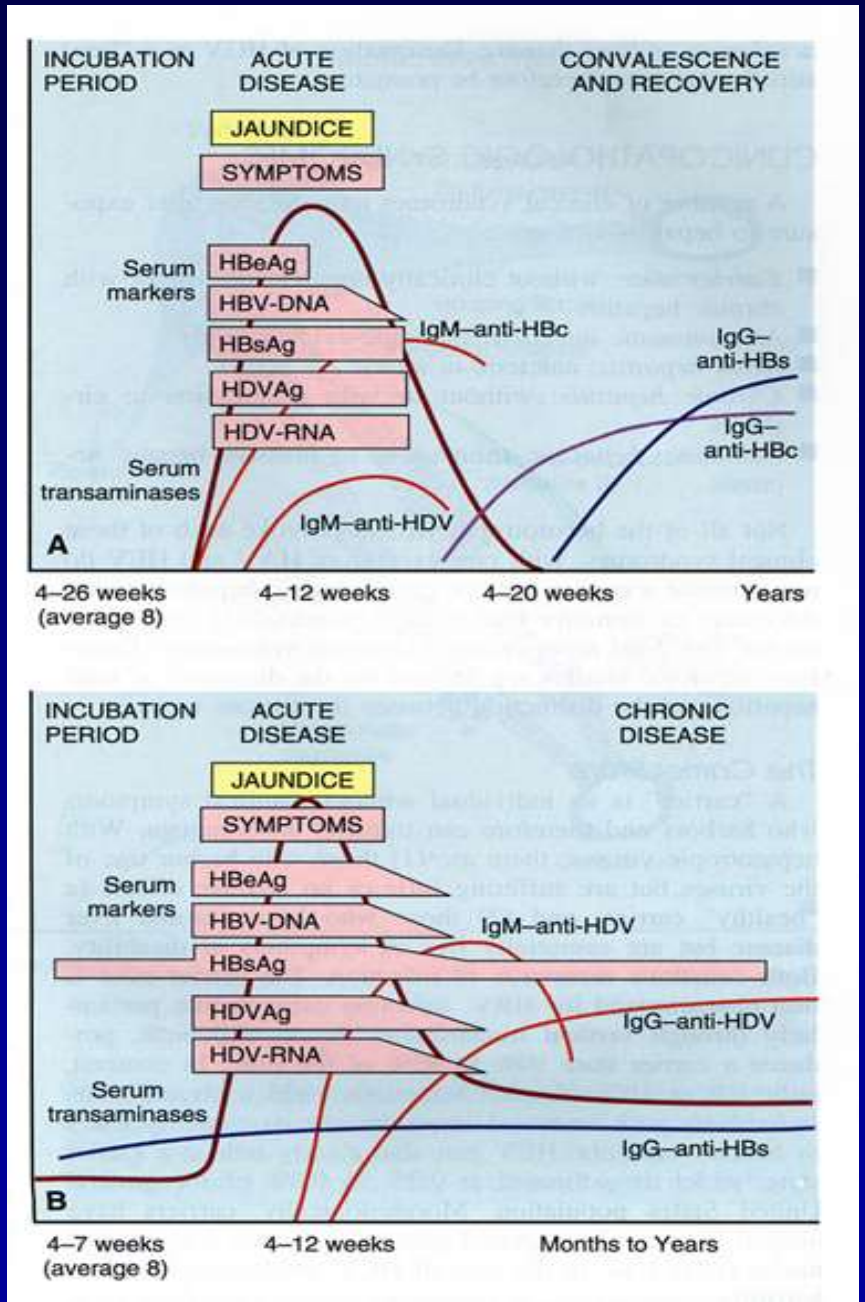
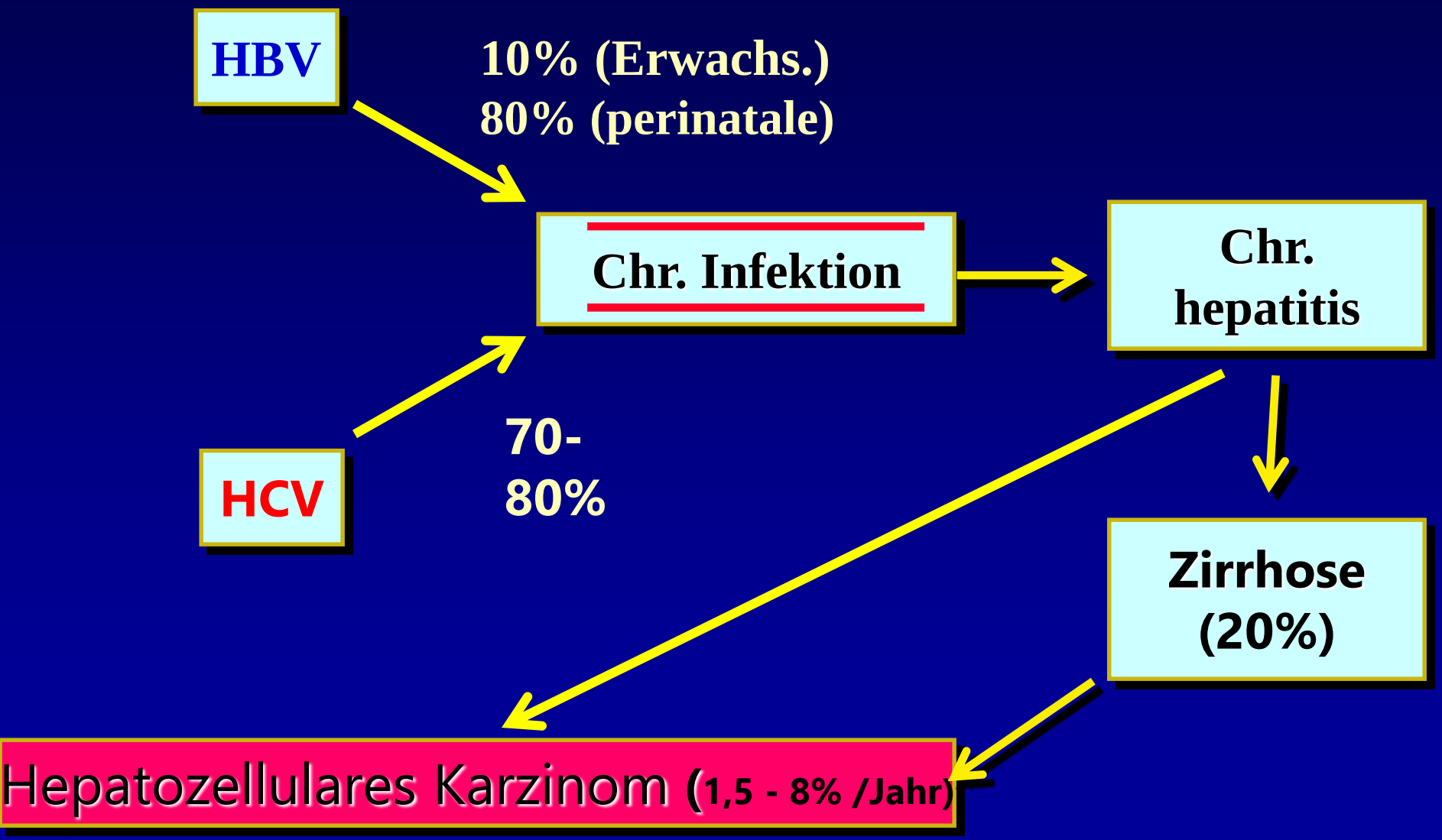


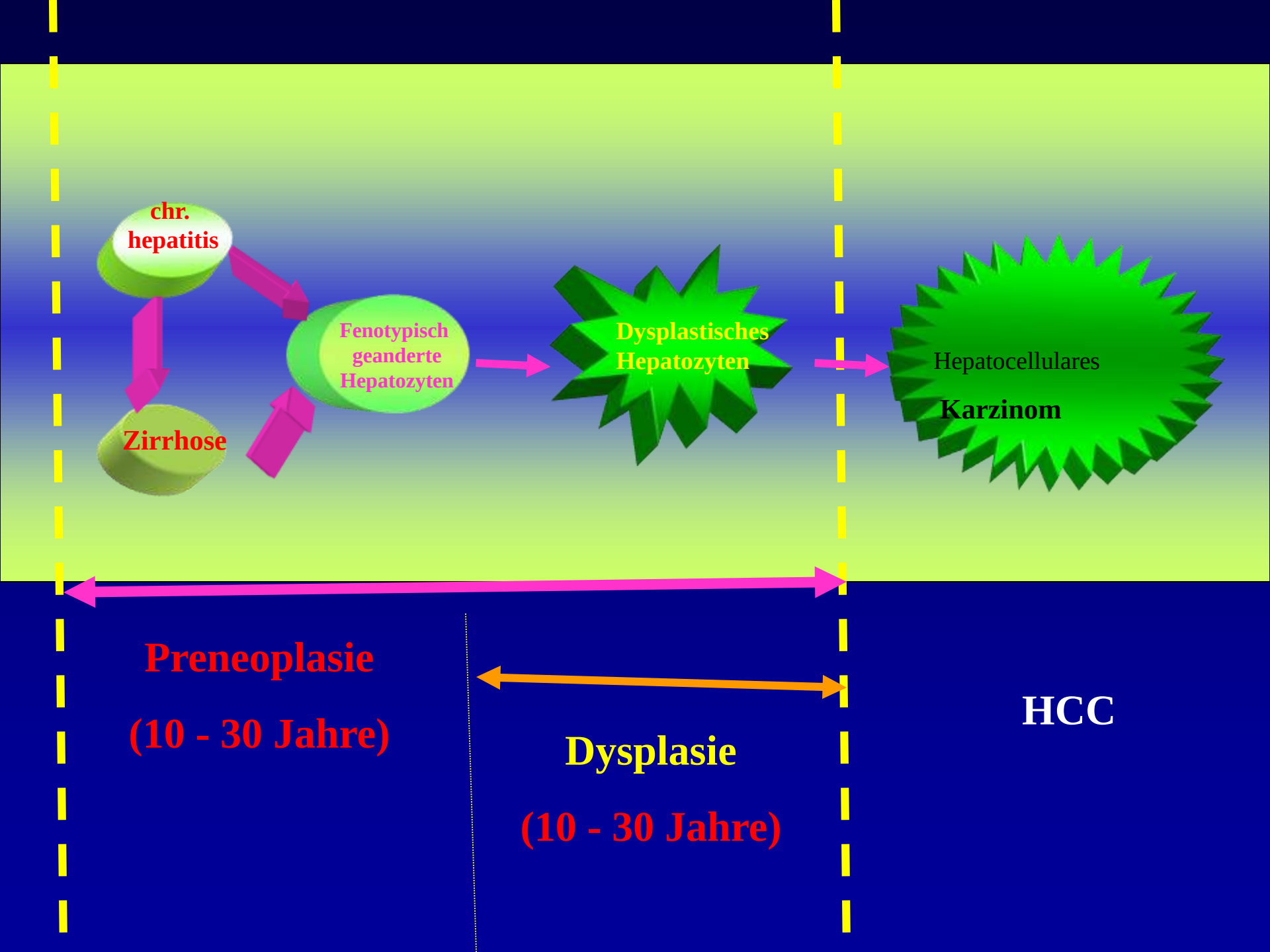
Figure 19–15

Verlauf der HDV Infektion

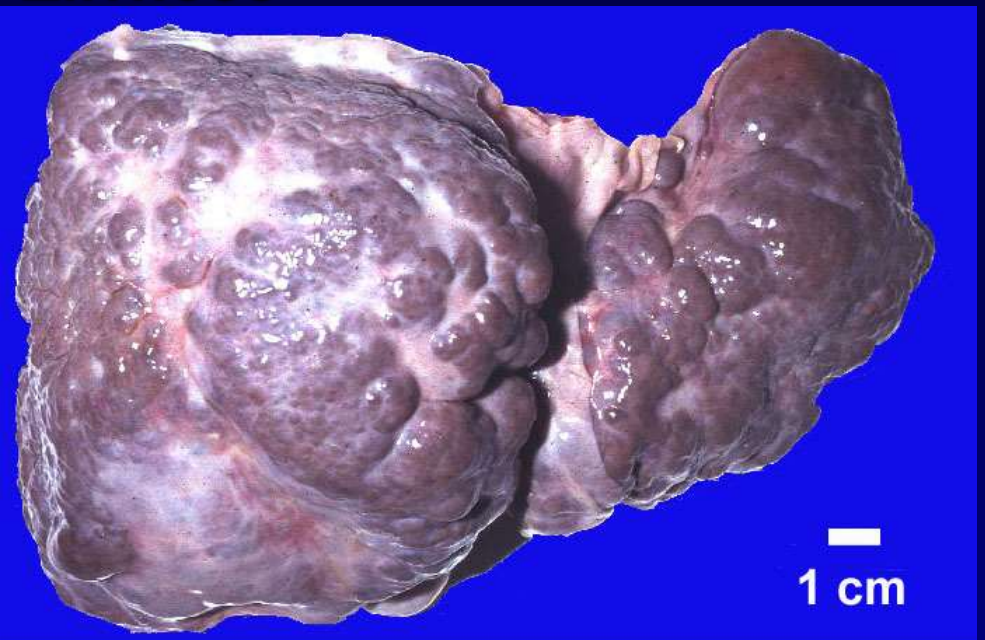


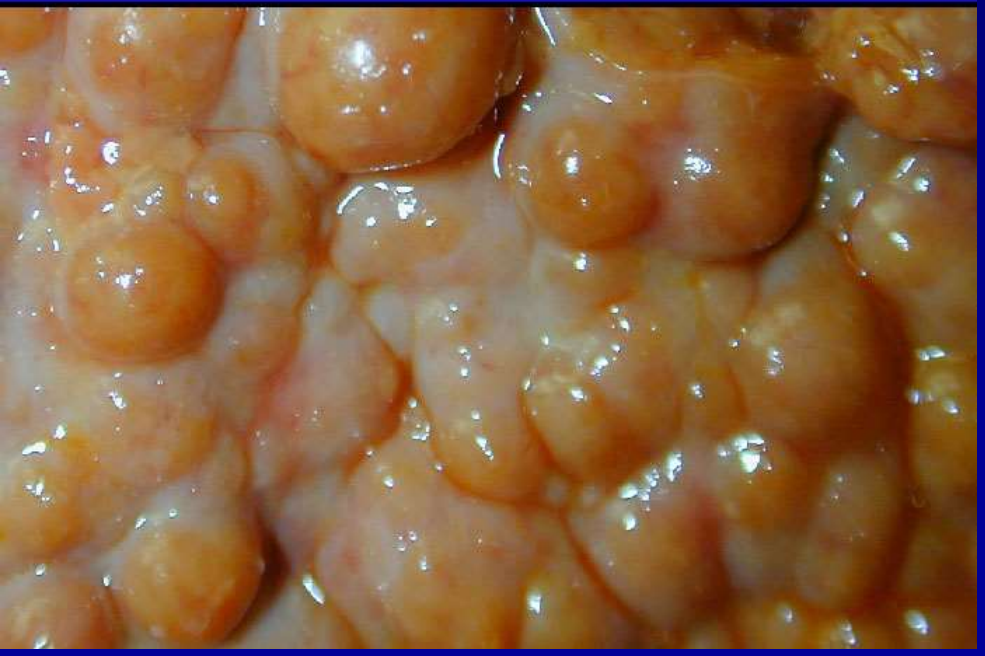
Folgen der chronischen HBV und HCV infektion




chr.
hepatitis
Zirrhose
Fenotypisch
geanderte
Hepatozyten
Dysplastisches
Hepatozyten
Hepatocellulares
Karzinom
Preneoplasie
(10 - 30 Jahre)
Dysplasie
(10 - 30 Jahre)
HCC

Zirrhose





HCC

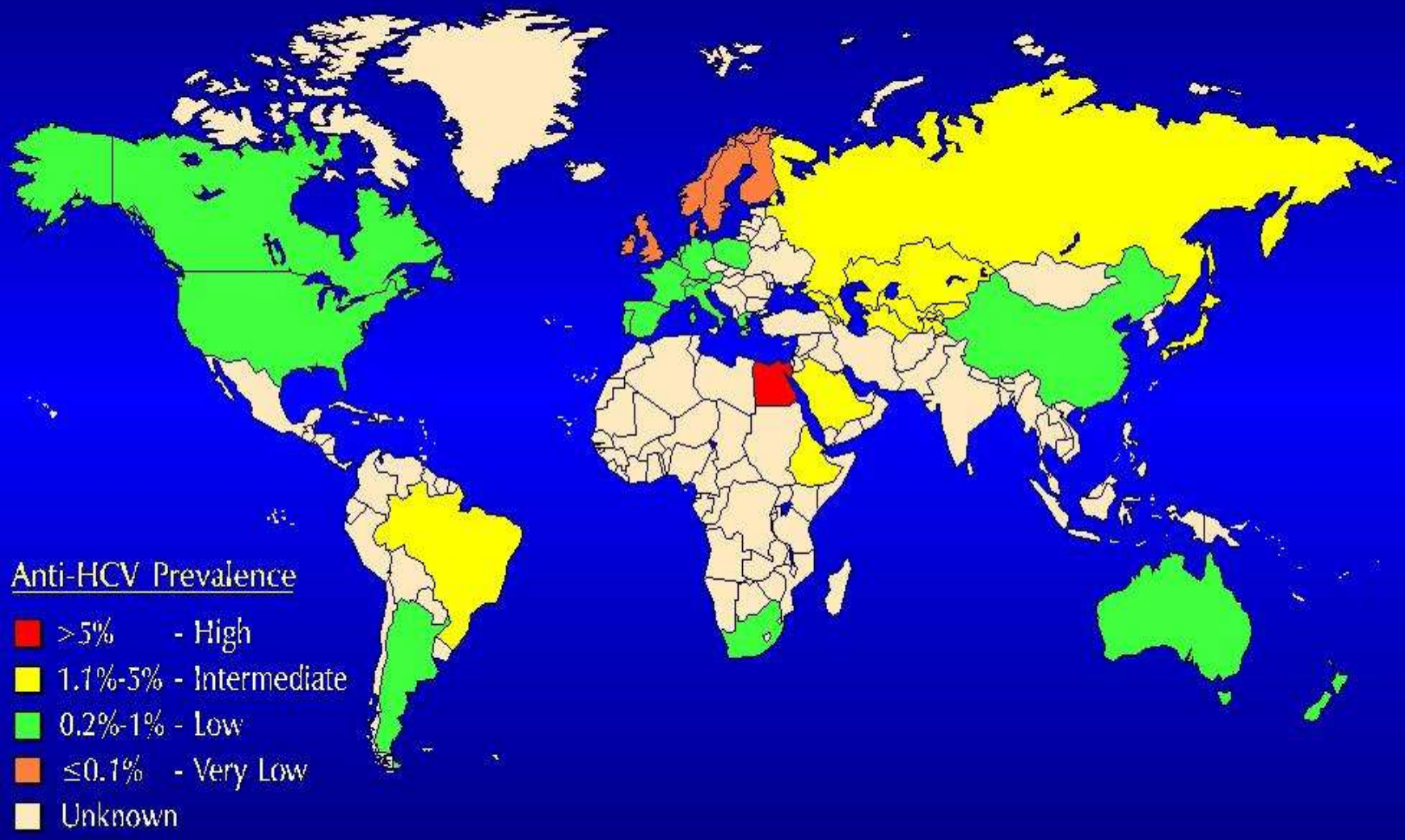
Die Folgen und Eigenschaften der HBV-DNS Integration

Folge	Eigenschaft
Chromosomale Instabilitat	Nachweisbar in 90 % der HBV assoziierte HCCs
Insertions Mutagenese	Random
Produkion inkomplette viralen Proteinen	vorhergehend der Entwicklung des HCC
Überproduktion der HBx Proteine	
Alteration zellularen Gene und Protoonkogene	

Die Rolle der HBx Protein

- Transaktivation der für Wachstum verantwortliche zellulare Gene (Protoonkogene, c-jun, c-fos, c-myc)
- Deregulation der „Kontrollpunkten”
- Tumorpromoter
- SAktivation vielen zytoplasmatischen und nuklearen Transduktion-kaskaden
- Es induziert Tumor HBx-transgene Mausen
- Inaktivation von Tumorsupress Gene (p53, RB, etc.), durch Bindung zu diesen Proteinen.

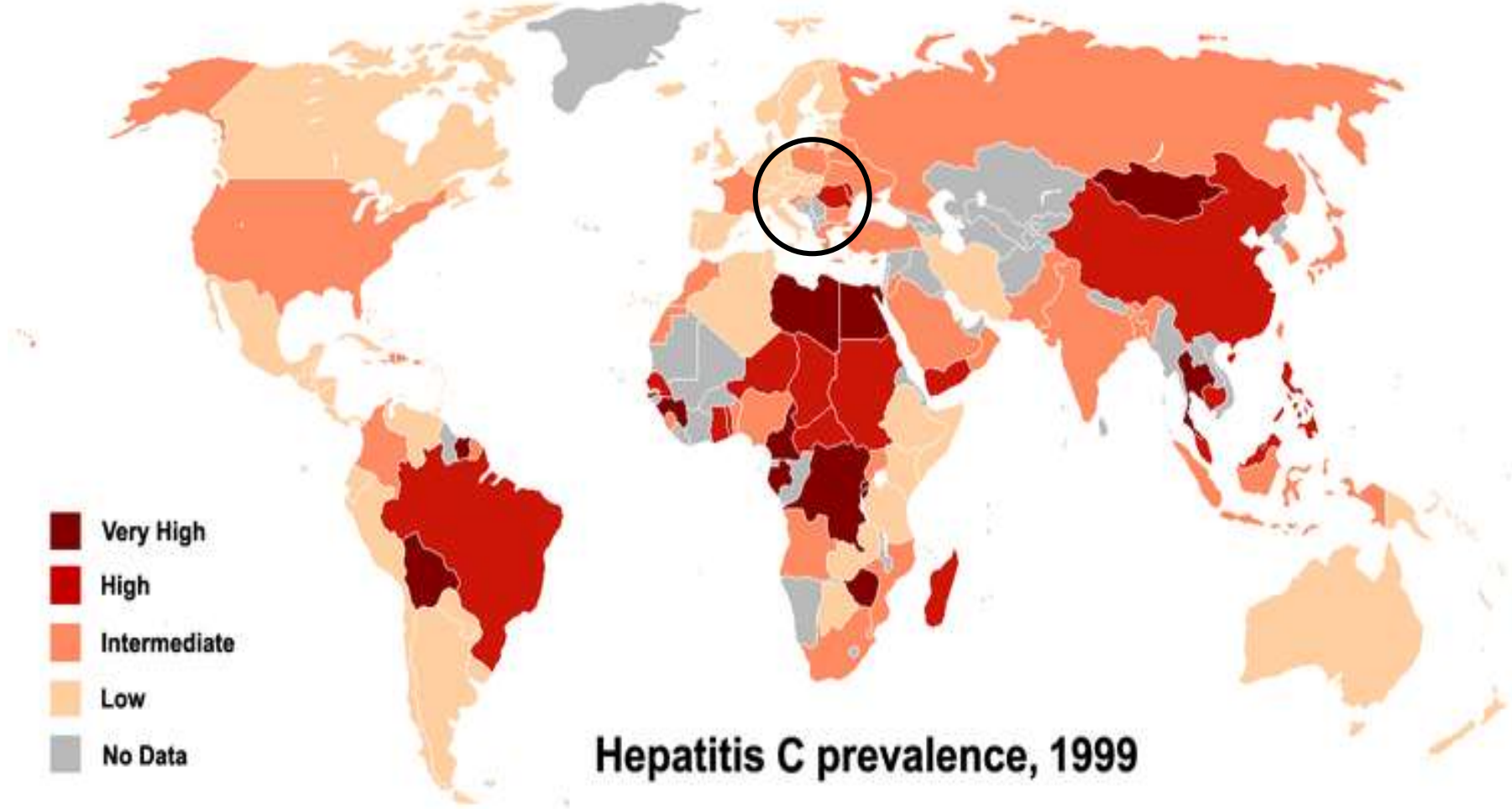
Prevalence of HCV Infection Among Blood Donors*



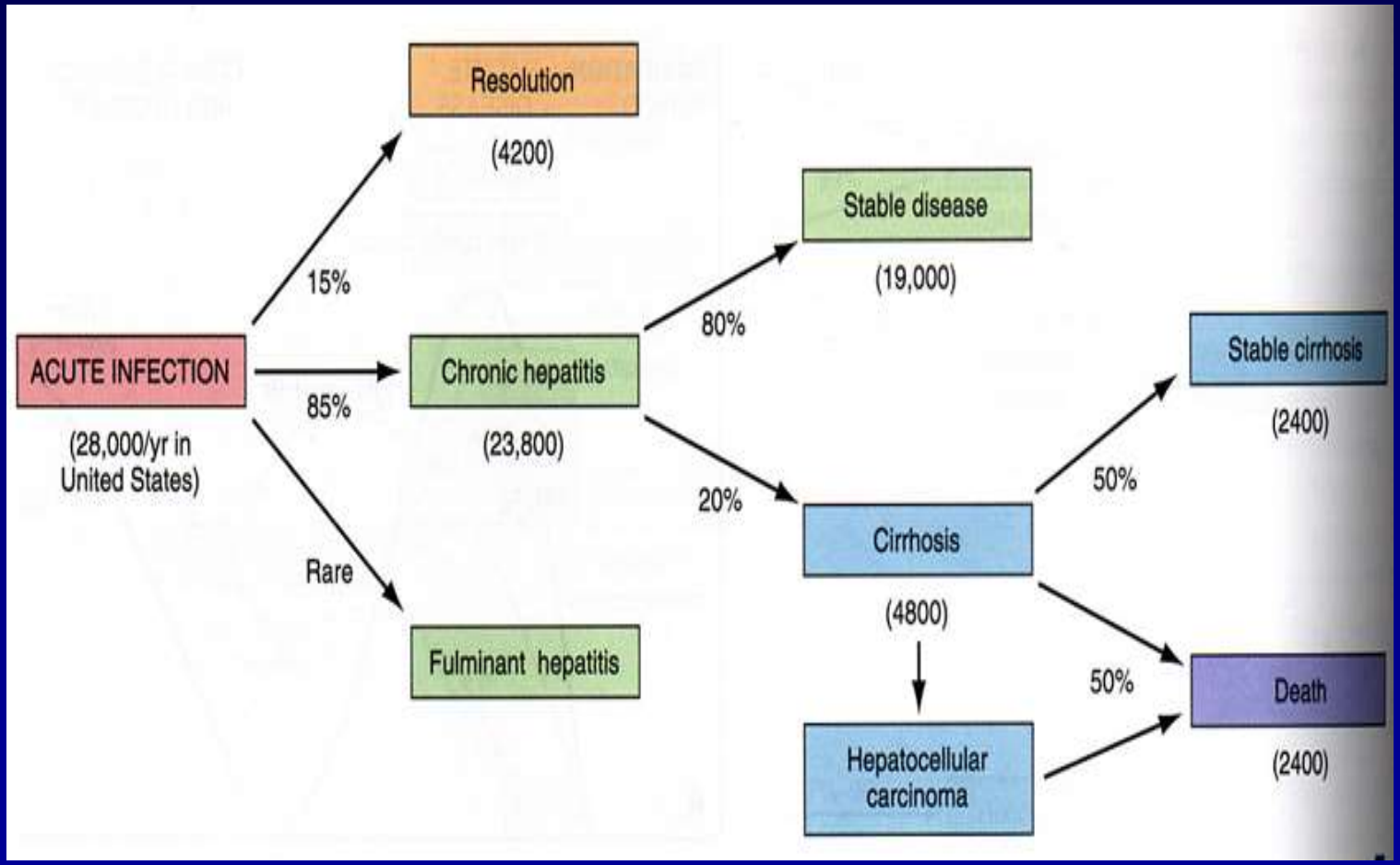
* Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1995.

CDC

Weltweites Prevalenz der HCV



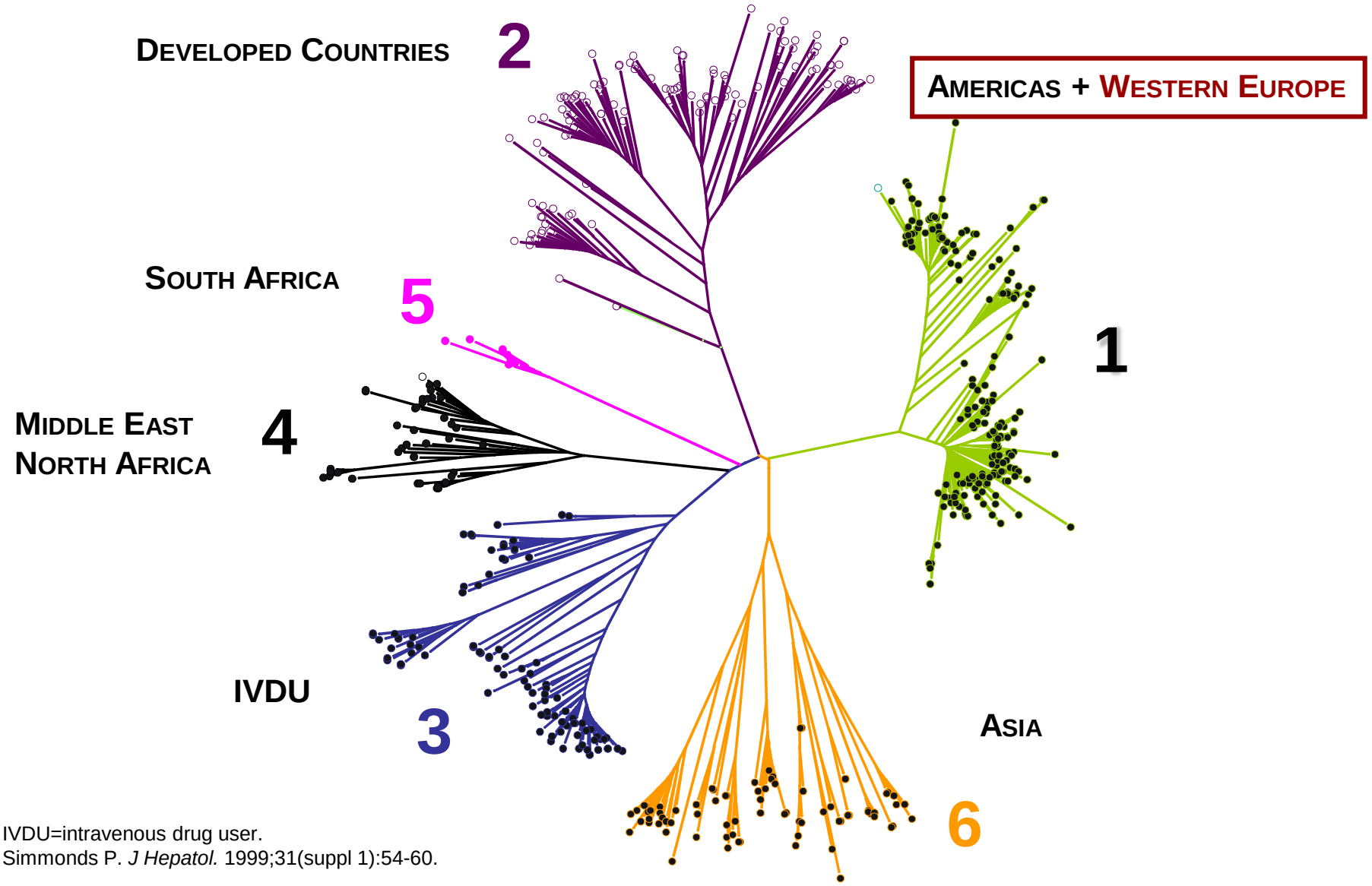
Verlauf der HCV Infektion



Terminologie: Hepatitis C virale genomische Heterogenitat

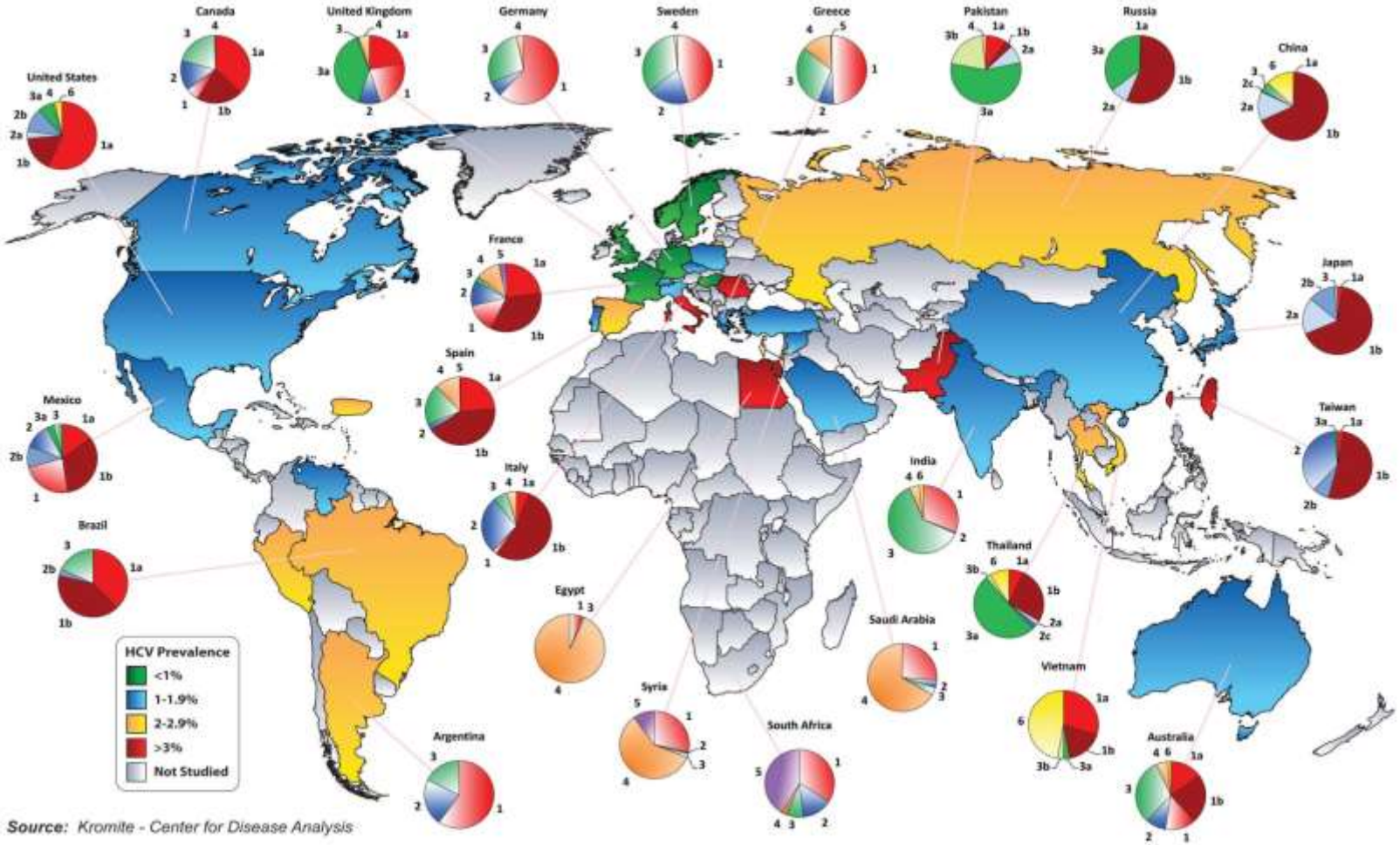
Terminology	Definition	Nucleotide similarity (%)
Genotype (1 - 6)	Major genetic group based on similary of nucleotide sequence	65.7 - 68.9
Subtype (a,b,etc.)	Genetically closely related viruses within of nucleotide sequence	76.9 -80.1
Quasispecies	Complex of genetic variants within individual isolates	90.8 -99

HCV Genotypen



IVDU=intravenous drug user.
Simmonds P. *J Hepatol.* 1999;31(suppl 1):54-60.

Genotype Prevalenz der HCV



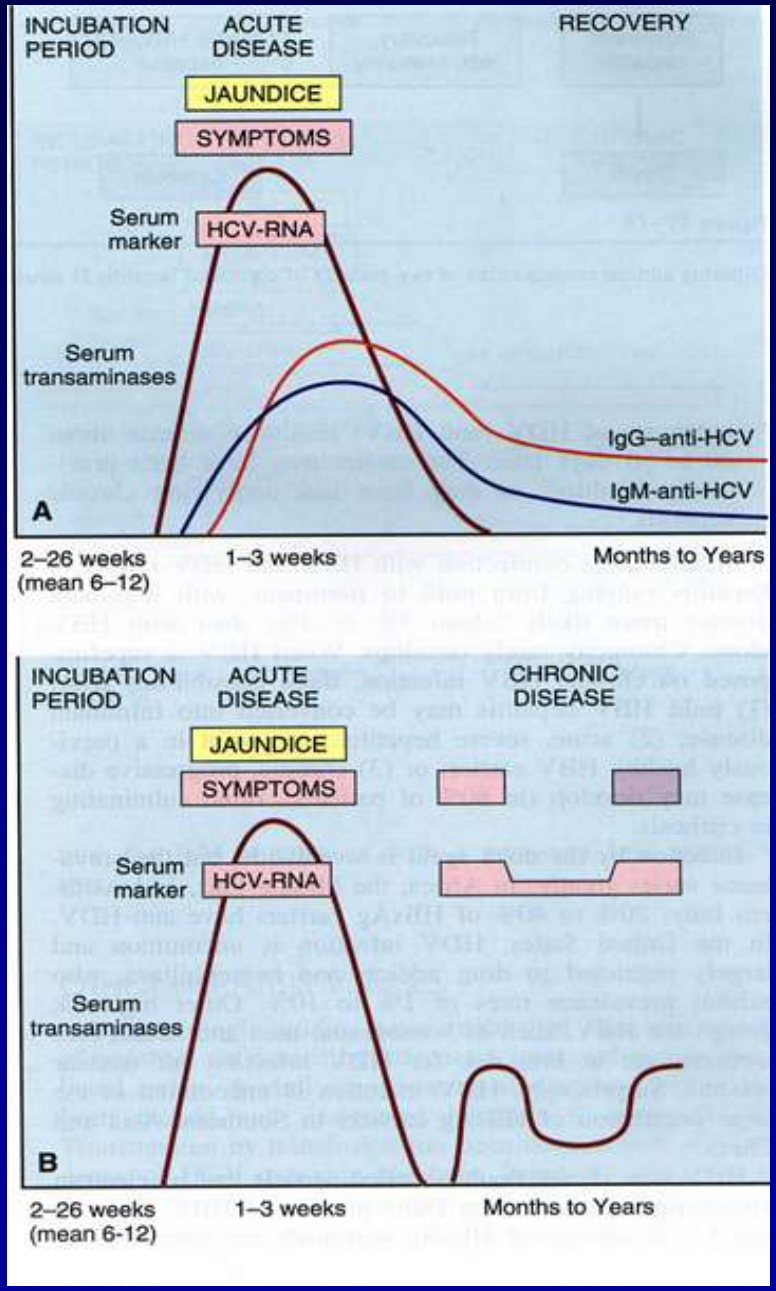
Negro F and Alberti A. The global health burden of hepatitis C virus infection. *Liver International.* 2011: 31(Suppl 2): 1-3.

O'Leary JG, Davis GL. Hepatitis C. *In:* Feldman M, Friedman LS, Brandt LJ, (szerk.). *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management.* 9. kiadás Philadelphia, PA: Saunders, Elsevier Inc.; 2010: 1313-35. oldal

Dienstag JL. Acute Viral Hepatitis. *In*: Longo *Gastroenterology*. … 349-377.

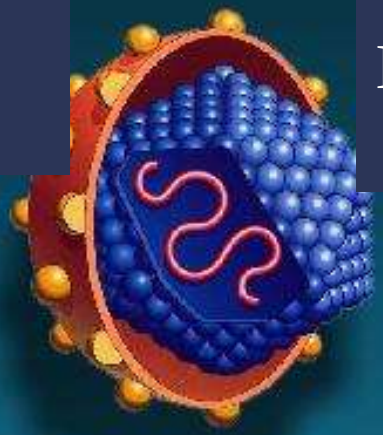
Kamal and Nassar. Hepatitis C Genotype 4: What We Know and What We Don't Yet Know. *Hepatology*. 2008; 47: 1371-83.

Verlauf der HCV Infektion



170-200 Millionen infiziert,
keine Schitzimpfung

Transmission: Blut, Sekrete,
Infizierte med. Gerate



„ Wolf in Schafshaut ”

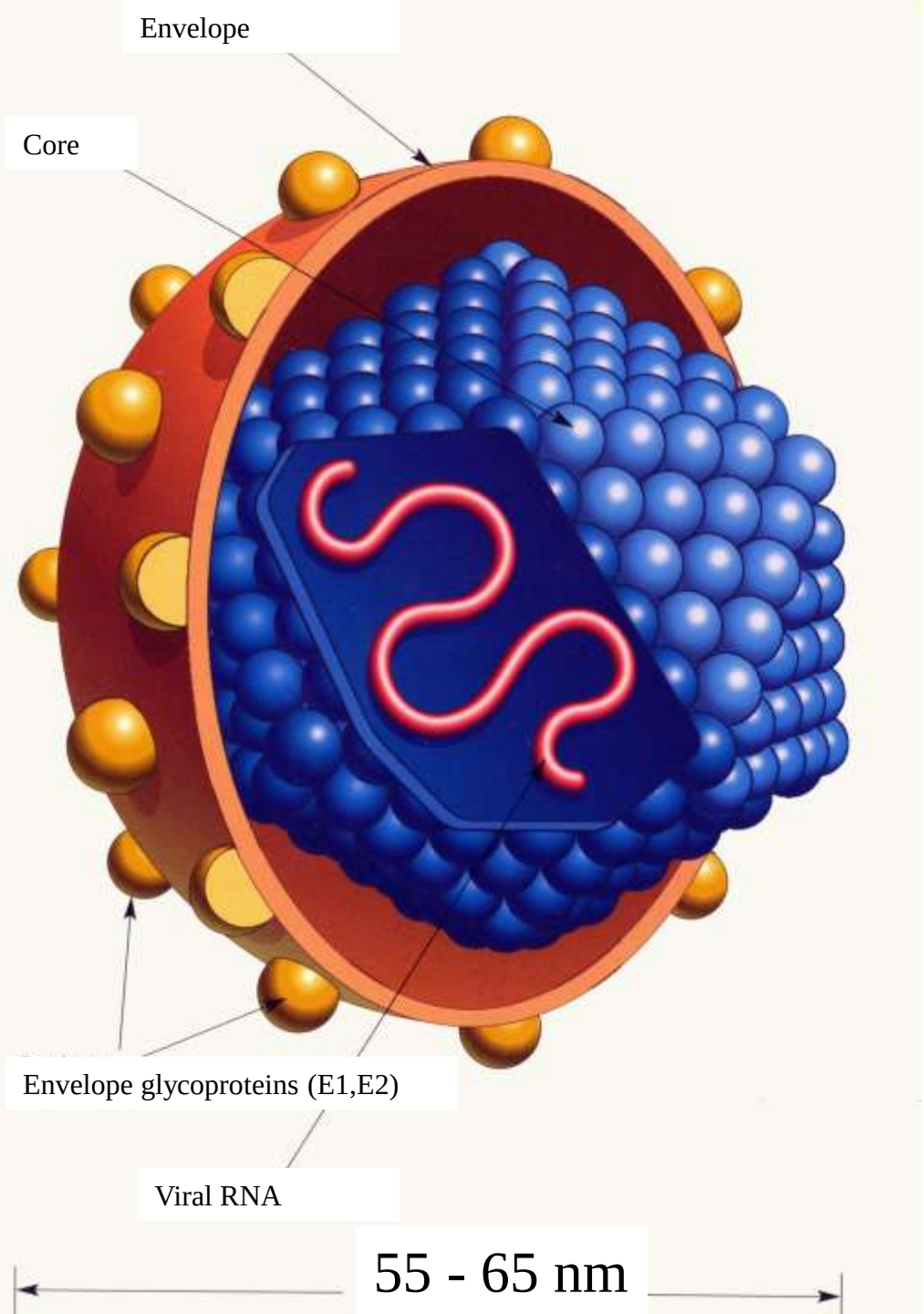
170-200 Millionen infiziert,
keine Schitzimpfung

Transmission: Blut, Sekrete,
Infizierte med. Gerate

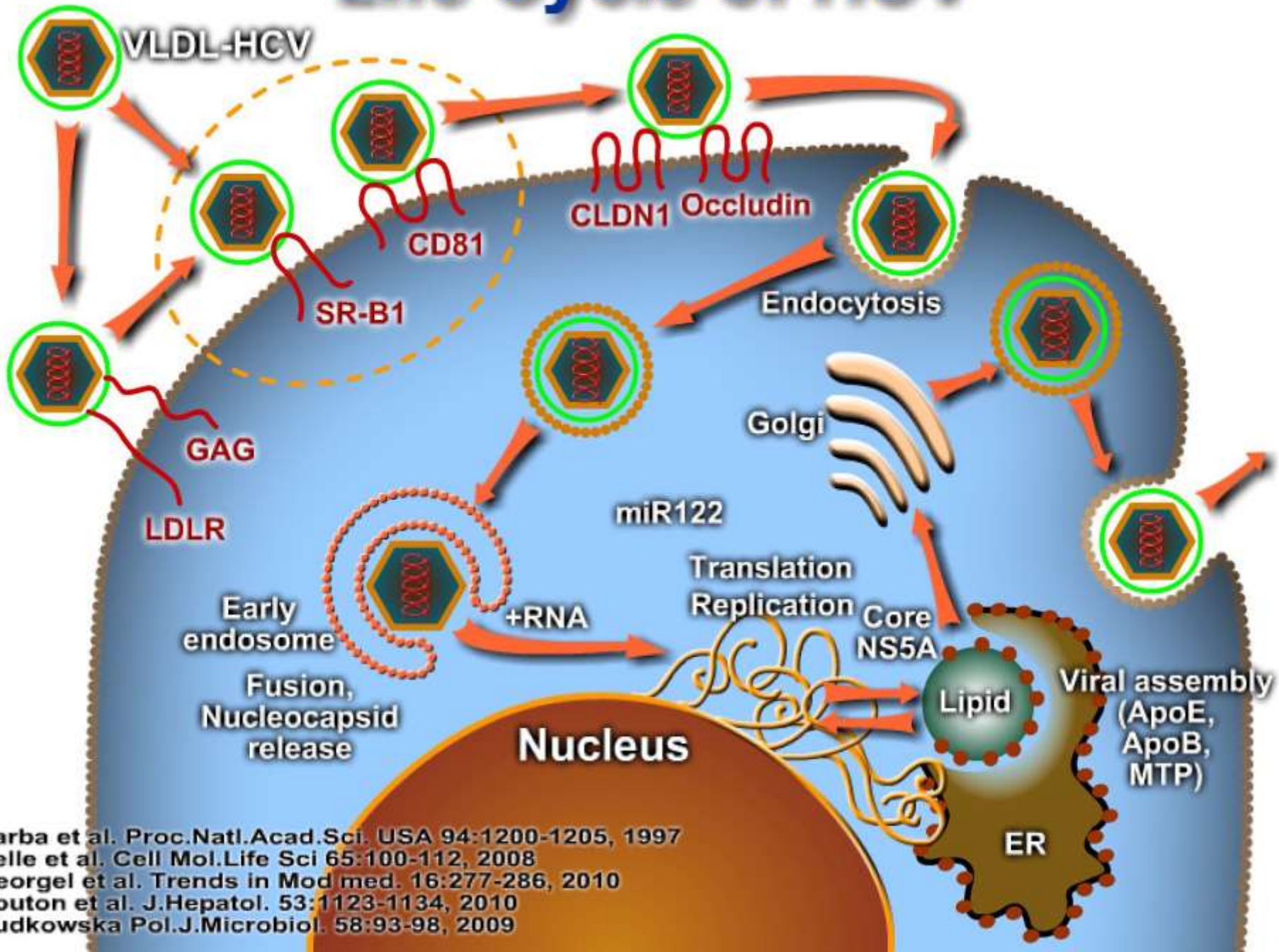
„ Wolf in Schafshaut ”

HCV

(**)

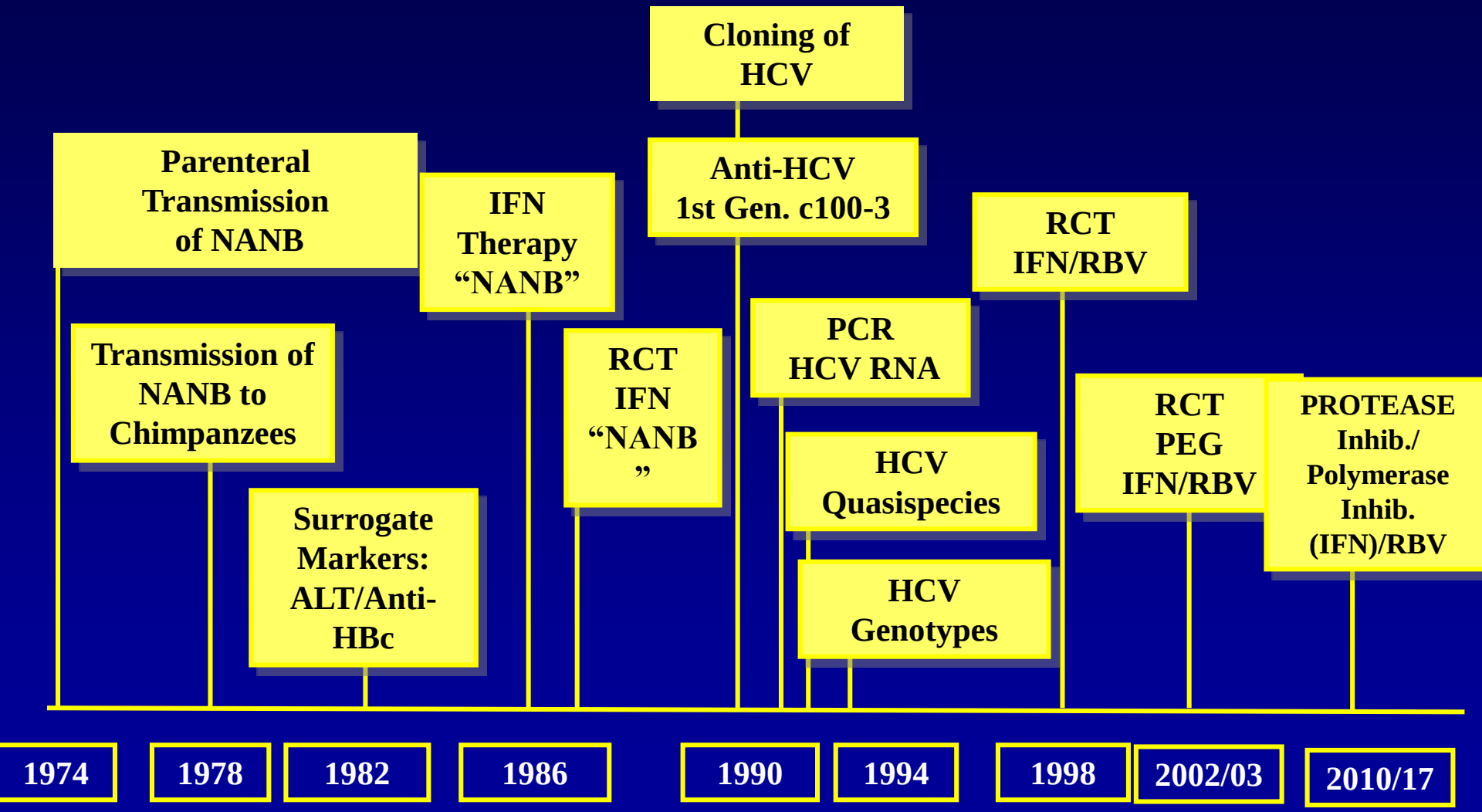

Envelope
Core
Envelope glycoproteins (E1,E2)
Viral RNA
55 - 65 nm

Life Cycle of HCV

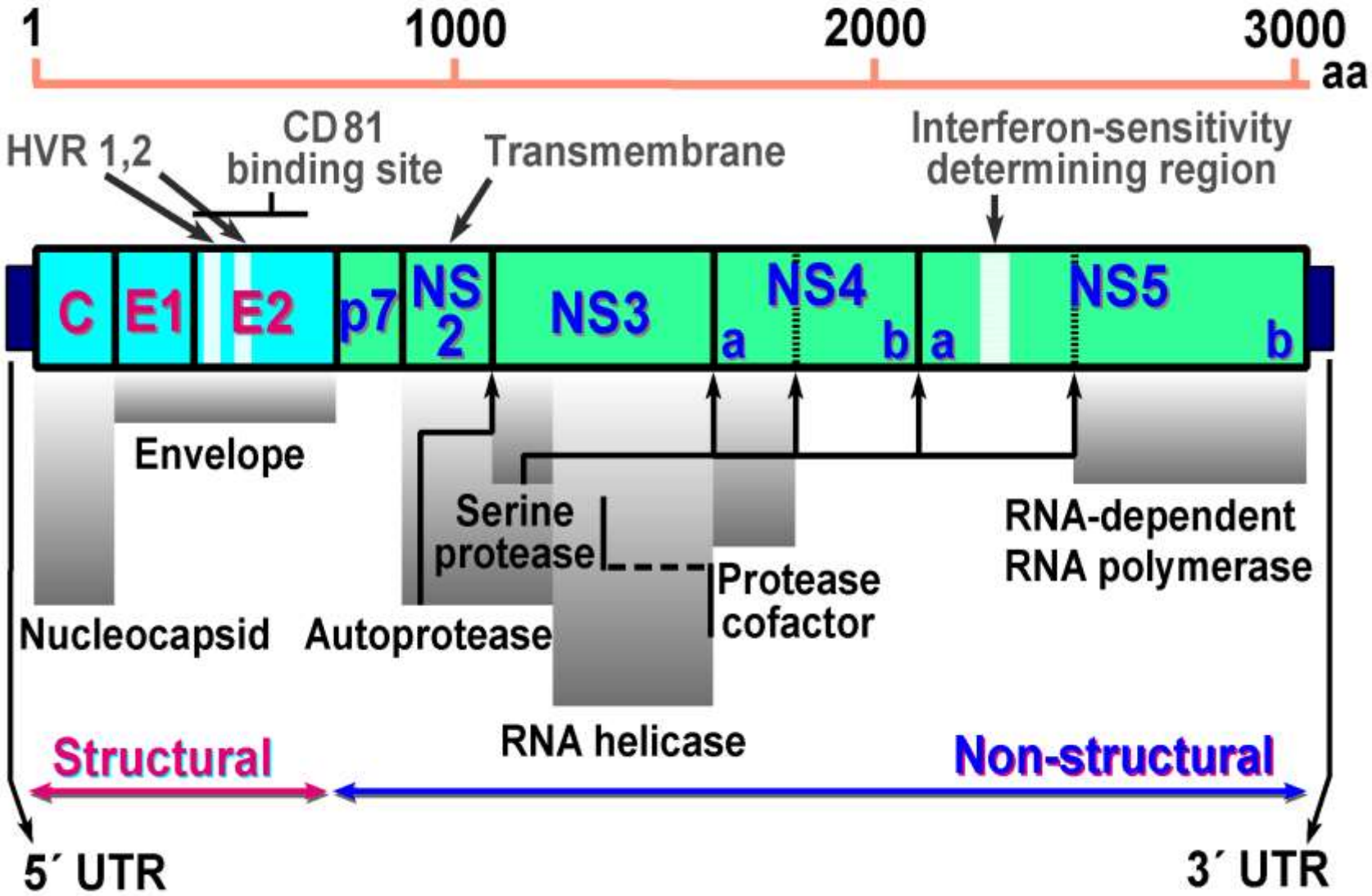


Barba et al. Proc.Natl.Acad.Sci. USA 94:1200-1205, 1997
Helle et al. Cell Mol.Life Sci 65:100-112, 2008
Georgel et al. Trends in Mod med. 16:277-286, 2010
Routon et al. J.Hepatol. 53:1123-1134, 2010
Budkowska Pol.J.Microbiol. 58:93-98, 2009

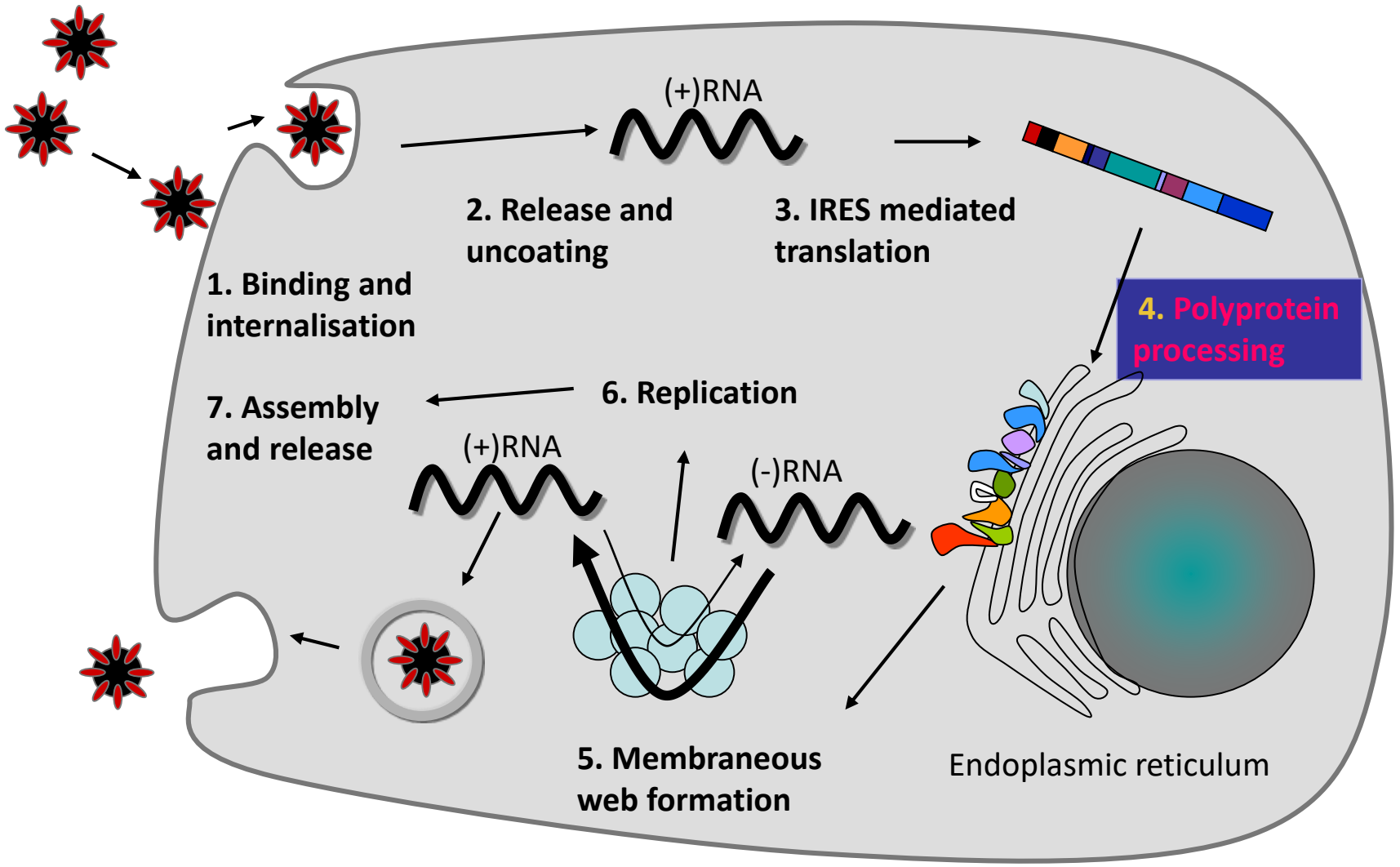
Milestones in Hepatitis C



Structure of HCV genome

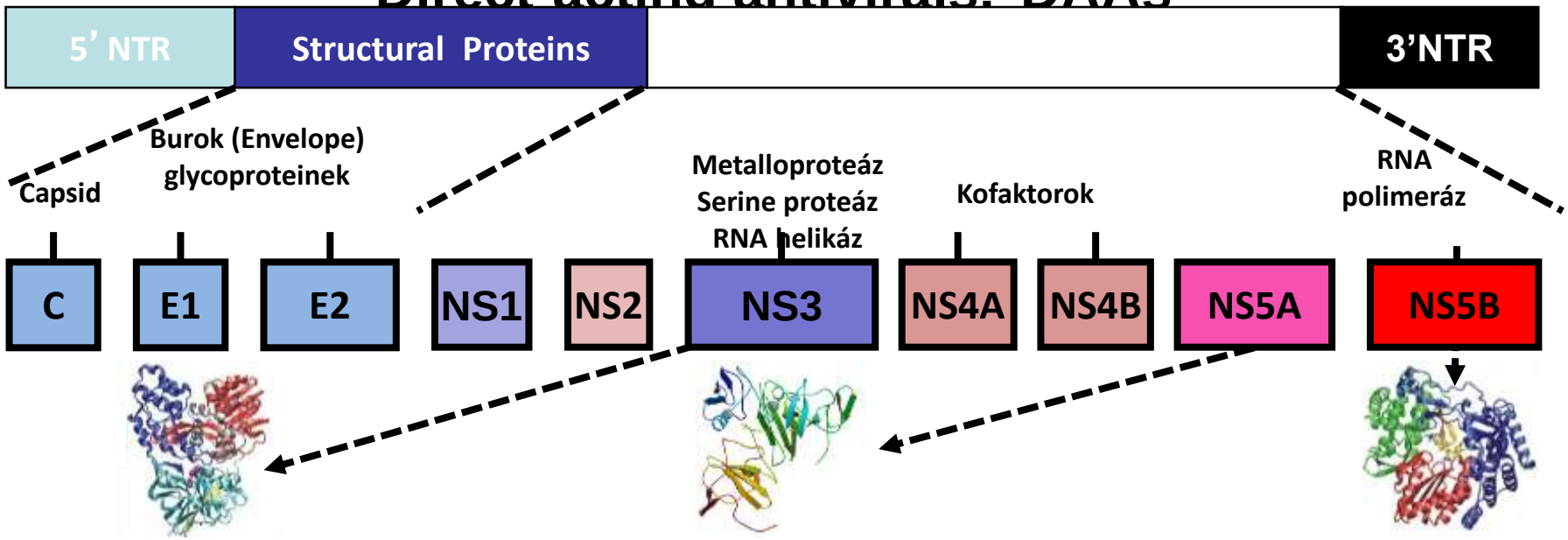


Life Cycle of HCV and Potential Direct Acting Antiviral (DAA) Targets



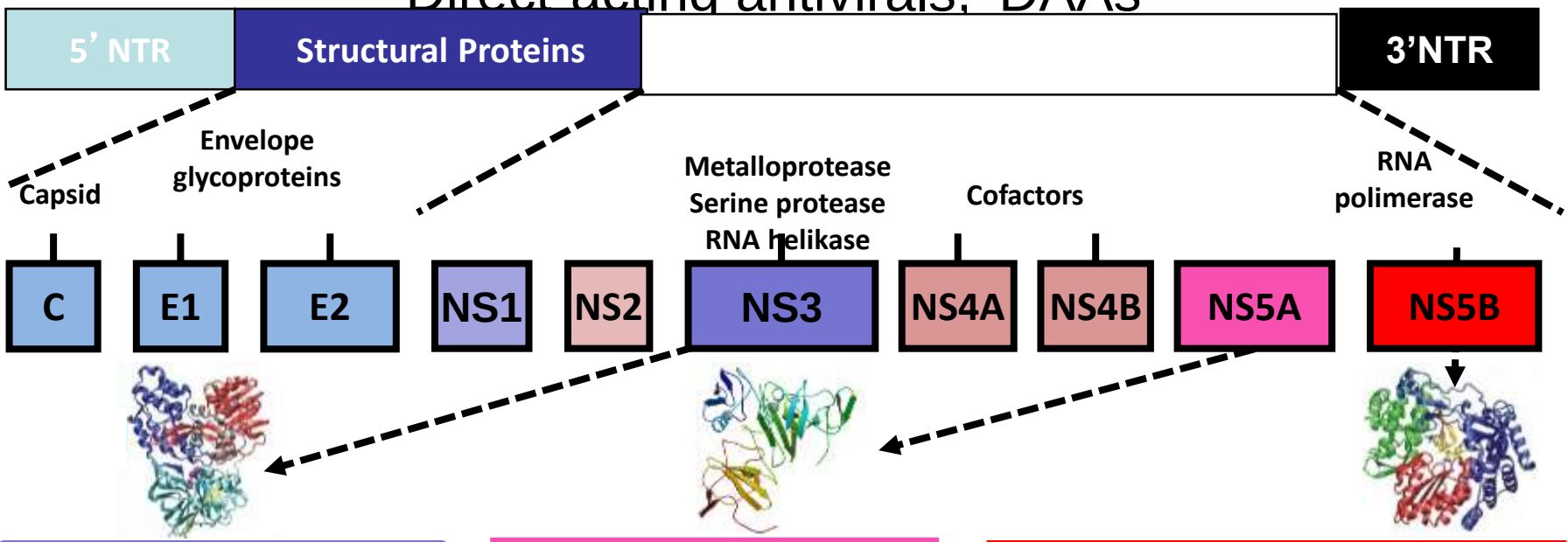
Adapted from Moradpour D, et al. *Nat Rev Microbiol* 2007;5:453-63

Direct-acting antivirals, DAAs



- Adapted from Schinazi R, *et al. Liver Int* 2014; **34** (Suppl 1):69–78.

Direct-acting antivirals, DAAs



Protease inhibitors

Paritaprevir (ABT-450)

Telaprevir

Boceprevir

Simeprevir

Faldaprevir

Asunaprevir

MK-5172

Sovaprevir

ACH-2684

NS5A inhibitors

Ombitasvir

Daclatasvir

Ledipasvir

GS-5816

ACH-3102

PPI-668

GSK-2336805

Samatasvir

MK-8742

Polimerase inhibitors

Nucs

Sofosbuvir

VX-135

IDX-20963

ACH-3422

GS-9669

TMC-647055

Non-Nucs

Dasabuvir

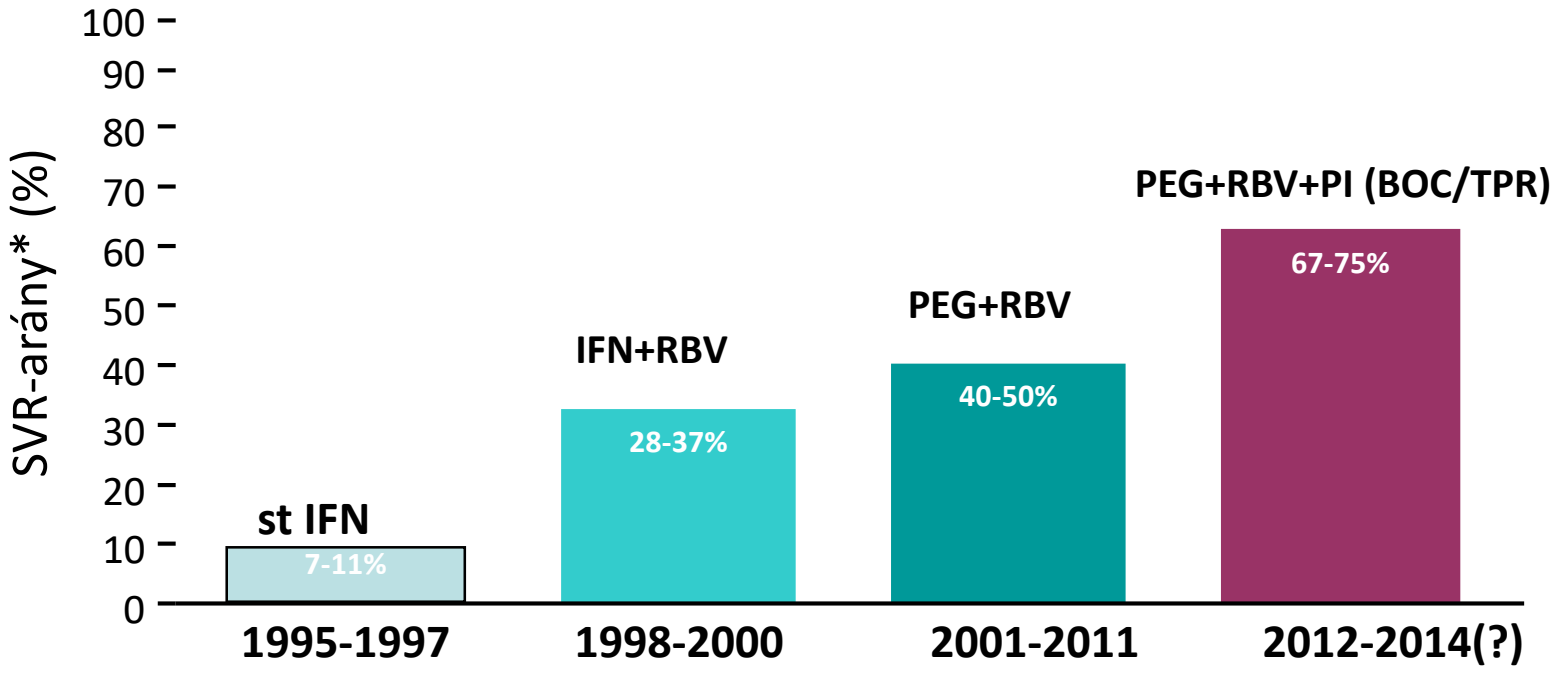
Deleobuvir

BMS-791325

PPI-383

- Adapted from Schinazi R, *et al. Liver Int* 2014; **34** (Suppl 1):69–78.

Steps in treatment of chronic hepatitis C
Naiv patients



*G1 HCV fertőzött, terápianaiv betegek

Hepatology Snapshot

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

58:1045-46, 2013

Hepatitis E virus infection: Multiple faces of an underestimated problem

Sven Pischke, Heiner Wedemeyer*

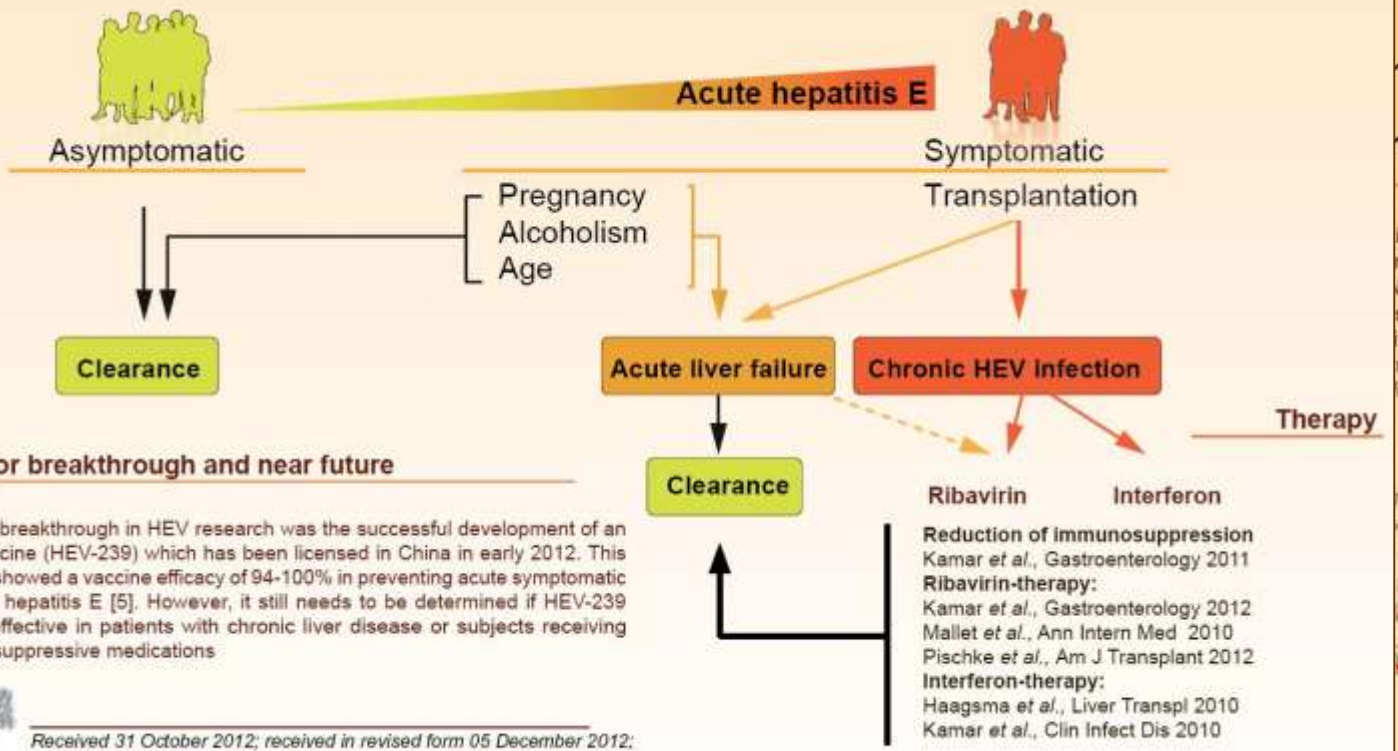
Medizinische Hochschule Hannover, Hannover, Germany

Key facts

- HEV is a relevant clinical problem also in industrialized countries
- In addition to waterborne infections, zoonotic and blood-borne

Transmission

Clinical course of exposed individuals



Diagnosis

is E is frequently diagnosed by the
n of HEV antibodies followed by testing for
NA in blood or stool. However, serological
show a wide variability in sensitivity and
ty and HEV antibodies may be negative
nocompromised individuals. Thus, direct
or HEV RNA is advised in all patients [1]

Therapy

Ribavirin **Interferon**

Reduction of immunosuppression
Kamar *et al.*, Gastroenterology 2011
Ribavirin-therapy:
Kamar *et al.*, Gastroenterology 2012
Mallet *et al.*, Ann Intern Med 2010
Pischke *et al.*, Am J Transplant 2012
Interferon-therapy:
Haagsma *et al.*, Liver Transpl 2010
Kamar *et al.*, Clin Infect Dis 2010

Major breakthrough and near future

A major breakthrough in HEV research was the successful development of an HEV vaccine (HEV-239) which has been licensed in China in early 2012. This vaccine showed a vaccine efficacy of 94-100% in preventing acute symptomatic cases of hepatitis E [5]. However, it still needs to be determined if HEV-239 is also effective in patients with chronic liver disease or subjects receiving immunosuppressive medications

reas where >25%
sporadic non-ABC hepatitis
due to hepatitis E virus

Received 31 October 2012; received in revised form 05 December 2012; accepted 10 December 2012

ELSEVIER

Journal of Hepatology **2013** vol 58 | 1045–1046

HEV: HISTORY

H.Alter HepDart, Dec.2013.

- 1978: Water-borne epidemic in Kashmir caused 20,000 icteric cases; 700 FH; 600 deaths; not HAV
- 1980: Epidemic hepatitis among Russian soldiers in Afghanistan; not HAV related
- 1983: Russian volunteer swallows fecal extract from 9 acute cases in the Afghan epidemic and recovers 27-30nm VLP from his acute phase stool (Balayan)
- CDC recovers identical VLP from macaques inoculated with acute phase stool; serial passage
- 1990: Bile from cyno macaques used in differential

How Might Non-Swine Handlers be Exposed to Contaminated Pork?
[Caution: This slide is not for the queasy]

- Gastro Elitism Movement: wild boar pappardelli, pigs feet Milanese
- Figatelli (raw pork sausage) : favorite in Southern France
- Liver slime from pig poop is pooled and used to irrigate soil and plants

  (don't forget to eat your veggies)
- Dunkin Donuts sells pork donuts in China
- Scrapple made from pig heads and liver
- 11% of raw pig liver in US markets tested HEV RNA+
- USDA: cook pork meat to 145F; organs to 160F

H.Alter HepDart, Dec. 2013

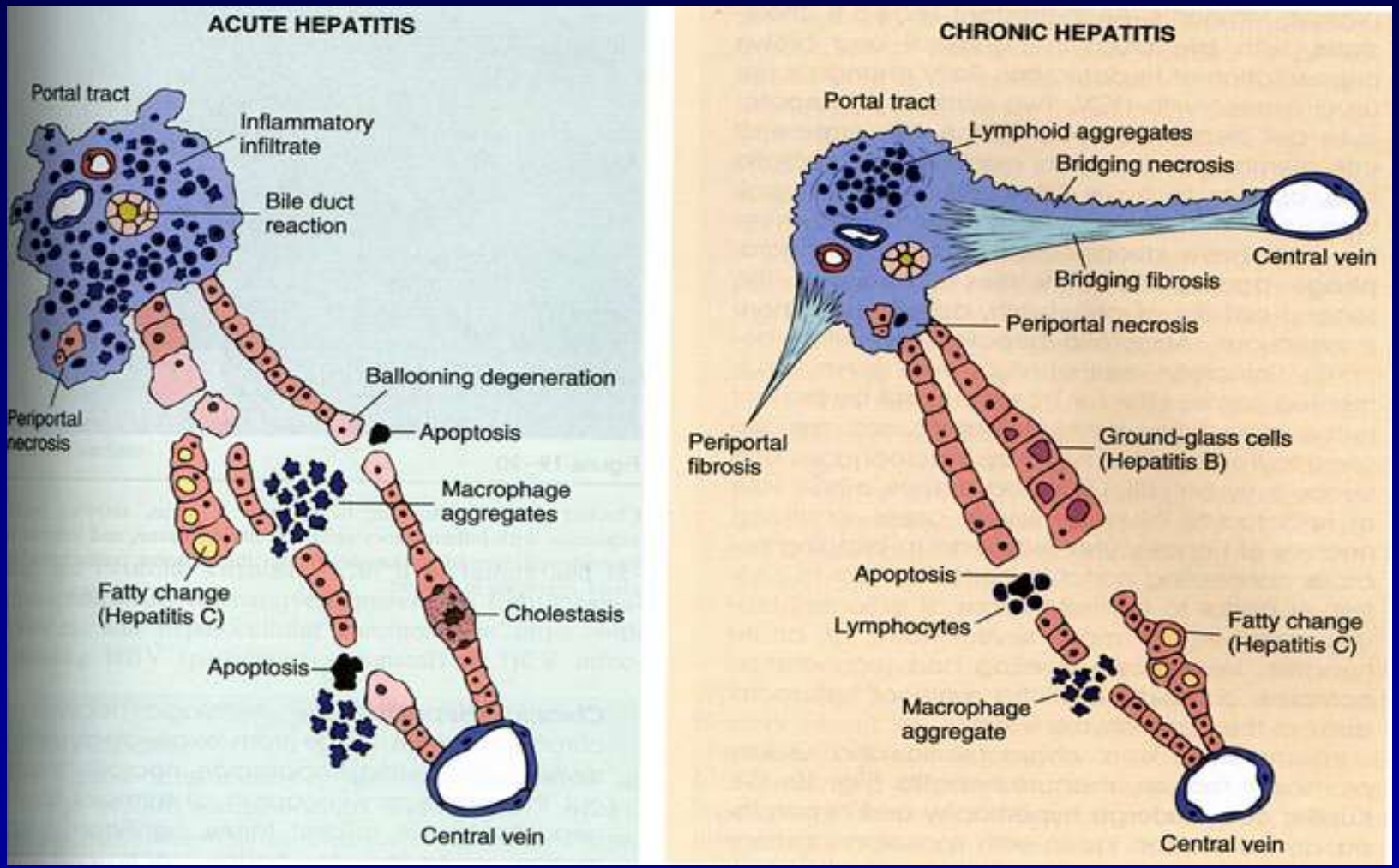
Leberreaktionen

- Intrazelluläre Akkumulationen
- Degenerative Zellläsionen
- Regeneration
- Fibrosen
- *Leberzirrhose*
- *Portalfeldkonfiguration*

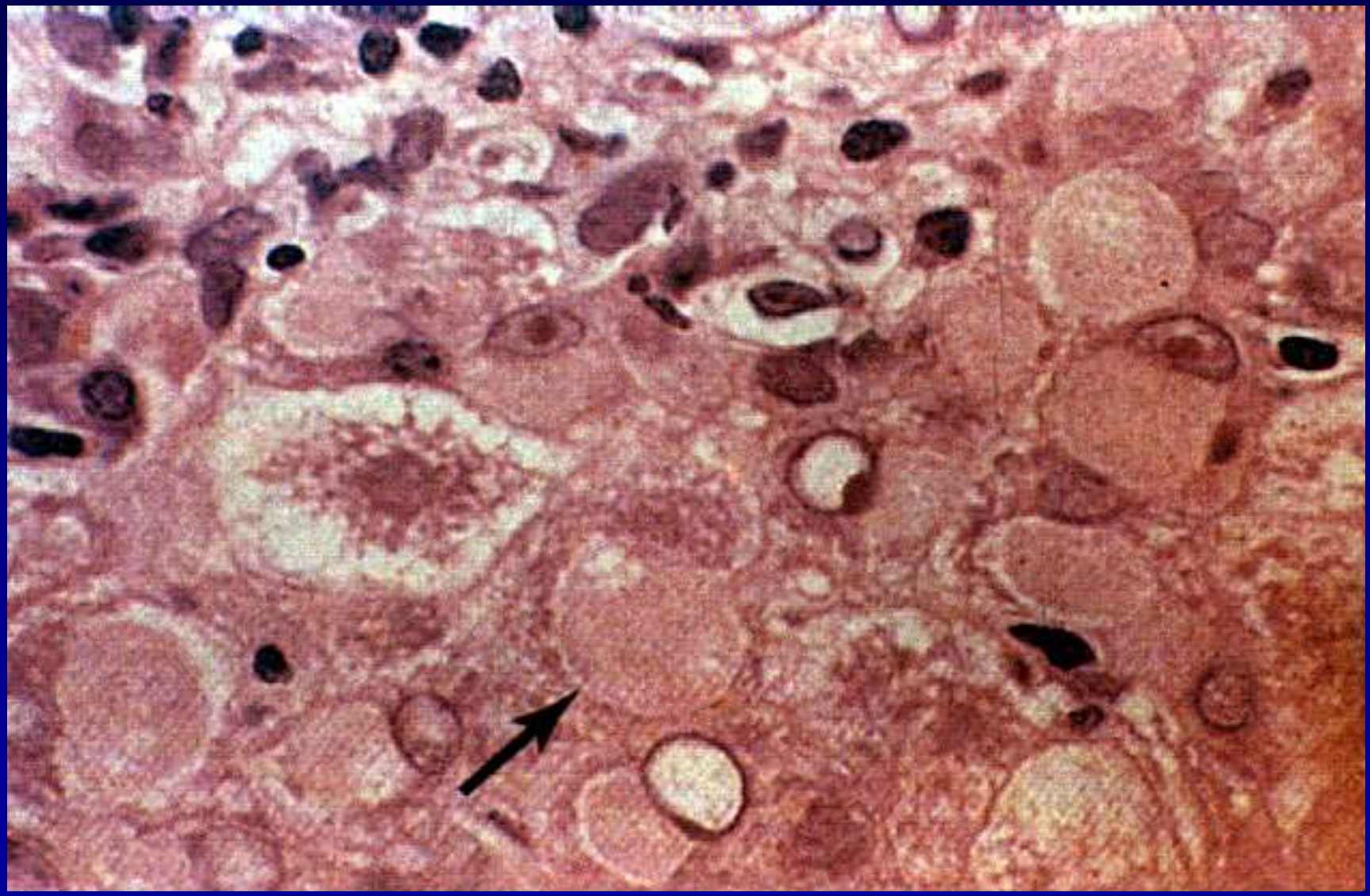
Akute Hepatitis (AH) histologisch

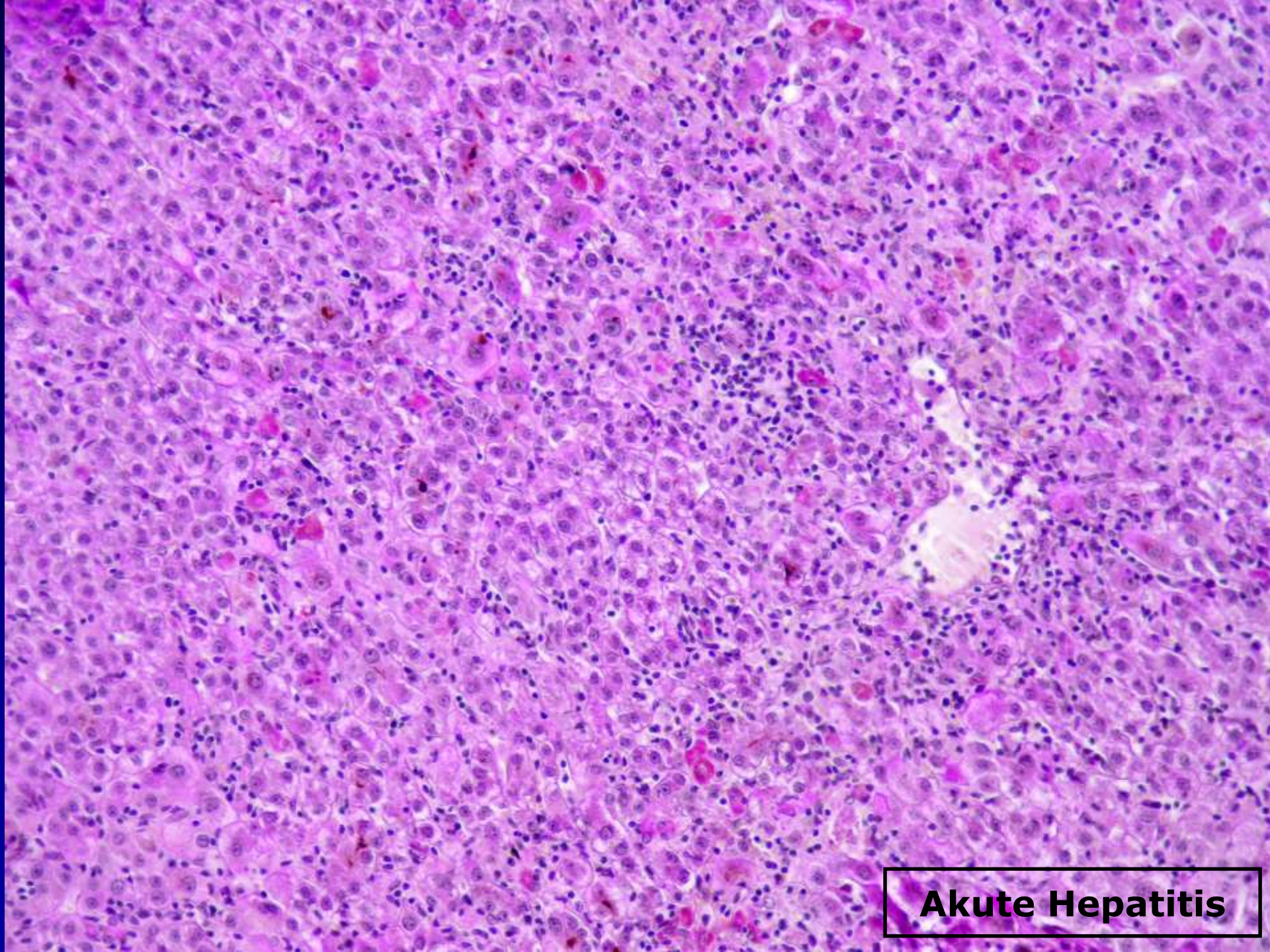
- AH mit Einzelzellnekrosen (klassische)
- AH mit konfluirenden Brückennekrosen
- AH mit panlobulären Nekrosen (fulminante)
- klassische AH mit Piecemeal-Nekrosen (Mottenfraßnekrose – Grenzlamelle ist durchbrochen) (Chronifizierung!)
- Adulte Riesenzellhepatitis

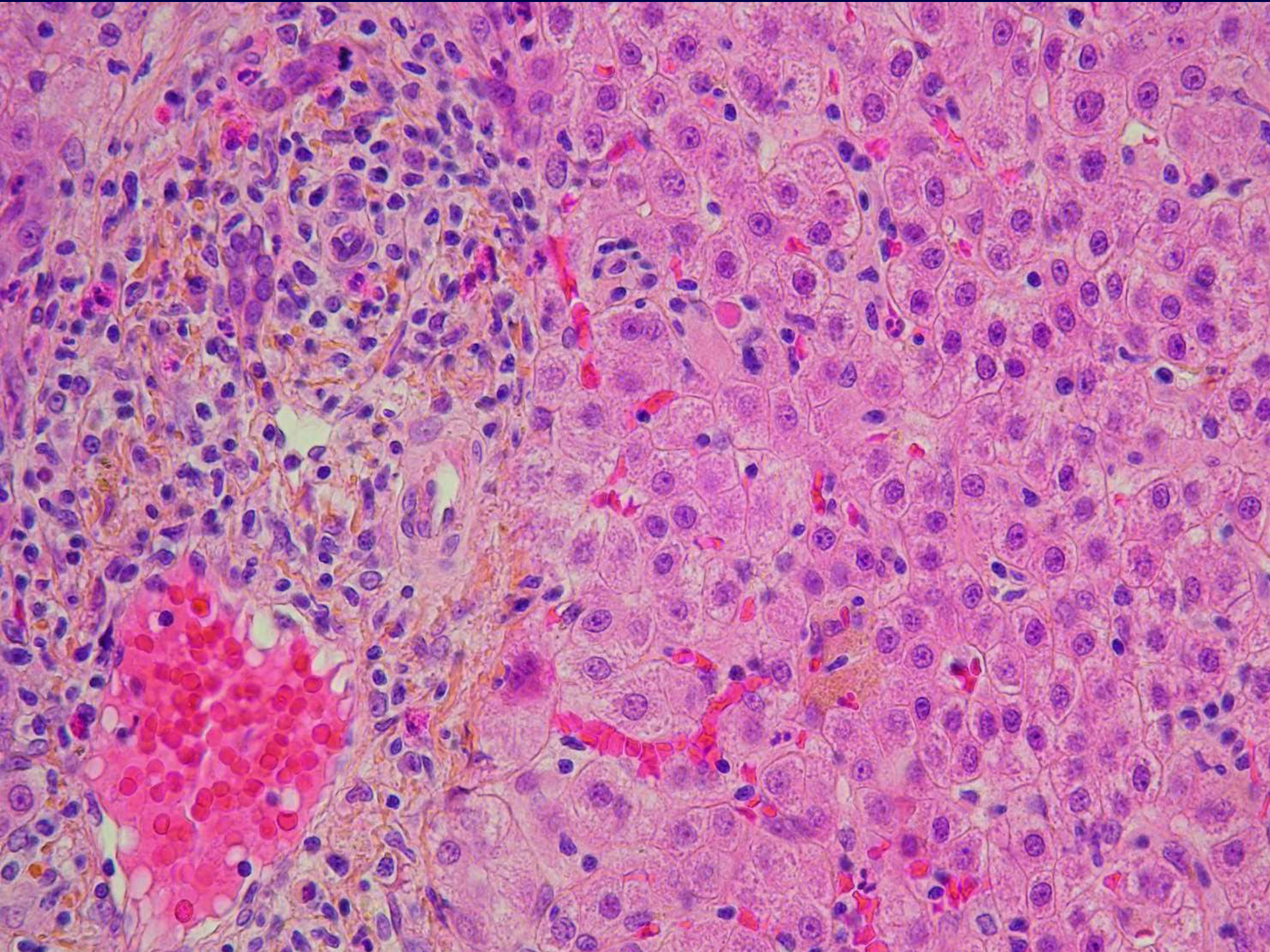
Hepatitiden

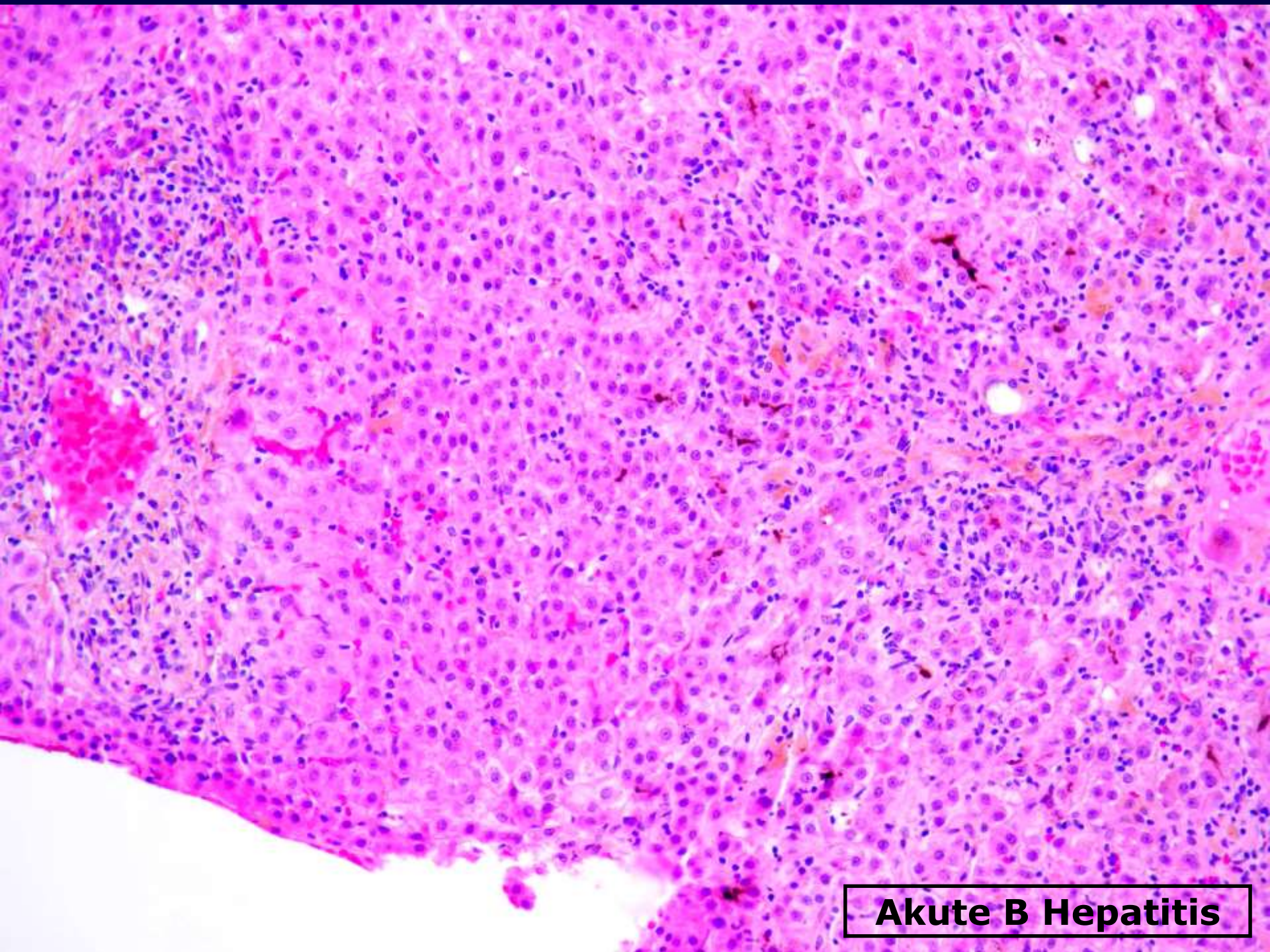


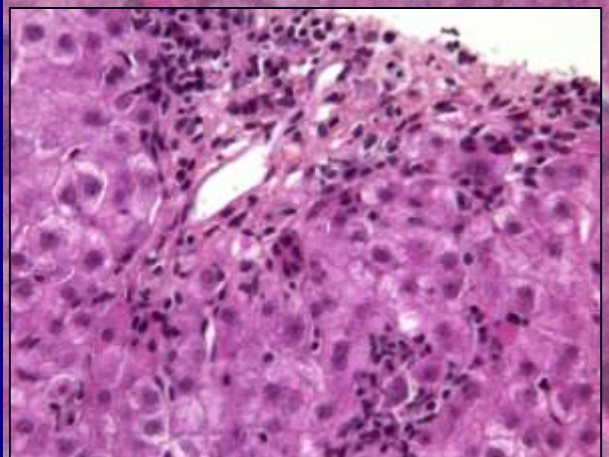
Hepatitiden



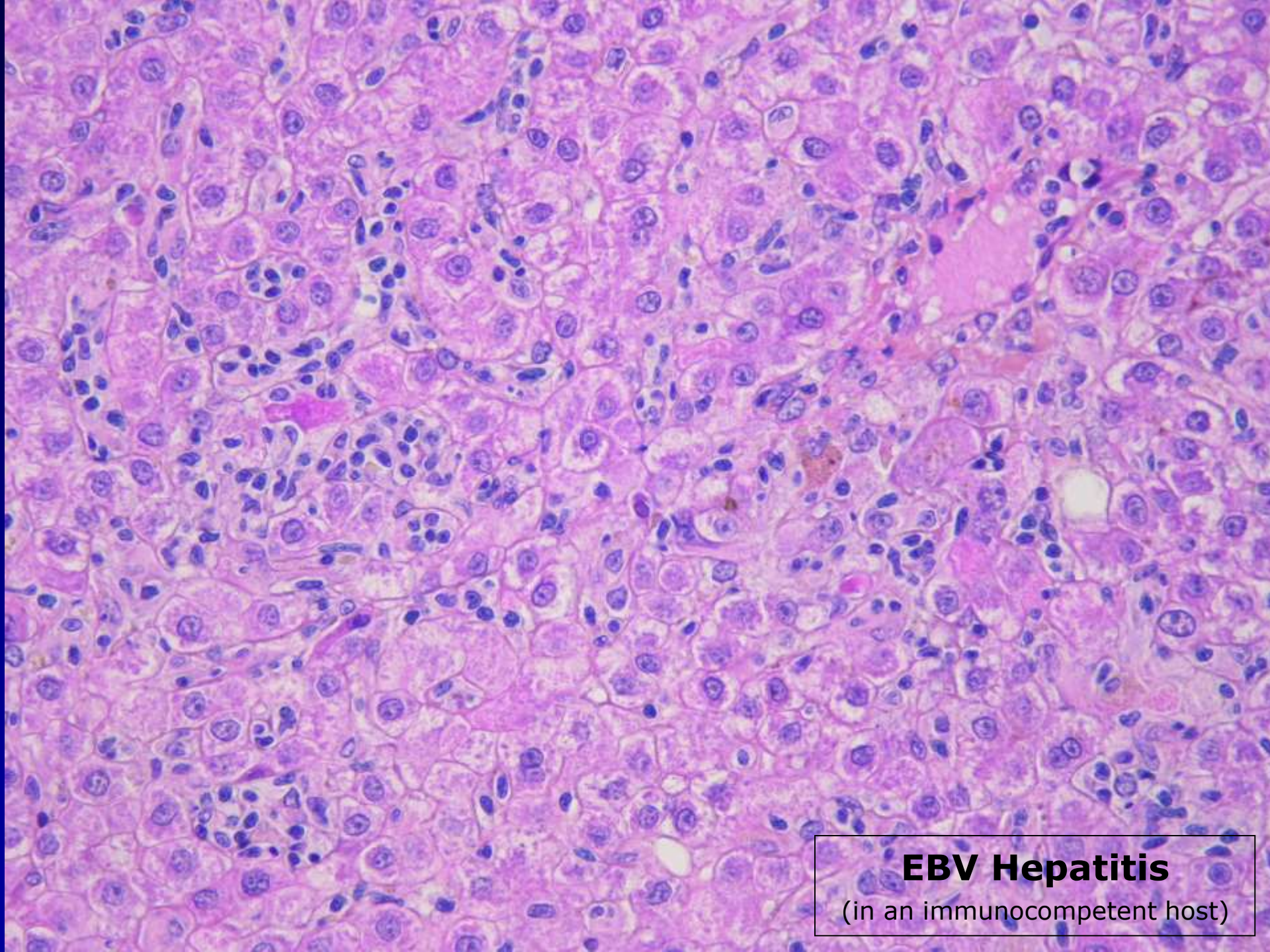

Akute Hepatitis

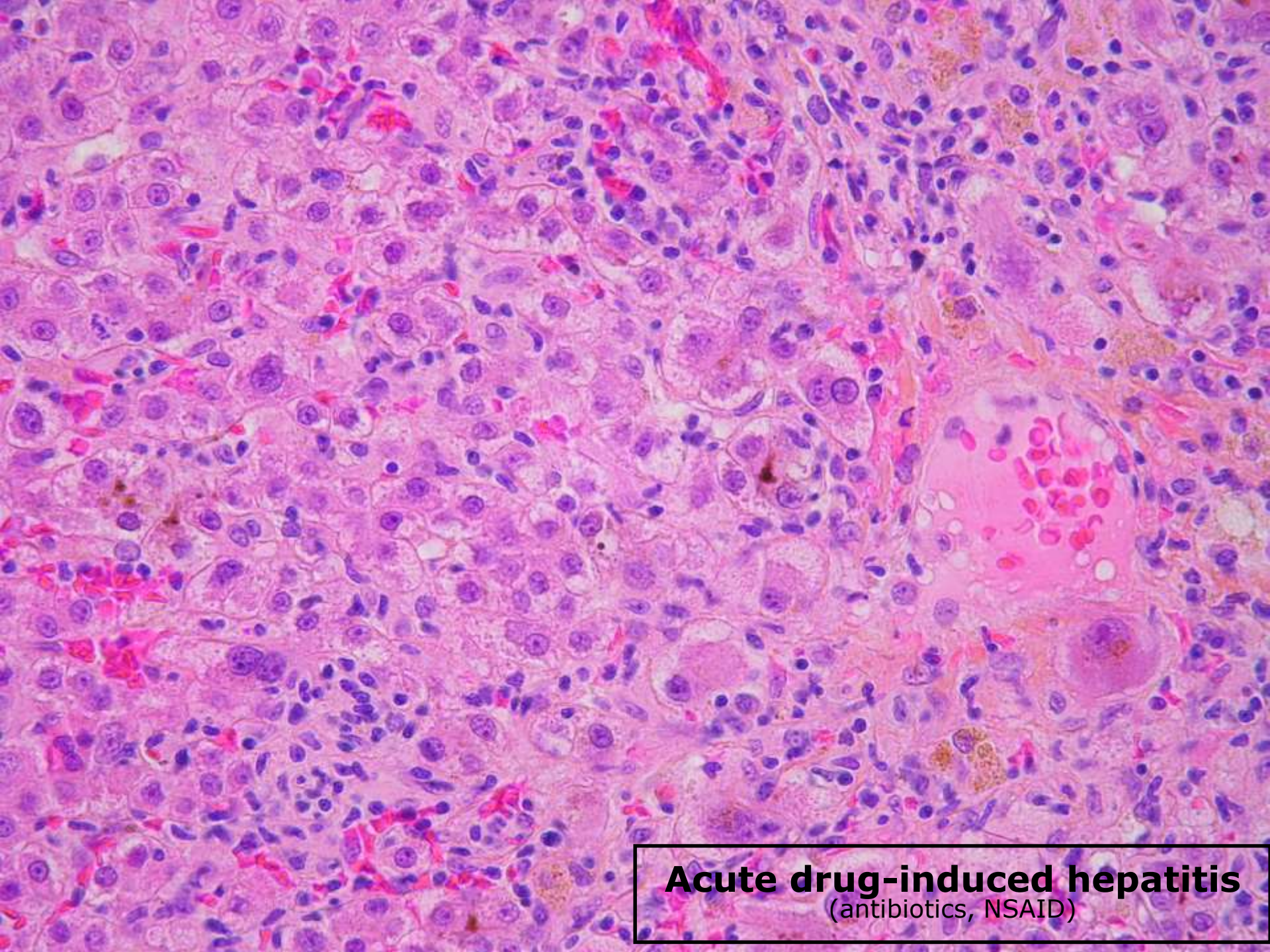


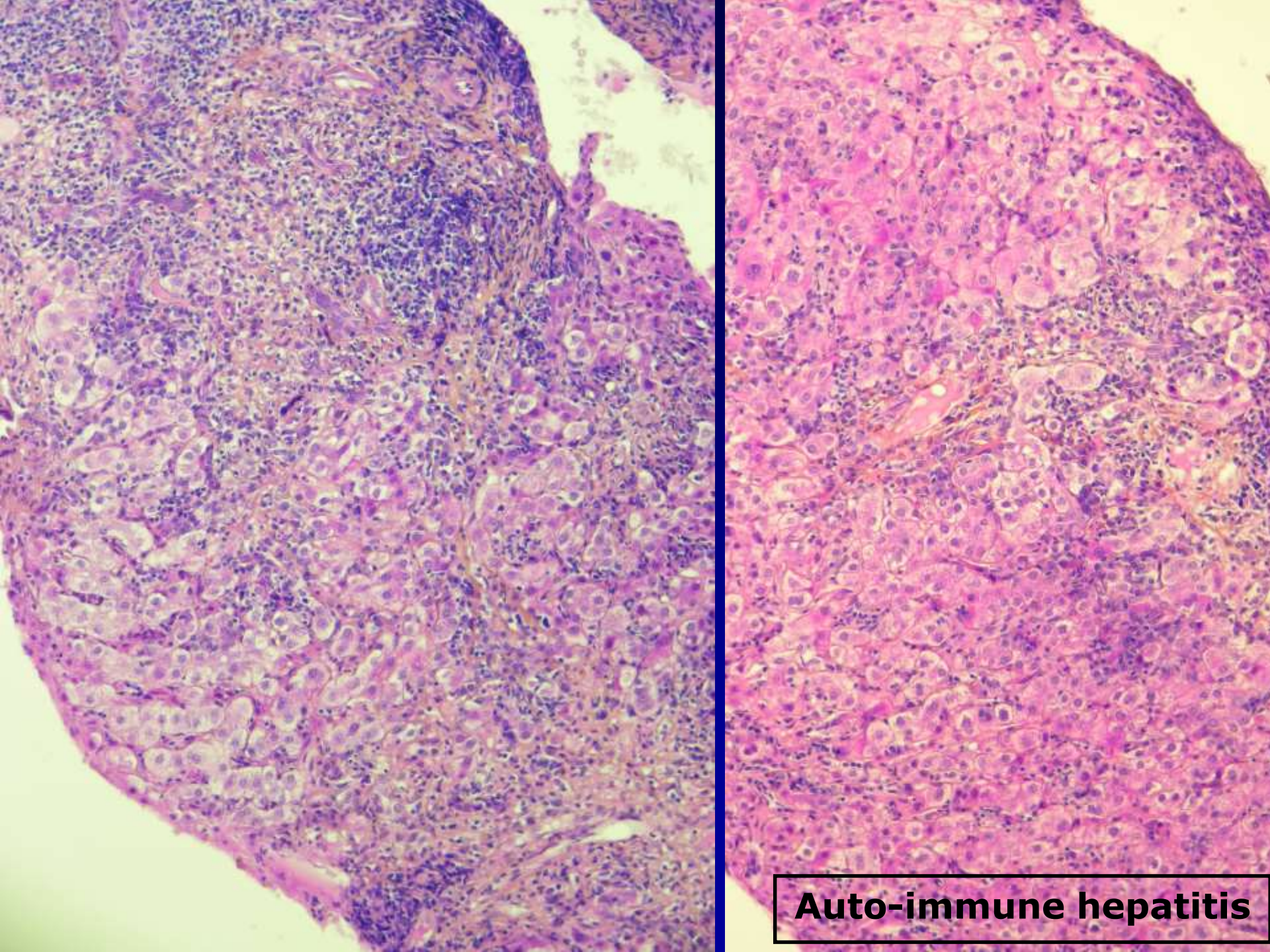

Akute B Hepatitis

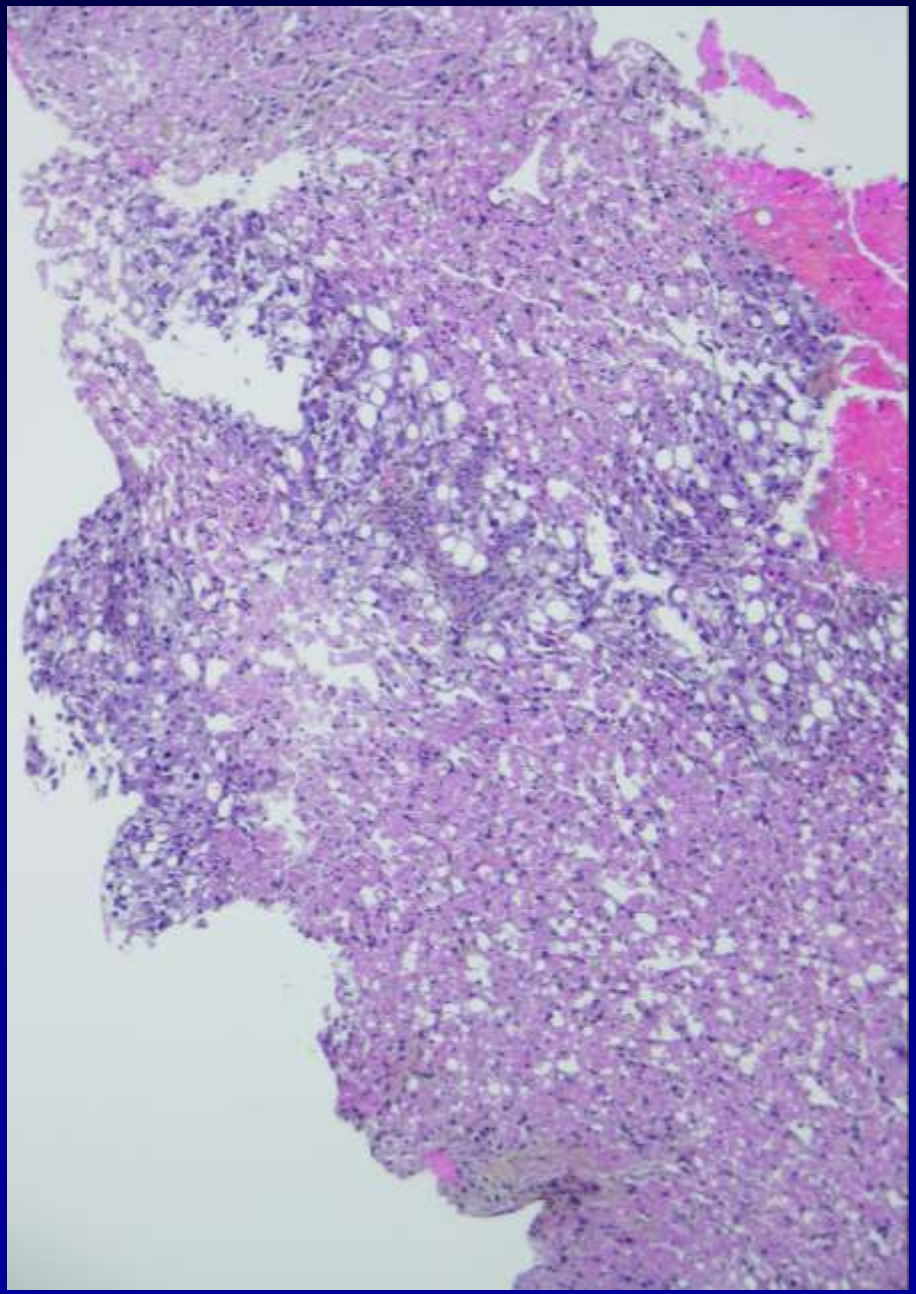


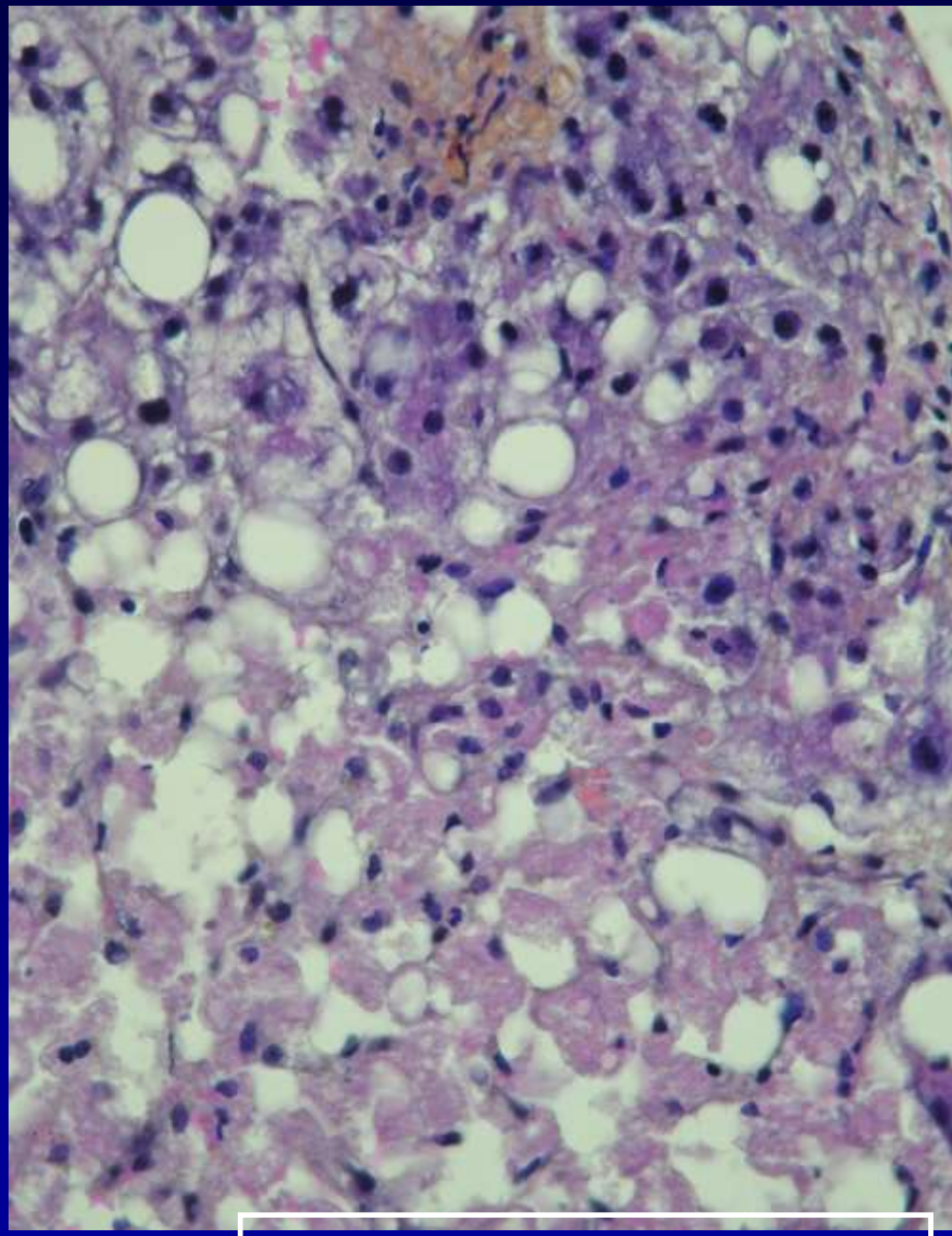
Akute C Hepatitis


EBV Hepatitis
(in an immunocompetent host)

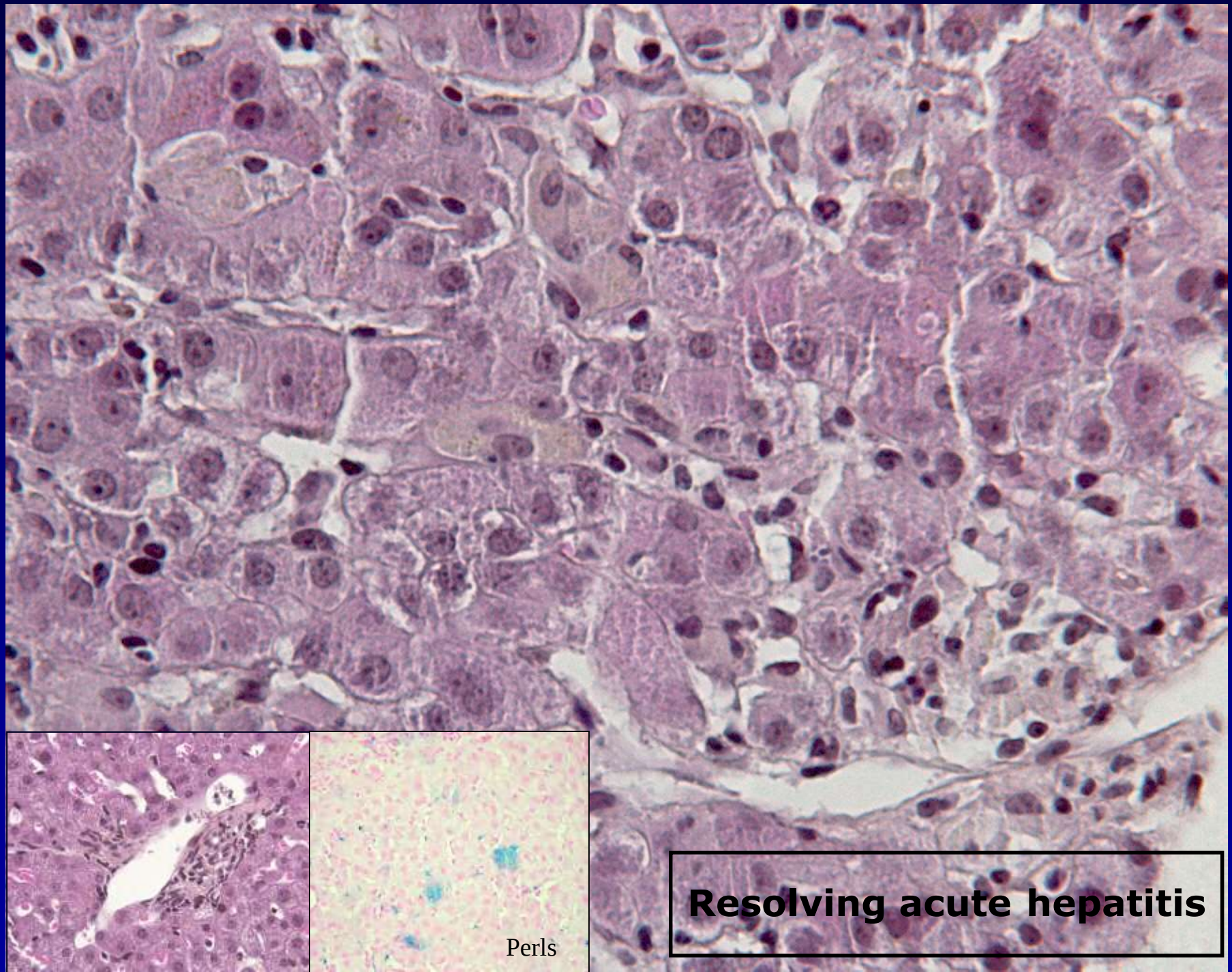

Acute drug-induced hepatitis
(antibiotics, NSAID)


Auto-immune hepatitis





Sub-massive hepatitis


Perls
Resolving acute hepatitis

Hepatitiden

- **Lobuläre Hepatitis: Einzelzellnekrosen, Councilman-Körperchen (Apoptose), Brückennekrosen, Mottenfassnekrosen**

- **Panlobuläre Hepatitis: Nekrosen in dem gesamten Läppchen = gelbe Leberdystrophie**

- **Chronische Formen:**

Chronisch persistierende Hepatitis

Chronisch aggressive Hepatitis

Chronische Hepatitis

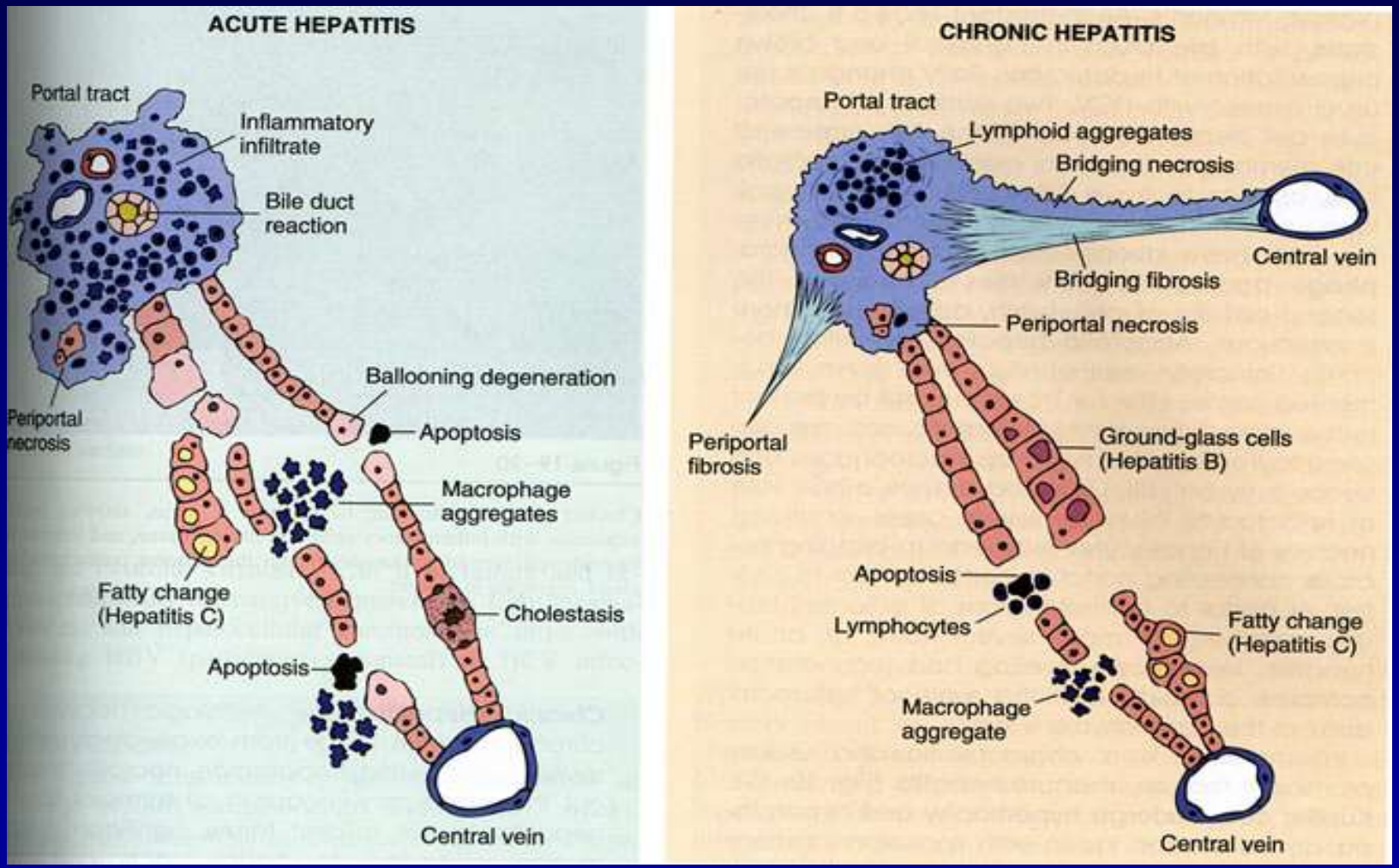
Ätiologie

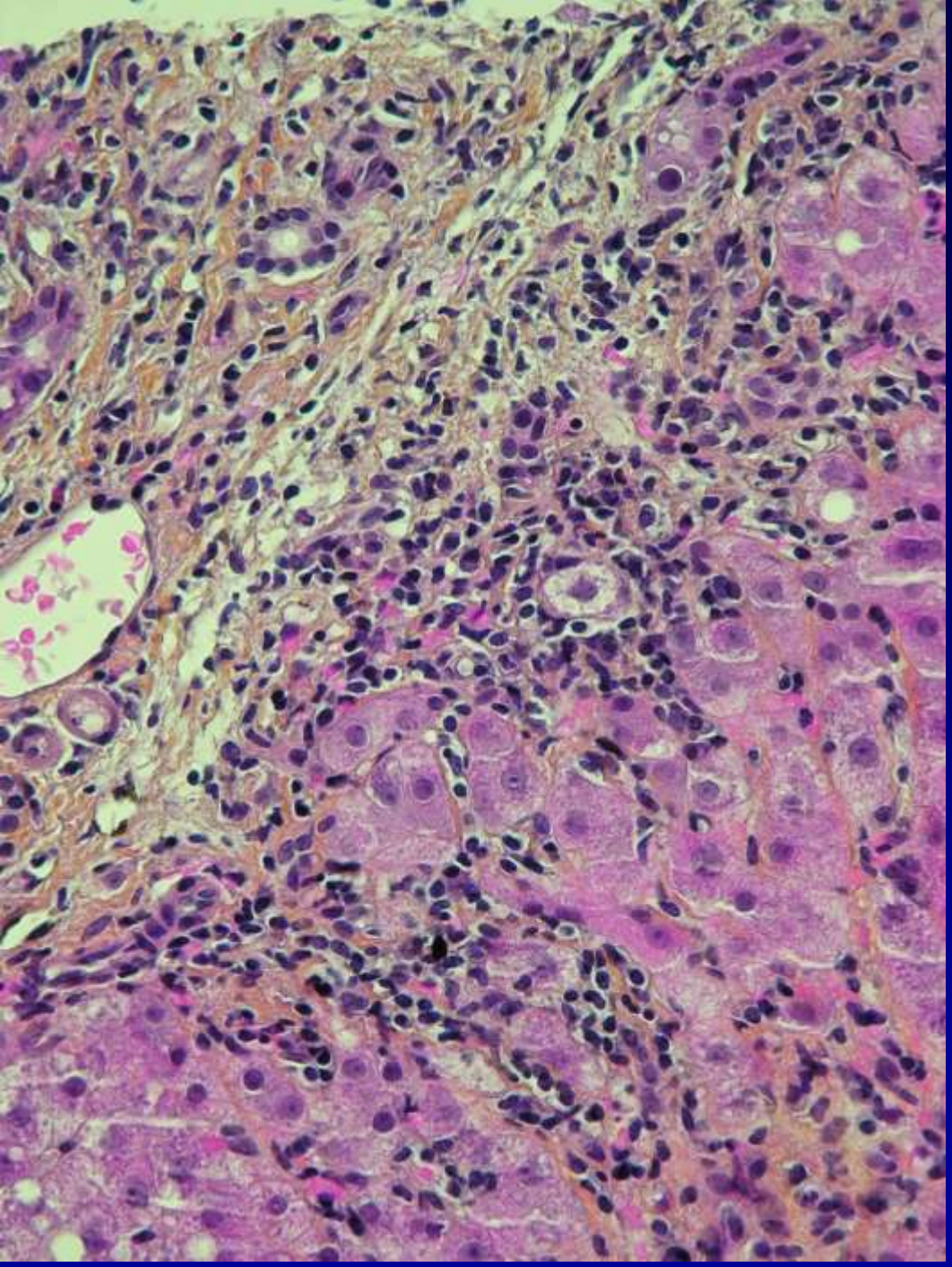
- virale
- autoagressive
- medikamentös-toxische
- metabole Formen
- kryptogene

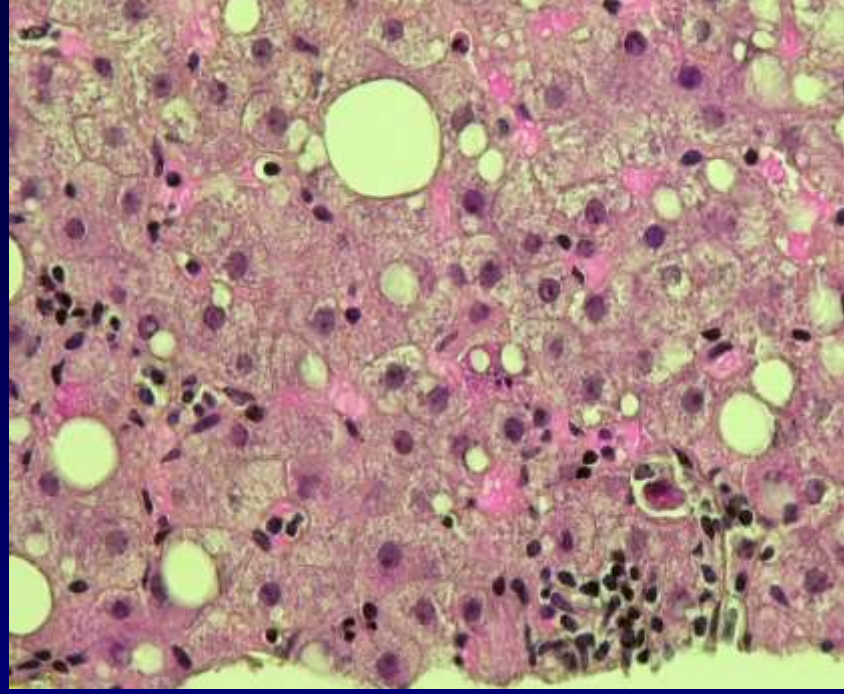
Chronische Hepatitis

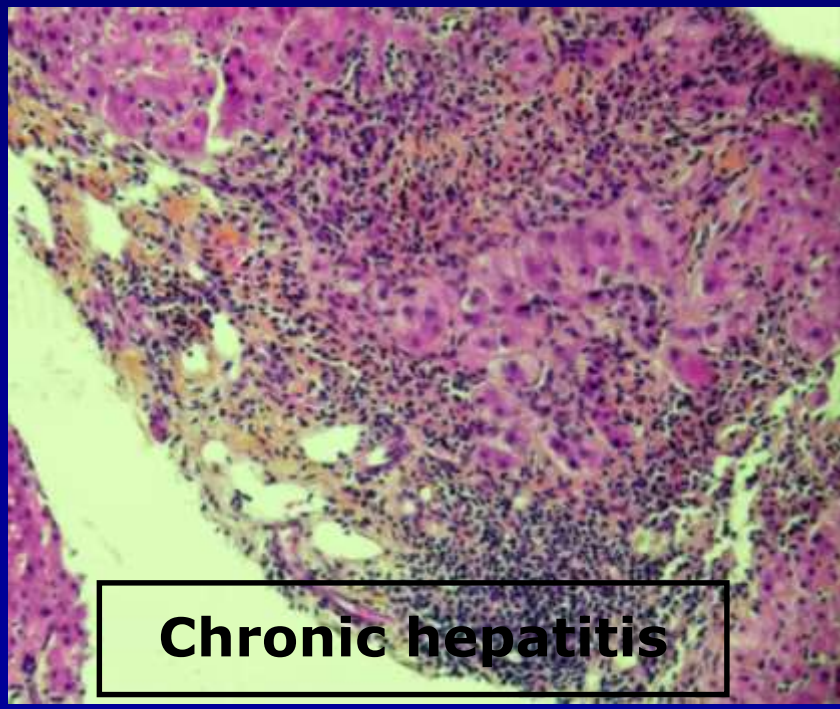
- Grading (Aktivität)
  - Ausmaß der Piecemeal-Nekrosen
  - und der assoziierten Entzündung
- Staging (Erkrankungsstadium)
  - Parenchymumbau
    - Fibrose
    - Zirrhose

Hepatitiden

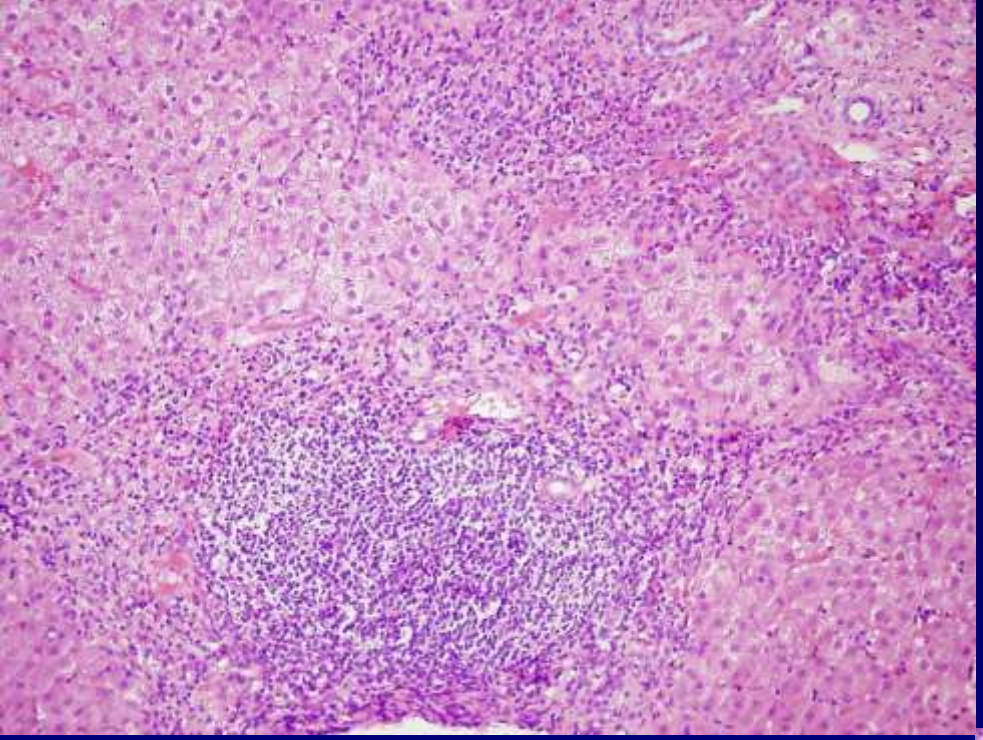






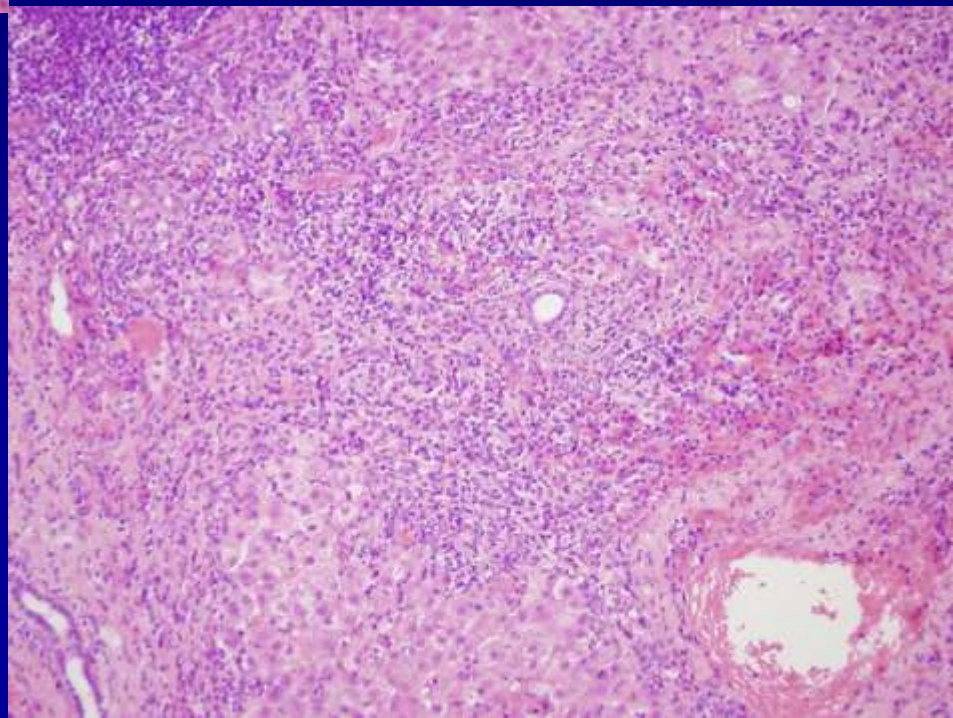


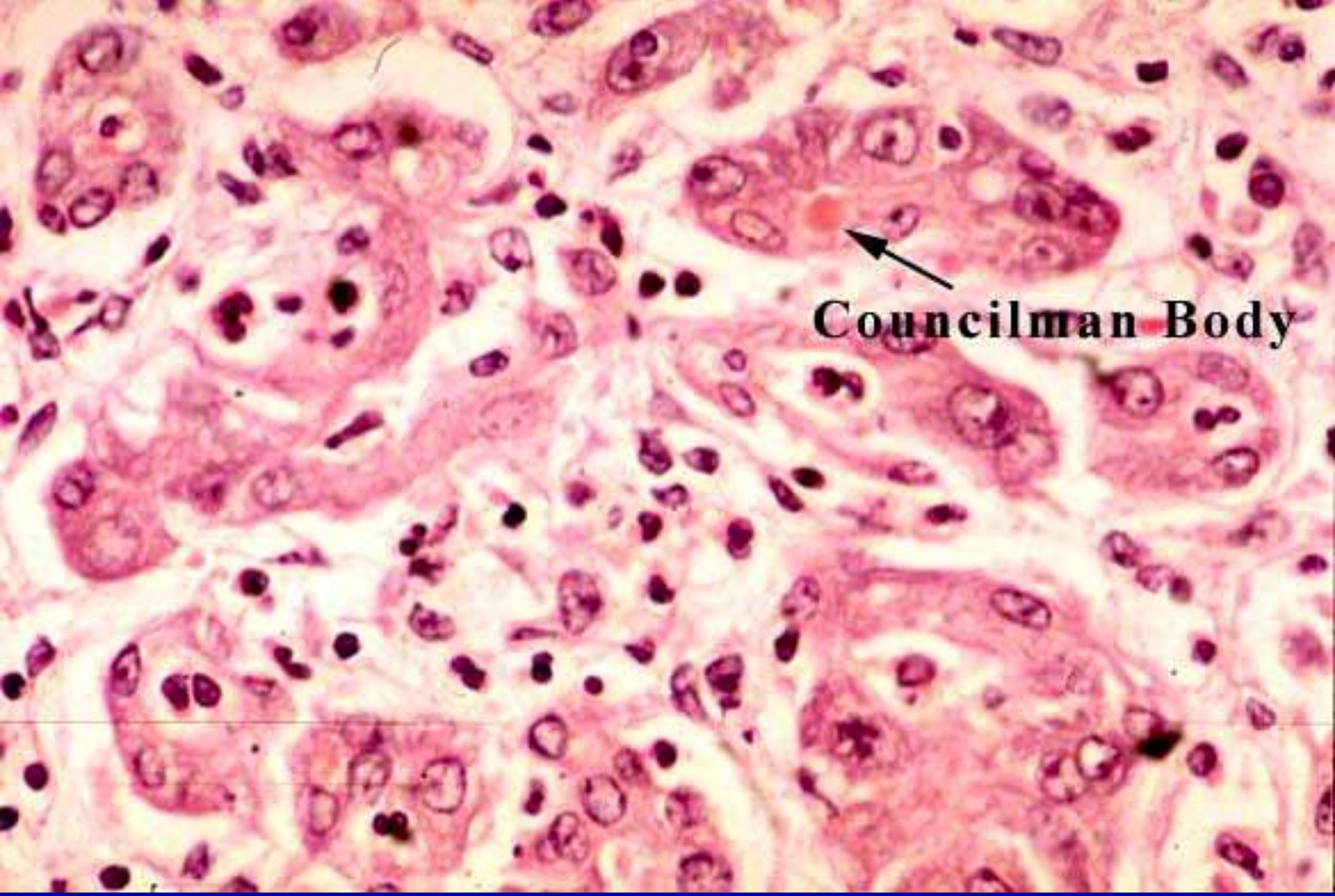
Chronic hepatitis



Brückennekrosen
Piecemeal-Nekrosen

Lymphozytenaggregat
(HCV Infektion)





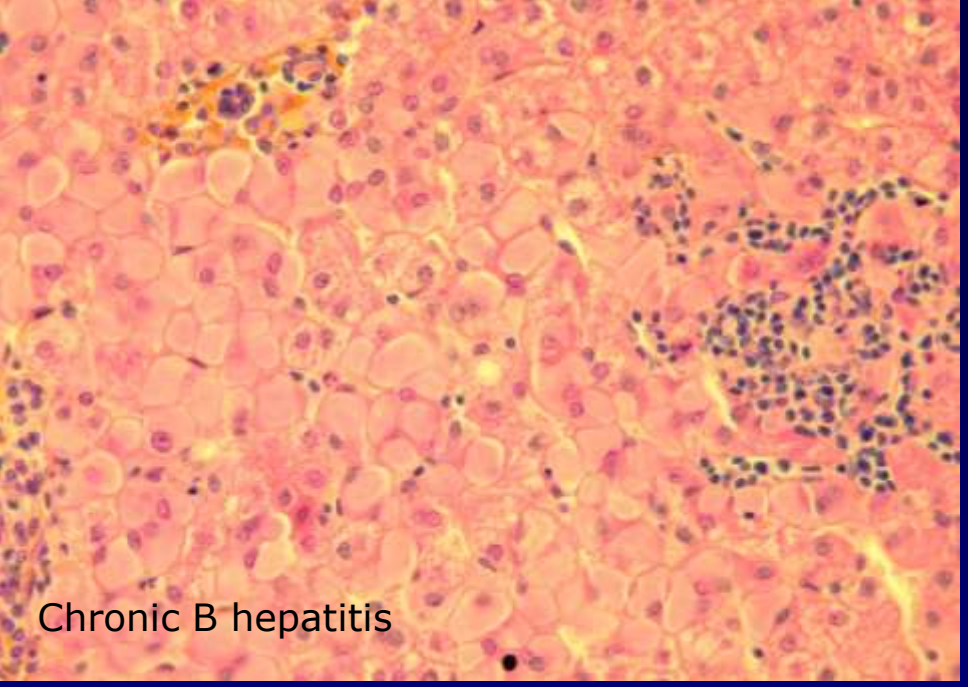
Apoptotischer Zelltod, HBV Infektion

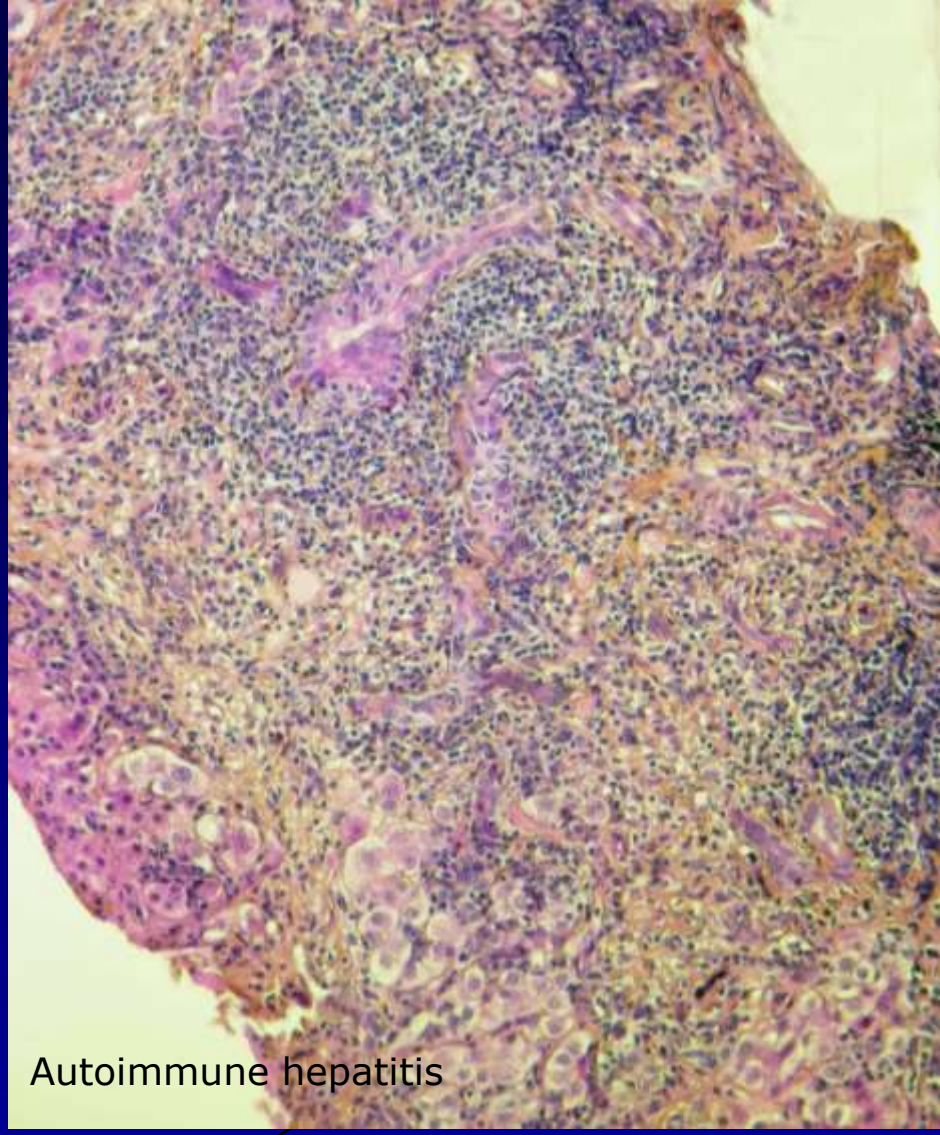
Chronische Hepatitiden

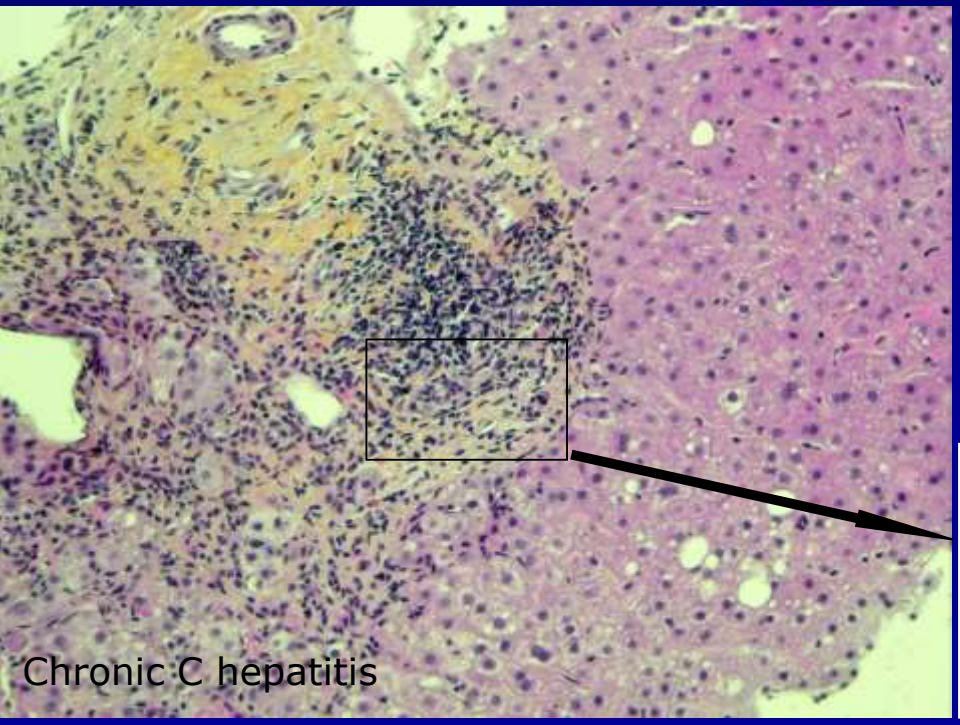
- **Chronisch persistierende Hepatitis: Proliferation der Kuppfer Zellen, verbreitete Periportalfeldern mit Infiltration. Läppchenarchitektur bleibt Erhalten.**

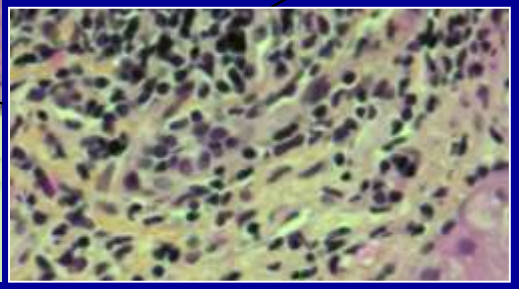
- **Chronisch aggressive Hepatitis: Inflammatorische Infiltrationen und Nekrosen von der Portalfeldern ausgehend, die auf die angreizenden Läppchen übergreift: MOTTENFRASSNEKROSE**

Es kann durch Bindegewebevermehrung zu Zirrhose kommen.


Chronic B hepatitis


Autoimmune hepatitis

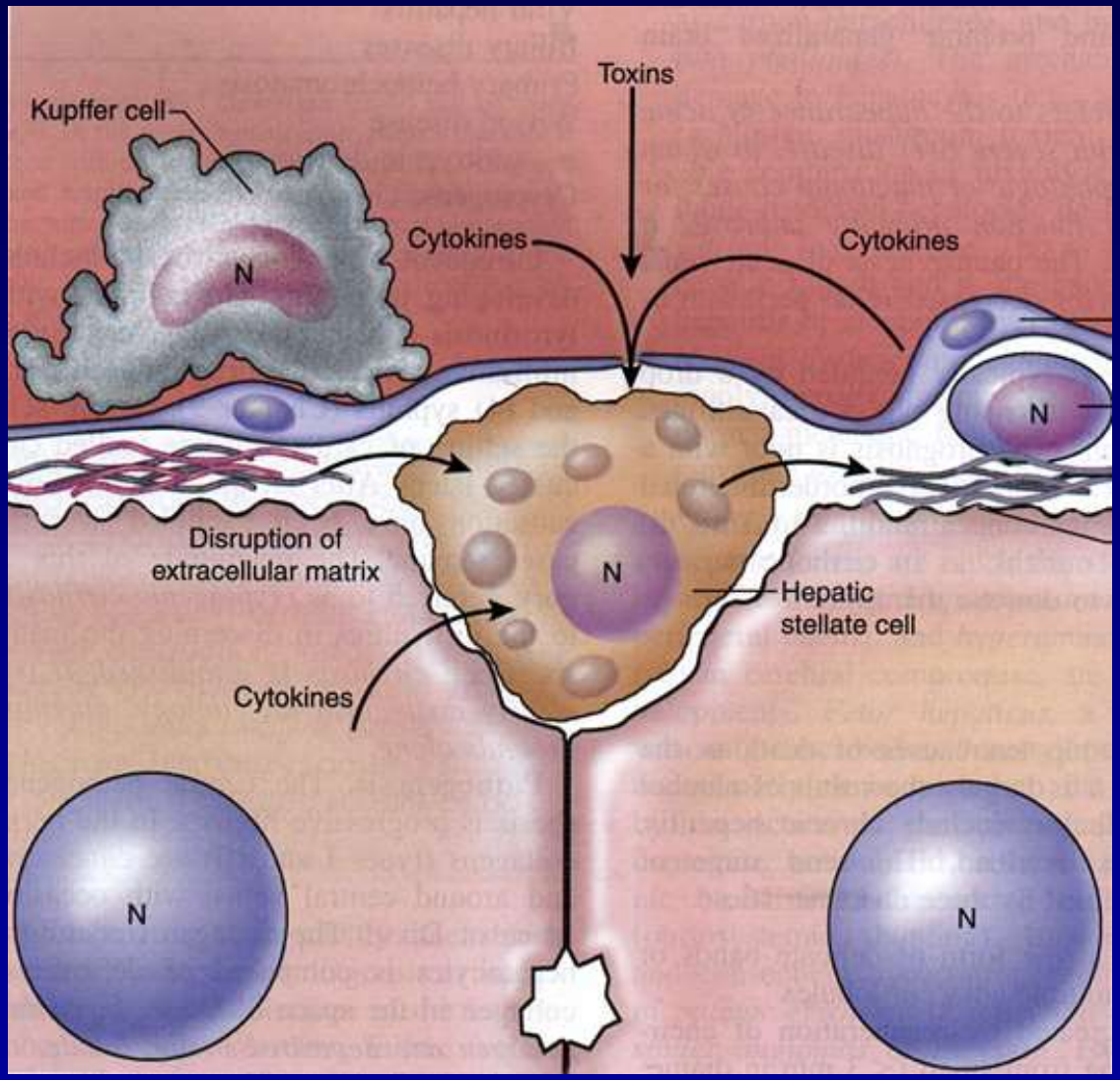

Chronic C hepatitis


Chronic C hepatitis

Fibrose

- **Bindegewebsvermehrung innerhalb des Parenchym der Leber. Ein Umbau der Läppchenstruktur erfolgt hier NICHT !!**
- **Maschendrahtfibrose: Kollagenfasern liegen eng um läppchenzentrale Hepatozyten. – Schädigungen durch Alkohol**
- **Perisinusoideale Fibrose: nach langer venösen Stauung**
- **Periportale Fibrose - Hepatitiden**
- **Passive Septen – nach den Brückennekrosen in den chronisch aggressiven Hepatitiden**
- **Aktive Septen – Fibroblasten wandern aus den Portal-Feldern in das Läppchen nach Mottenfrassnekrose**

FIBROSE


Toxins
Kupffer cell
Cytokines
Cytokines
N
N
N
Disruption of
extracellular matrix
Hepatic
stellate cell
Cytokines
N
N

Zirrhose

- **Reaktive Bindegewebsvermehrung und folgende**

strukturelle Umbau der Leberarchitektur !!
knotiger Leberumbau - Umbau der Läppchenstruktur ! mit Störung der Organdurch-Blutung und Funktion !
Vaskuläre und parenchymatöse Dekompensation ist das Endstadium.

- **40-50 % in der westlichen Welt alkoholisch bedingt, 30 % entstehen posthepatitisch**
- **in Süd-Ost Asien und Süd-Afrika ist durch HBV und HCV verursacht.**

Leberzirrhose

- Irreversibler Endzustand
- nach verschiedenen Erkrankungen
- fein-, grob-, gemischtknotig
- fibrotische Parenchymumbau (Pseudoläppchen)
- zerstörte funktionelle Histoarchitektur und Hämodynamik

Leberzirrhose

Ätiologisch

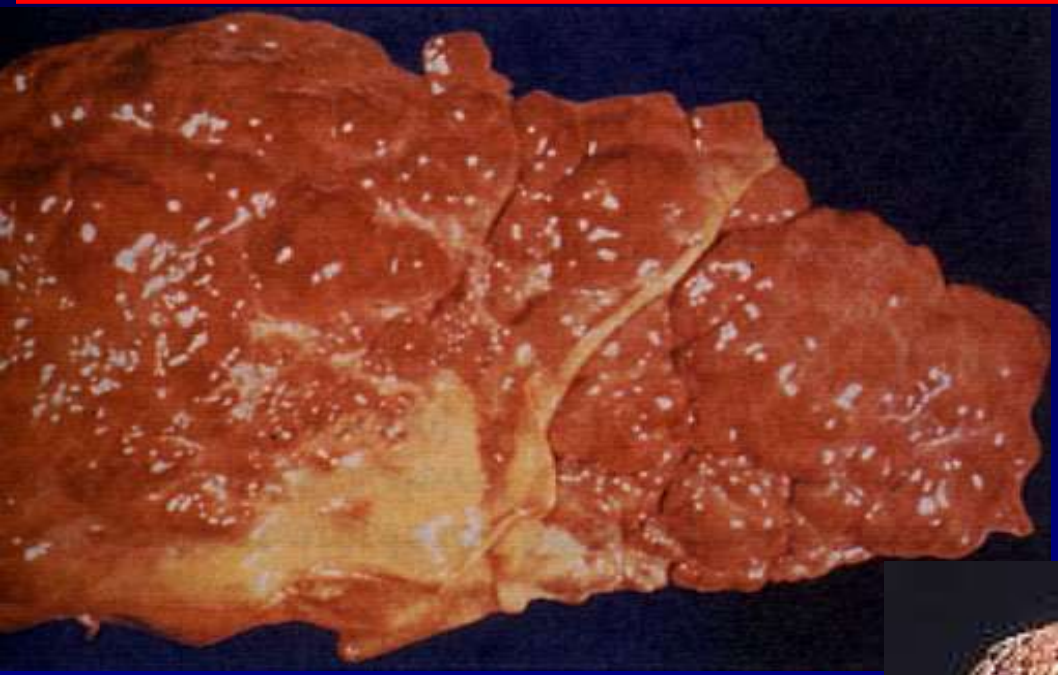
- Alkoholische (60%)
- Hepatitische (20%)
- Metabolische (Stoffwechselstörungen)
- Biliäre (primär oder secundär)
- Medikamentös-toxische
- Stauungszirrhose
- Kryptogene (10-20%)

Leberzirrhose

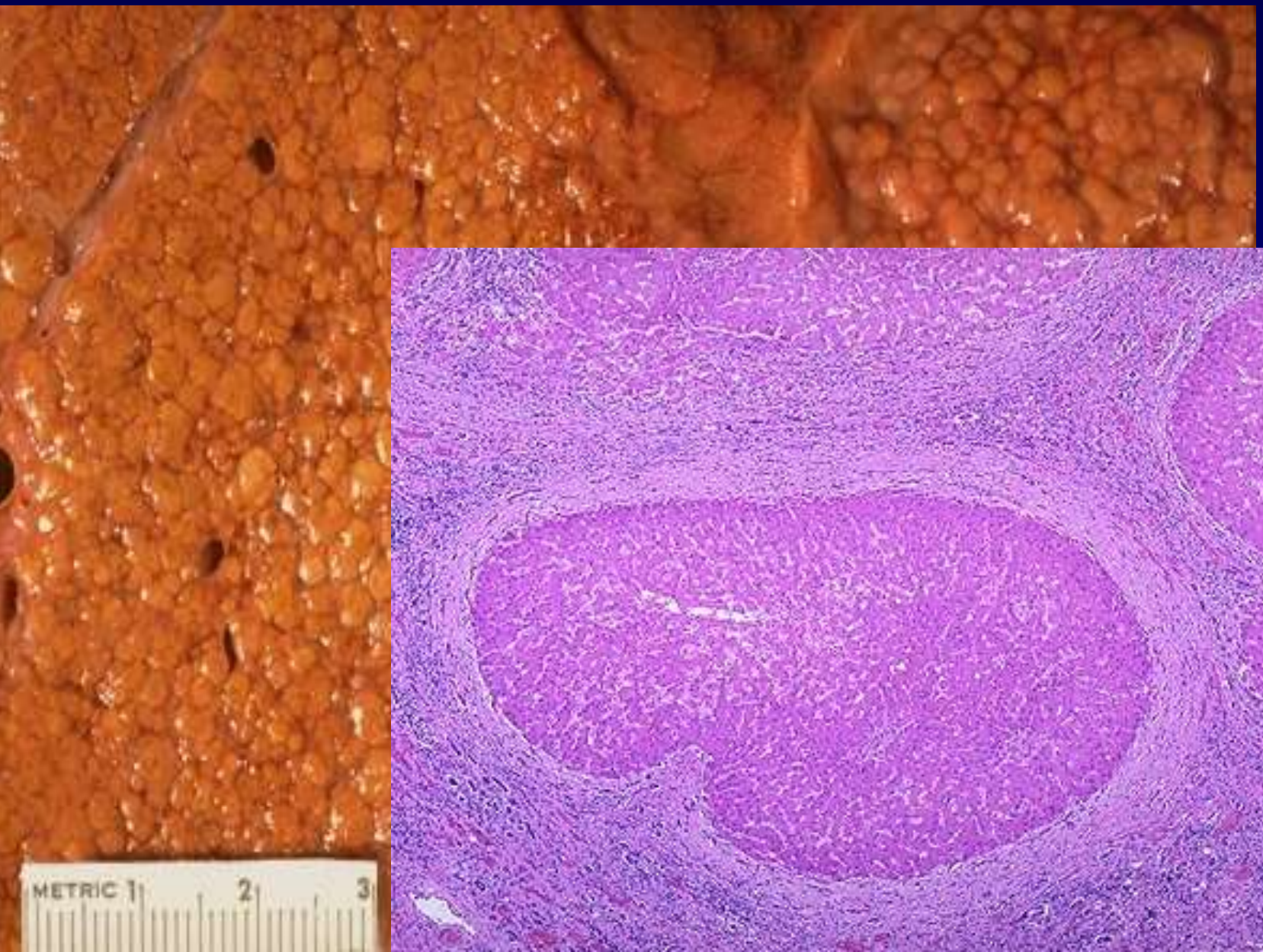
Folgekrankheiten

- Zirkulationsstörung (portokavale Shunt-Bildungen)
- Ascites
- Leberinsuffizienz (hepatischer Diabetes, Lactatazidose, Östrogen!)
- Hepatische Enzephalopathie (Leberkoma)
- Hepatorenales Syndrom
- Hepatopulmonales Syndrom
- Hepatozelluläres Karzinom

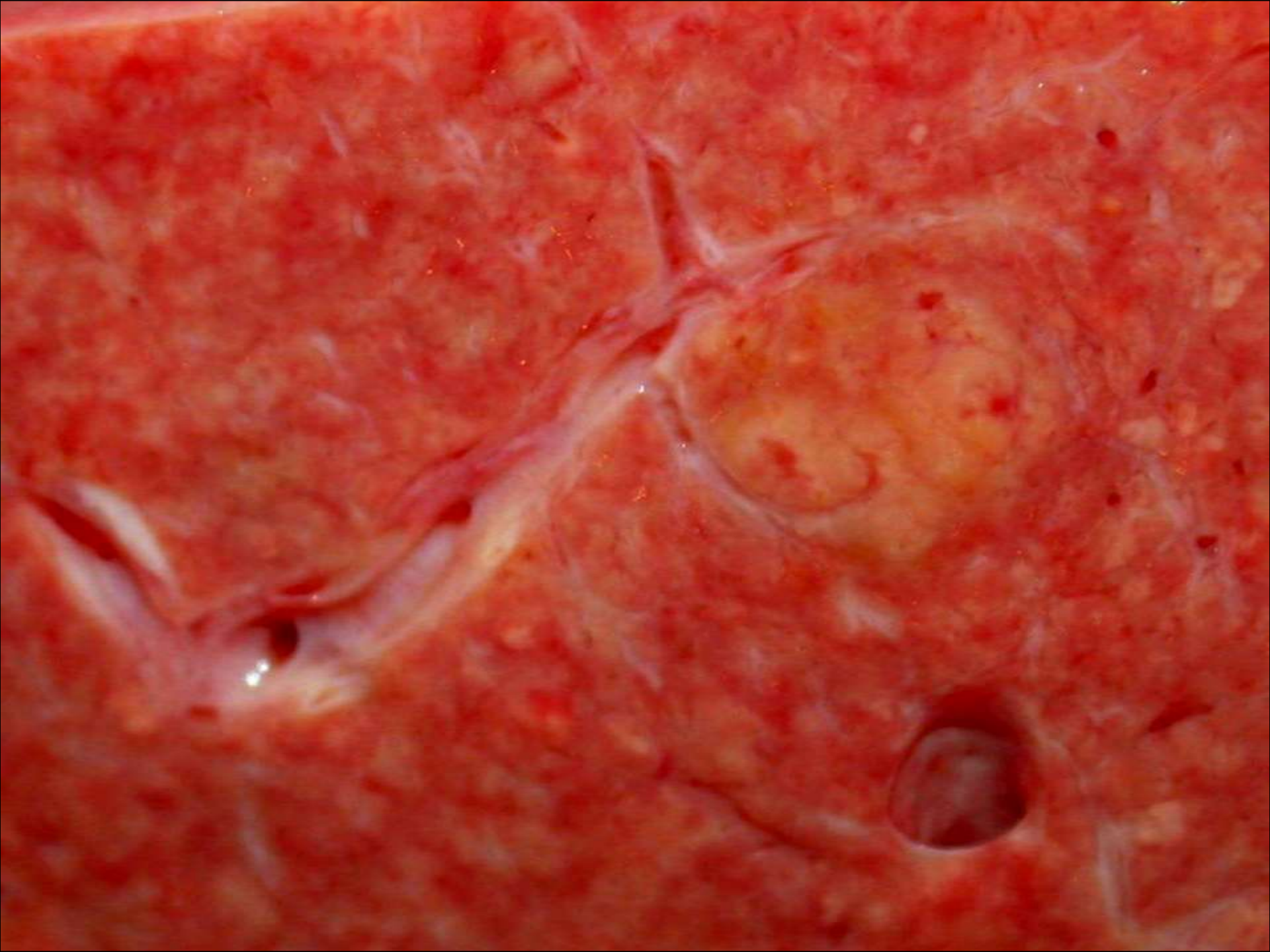
ZIRRHOSE

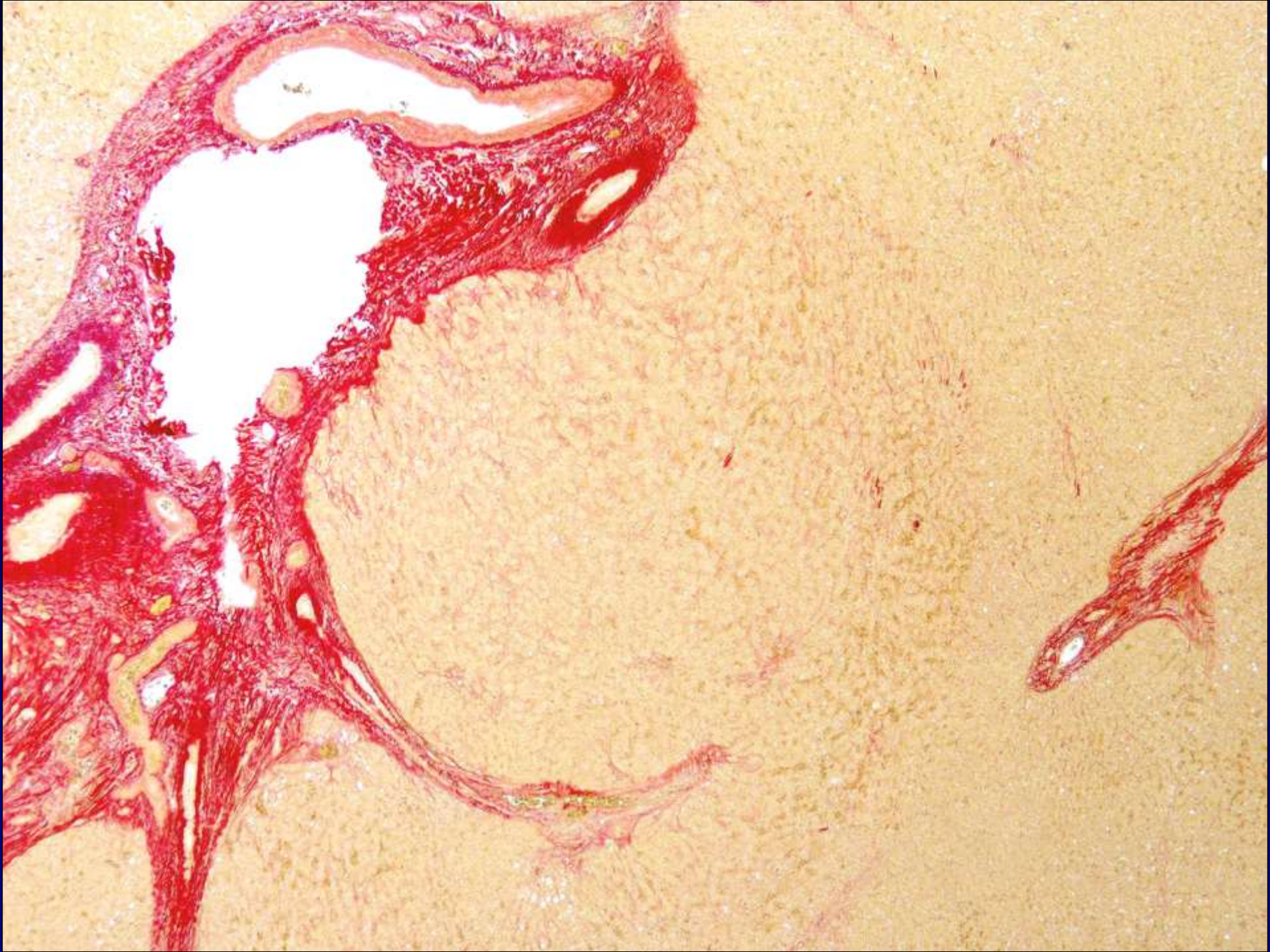


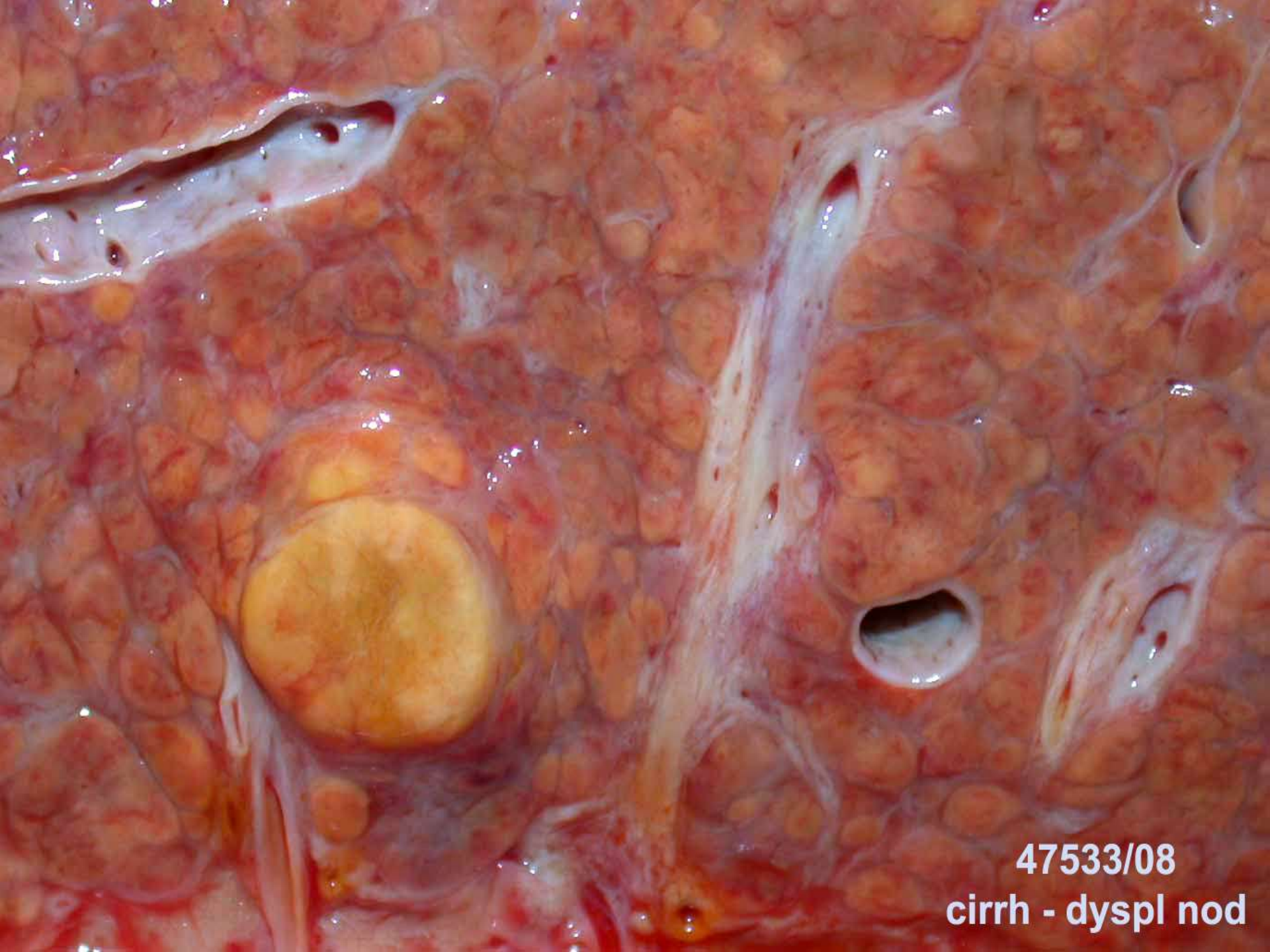
ZIRRHOSE

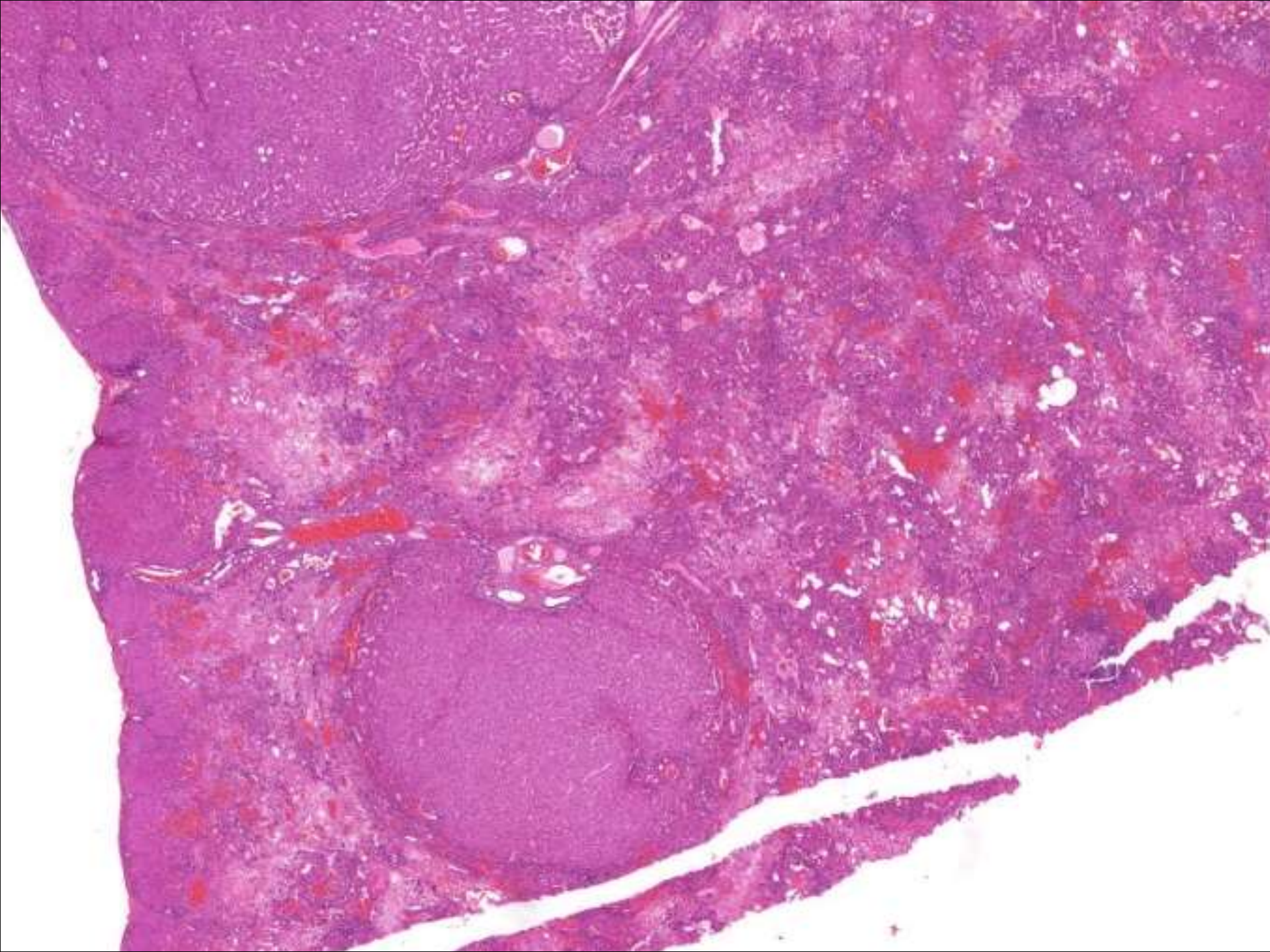



nod. regenerative Hyperplasie





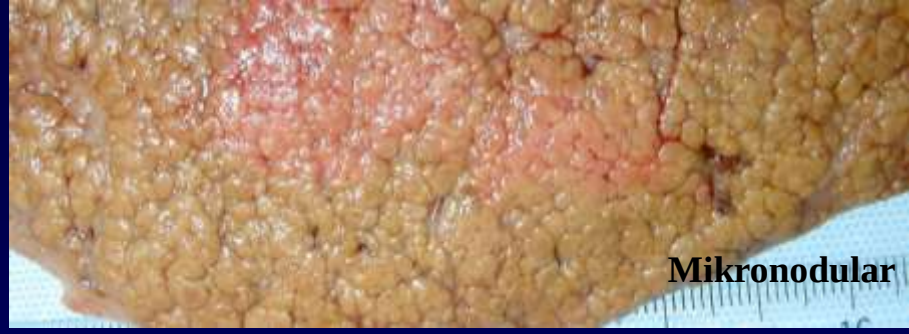

47533/08
cirrh - dyspl nod

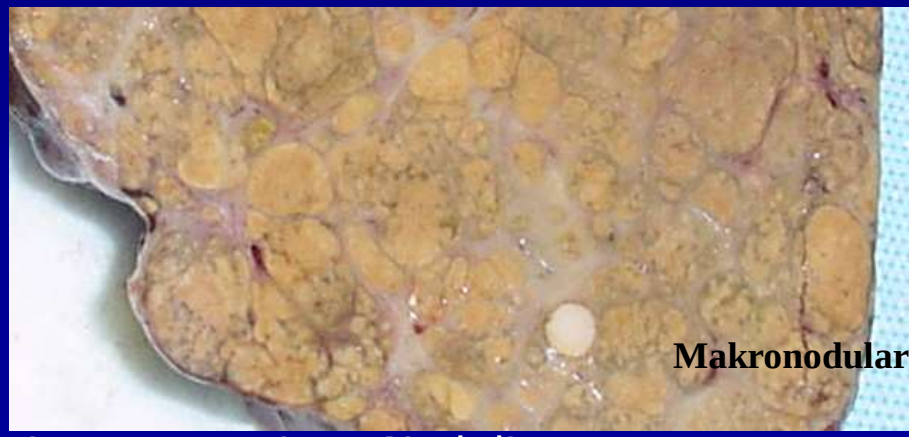


ZIRRHOSE

- alkoholisch
- posthepatitisch
- metabolisch: Hämochromatose, Morbus Wilson
- medikamentös, toxisch (z. B. Aflatoxine, Arsen)
- biliäre Zirrhose

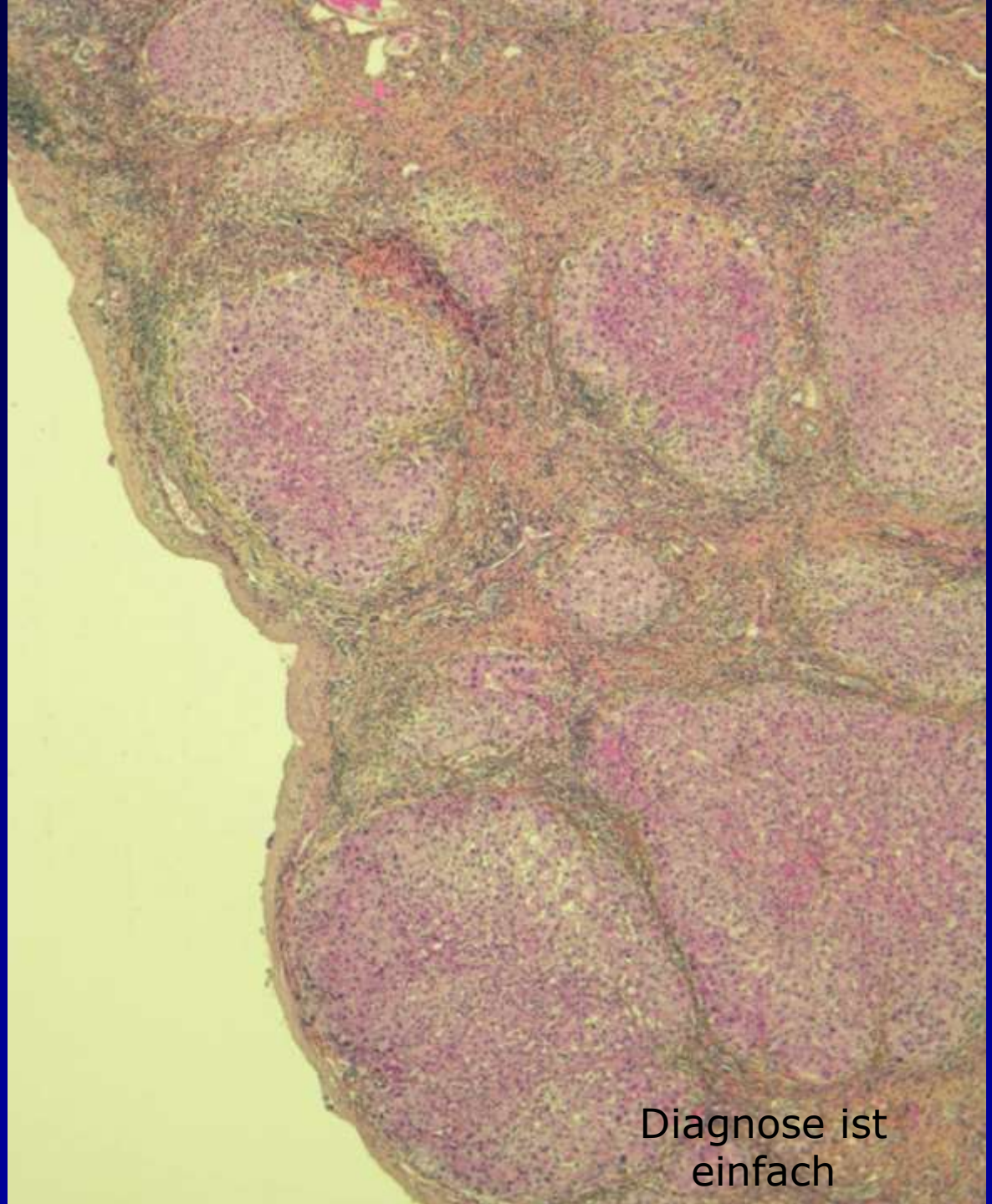
- Nekrose (toxischer oder entzündlicher Genese)
- Fibrose
- Regeneration – knotige Regenerate
- PSEUDOLOBULI !!!
- Nekrosen
- knotige, pseudolobuläre Regeneratbildung
- bindegewebige Septen mit gestörter Läppchenarchitektur
- und Gefässversorgung



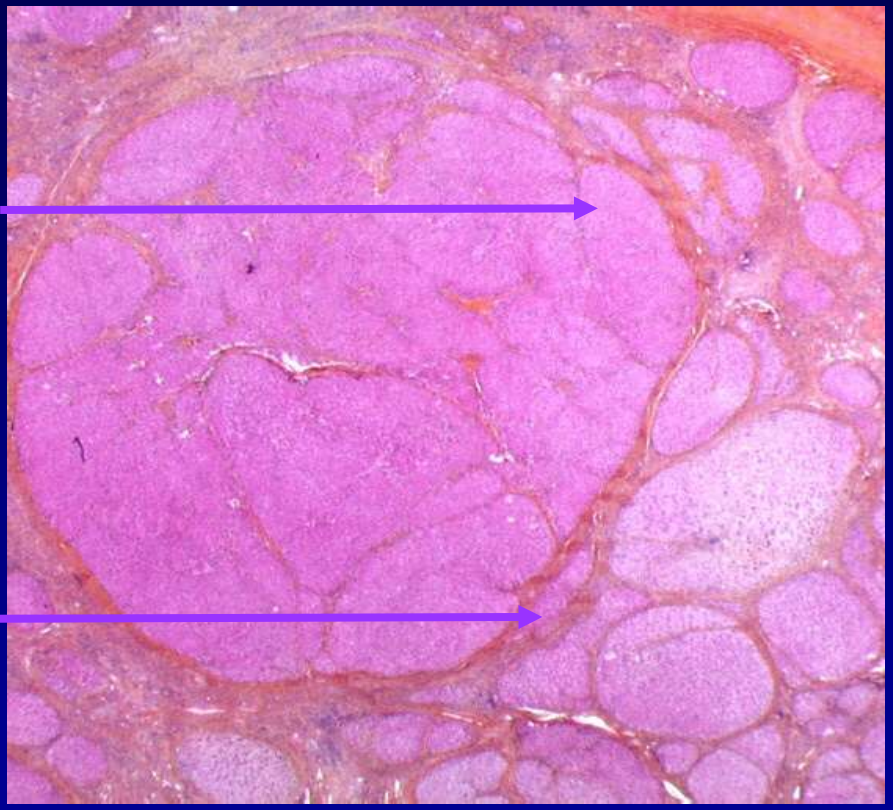


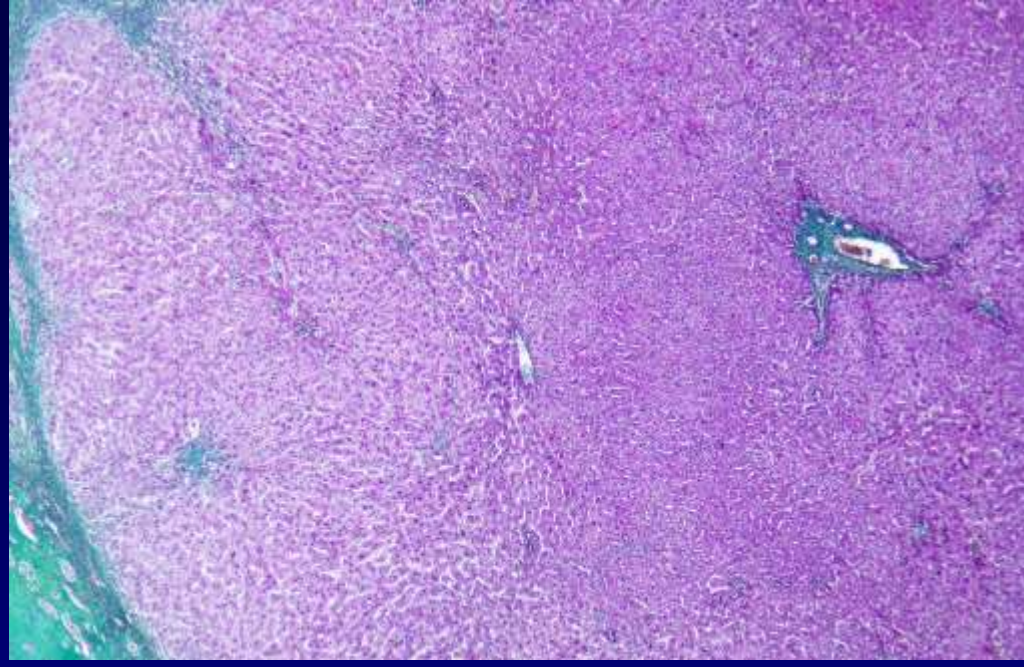
Zirrhose

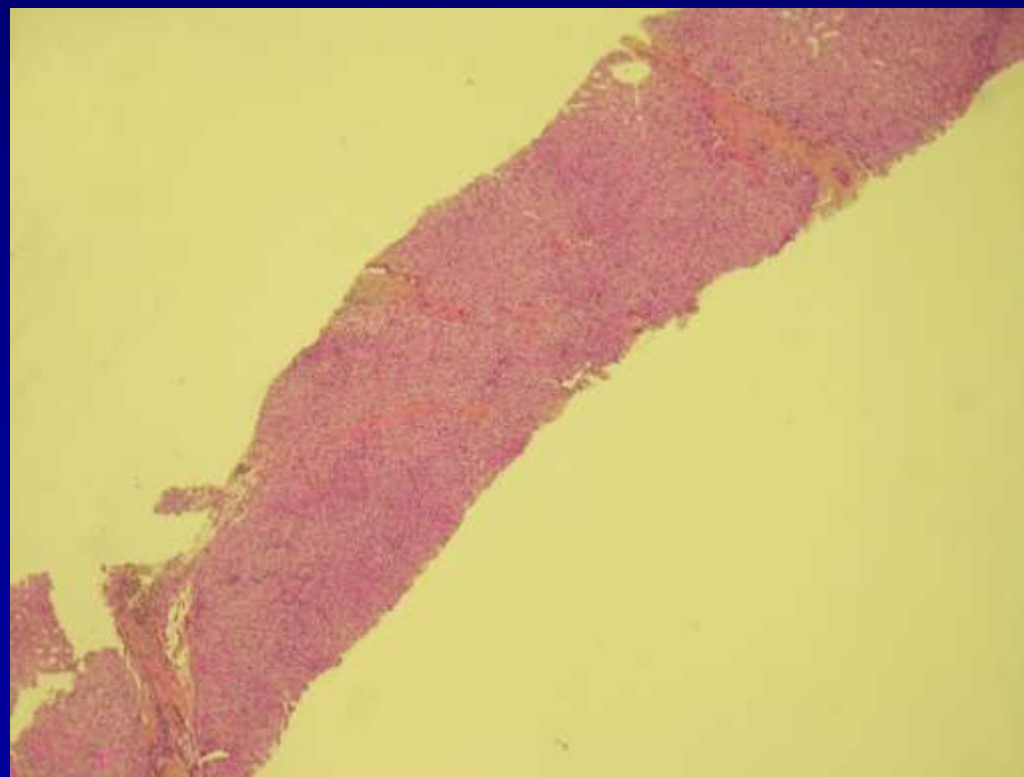
Diffuse Fibrose mit regenerativen Noduli



Diagnose ist
einfach







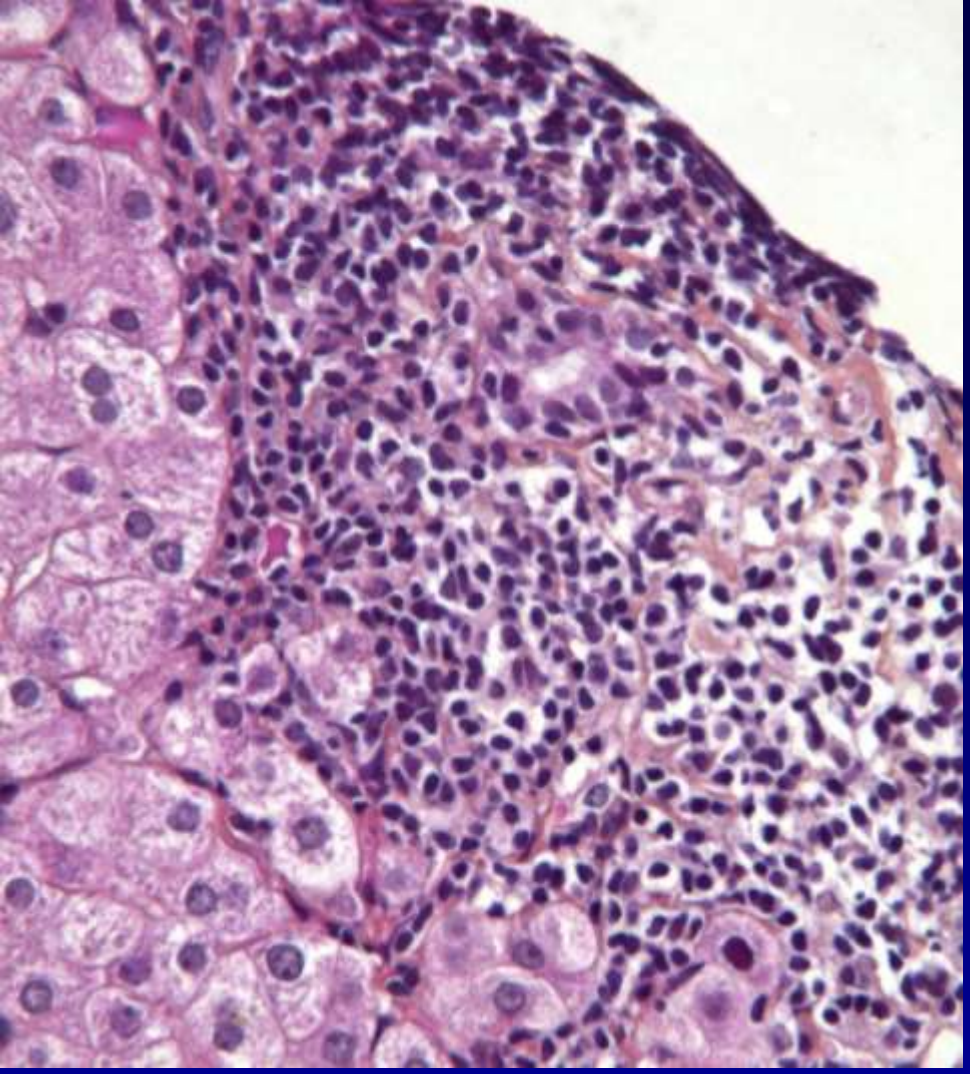
Diagnose ist problematisch im Fall der makronodularen Zirrhose

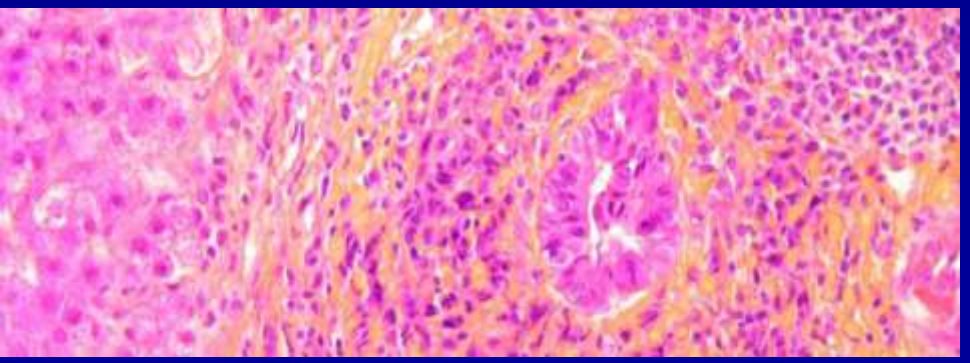
Biliäre Zirrhose

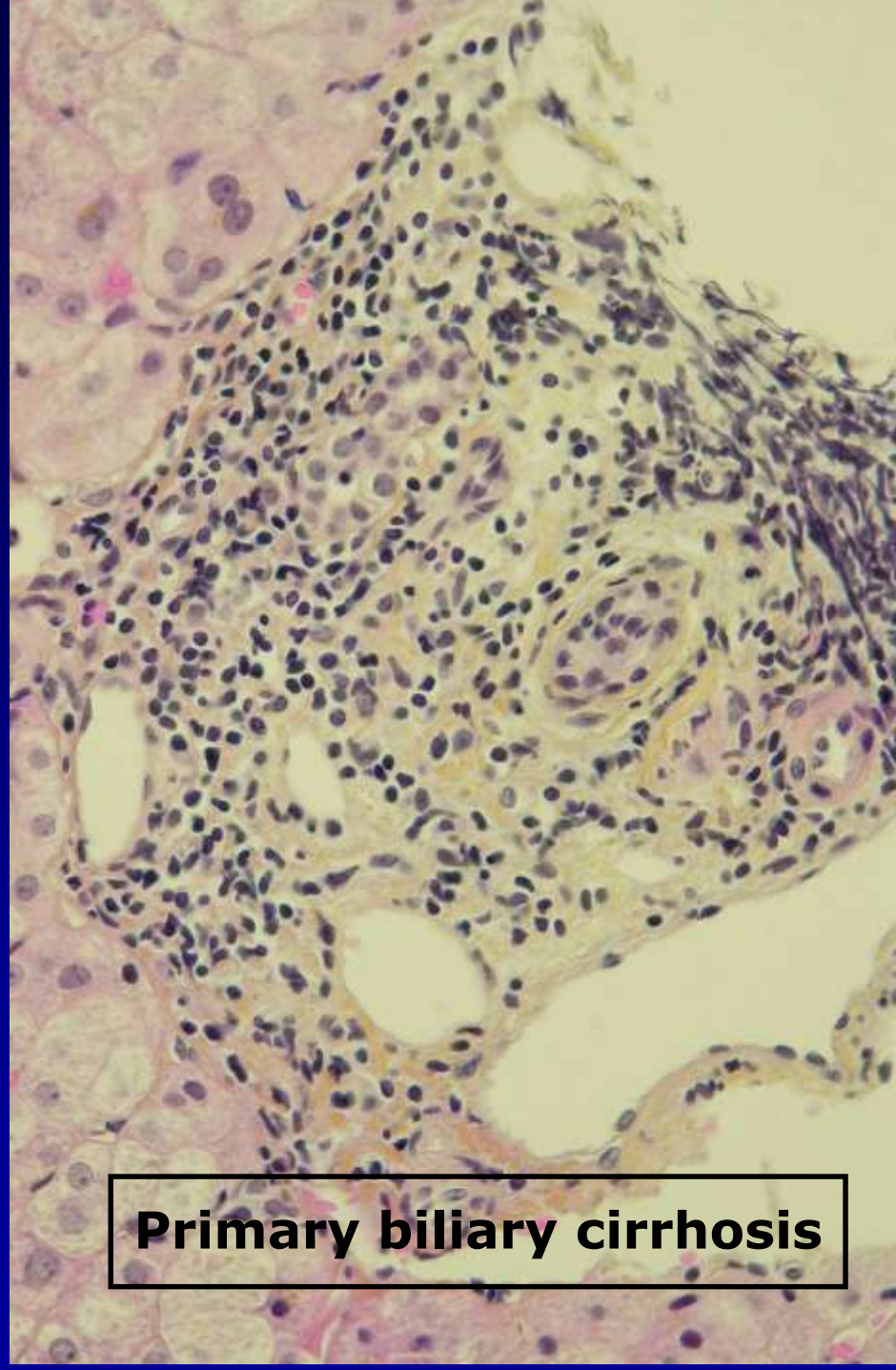
Primare biliare Zirrhose:
Autoimmune Krankheit, Frauen haufiger betroffen, (40-60 Jahre)

I.Portalfeld entzündlich infiltriert, ödematös, granulomatöse Lasionen. Gallengangsnekrosen. In der Grenzlamelle Kupfer Assoz. Proteine !! (Shikata Orzein Farbung - Frühzeichen !)
II. Gallengangnekroses und Gallengangprolierationen
III. Zerstörte Gallengange und Portalfeldfibrose, Verödung. Von Portalfeld ausgegangene Septale und Brückenfibrose
IV: Biliare Zirrhose, Narben, Gallenstauung, Fehlende Gallengange (Vanishing bile ducts)

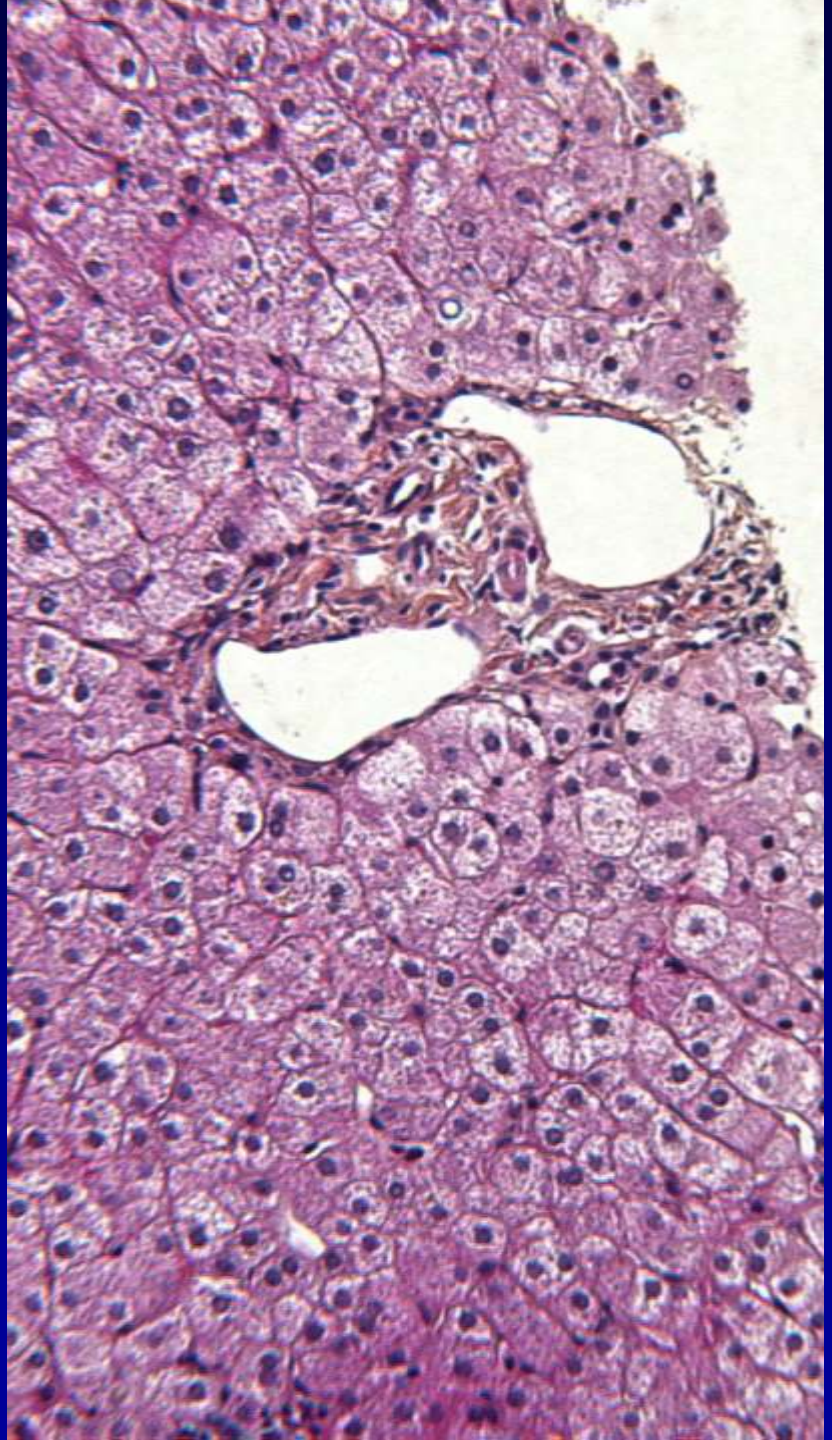
Sekundare biliare Zirrhose:
Gallenabfluss-störung induzierte sekundare Zirrhose

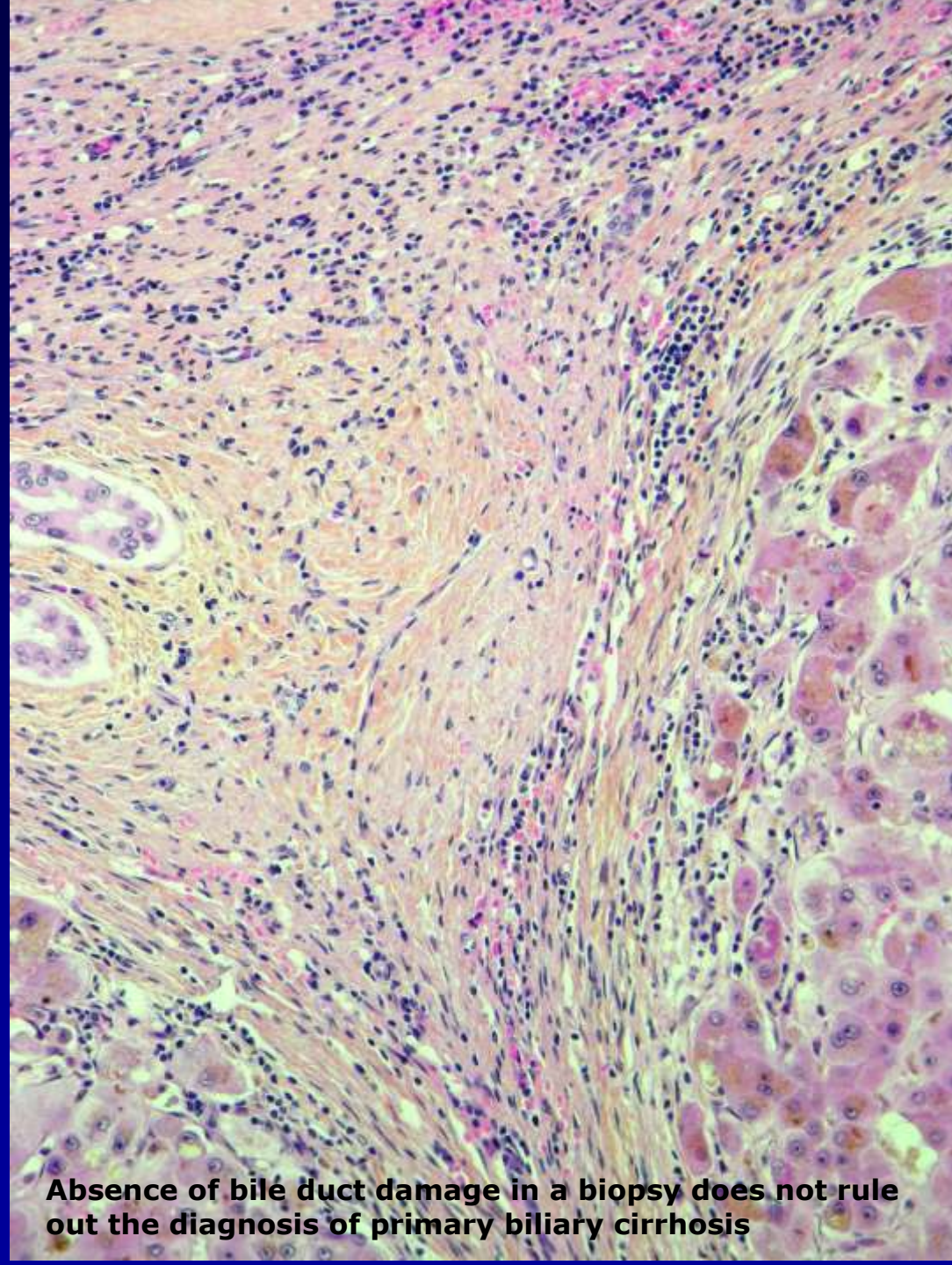




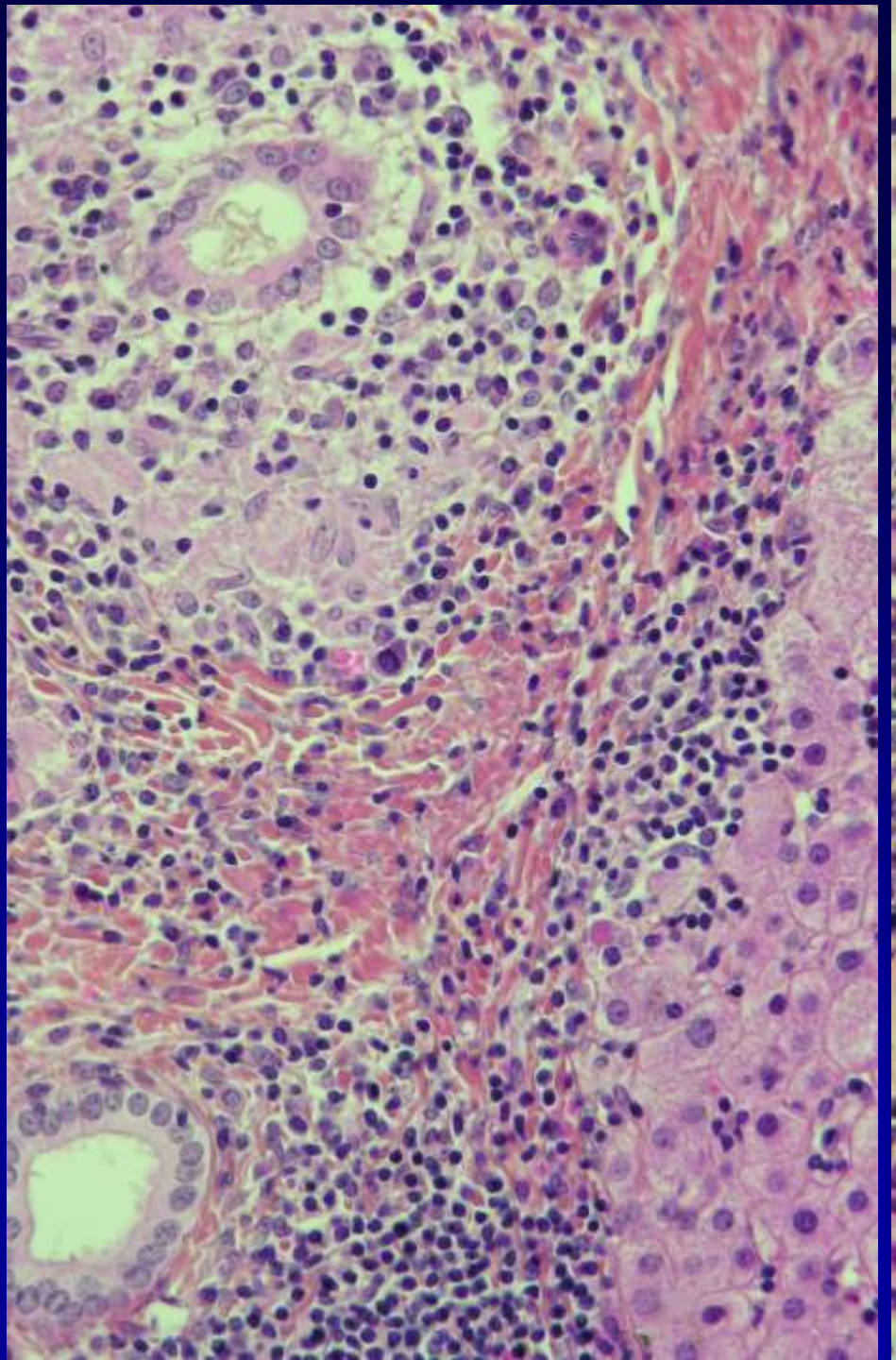


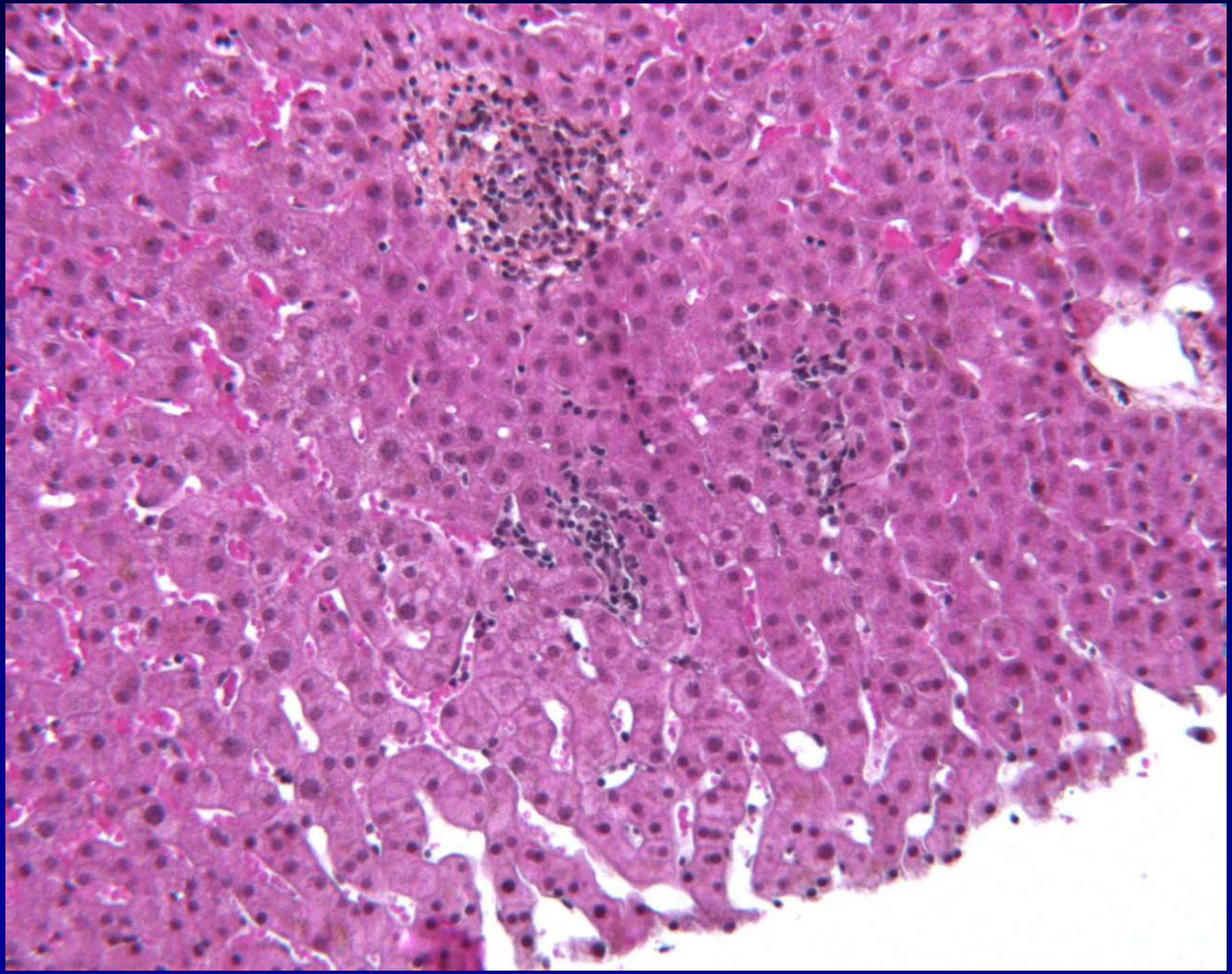
Primary biliary cirrhosis





Absence of bile duct damage in a biopsy does not rule out the diagnosis of primary biliary cirrhosis





Primary biliary cirrhosis - Primary sclerosing cholangitis

Staging

Scheuer[1]

Stage 1: florid duct lesion (portal inflammation)

Stage 2: ductular proliferation (portal fibrosis)

Stage 3: septal fibrosis (usually decreased inflammation)

Stage 4: cirrhosis

Ludwig et al.[2]

Portal stage (inflammation without fibrosis)

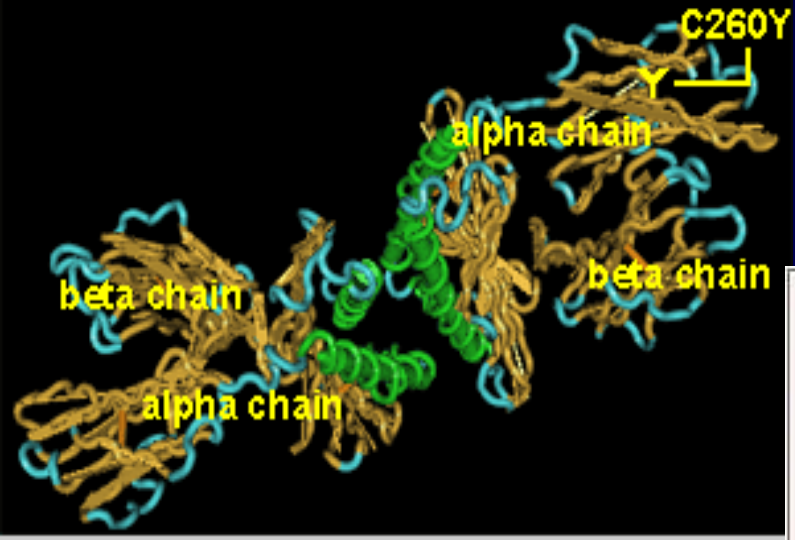
Peri portal stage (piece meal necrosis or fibrosis)

Septal stage (bridging fibrosis)

Cirrhosis

1. **Scheuer PJ. Proc R Soc Med 1967 ; 60 : 1257-60.**
1. **Ludwig J. et al. Virchows Arch. A 1978 ; 379 : 103-112.**

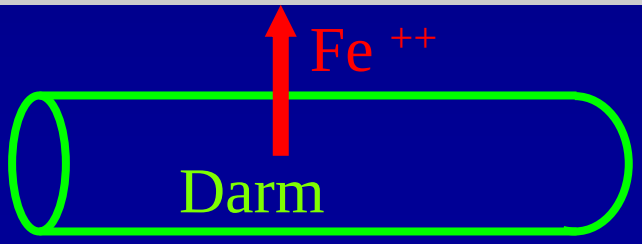
Haemochromatose (Bronz Diabetes)



The HFE protein is similar in structure to MHC class I, consisting of two pairs of alpha and beta chains.
In the mature HFE protein, the mutation is called C260Y. This is because the body's processing of the protein removes 22 amino acids to produce the mature protein.

The C260Y mutation occurs in the alpha 3 domain and disrupts the association between the chains.

Mutant HFE is unable to bind to the iron-loaded transferrin receceptor. Without this interaction, the receptor brings more iron into the cells.



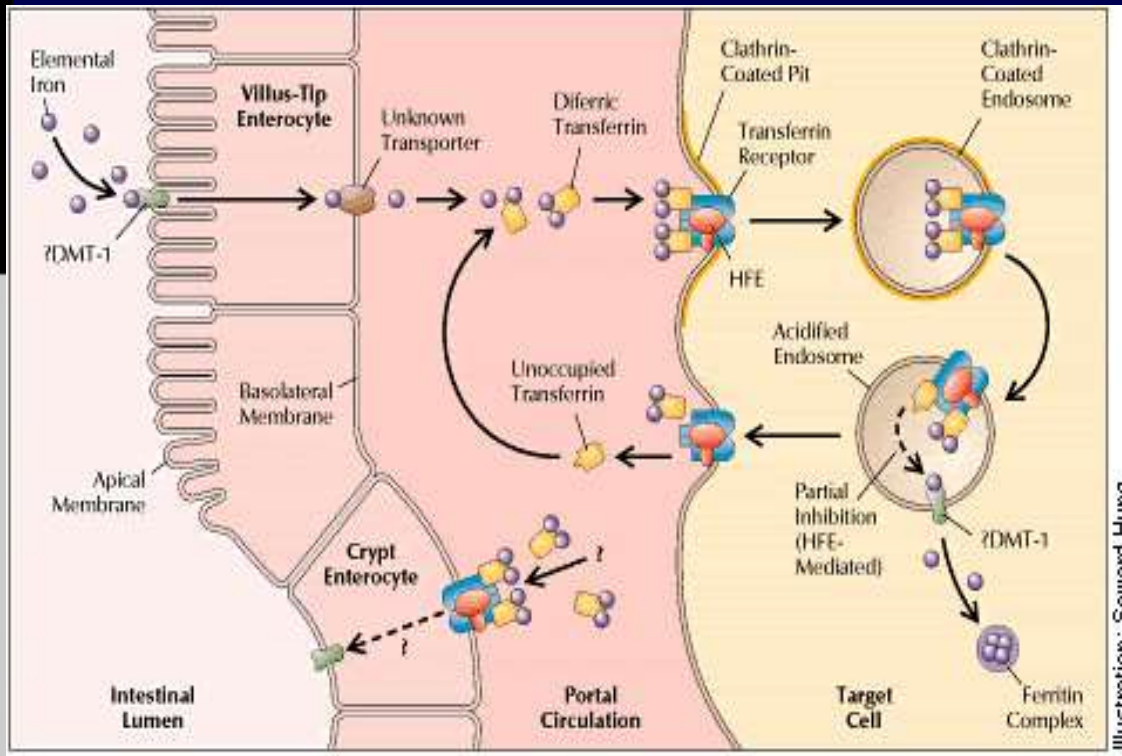
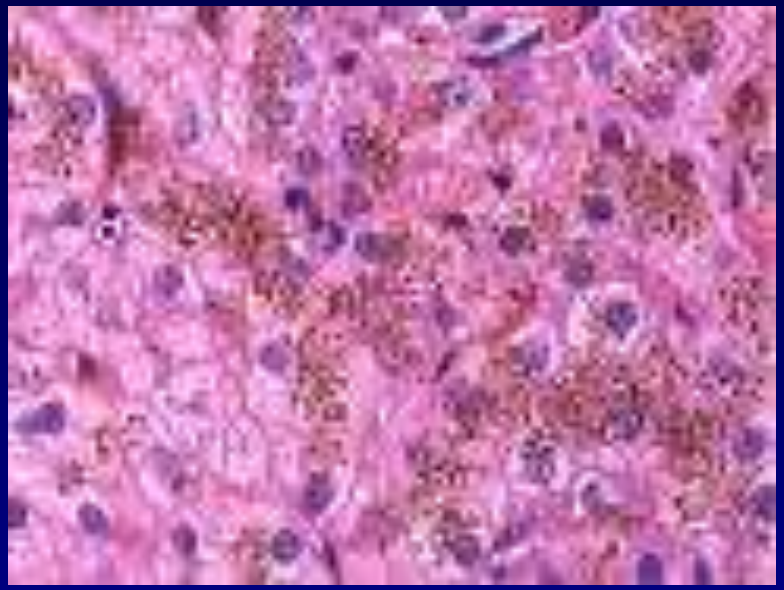
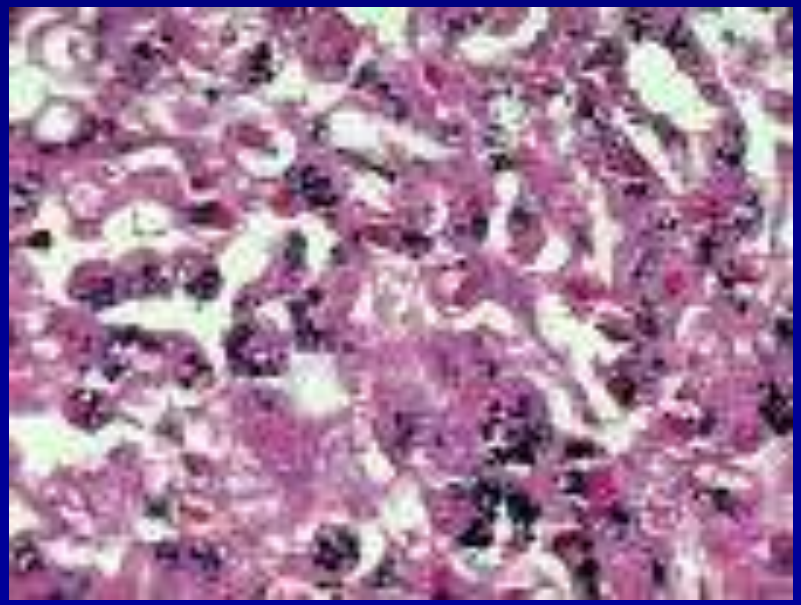


Figure 1. Emerging details of iron metabolism permit at least partial understanding of the function of the HFE protein—and of HFE's absence or dysfunction in causing hereditary hemochromatosis. From the intestinal lumen (left), dietary iron is transported into enterocytes, most likely by the newly described transporter DMT-1. From there iron enters the portal circulation for delivery—by transferrin—to target cells such as hepatocytes and erythroblasts (right). Internalized by endocytosis, the iron is eventually transported from endosomes into the cytoplasm, often for storage in ferritin. Meanwhile, transferrin and its receptor are recycled to the cell surface. HFE binds to the transferrin receptor. Once bound, it inhibits the release of iron, so that an increased fraction of iron-bound transferrin recycles back out of the cell. In the absence of HFE, the cell may become iron-overloaded. A more primary problem may affect the intestinal lining. Here, HFE is hypothesized to act in undifferentiated crypt enterocytes (bottom left), the precursors of villus-tip enterocytes, so as to regulate uptake of plasma iron. Each crypt cell becomes a sensor of the body's iron load, perhaps to program its subsequent expression of DMT-1 (dashed arrow). If HFE function is lost, iron sensing may be disrupted. Falsely sensing low body iron, the crypt cell may overexpress DMT-1, facilitating excessive lumenal iron absorption by mature enterocytes.

Hämochromatose

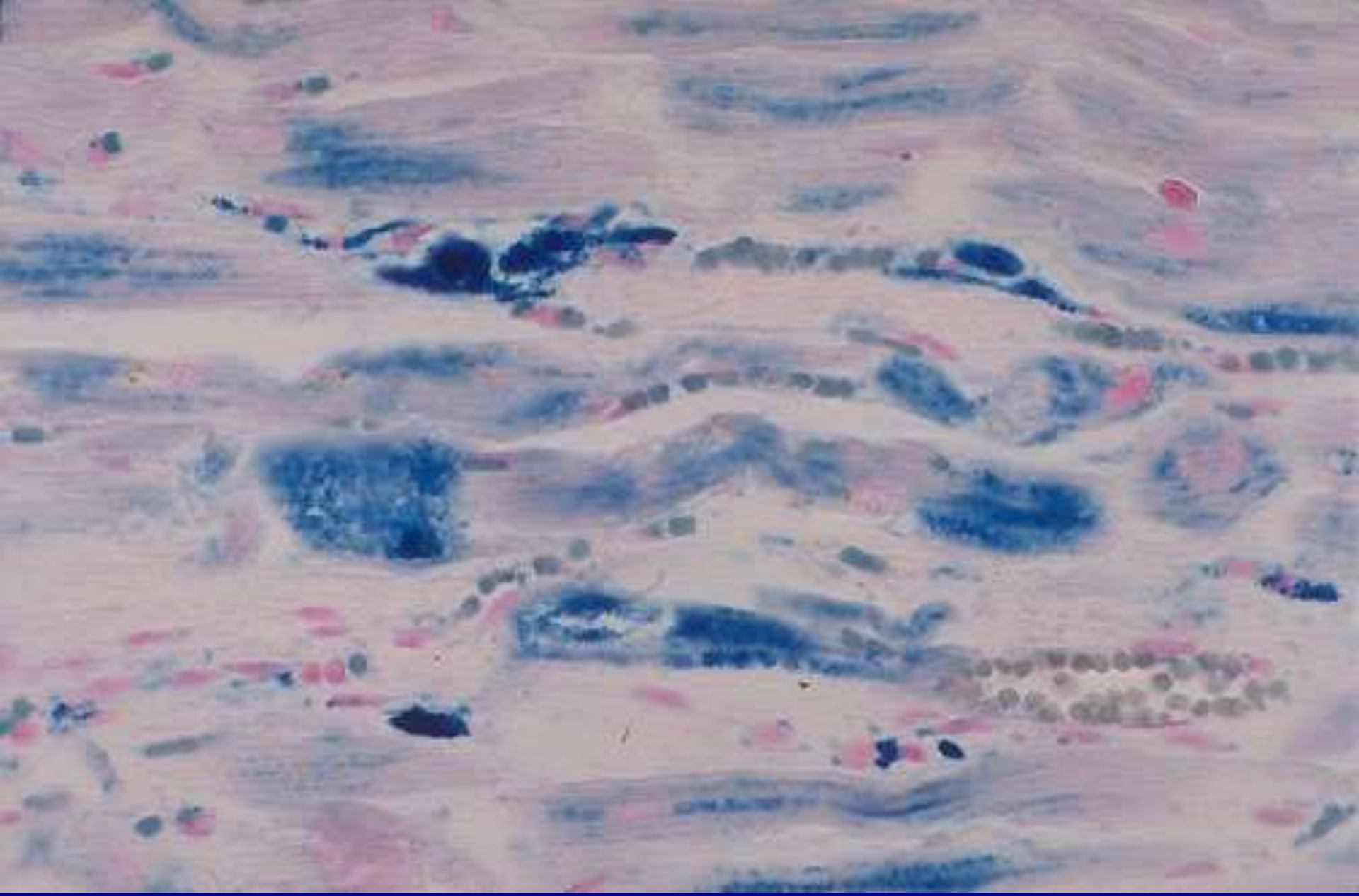




Hämochromatose - Bronzdiabetes

»Eisenspeicherkrankheit« infolge Eisenüberladung des Organismus
v.a. in der parenchymatösen Organe
Ursache: Unfähigkeit des RHS, das Eisenangebot zu bewältigen
Formen: *idiopathische* a) »adulte« Hämochromatose familiär auftretend
b) perinatale, angeboren manifeste Form
erythropoetische Hämochromatose bei Blutbildungsstörungen
Steigerung der Eisenresorption
Hypersiderämie und Eisenablagerung (Siderose)
Leberzirrhose (Pigmentzirrhose)
bronzeartiger Hautverfärbung
Ausfallserscheinungen endo- und exokriner Drüsen
Hypogonadismus
insulinabhängiger Diabetes mellitus =
»Bronzediabetes«
Herzinsuffizienz
Haarverlust

erworbene Hämochromatose z.B. Transfusions-Hämochromatose



hemochromatosis, with excessive iron deposition - Prussian blue iron stain the excessive deposition of iron leads to heart enlargement and failure

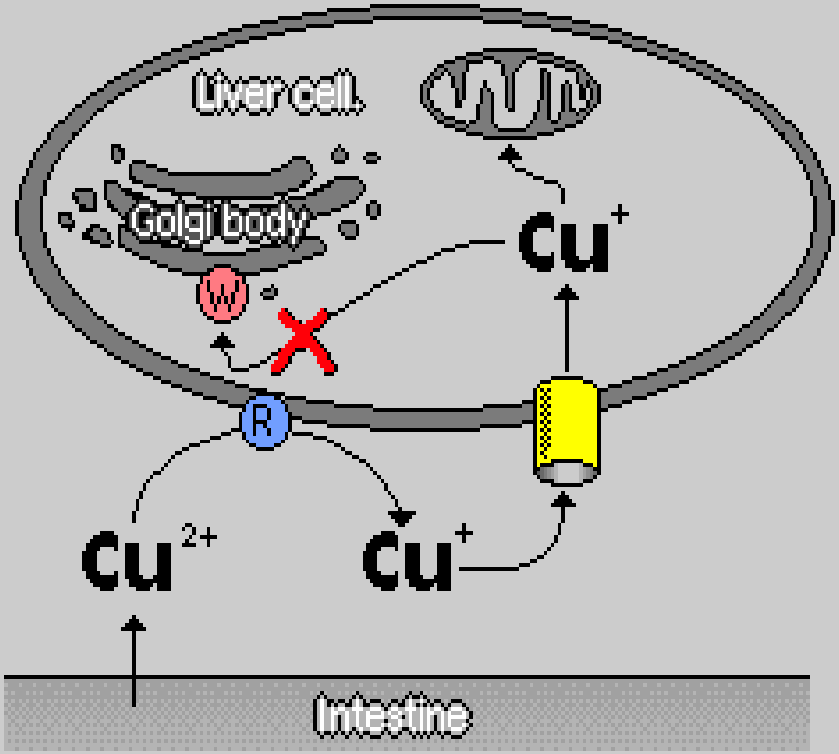
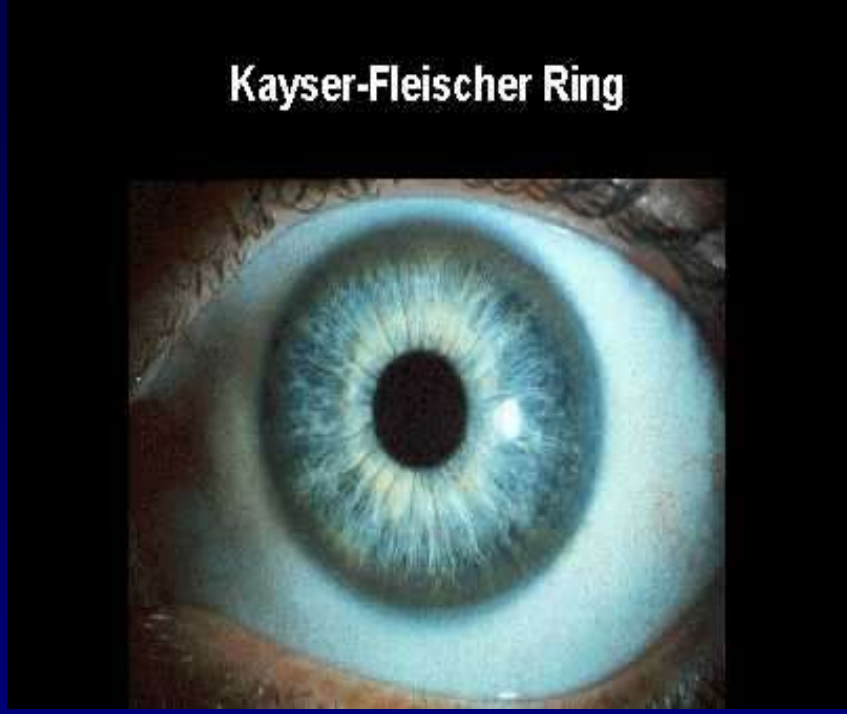
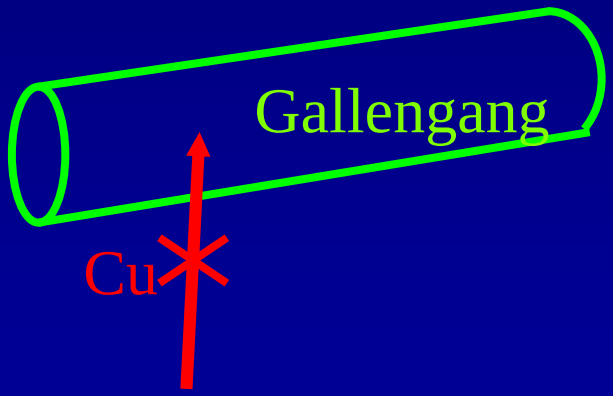


Fig 13.01.01 – The normal routes of copper processing in the liver. Abbreviations – W – Wilson Cu ATPase; R – Reductase. Adapted from Didonato M., 1997)



Wilson Krankheit
(hepatolenticulare Krankheit)
(Kupfer-speicherung Krankheit)

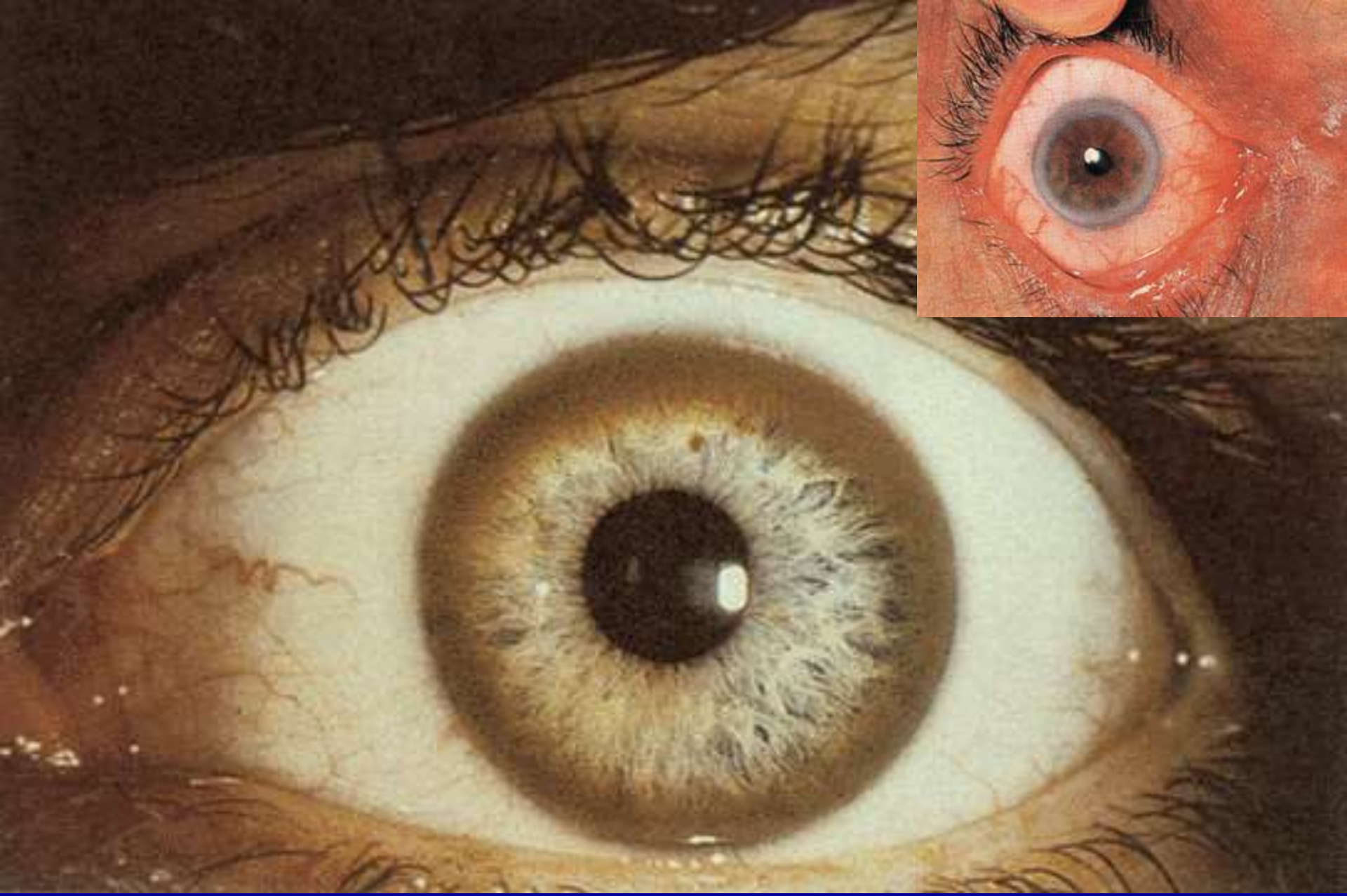


Wilson Krankheit - hepatolentikuläre Degeneration

autosomal-rezessiv erbliche Defektparaproteinämie
Störung der Coeruloplasmin-Synthese
    Serumspiegel < 10 mg/100 ml; normal 23-44
Kupferanreicherung im Gewebe
beginnt im 1.-2. Ljz.
extrapyramidale Symptome: Tremor, Rigor, Ataxie, Dysarthrie, Kontrakturen infolge Degeneration der Stammganglien (»Linsenkerndegeneration«) pathognomonisch:
Kayser-Fleischer Ring
    Leberzirrhose
    Aminoazidurie - Blockierung der Tubulusenzyme durch Kupfer
    graubrauner Hautpigmentierung
    Störung des Kohlenhydratstoffwechsels
        Hyperinsulinismus
    intellektueller und psychischer Verfall

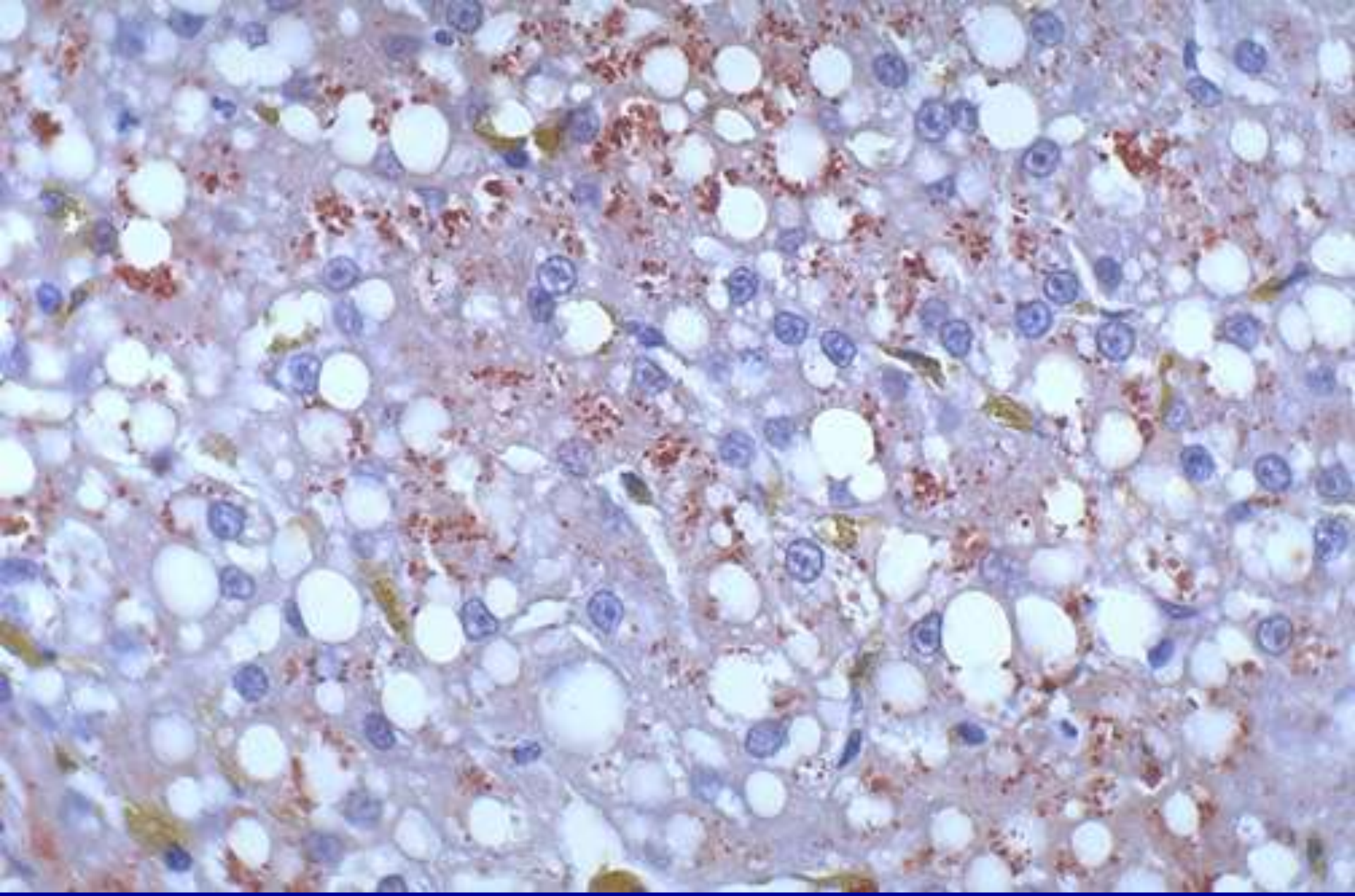
Kayser-Fleischer Ring

bräunlich-grünlicher Limbus-naher Hornhautring
    1-3 mm breit
bedingt durch Kupfereinlagerung



Kayser-Fleischer Ring

Arcus senilis



excessive lysosomal copper in a patient with the rare autosomal recessive disorder Wilson's disease

Hämochromatose

- Siderophilie, autosomal-rezessiv
- Mukosablock aufgehoben: 1 mg pro T. -
- Gesamtkörpereisengehalt: 3 g zu 20 g
- Leber: Hepatomegalie, Leberzirrhose, Karzinom
- Sekundäre Kardiomyopathie - Myokardfibrose
- Hyperpigmentation der Haut – Pankreasfibrose

BRONZDIABETES

Diff. Dg.: sekundäre Siderose – Berliner Blau Färbung

- Morbus Wilson: Hepatolentikuäre Degeneration !!
- autosomal rezessiv
- verminderte Ausscheidung der Kupfer !! Pathologische Kupferspeicherung !!
- Leber: Hepatitis – Zirrhose, Gehirn, Augen, Niere

ZIRRHOSE

- **postnekrotische Zirrhose: postinfektiös o. Toxisch**

Grobhöckrig, unregelmässige Pseudolobuli

- **posthepatitische portale Zirrhose: nach chronisch-**

aggressiven Virushepatitiden

- **Primär biliäre Zirrhose - Autoimmunerkrankung**

Zerstörung der Gallengangsepithelien mit periduktaler Fibrose

- **sekundär Biliäre Zirrhose – rezidivierende Gallengang-**

Störungen. (Mukoviszidose oder Infektionen)

„grüne „ biliäre Zirrhose

- **Pigmentzirrhose – nach vermehrter Eisenspeicherung**

infolge einer Hämochromatose

Komplikationen der ZIRRHOSE

- **Ikterus**
- **endokrine Störungen - Gynäkomastie**
- **verminderte Syntheseleistung:**

Mangel an Gerinnungsfaktoren — Blutungen
Albumin — Ödem
Apoferritin — Hämosiderose

- **portale Hypertonie – Milzstau**

Ösophagusvarizen, Caput medusae, Hämorrhoiden, Pfortaderthrombose – (Pylethrombose) oder Abdominalvenenthrombose

- **Ascites**
- **Hepatische Enzephalopathie**

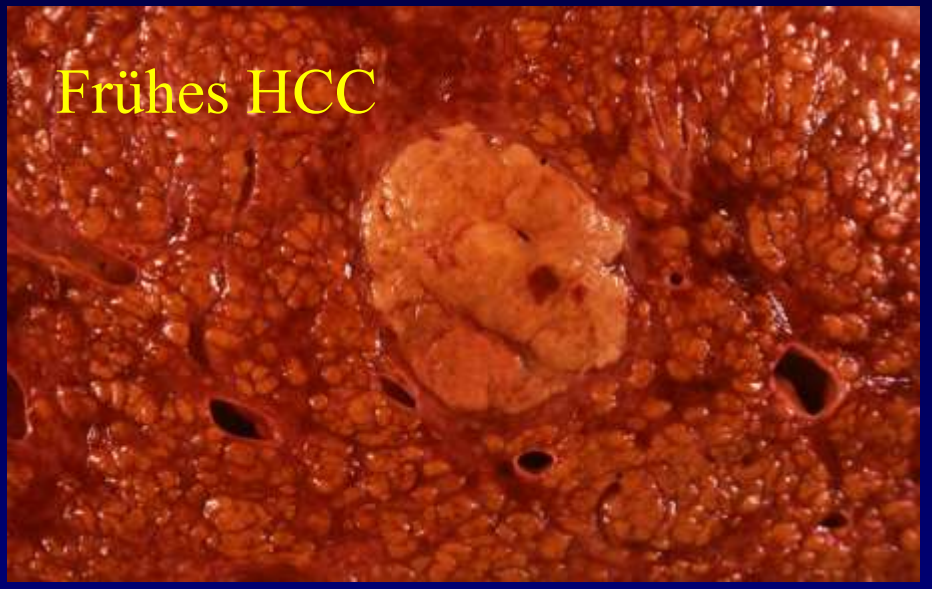
Komplikationen der ZIRRHOSE

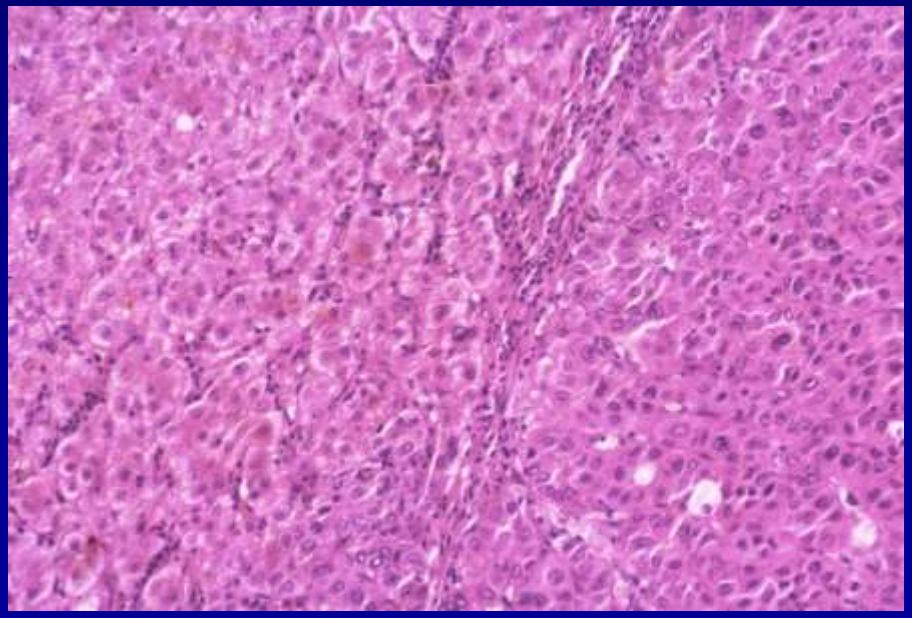
- **Leberausfallkoma: Verlust der Fähigkeit zum Abbau toxischer Stoffe**

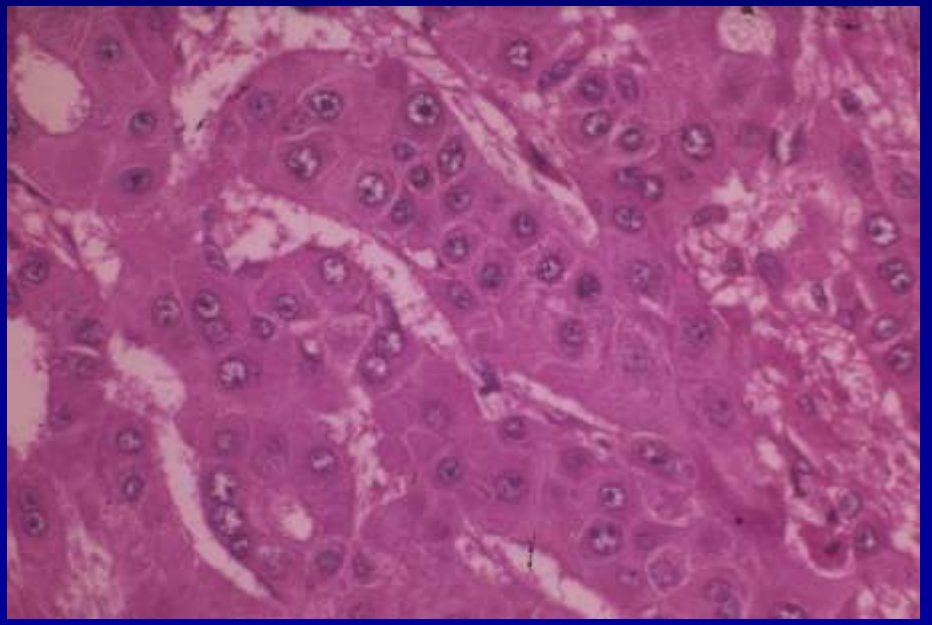
Leberzerfallskoma: Zerfallsprodukten bie massiver Zellzerstörung. (Knollenblätterpilz, fulminante Virushepatitis). Aszites

- **Leberkarzinom !!!**

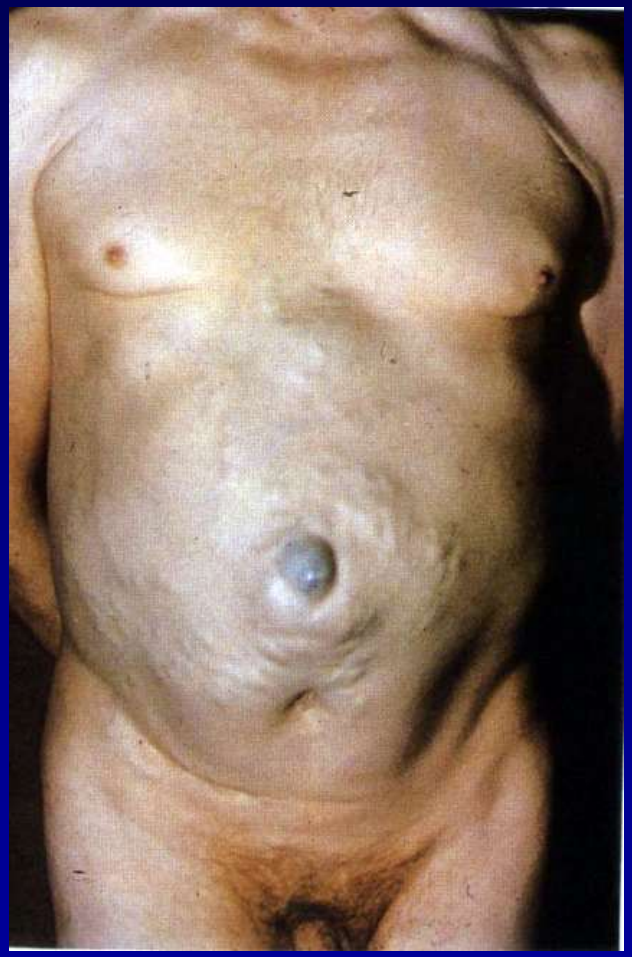

182-82

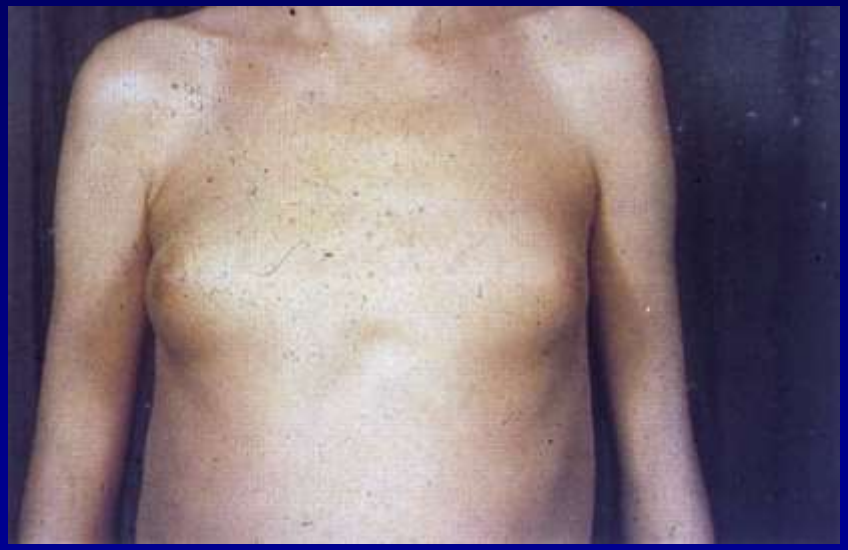

Frühes HCC





PATHOLOGIE der LEBER





Letzte Chance bei Leberzirrhose: Leberverpflanzung - TX