Hepatitis research in Hungary: from identification to treatment

Prof. Dr Zsuzsa Schaff

Semmelweis University

Member of the Hungarian Academy of Sciences

Elimination of Viral Hepatitis in Hungary: Lessons learnt and the way forward

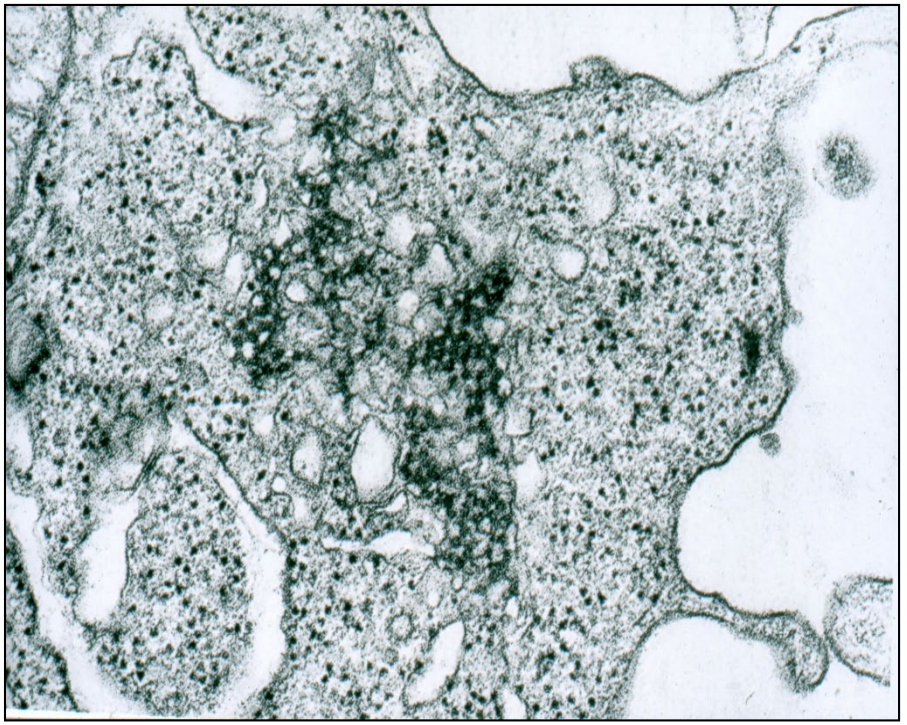
Budapest, Hungary

30-31 October 2019

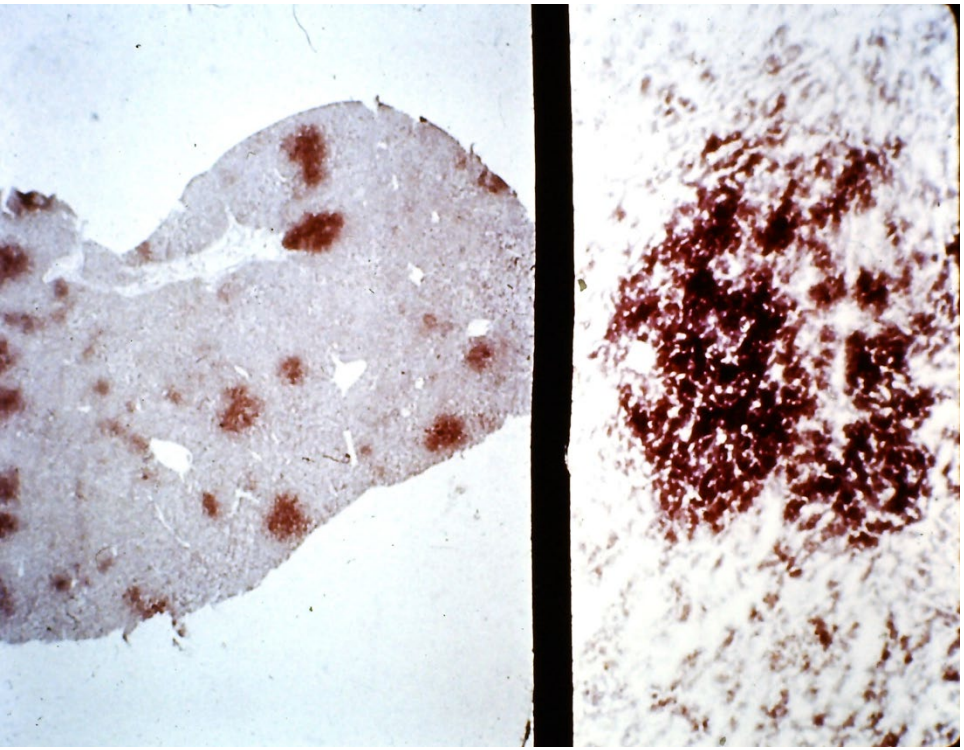
Viral Infections and Cytokines

- Several cytokines are released after in vivo and in vitro after virus infection

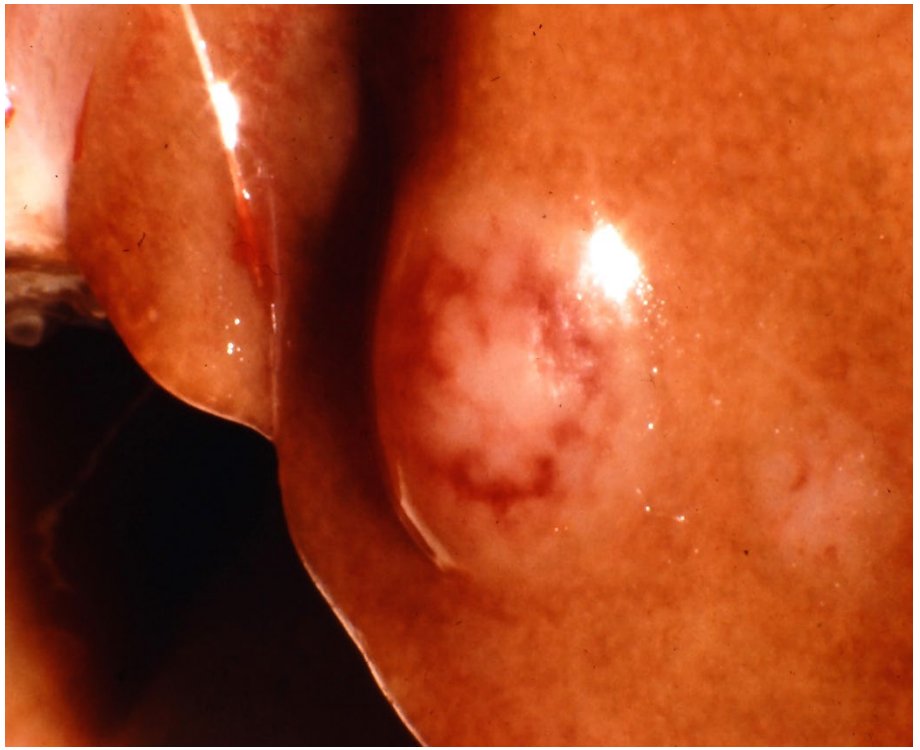
Schaff Z et al.
Cancer Research *32: 2696.1972,*
Lab Invest *29:577-586 1973,*
JNCI *51:293-297, 1973,*
JNCI *51:1751-60 1973,*
J Invest Derm *63:407-410 1974,*
Int J Cancer *18: 697-702 1976,*
Ultr Path *3:169-173 1982,*
Lancet *1:1336 1983,*
Hepatology *6:966-970 1986*



Chemical and virus-induced hepatocarcinogenesis



DEN-induces foci in rat liver
GGT reaction



MC-29 induced turkey hepatoma

Schaff et al. Virchows Arch A 1971, 1982, Acta Morph 1978

DONALD EARL HENSON, M.D.

Program Director
Early Detection Branch
Division of Cancer Prevention and Control
National Cancer Institute
Bethesda, Maryland

JORGE ALBORES-SAAVEDRA, M.D.

Professor of Pathology
Director, Division of Anatomic Pathology
University of Texas
Southwestern Medical Center
Dallas, Texas

PATHOLOGY OF INCIPIENT NEOPLASIA

Second Edition

Volume 28 in the Series
MAJOR PROBLEMS IN PATHOLOGY

Chapter

8

LIVER

ZSUZSA SCHAFF, KAROLY LAPIS, AND DONALD EARL HENSON

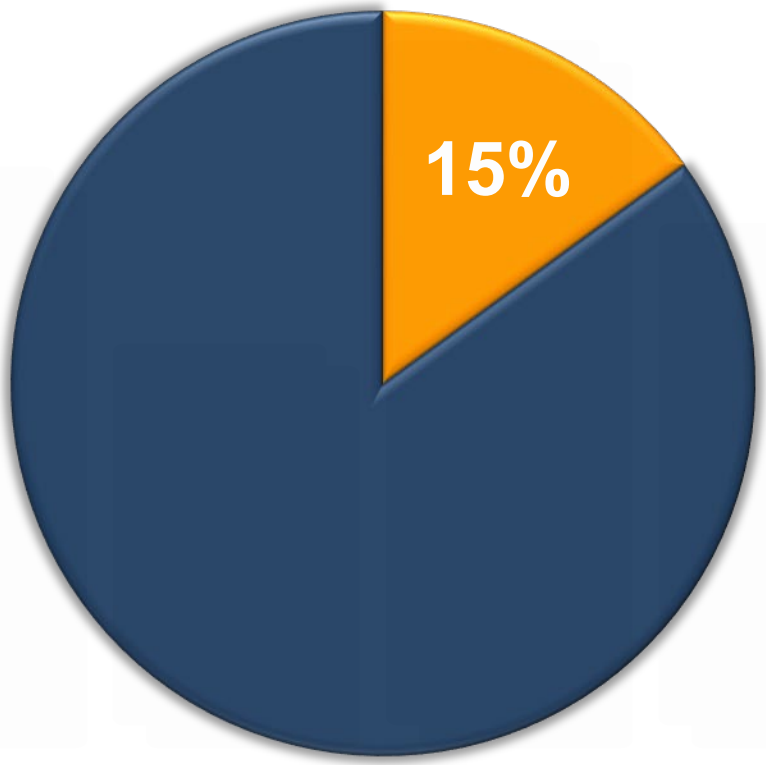
W. B. SAUNDERS COMPANY
HARCOURT BRACE JOVANOVICH, INC.
Philadelphia London Toronto Montreal Sydney Tokyo

Epidemiology of Hepatocellular Carcinoma

1983), 53 years in American blacks, and 61 years in American whites. HCC among chil-

1993. pp. 151-166.

Etiology of Cancer



- 15%
  - Viruses
  - Bacteria
  - Paracytes

Cancer Incidence and Mortality Worldwide

New Tumor cases in 2018: 18,1 million

Mortality 2018: 9,6 million

New Tumor cases in 2013: 14,9 million

Mortality in 2013: 8,2 million

New tumor cases in 2008: 12,7 million

Mortality in 2008: 7,6 million

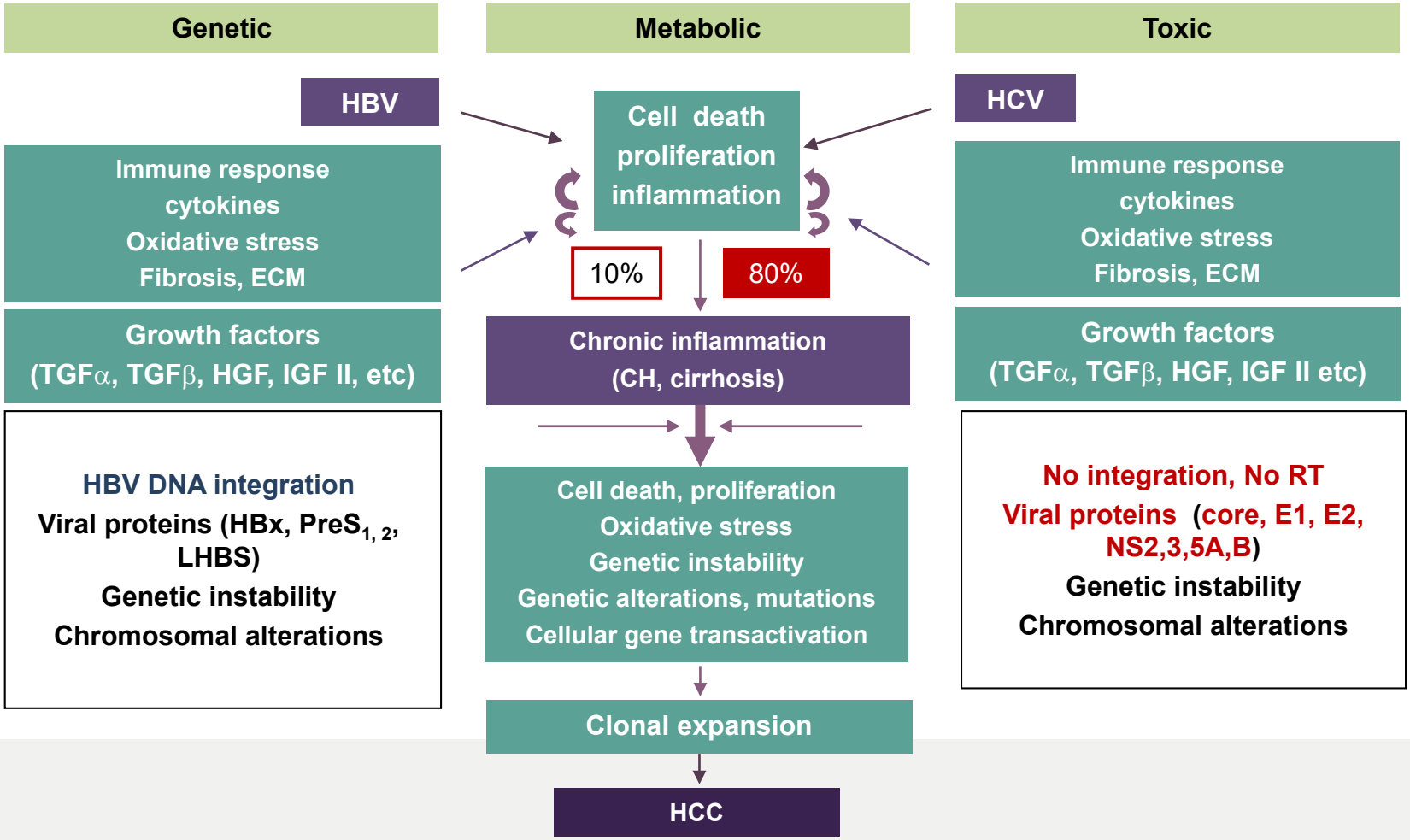
New tumor cases in 2002: 11 million

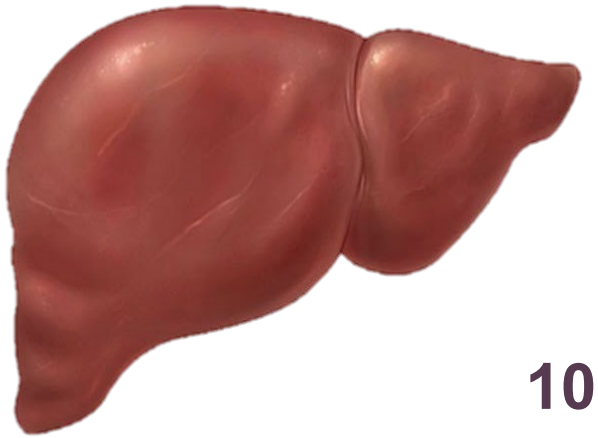
Mortality in 2002: 7 million

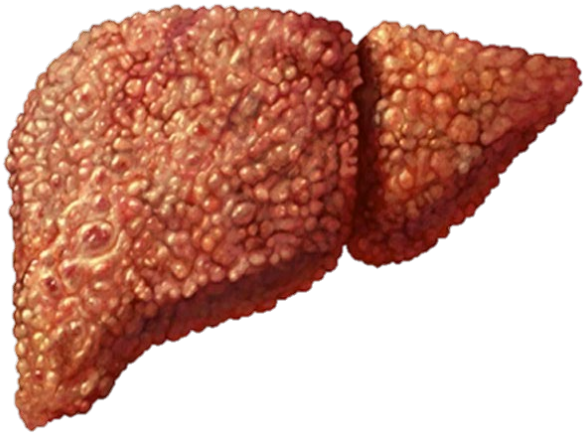
Ferlay J et al. Lyon, France: IARC Press; 2004.

GLOBOCAN 2008 (IARC 2010), JAMA Oncol.2015, CA Cancer J.Clin. 2018 Sept

Pathomechanism of virus-induced liver cancer (HCC)







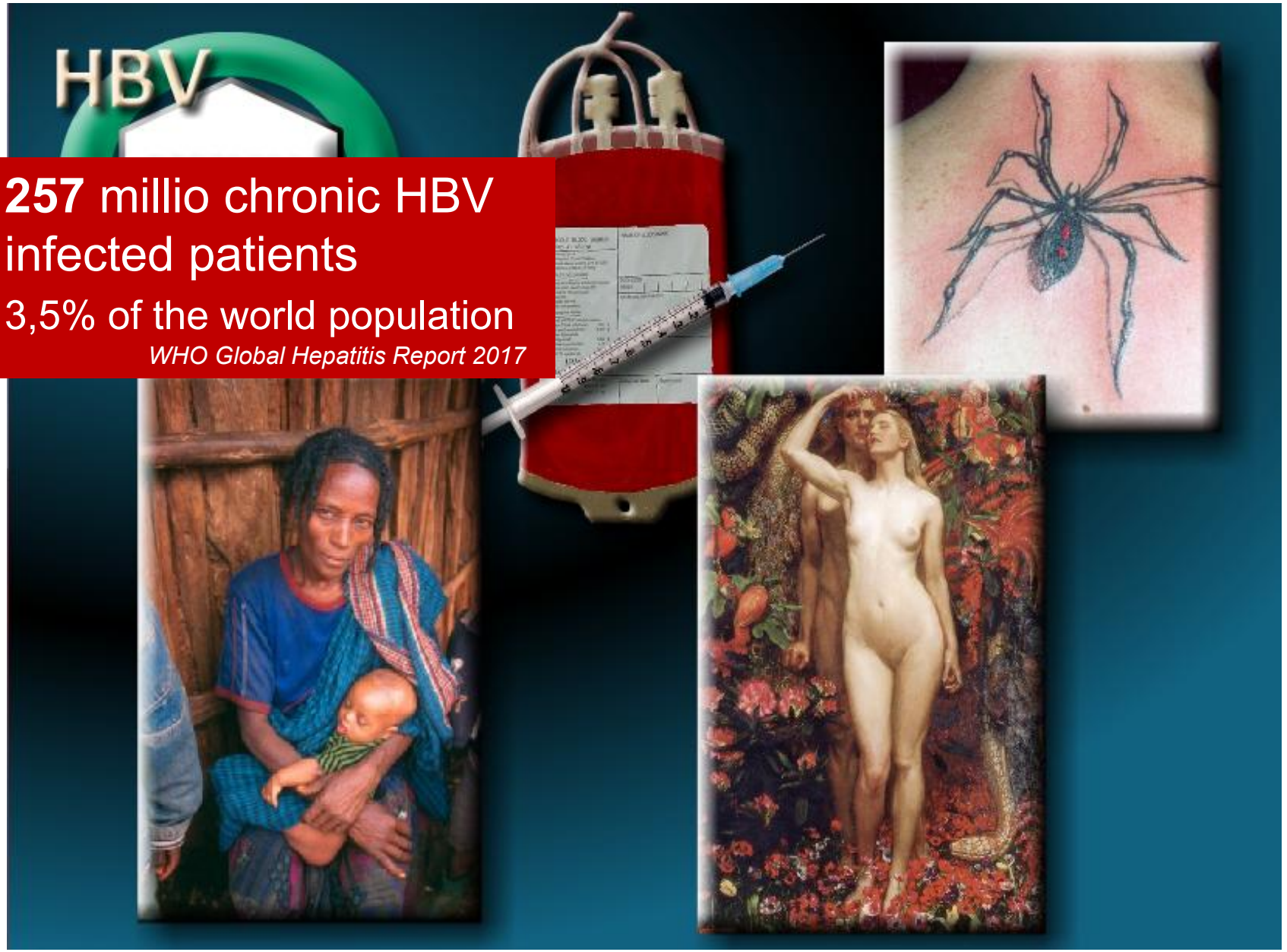
10-20 yrs

HBV

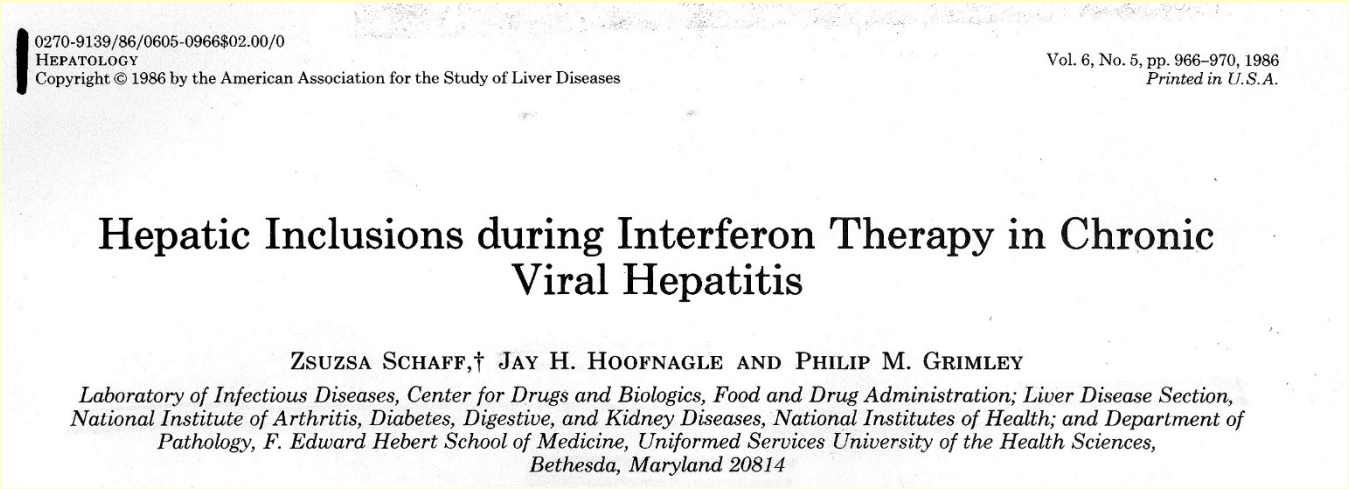
10%
Chronic
inflammation

Cirrhosis

Hepatocellular
carcinoma (HCC)


HBV
- **257** millio chronic HBV infected patients
- 3,5% of the world population
WHO Global Hepatitis Report 2017

- Interferon therapy in CH-B *Hepatology 6:966-970 1986*



0270-9139/86/0605-0966$02.00/0
HEPATOLOGY

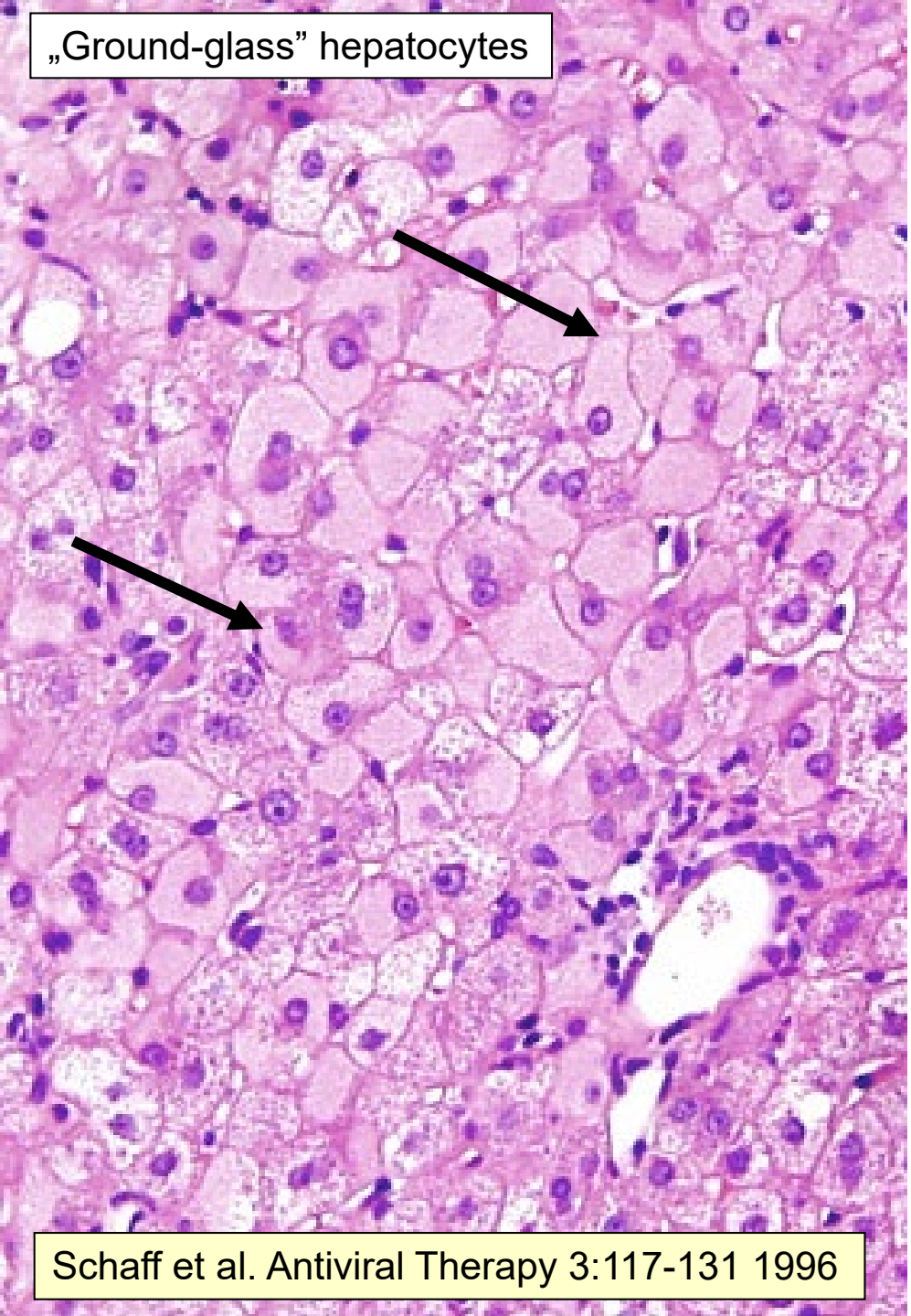
Vol. 6, No. 5, pp. 966–970, 1986
Printed in U.S.A.

Hepatic Inclusions during Interferon Therapy in Chronic Viral Hepatitis

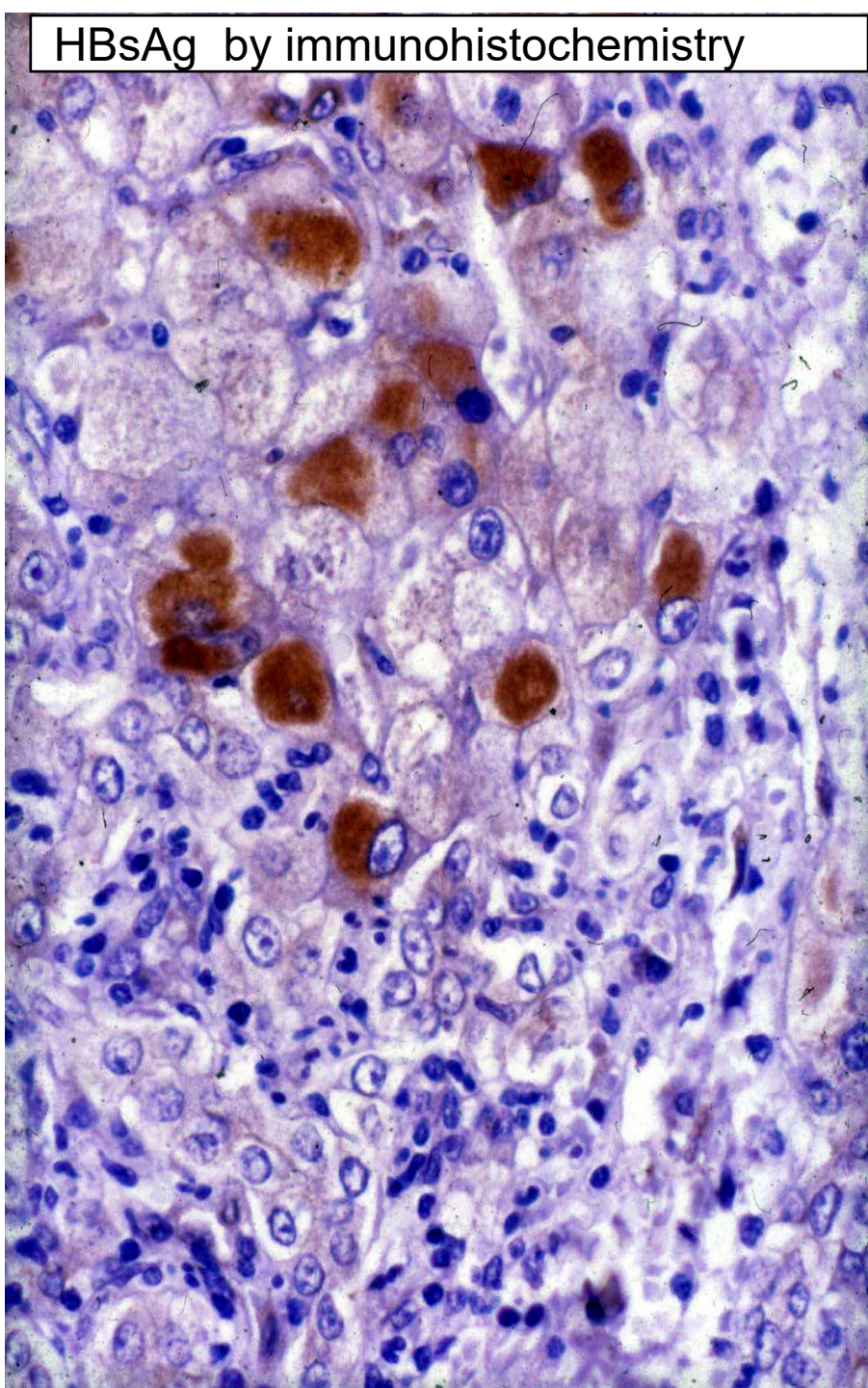
ZSUZSA SCHAFF,† JAY H. HOOFNAGLE AND PHILIP M. GRIMLEY

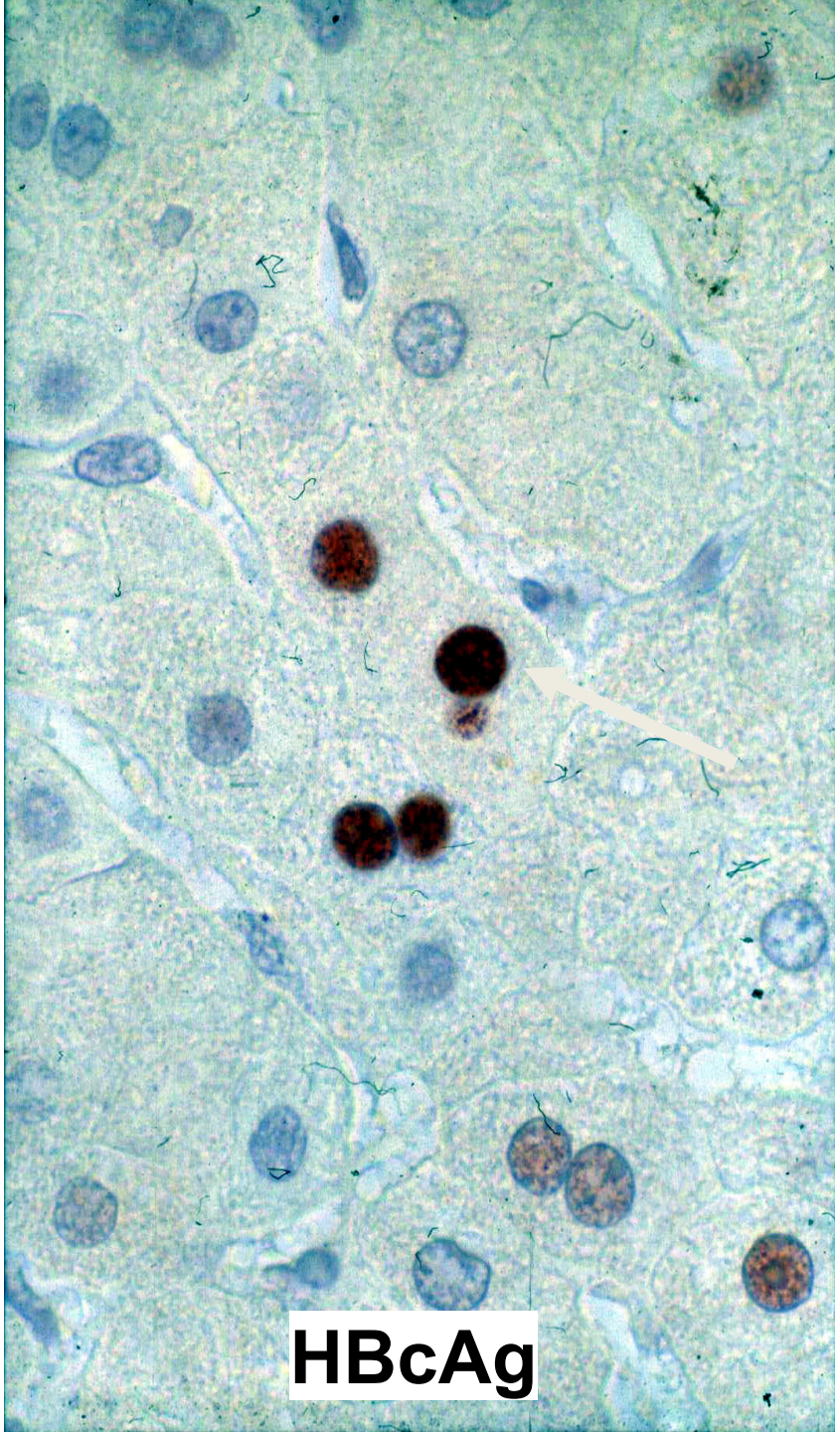
Laboratory of Infectious Diseases, Center for Drugs and Biologics, Food and Drug Administration; Liver Disease Section, National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases, National Institutes of Health; and Department of Pathology, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814

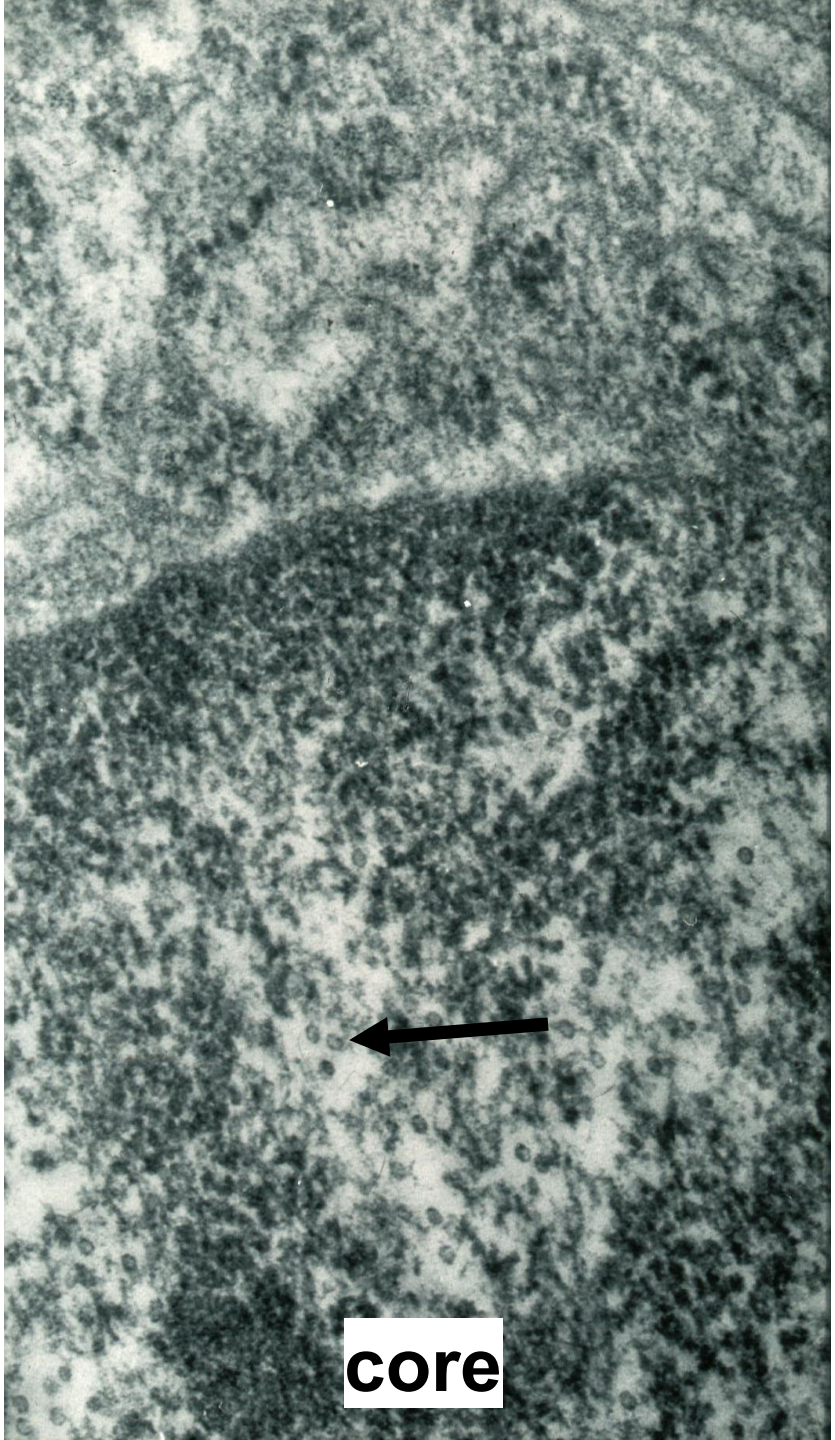
IFN treatment induces increased expression of HLA class I antigenes leading to elimination of infected hepatocytes (Hepatology 6:349-353 1986)

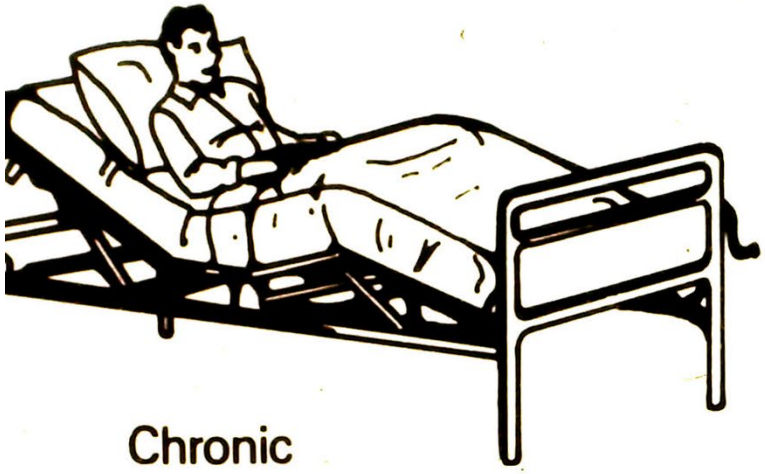


Schaff et al. Antiviral Therapy 3:117-131 1996



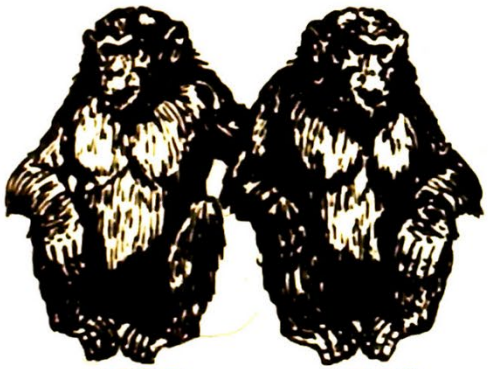

HBcAg


core



Chronic
Non-A, Non-B Hepatitis

Broken Pipette



#922 #930

Non-A,Non-B hepatitis

Lancet 1978 8062: 463-466

Reprinted from TRANSFUSION, May-June 1984
Vol. 24, No. 3

Additional evidence for more than one agent of human non-A, non-B hepatitis

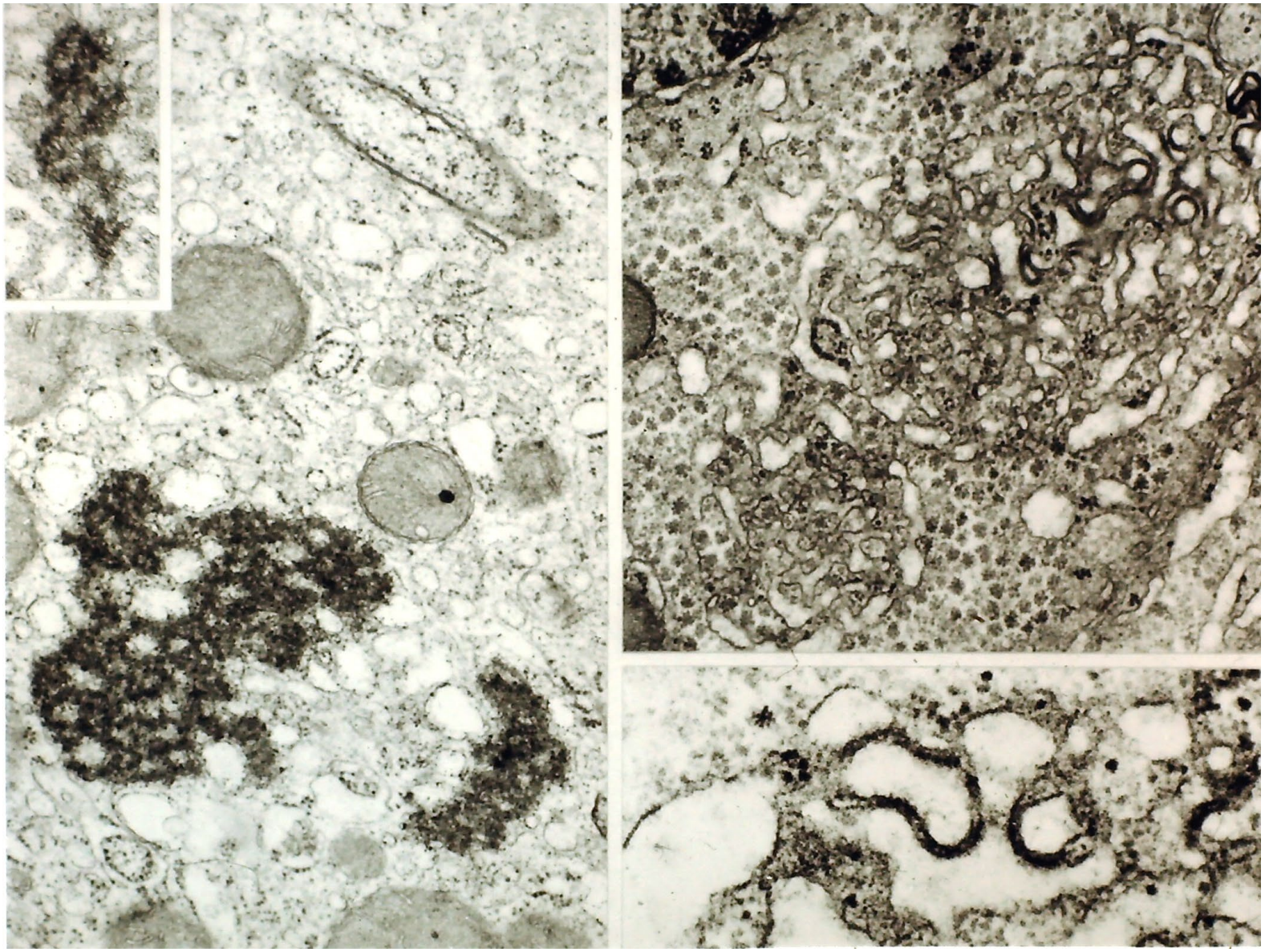
Transmission and passage studies in chimpanzees

E. TABOR, P. SNOY, D. R. JACKSON, Z. SCHAFF, P. M. BLATT AND R. J. GERETY

Evidence supporting the existence of two agents of human non-A, non-B hepatitis was obtained by the inoculation of chimpanzees sequentially with serum from a chronically infected human (Inoculum I) and with fibrinogen prepared from pooled plasma (Inoculum IV), each of which had transmitted non-A, non-B hepatitis to humans. Passage inoculations of serum samples obtained during the acute stages of chimpanzee infections transmitted by either the agent in Inoculum I or IV also transmitted non-A, non-B hepatitis to additional chimpanzees. Transmission and passage of the agent in Inoculum IV were conducted in chimpanzees which previously had recovered from infection by the agent in Inoculum I. Cytoplasmic tubules in hepatocytes, which have been described during non-A, non-B hepatitis, were observed by electron microscopy in liver biopsies obtained during all infections transmitted by the agent in Inoculum I. These cytoplasmic tubules were not detected in liver biopsies from chimpanzees infected by Inoculum IV, except in one chimpanzee inoculated by Inoculum IV without prior exposure to the agent in Inoculum I. The cytoplasmic tubules observed in this study were found to be composed of transverse bands arranged with a periodicity of approximately 17 nm. These studies suggest that two different agents or distinct serotypes of human non-A, non-B hepatitis may have been present in these inocula, although reactivation of latent infection or reinfection could not be ruled out completely. **TRANSFUSION** 1984;24:224-230.

Ultrastructural alterations in nonA-nonB hepatitis vírus infection

Schaff et al. Virchow's Arch 45: 301-312 1984

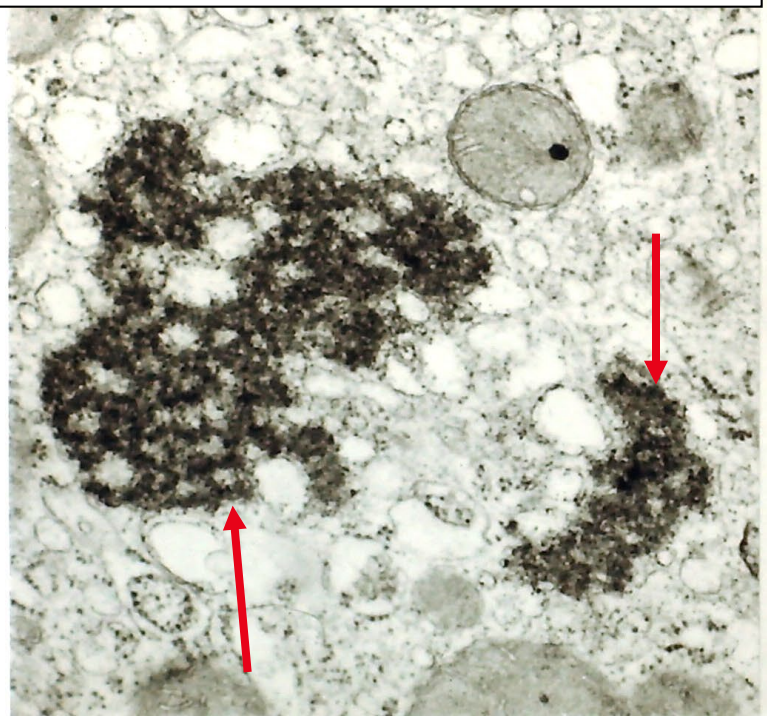


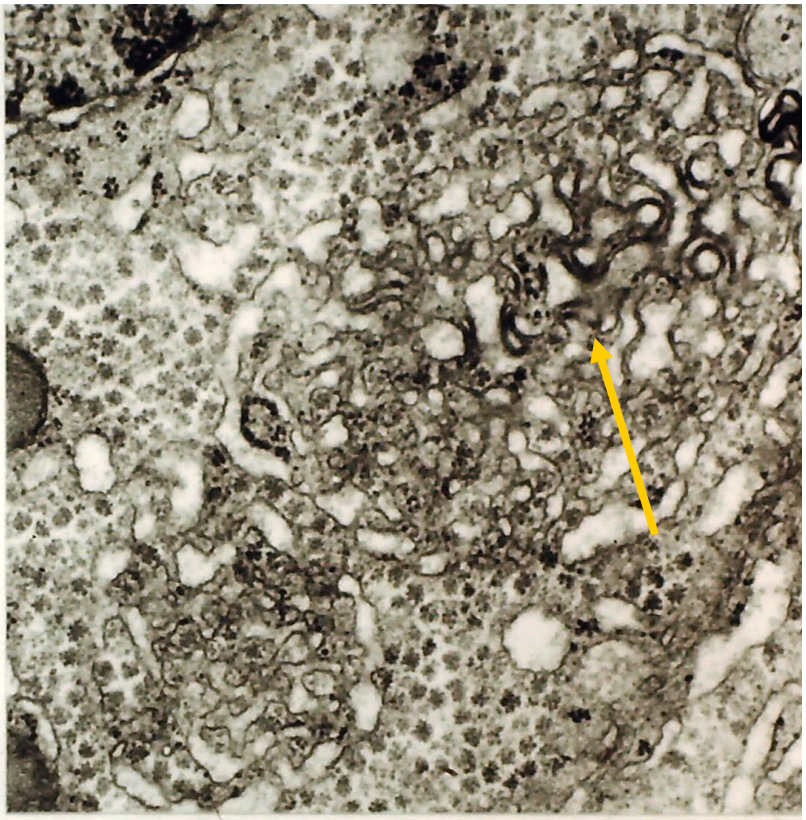
A nonA-nonB hepatitis vírus fertőzés ultrastrukturális jelei

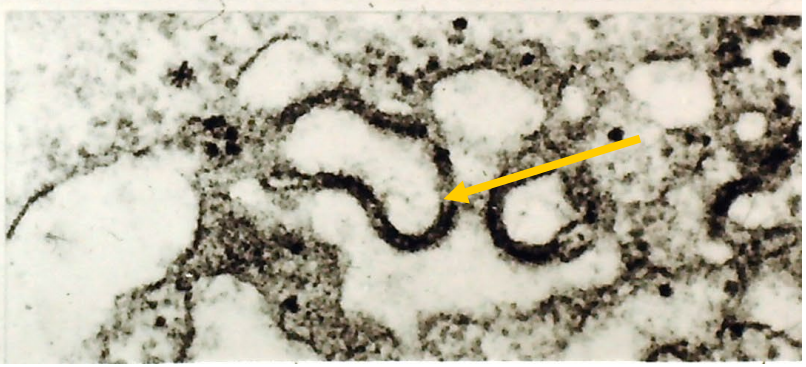
Schaff et al. Virchow's Arch 45: 301-312 1984

Membran-associated replication complex

Virális proteinek
Replikálódó virális RNS
Alterált celluláris membránok







Viral Hepatitis and Liver Disease, pages 580–587

Morphology, Immunohistochemistry, and In Situ Hybridization of Experimental and Human Non-A, Non-B Hepatitis

ZSUZSA SCHAFF, BELINDA SETO, WILLIAM G. COLEMAN, JR., AND KAROLY LAPIS
First Institute of Pathology and Experimental Cancer Research, Semmelweis Medical University, Budapest, Hungary (Z.S., K.L.); Hepatitis Laboratory, Division of Blood and Blood Products, Center for Drugs and Biologics, Bethesda, Maryland (B.S.); Section on Pharmacology, Laboratory of Biochemical Pharmacology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland (W.G.C.)

Bradley DW, Cook EH, Gravelle CR, McCaustland KA, Maynard JE, Miller MF, **Schaff Zs:**
Non-A, non-B hepatitis in experimentally infected chimpanzees: Comparative morphology of virus-induced ultrastructural changes
In: Hepatitis Viruses and Hepatocellular Carcinoma: Approaches Through Molecular Biology and Ecology, New York: **Academic Press, 1985, pp. 225-251**

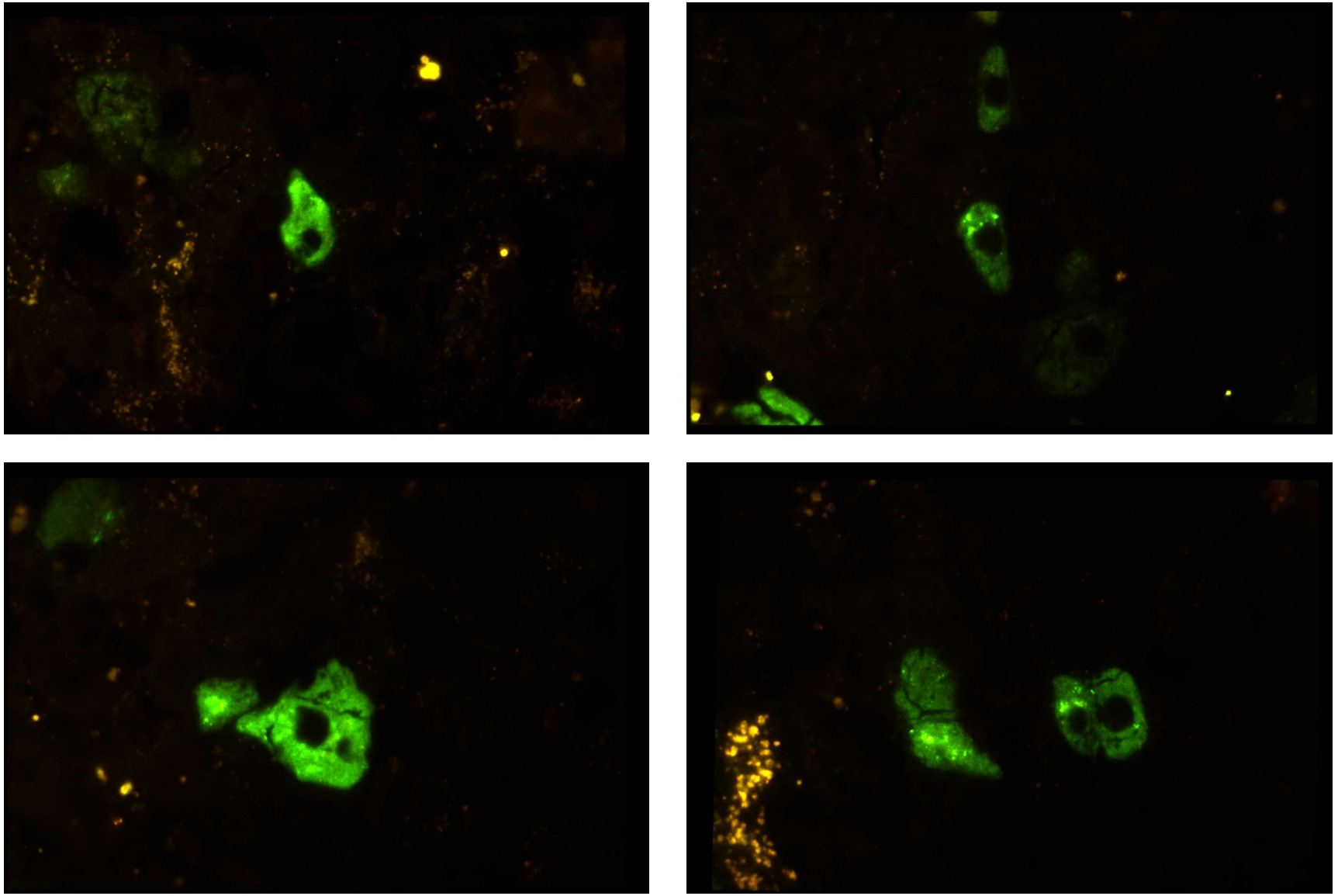
Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome

1.QL Choo,
2.G Kuo,
3.AJ Weiner,
4.LR Overby,
5.DW Bradley,
6.M Houghton
See all authors and affiliations

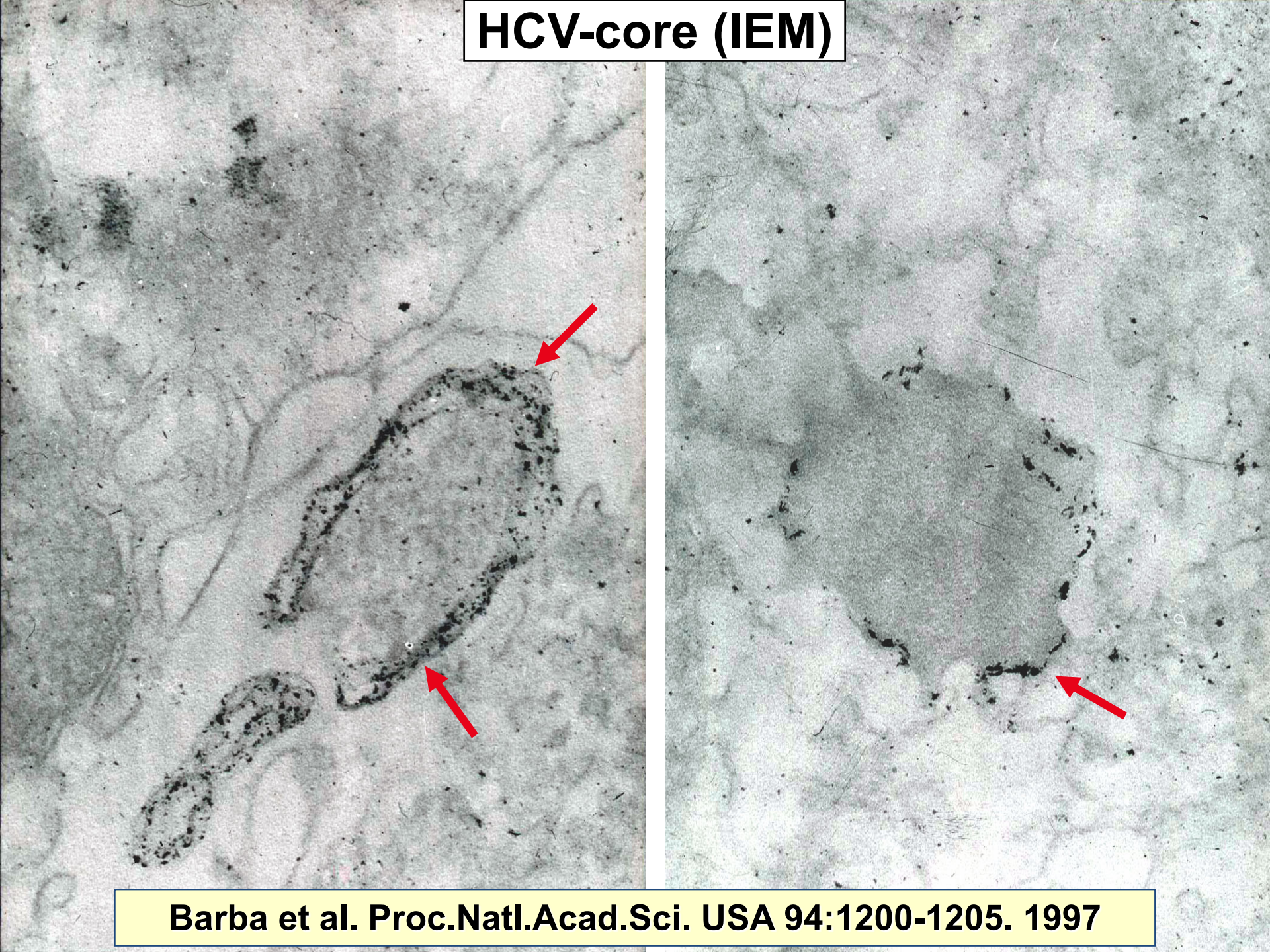
Science 21 Apr 1989:
Vol. 244, Issue 4902, pp. 359-362
DOI: 10.1126/science.2523562

Localisation of HCV by immunofluorescence

H.Alter, K.Krawczinsky, D.Bradley, Zs.Schaff



HCV-core (IEM)



Barba et al. Proc.Natl.Acad.Sci. USA 94:1200-1205. 1997

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 1200–1205, February 1997
Cell Biology

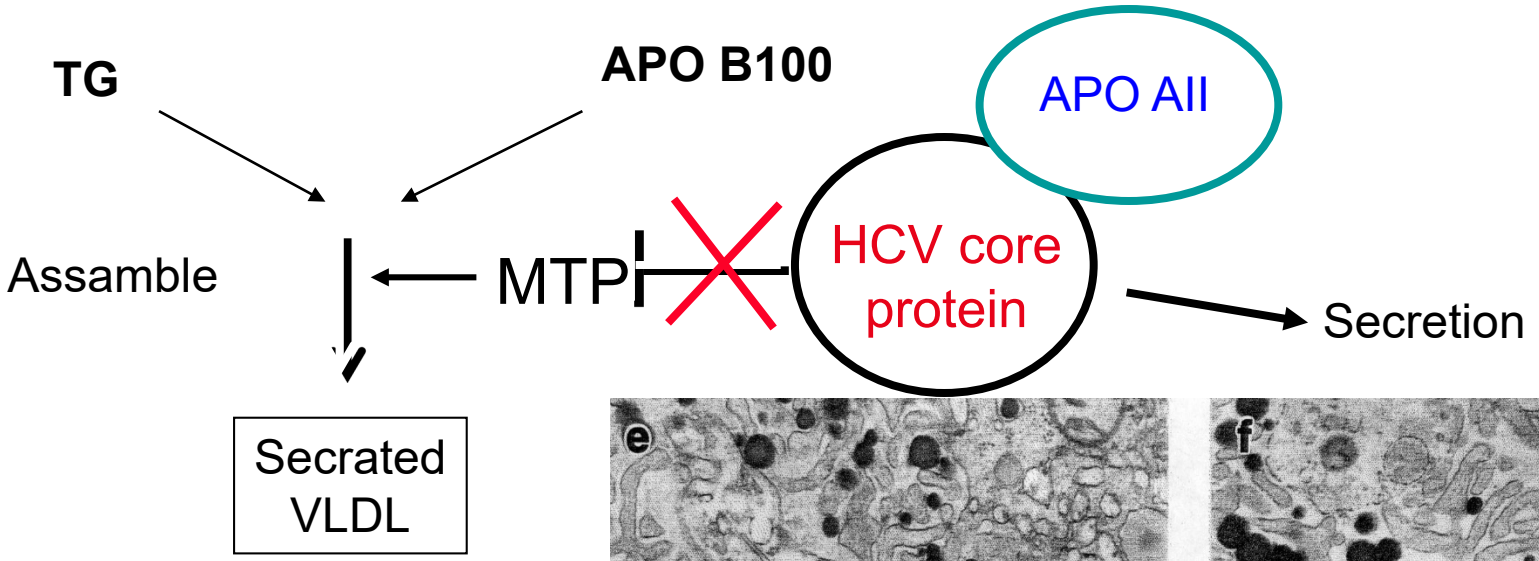
Hepatitis C virus core protein shows a cytoplasmic localization and associates to cellular lipid storage droplets

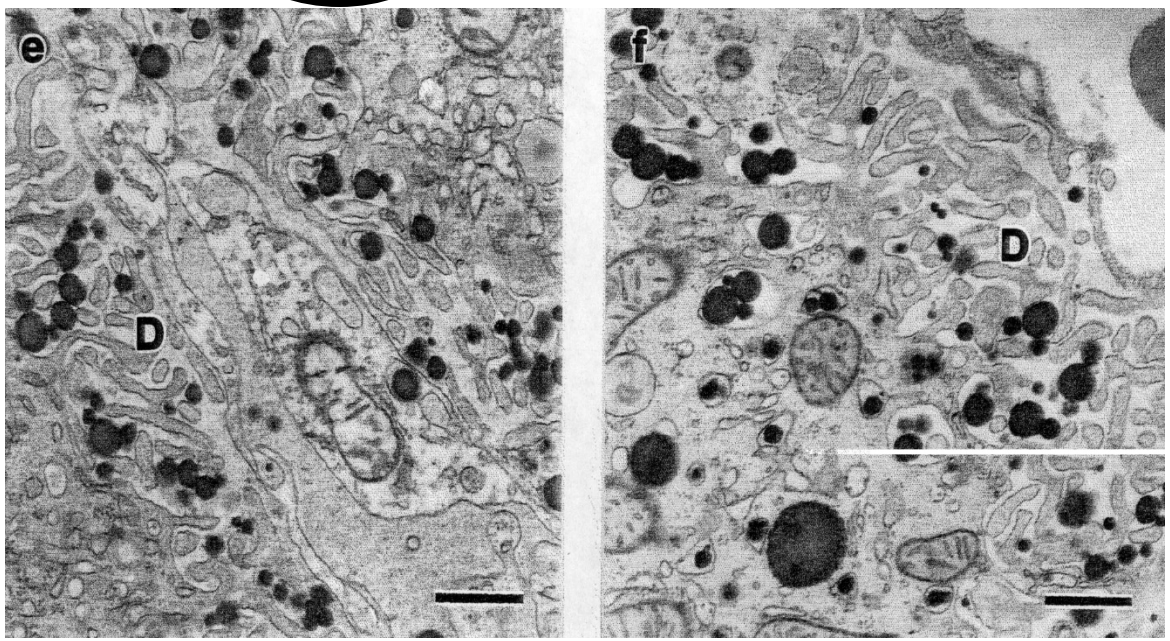
G. BARBA*, F. HARPER†, T. HARADA‡, M. KOHARA§, S. GOULINET¶, Y. MATSUURA‡, G. EDER‖, ZS. SCHAFF**, M. J. CHAPMAN¶, T. MIYAMURA‡, AND C. BRÉCHOT*††

*Liver Cancer and Molecular Virology, Institut National de la Santé et de la Recherche Médicale, Unité 370, 75015 Paris, France; †Functional Organization of the Nucleus, Unité Propre de Recherche 9044, 94801 Villejuif, France; ‡Departement of Virology II, National Institute of Health, Tokyo, 162, Japan; §Department of Microbiology, The Tokyo Metropolitan Institute of Medical Science, Tokyo, 113, Japan; ¶Lipoproteins and Atherogenesis, Institut National de la Santé et de la Recherche Médicale, Unité 321, 75013 Paris, France; ‖Departement of Clinical Research Gastroenterology and Hans Popper Primate Center, Immuno AG, Vienna, 1220, Austria; and **Institute of Pathology and Experimental Cancer Research, Semmelweis Medical University I, 1085, Budapest, Hungary

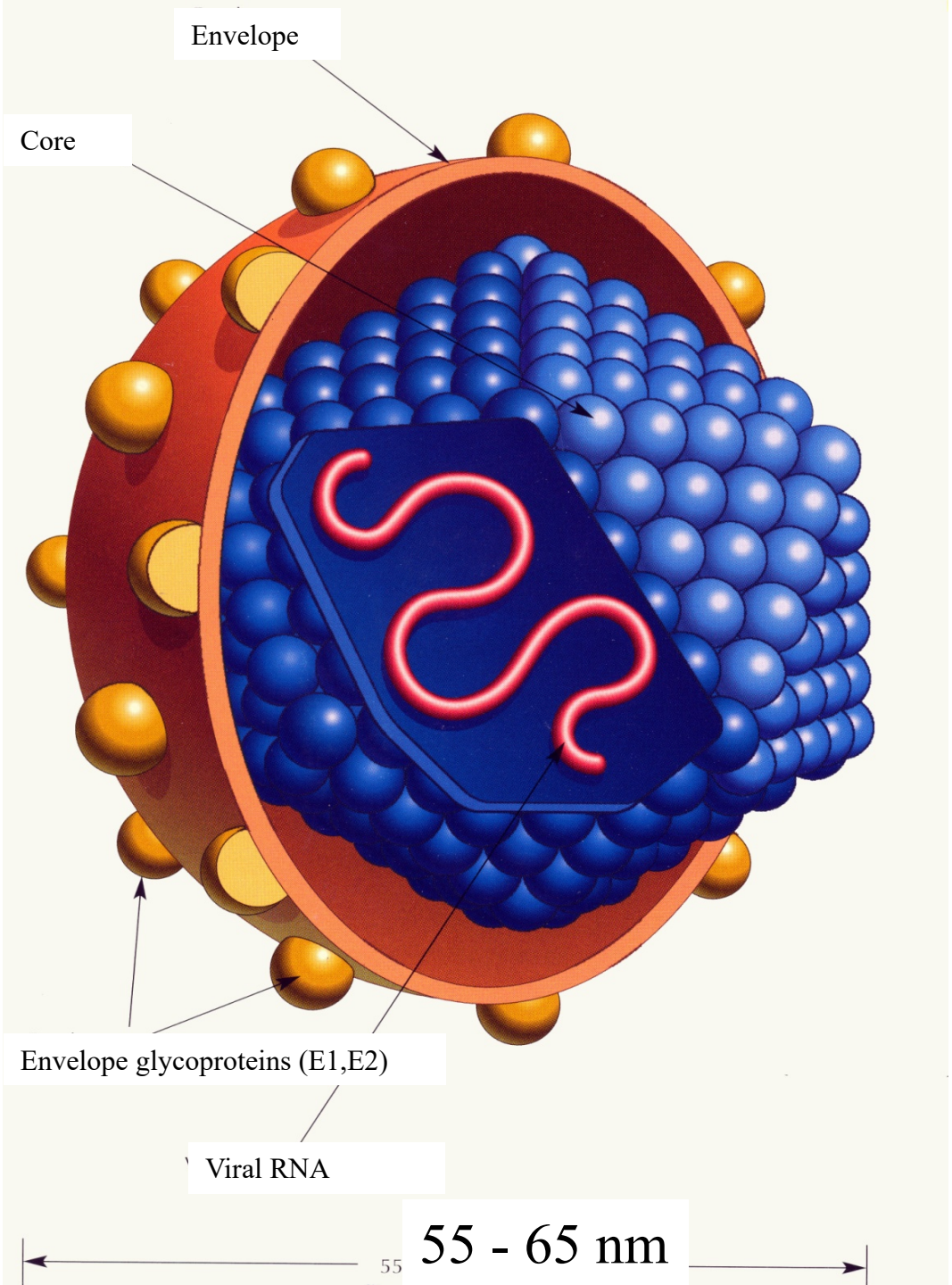
Communicated by William Rutter, University of California, San Francisco, CA, December 5, 1996 (received for review April 10, 1996)

HCV core protein/Apo AII
Double transgenic mice





Perlemutter et al.HCV core protein inhibits microsomal triglycerid transfer protein activity and VLD LP secretion: a model of viral-related steatosis FASEB J 16:185-194 2002



HCV

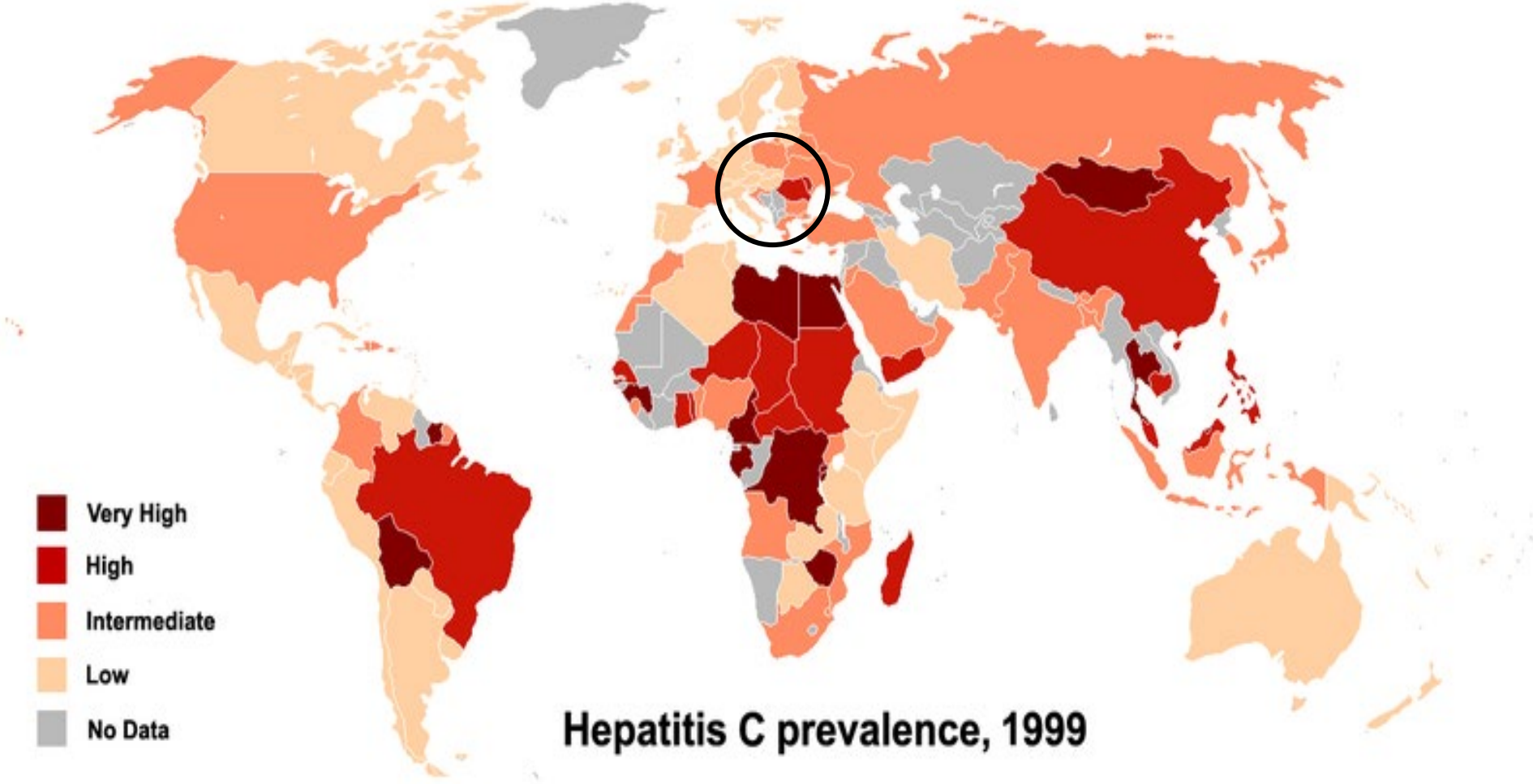
Hepacivírus

Flaviviridae

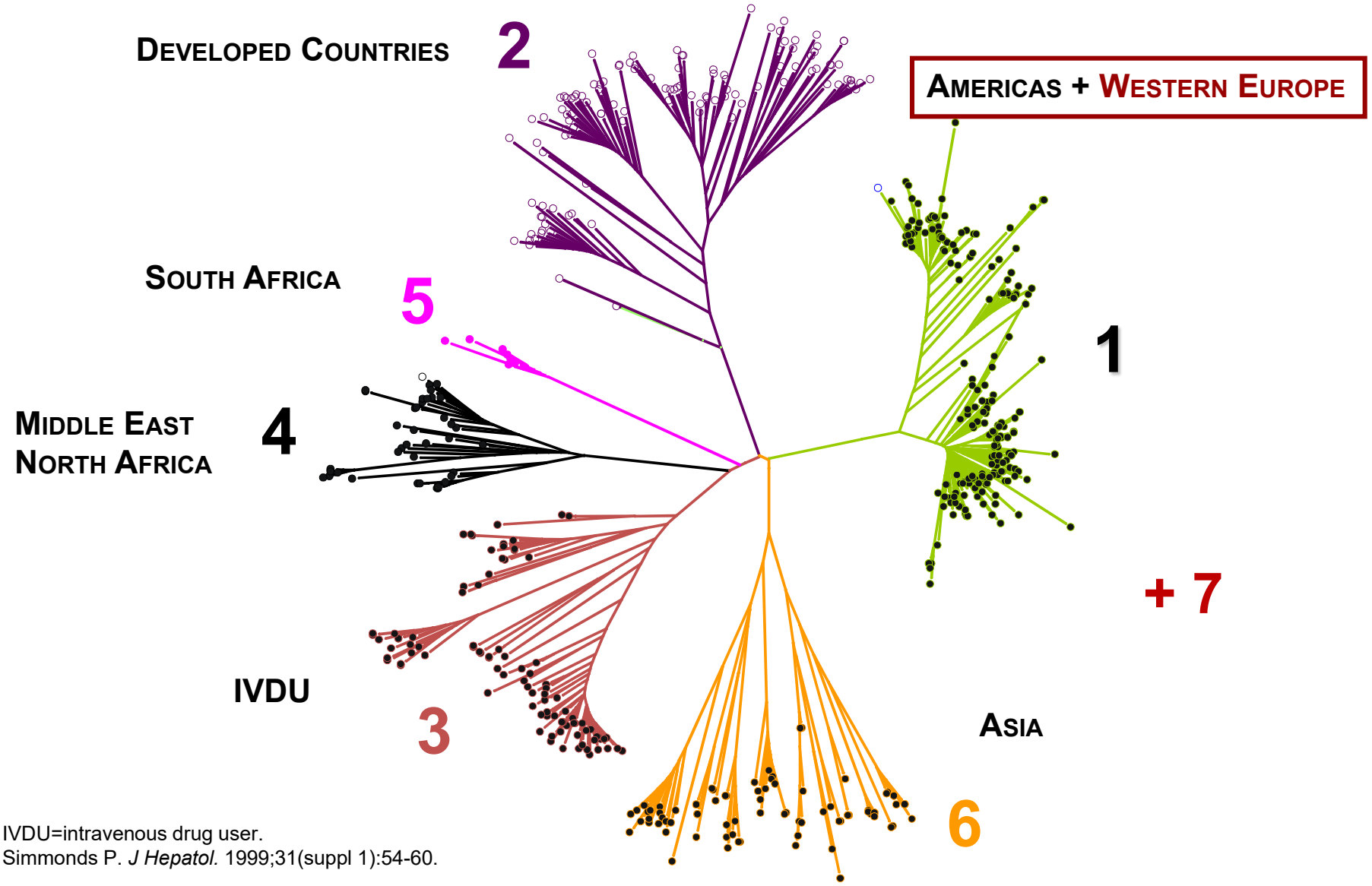
ssRNS

Great genomic variability
(7 genotypes, >100 subtypes)

HCV prevalence worldwide



HCV Genotypes



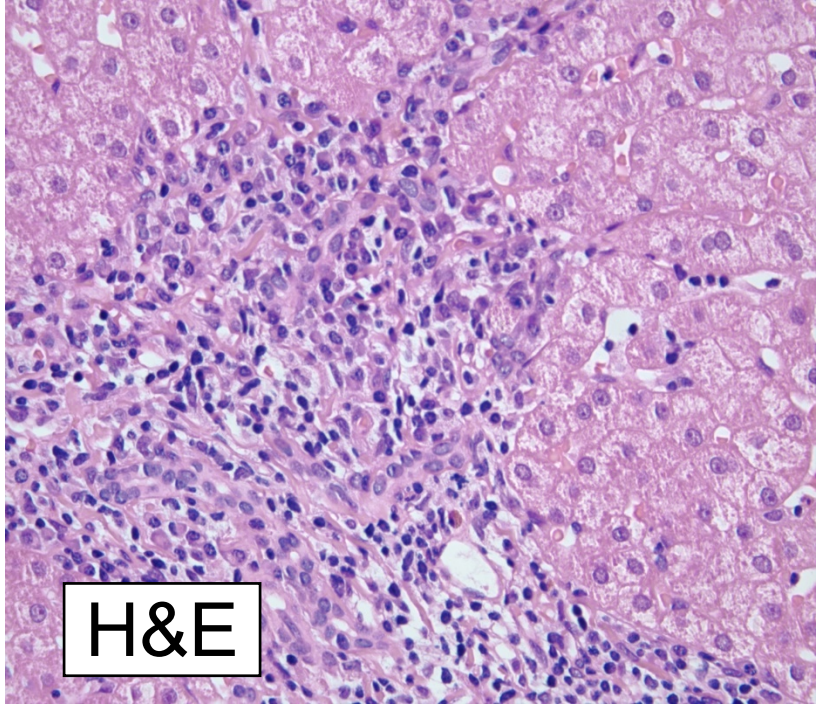
IVDU=intravenous drug user.
Simmonds P. *J Hepatol.* 1999;31(suppl 1):54-60.

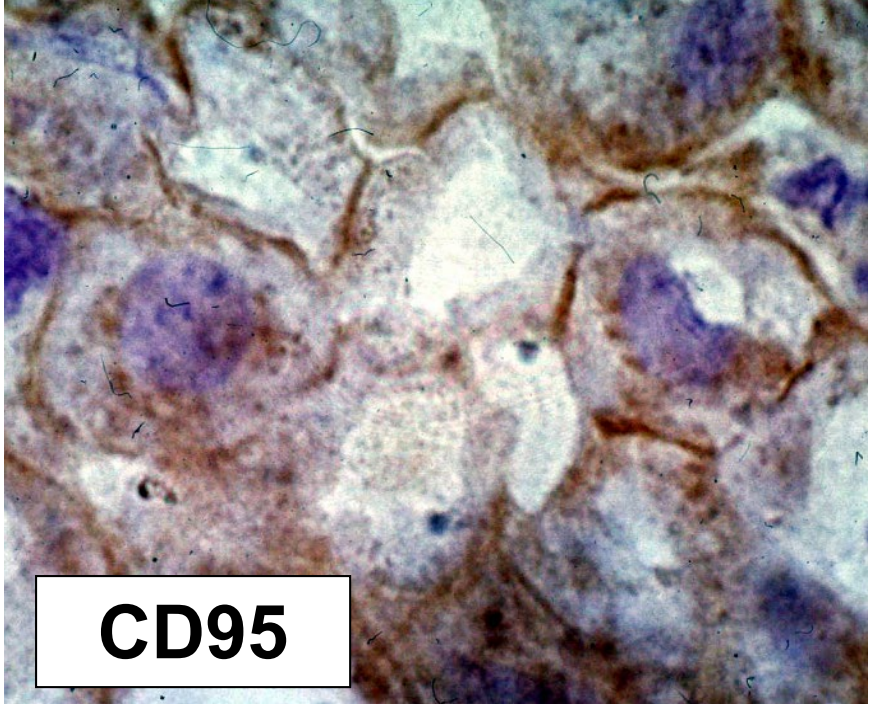
HCV genotypes in Hungary 2000-2017
(based on 5917 patients)

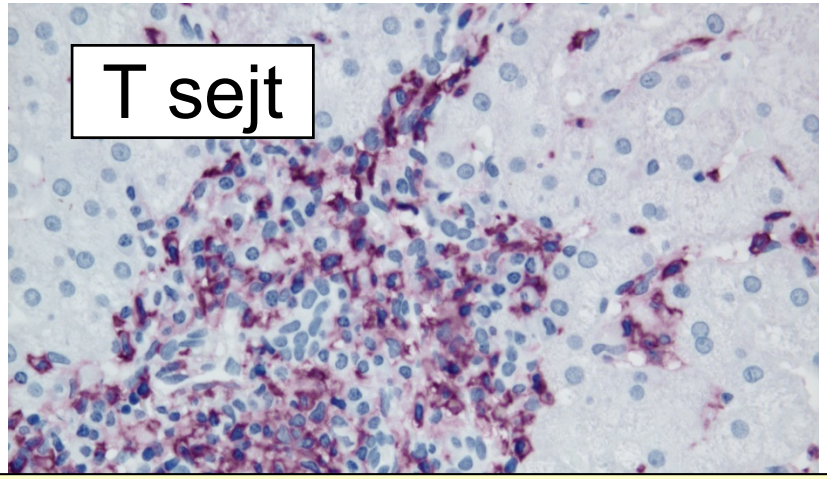
• 1a	5,6%
• 1b	84,6%
• 1a+1b	5,1%
• 3	1,8%
• Mixed	1,6%
• Not differentiated	1,1%

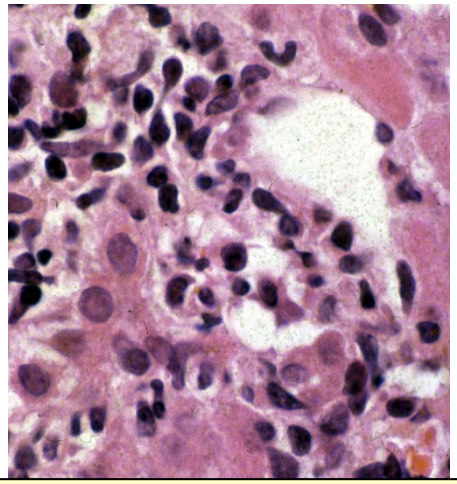
95,3%

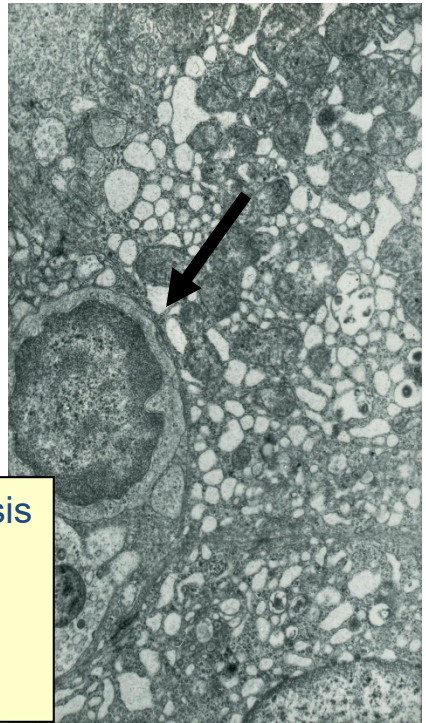
Judit Gervain et al. Orvosi Hetilap 2018. Suppl.2.



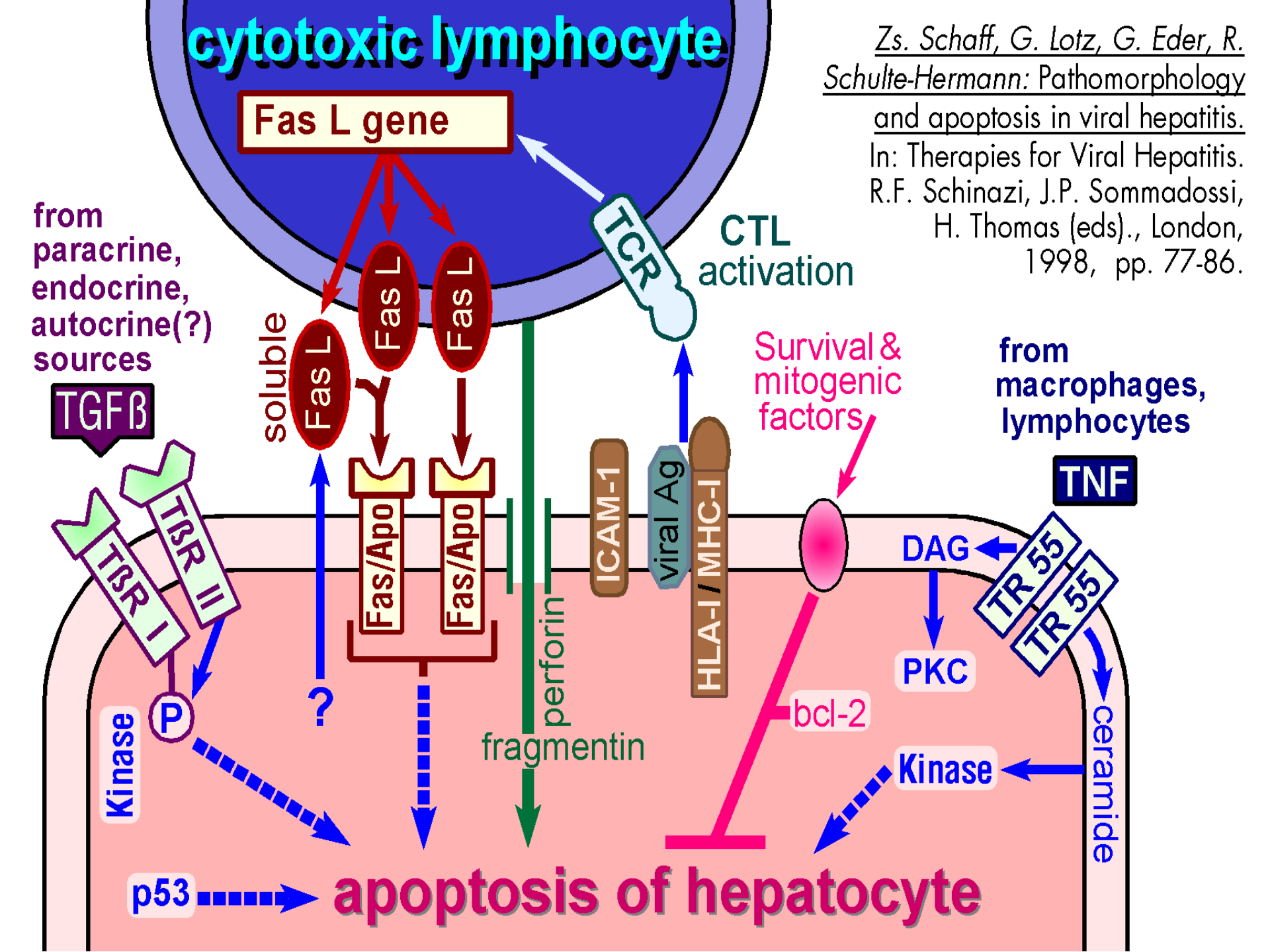






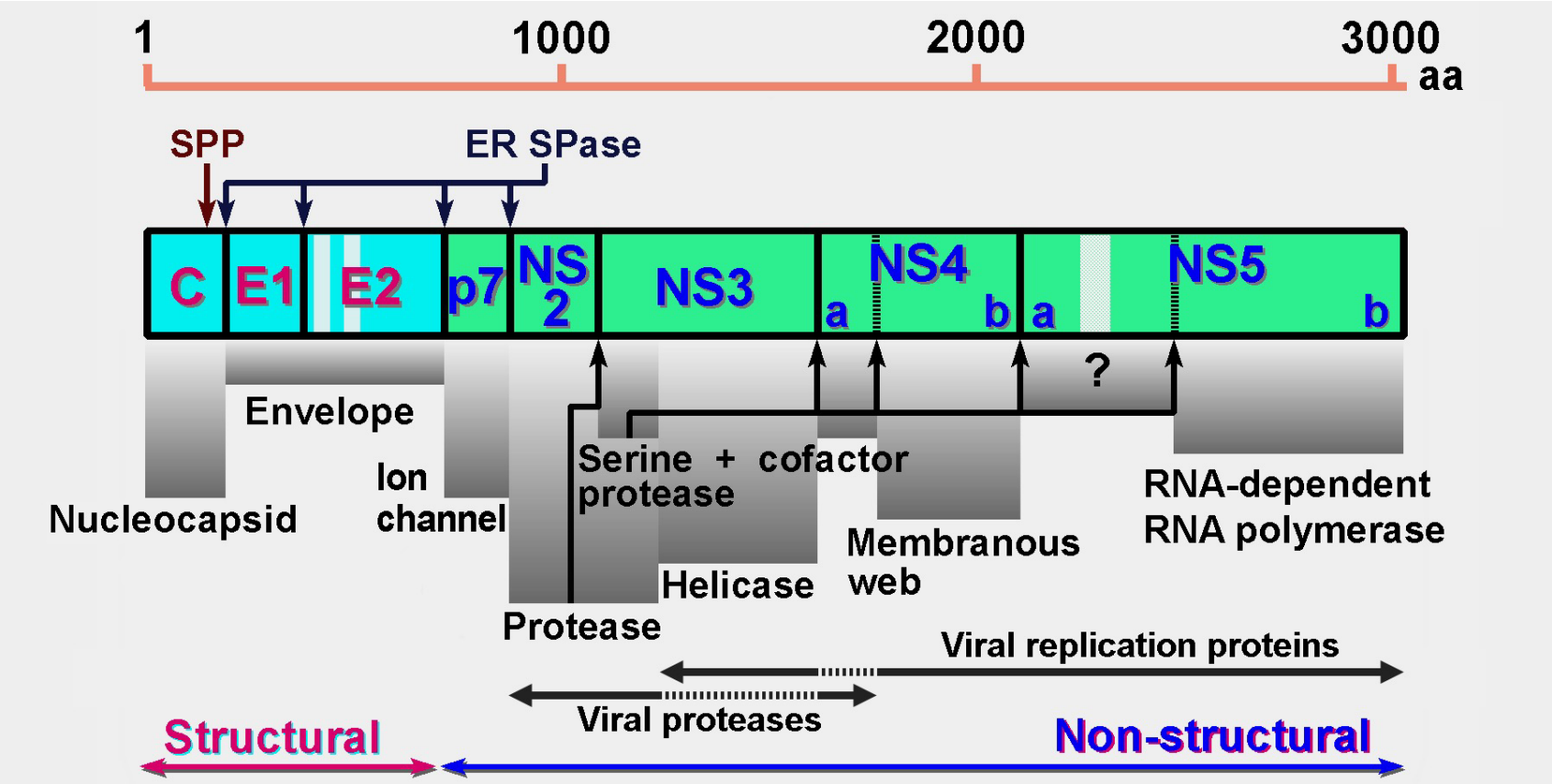


Schaff, Zs., Lotz, G., Eder G., Schulte-Hermann, R.: Pathomorphology and apoptosis in viral hepatitis In:Therapy of Viral Hepatitis, London 1998 77-86
Eder G., Schaff Zs. FAS antigen (APO1/CD95) expression in experimental HCV infection in chimpanzees Hepatology 24:218A 1996



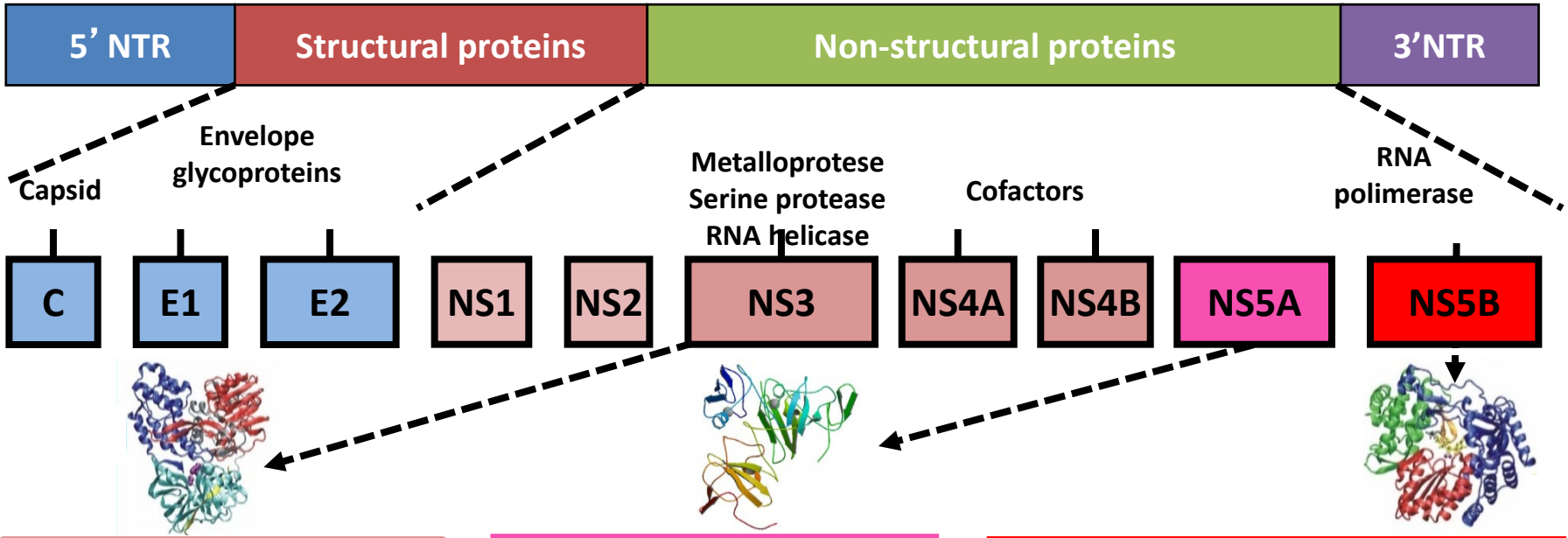
Zs. Schaff, G. Lotz, G. Eder, R. Schulte-Hermann: Pathomorphology and apoptosis in viral hepatitis. In: Therapies for Viral Hepatitis. R.F. Schinazi, J.P. Sommadossi, H. Thomas (eds)., London, 1998, pp. 77-86.

Structure of HCV polyprotein



Szabó et a. POR 9: 215-225, 2003

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

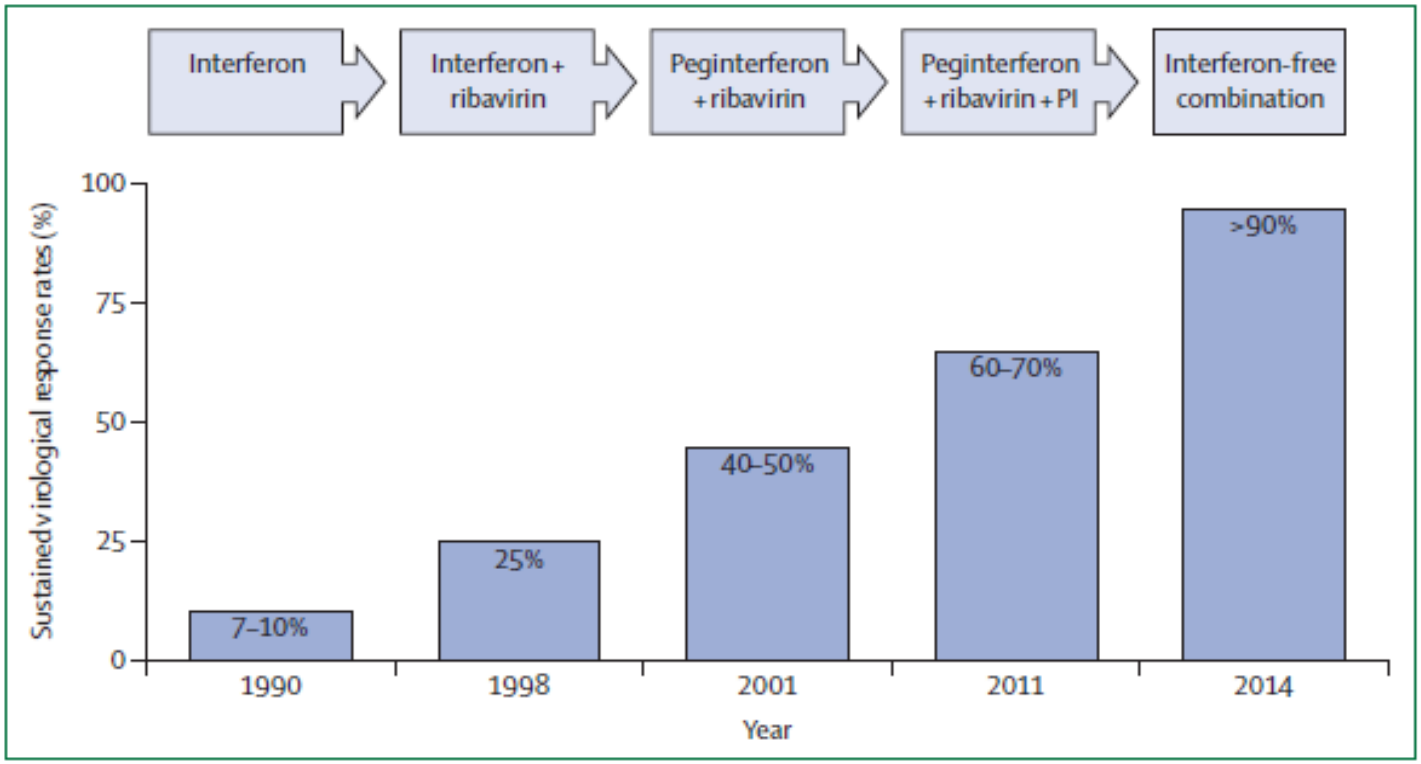


Figure 1: **Changes in standard of care for HCV, and improvements in numbers of sustained virological responses**
Data from references 9–12. PI=protease inhibitor.

Webster et al. Lancet Febr.14. 2015.

HCV: „Báránybőrbe bújt farkas”

(„wolf in lamb’s clothing – wolf in sheep’s clothing”)

- Milder and more prolonged (15-30 yrs)
- Transmission: transfusion, sexual (rare), perinatal (rare)

- 71 million infected
- 80% progression into chronicity
- No vaccine

National Hepatitis Elimination Board
2018. December 13th, Budapest