Adventure of Delta

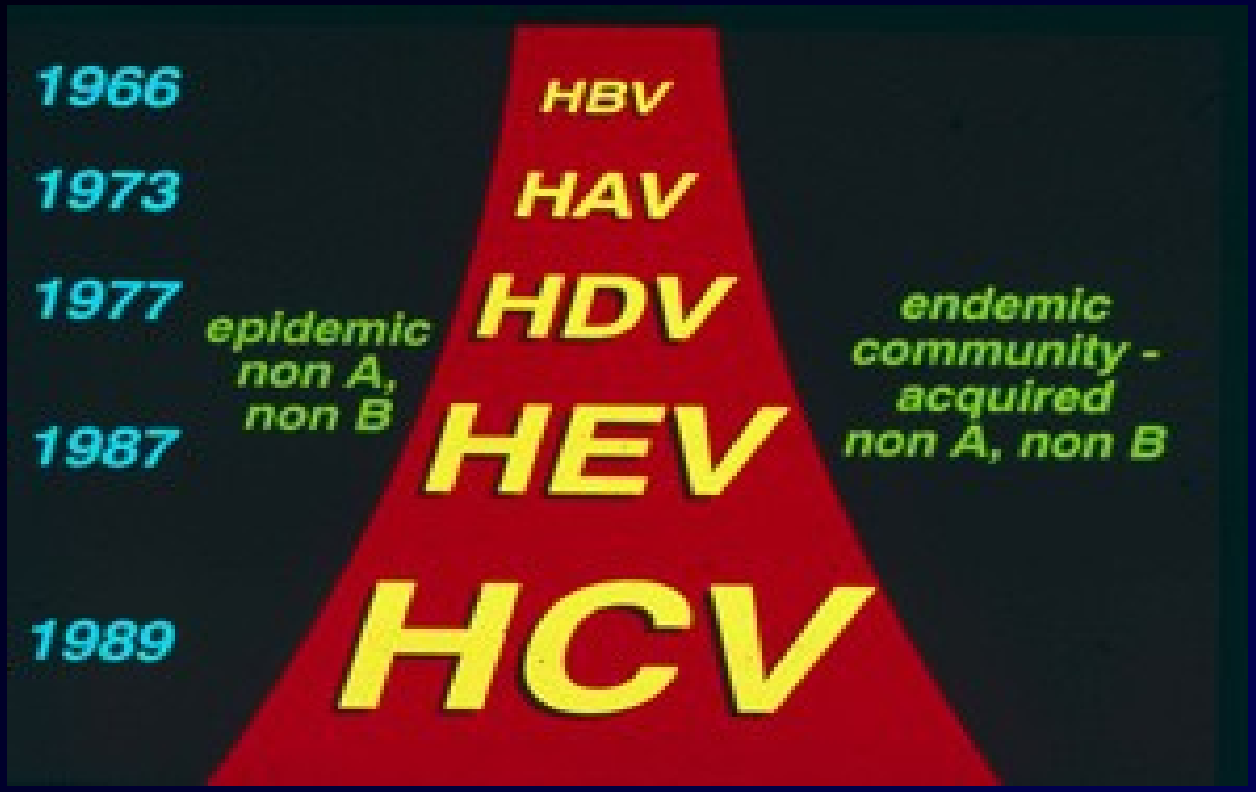
Mario Rizzetto

9 PHC

Paris, January 12, 2016

Hepatitis D (delta) Virus

- ✓ one of the 5 major hepatotropic viruses
- ✓ infection only in HBsAg +
- ✓ worldwide epidemiology,
  15-20 millions infected,
- ✓ severe liver disease


1966
1973
1977
1987
1989
HBV
HAV
HDV
HEV
HCV
epidemic
non A,
non B
endemic
community -
acquired
non A, non B

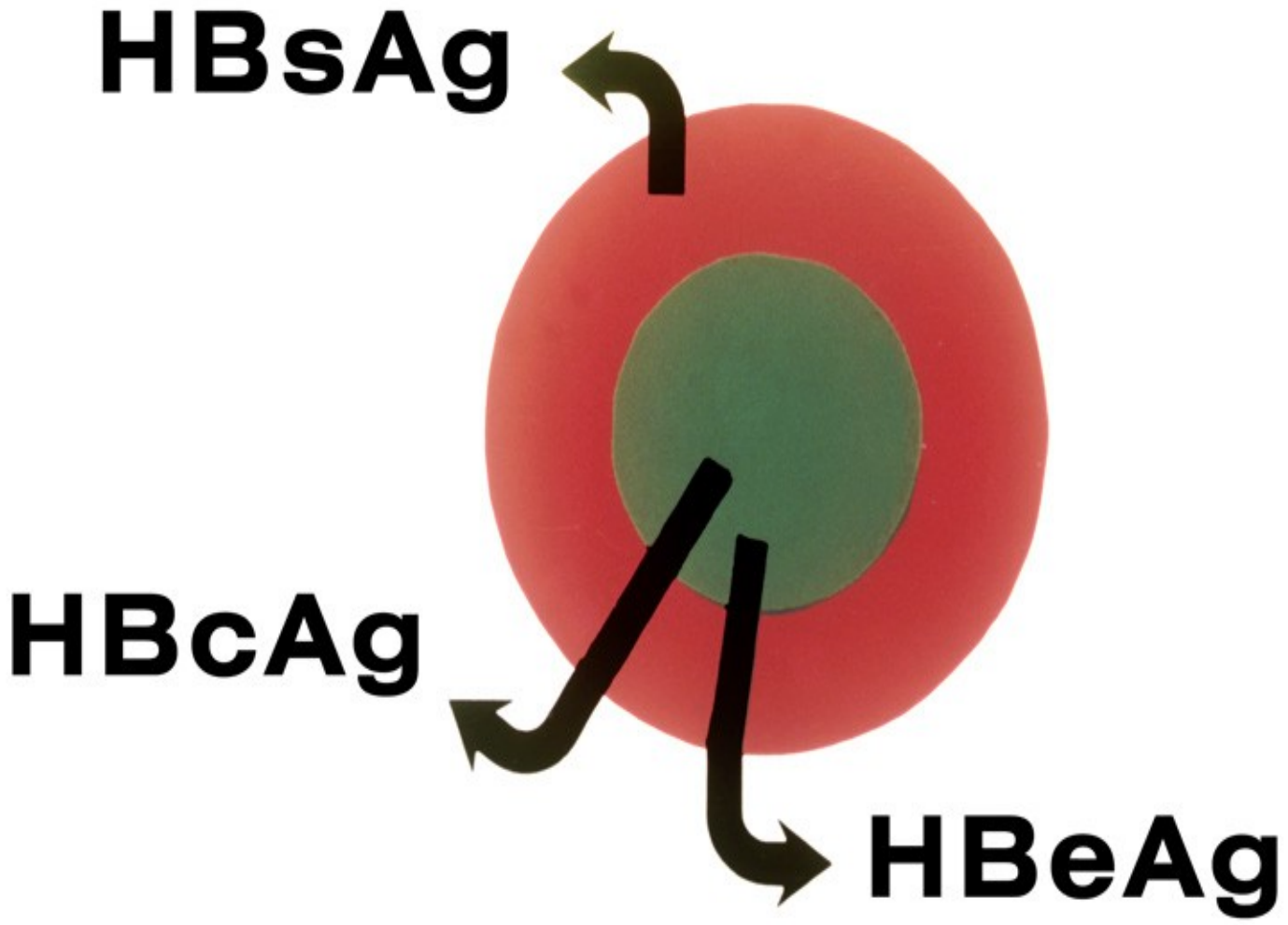
ADVENTURE

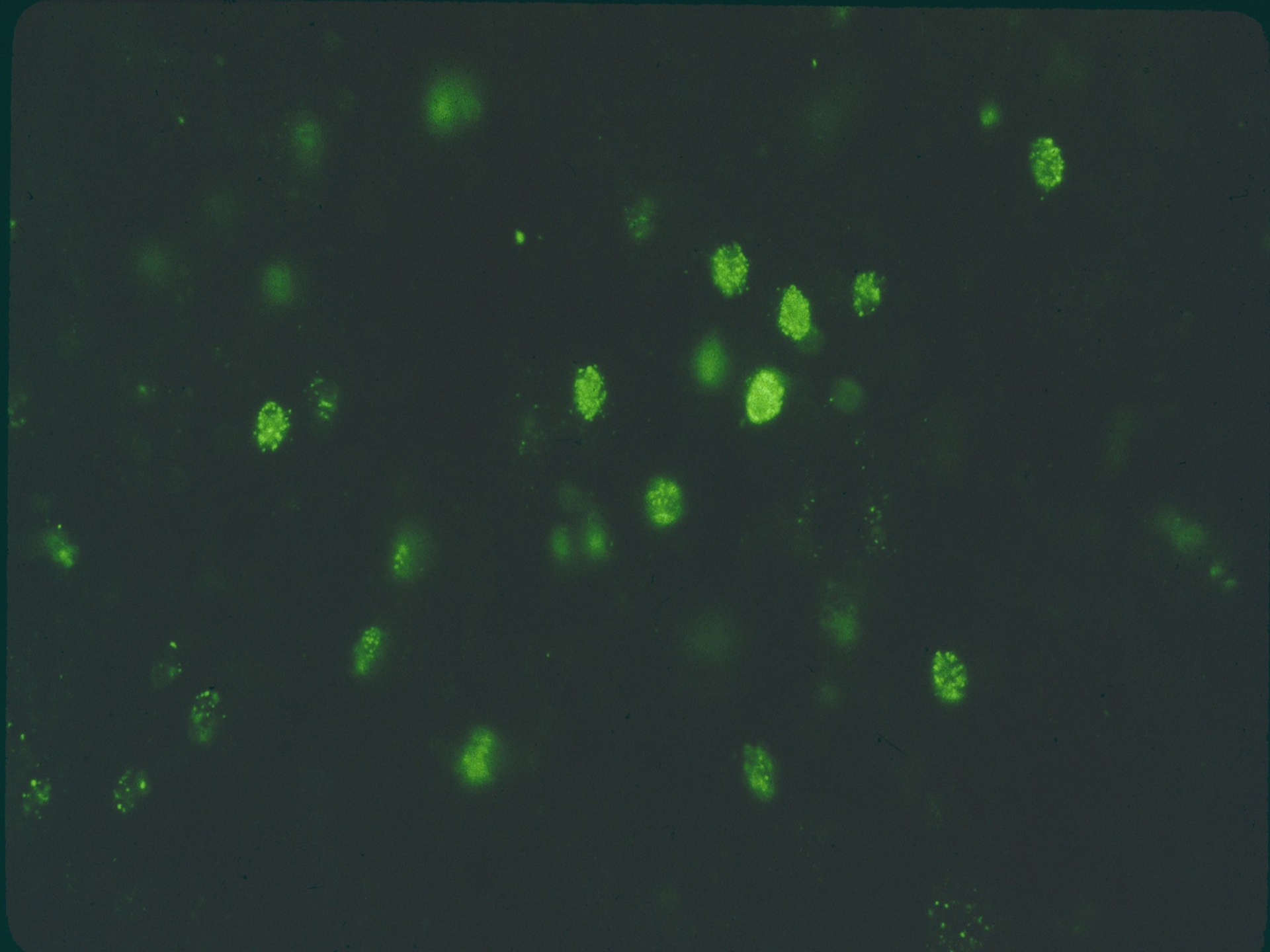
"a risky undertaking"

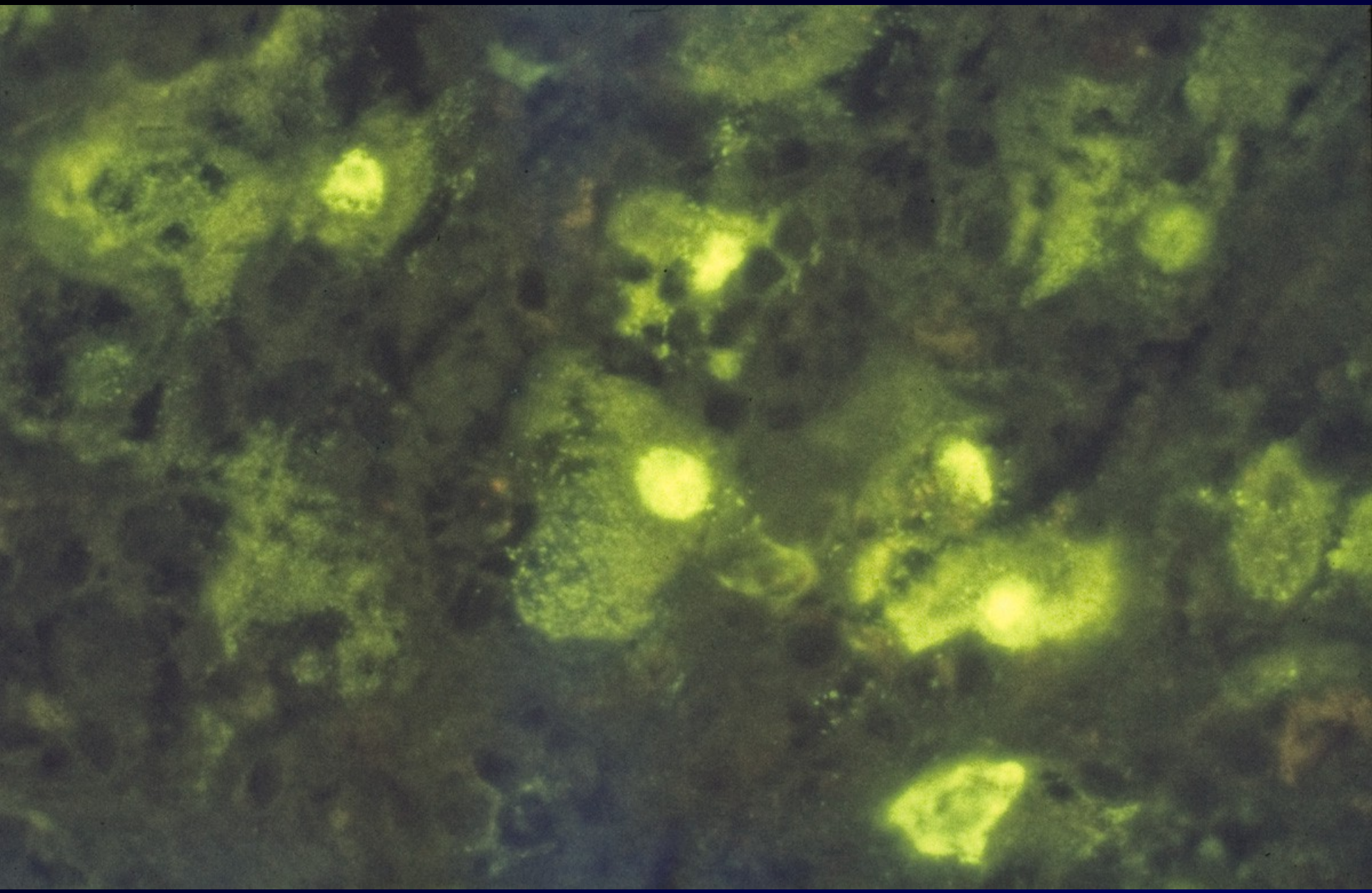
"an unusual and exciting experience"

American Heritage

HEPATITIS B VIRUS







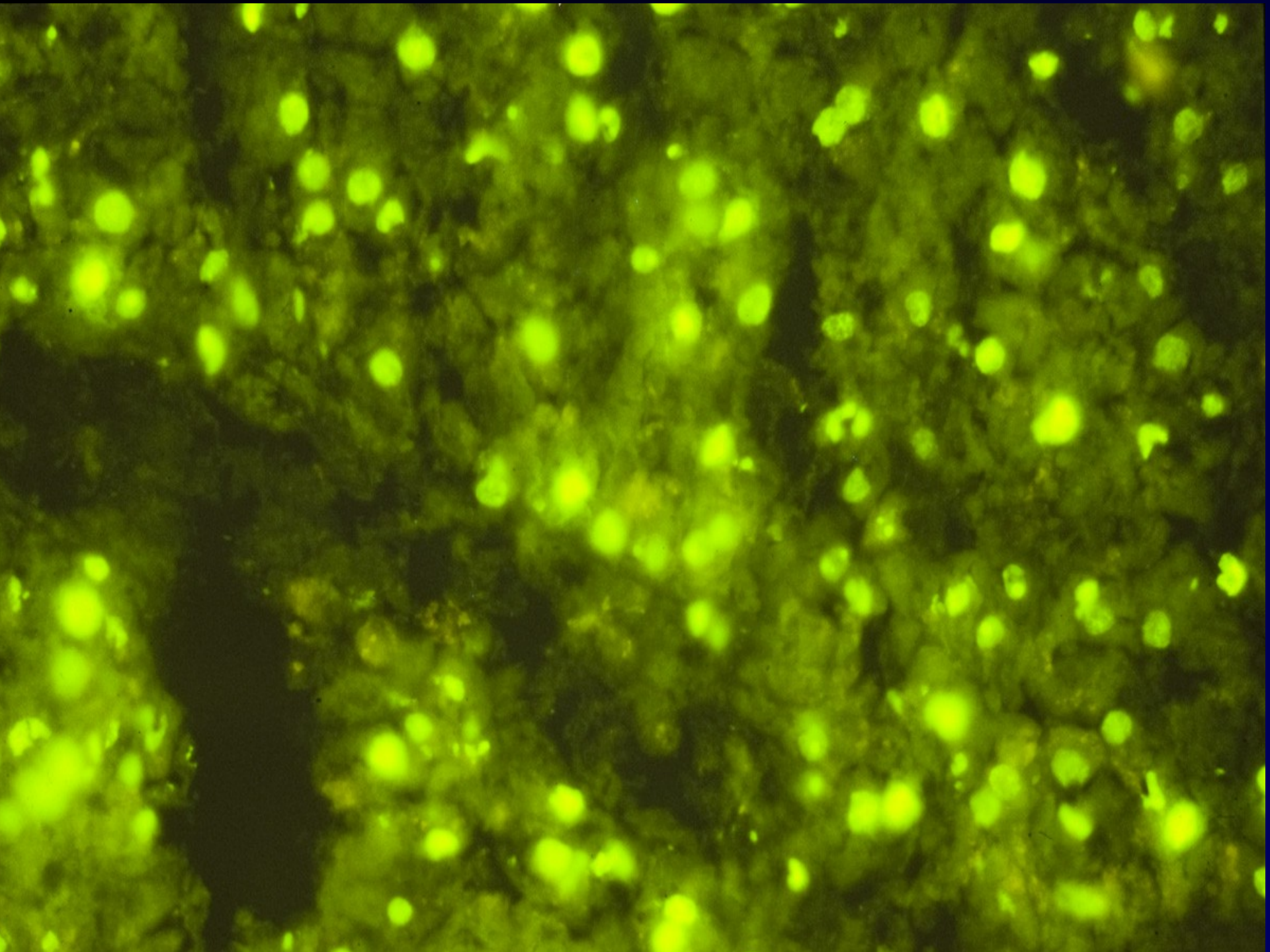
Gut, 1976, 17, 837-843

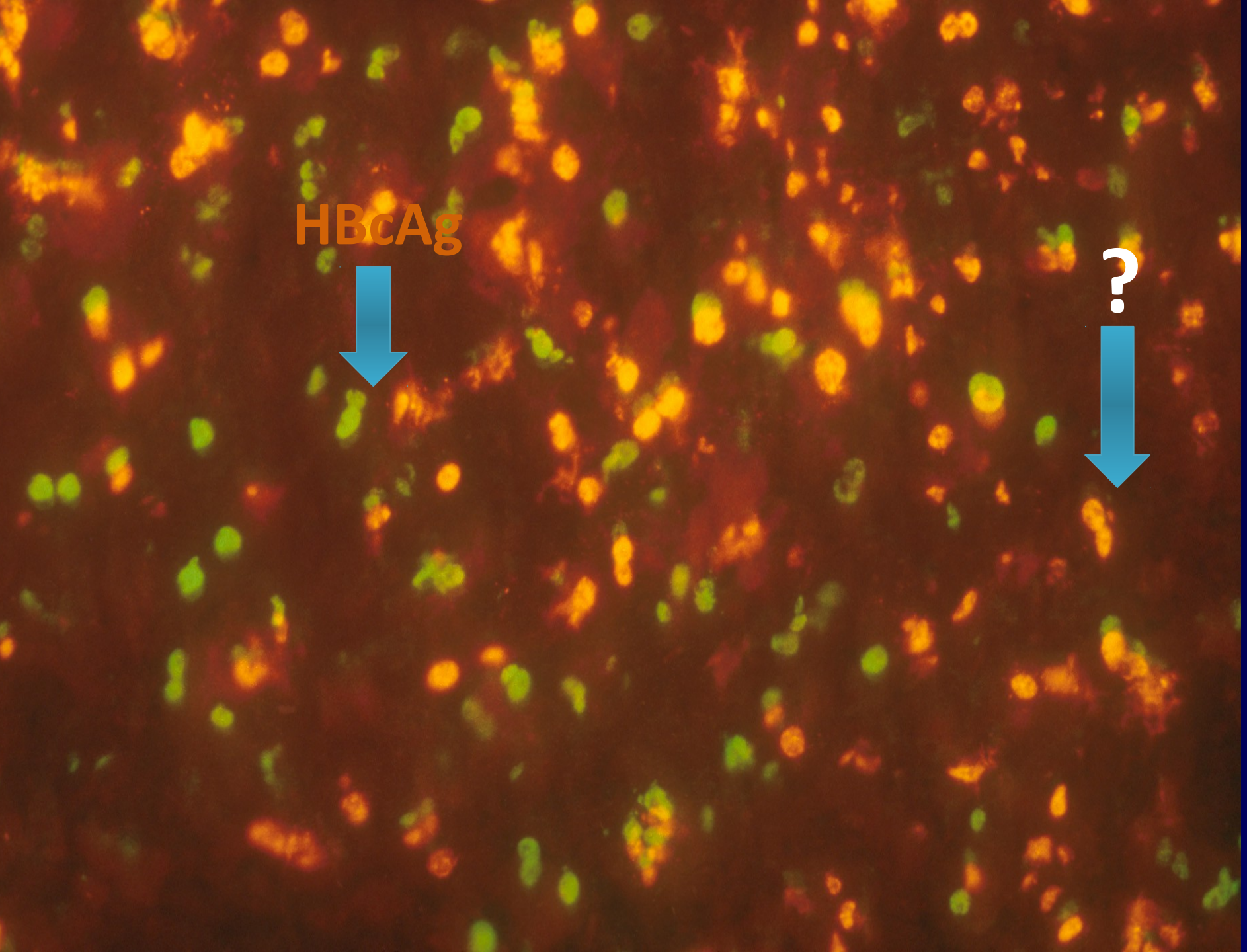
Complement fixing hepatitis B core antigen immune complexes in the liver of patients with HB_s antigen positive chronic disease

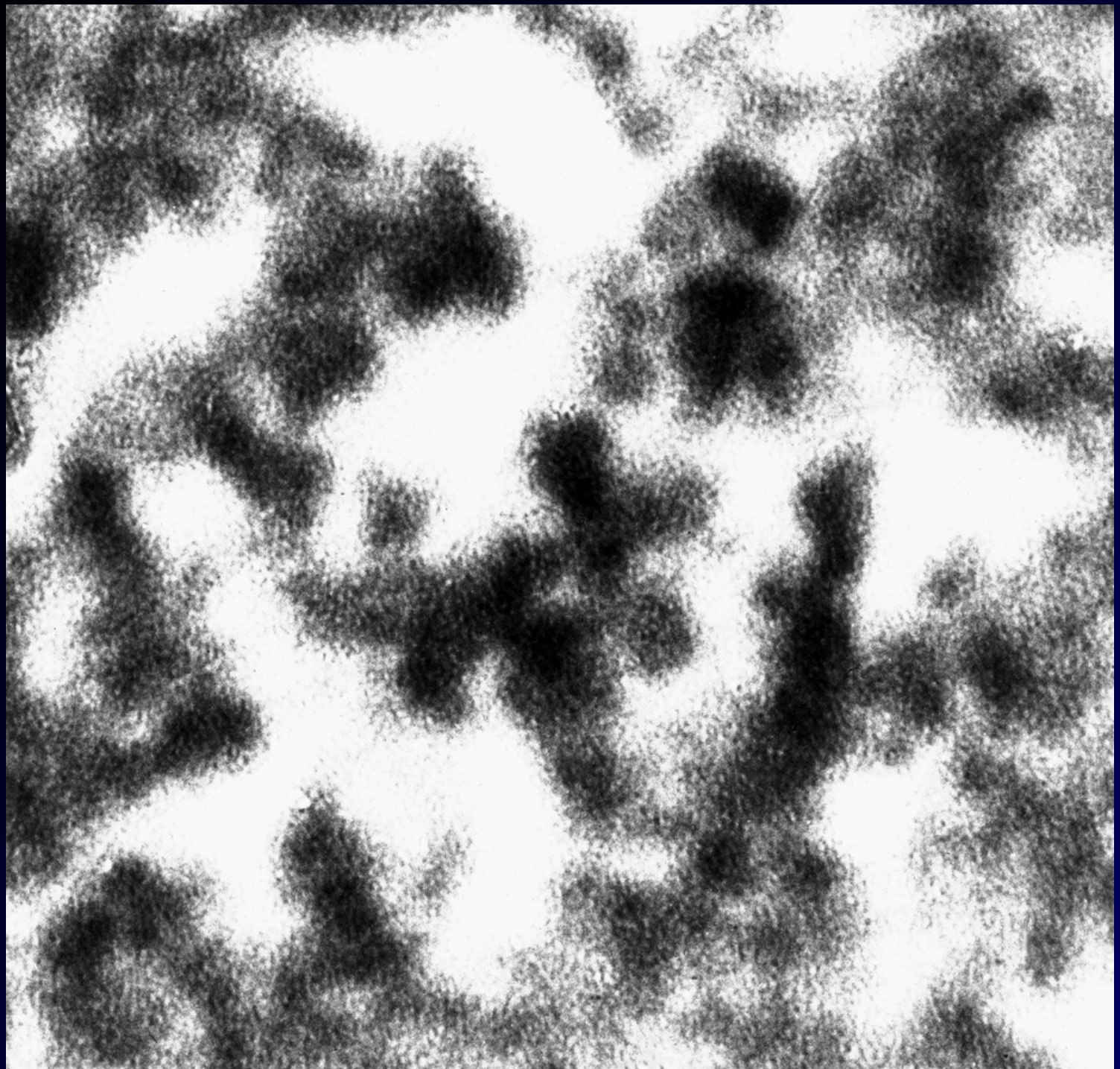
M. RIZZETTO, F. BONINO, O. CRIVELLI, M. G. CANESE, AND G. VERME

From the Department of Gastroenterology, Ospedale Mauriziano Umberto I, Turin, and the Centre for Electron Microscopy, III Chair of Morbid Anatomy, University of Turin, Italy

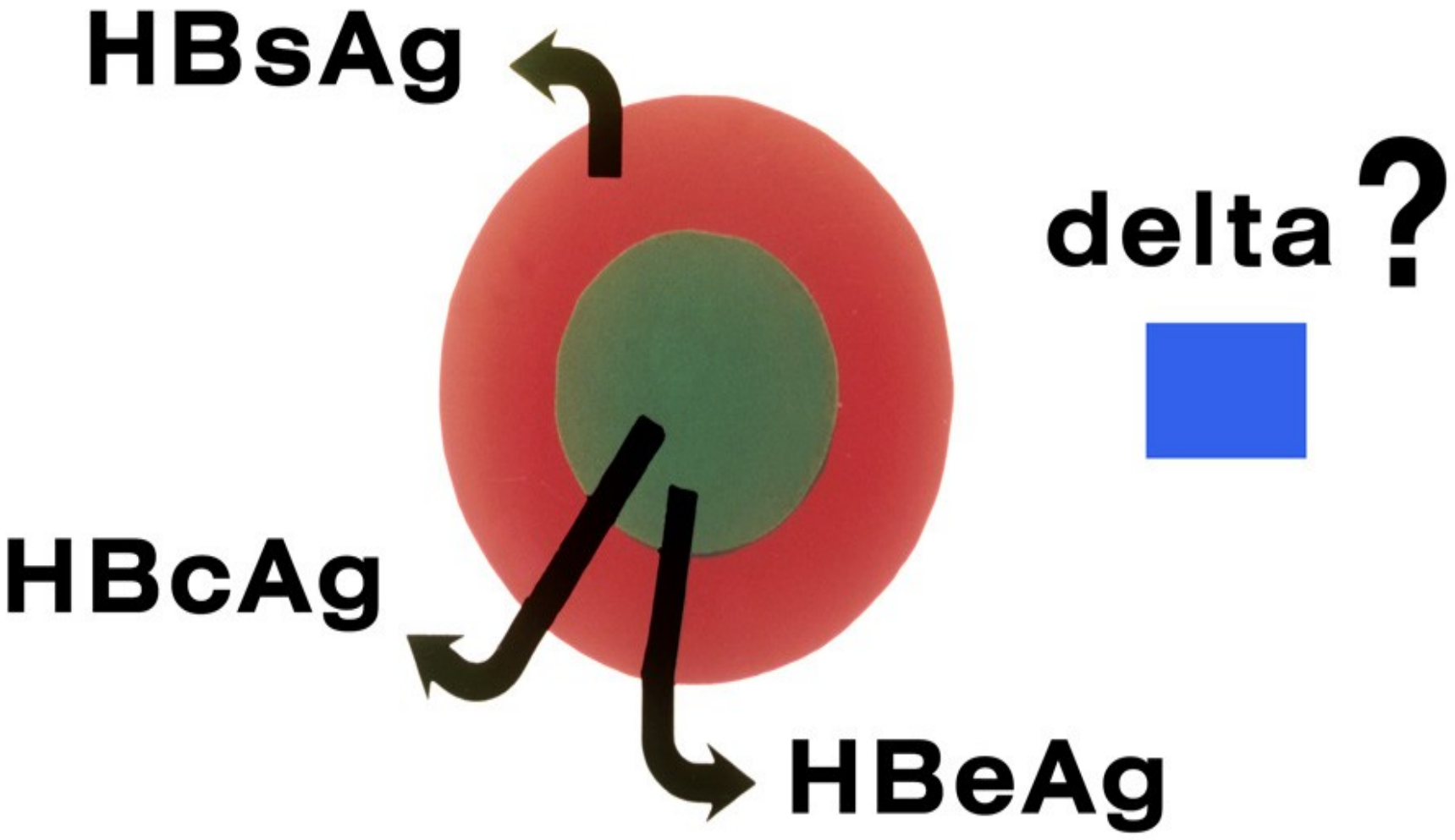
SUMMARY One hundred and fifty-two biopsies from serologically HB_sAg positive and negative patients with liver disease were studied in immunofluorescence for the presence of the surface (HB_s) and the core (HB_c) antigenic determinants of the hepatitis B virus, of immunoglobulins and complement (C) deposits, and for the capacity to fix human C. Circumstantial evidence is presented suggesting that HB_c immune-complexes are a relevant feature in the establishment and progression of chronic HB_sAg liver disease. C fixation by liver cells was shown in all HB_c positive patients with chronic hepatitis; an active form was present in every case, except two with a persistent hepatitis, an inverse ratio of HB_c to C binding fluorescence being noted between active chronic hepatitis and cirrhotic patients. HB_c without C fixation was observed in only three patients in the incubation phase of infectious hepatitis. IgG deposits were often found in HB_c containing, C fixing nuclei. No C binding or IgG deposits were observed in acute self-limited type B hepatitis, in serologically positive patients with normal liver or minimal histological lesions, with and without HB_s cytoplasmic fluorescence in their biopsy, or in serologically negative individuals.




HBcAg
?



HEPATITIS B VIRUS



Reprinted from the Journal of the British Society of Gastroenterology—GUT
Volume 18, page 997, 1977.

Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

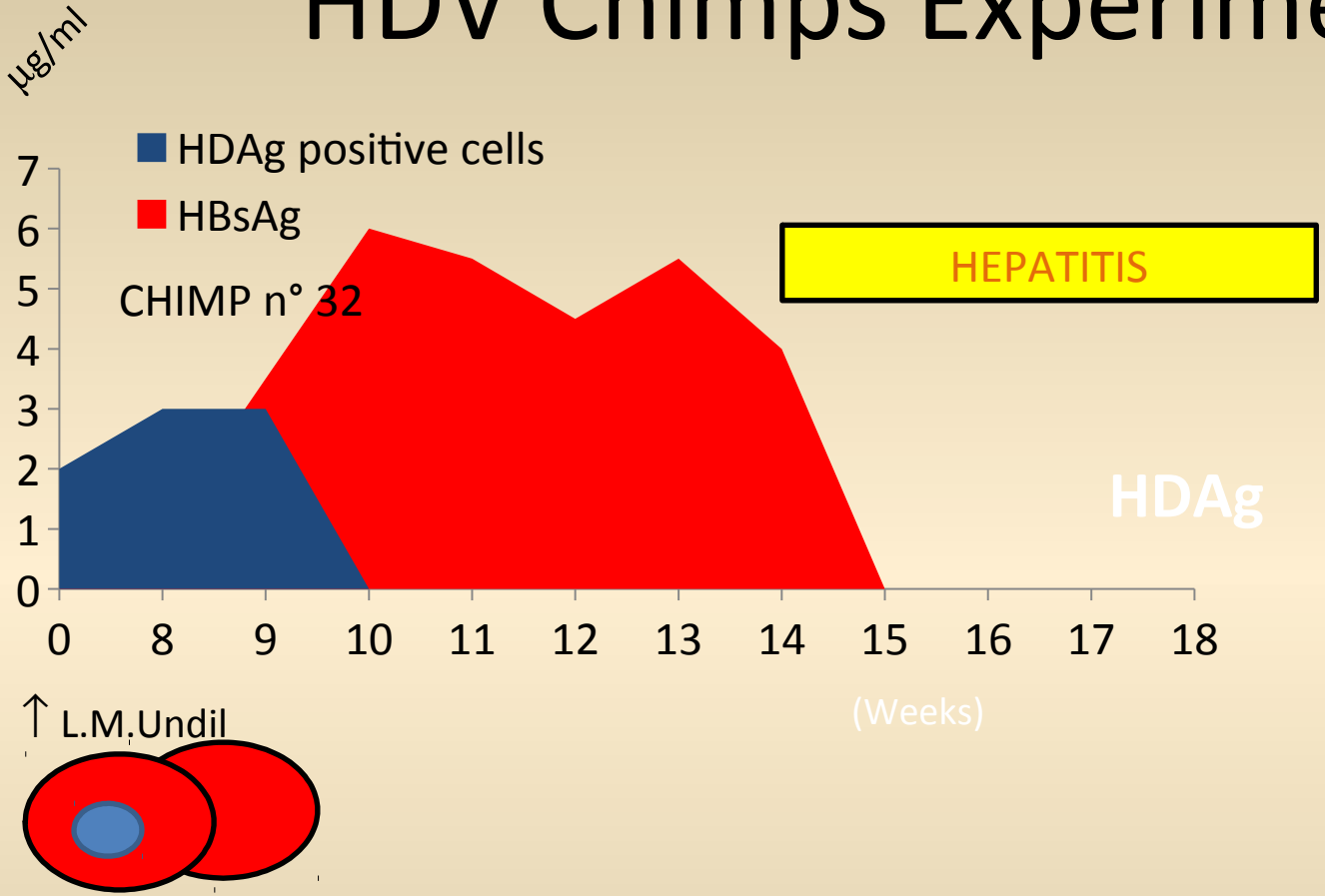
M. RIZZETTO, M. G. CANESE, S. ARICO, O. CRIVELLI, C. TREPO, F. BONINO AND G. VERME

John Gerin

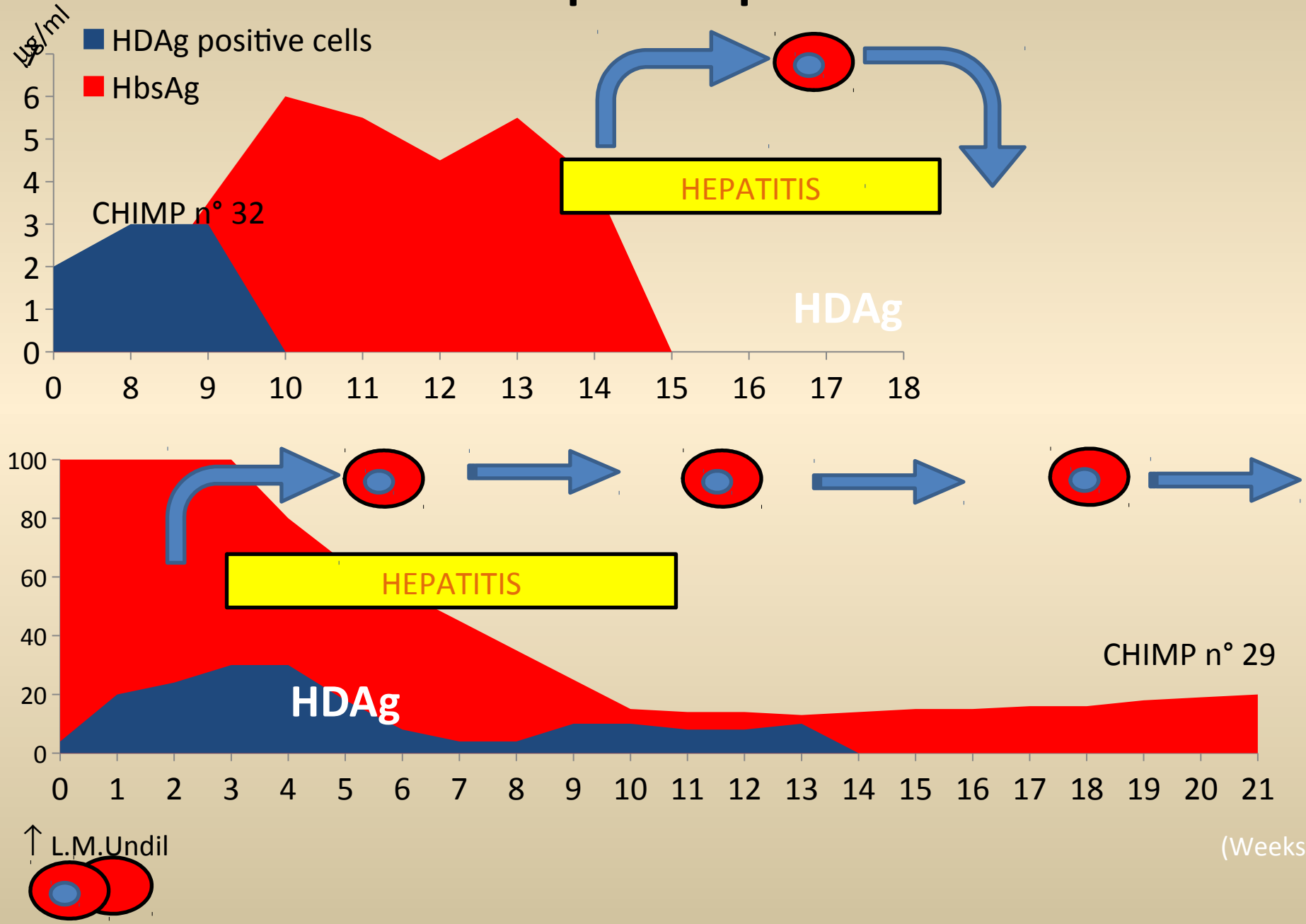
Robert Purcell

James Shih

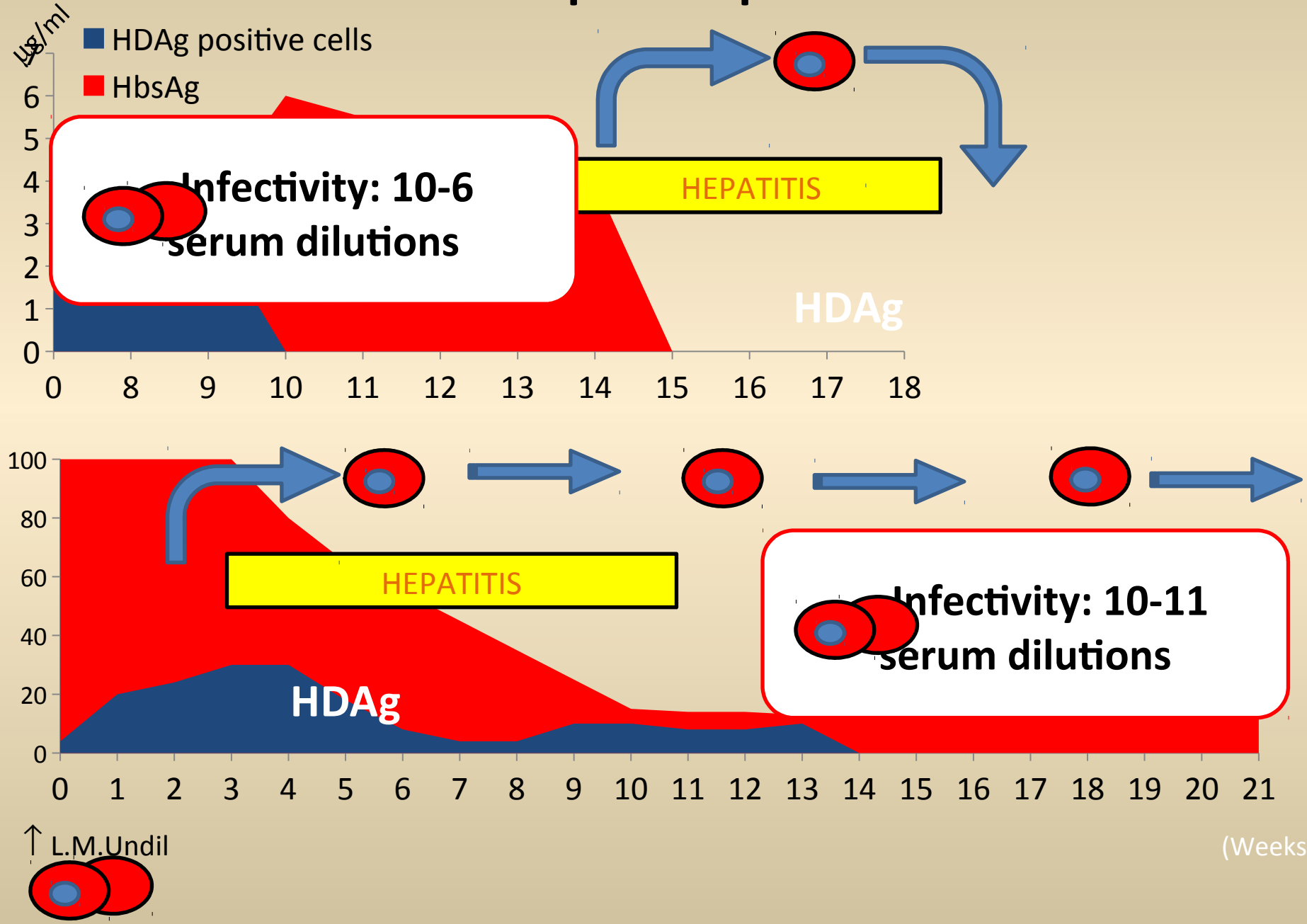
HDV Chimps Experiments

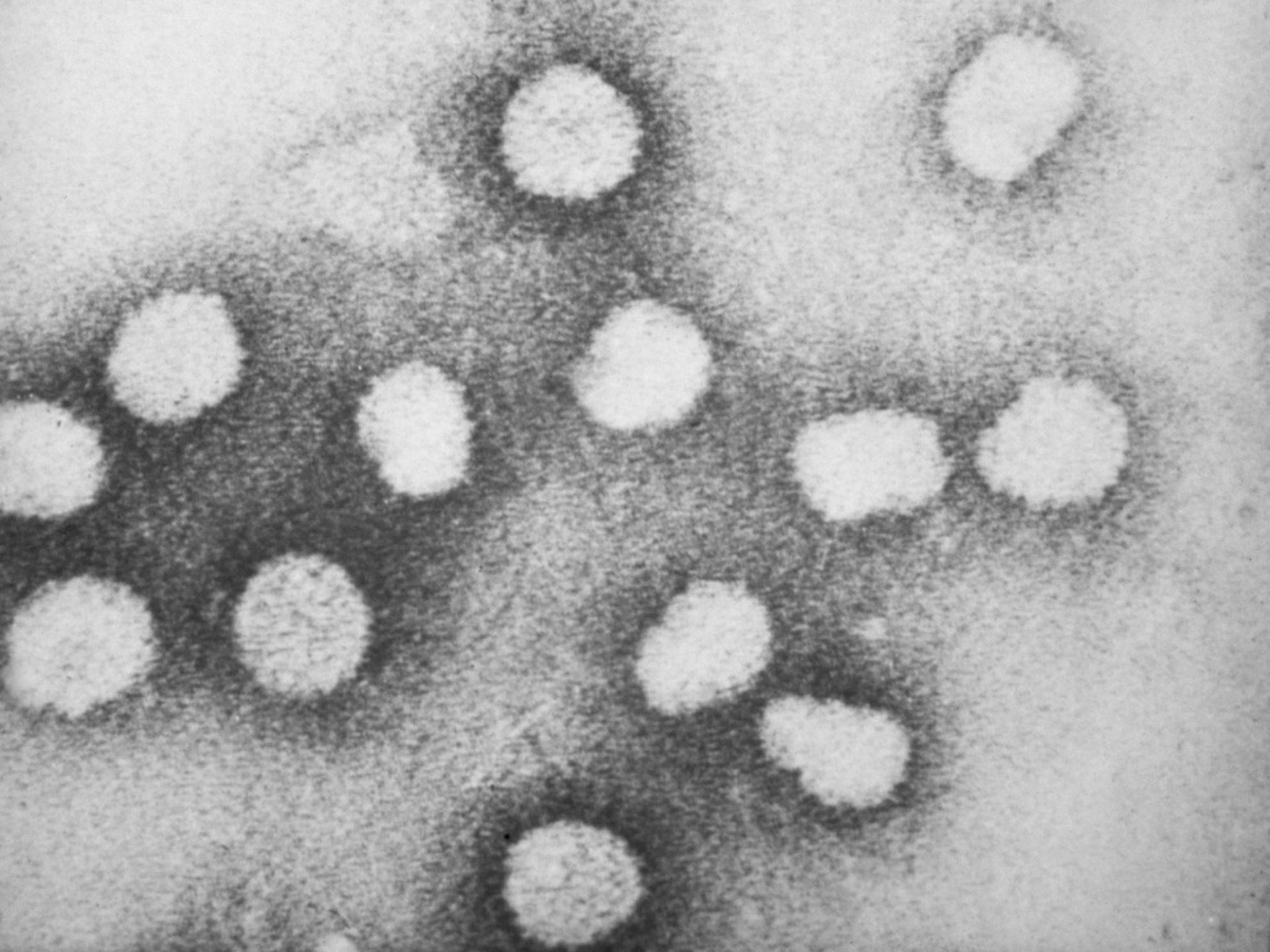


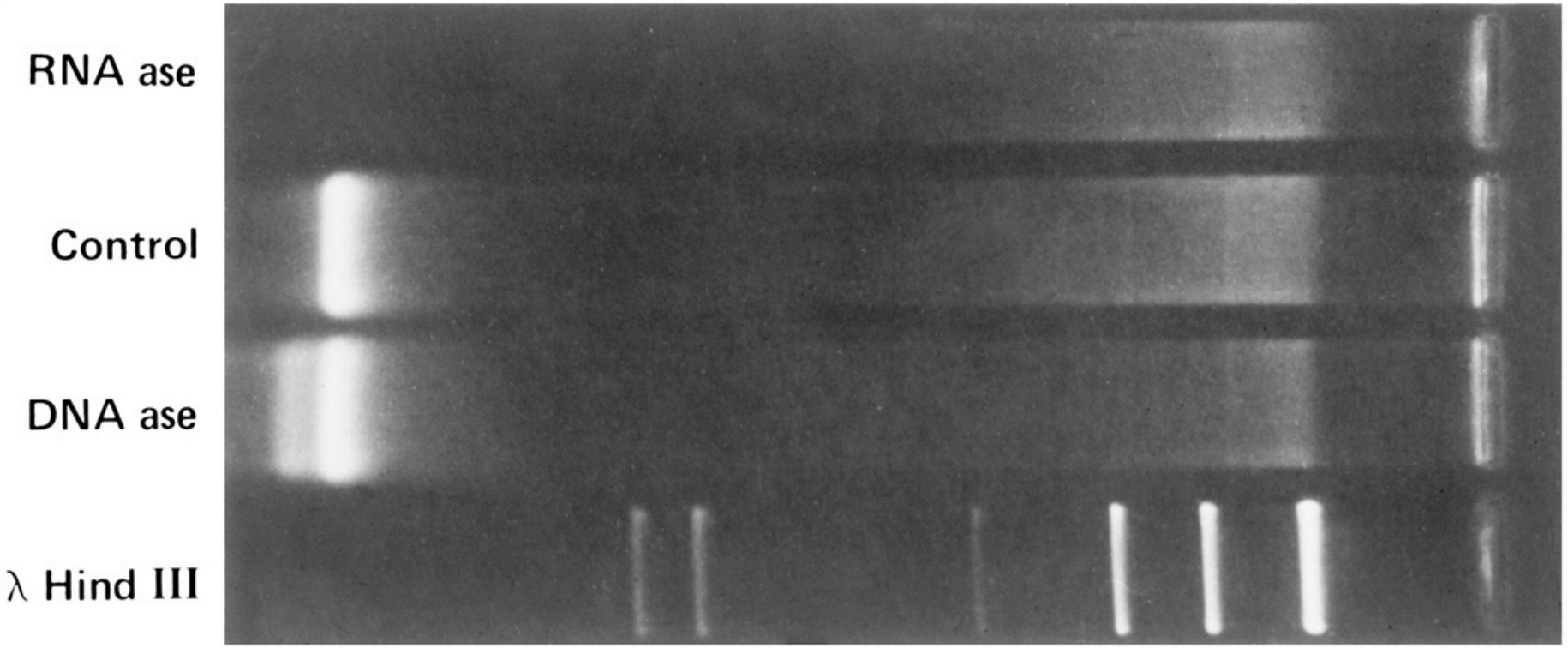
HDV Chimps Experiments



HDV Chimps Experiments

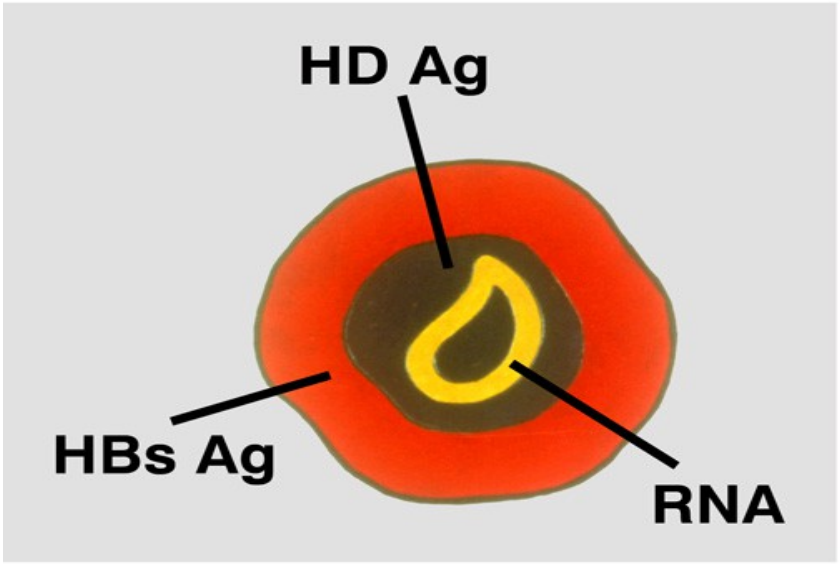


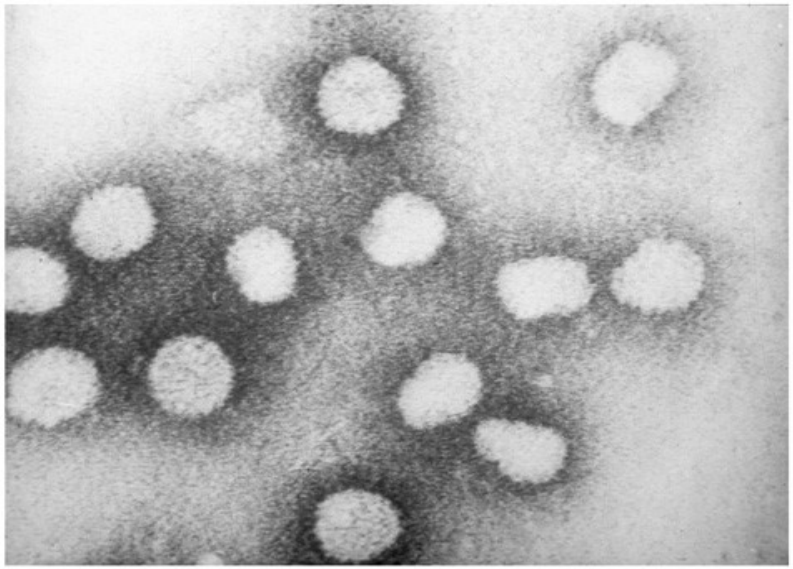



RNA ase
Control
DNA ase
λ Hind III

1980

HEPATITIS DELTA VIRUS





Classification: Genus Deltavirus

Virion: 36 nm, enveloped (HBsAg)

Genome: 1.7 Kb RNA single-stranded,

Pej-Jer Chen

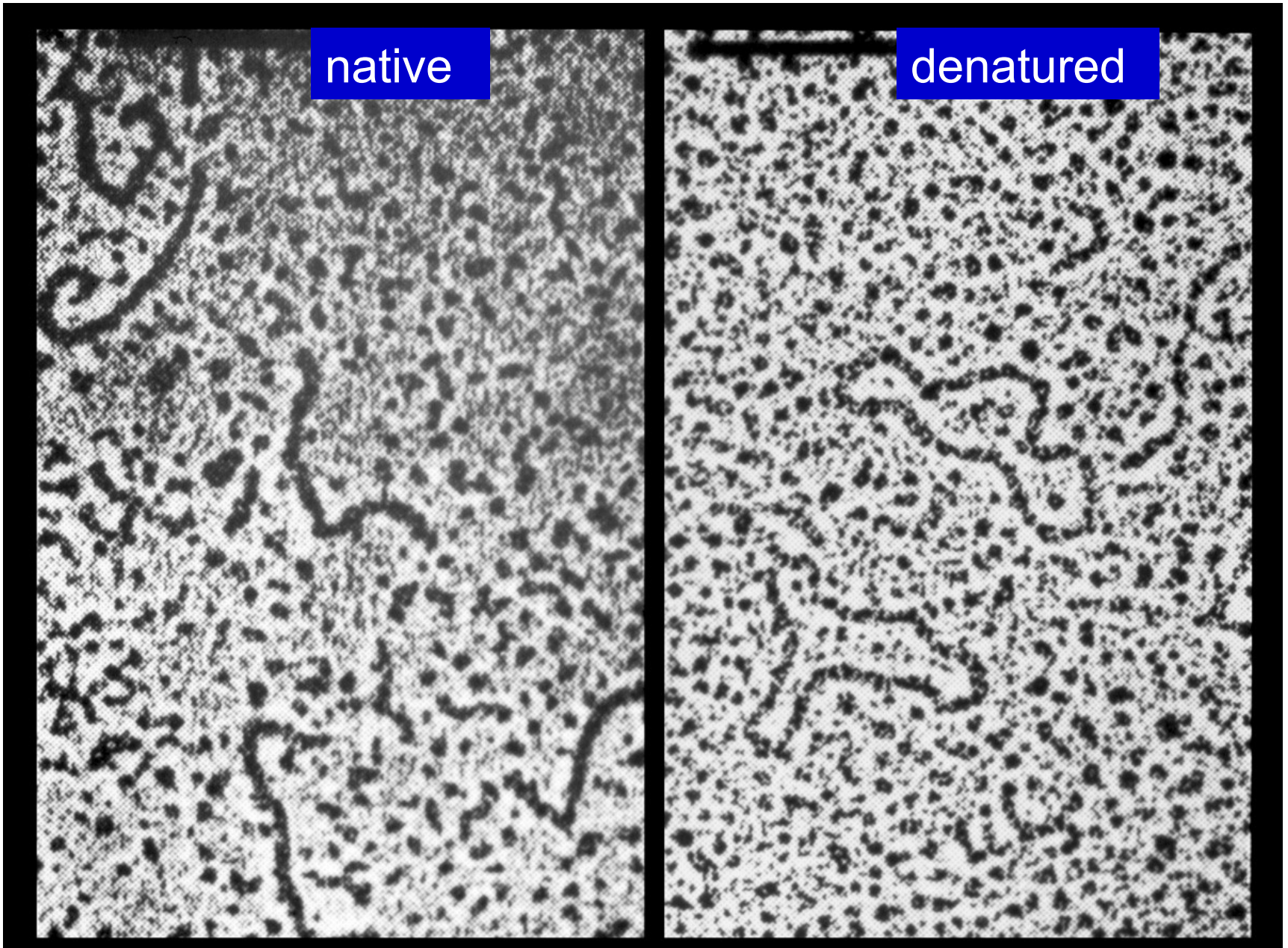
Paul Deny

Michael Houghton

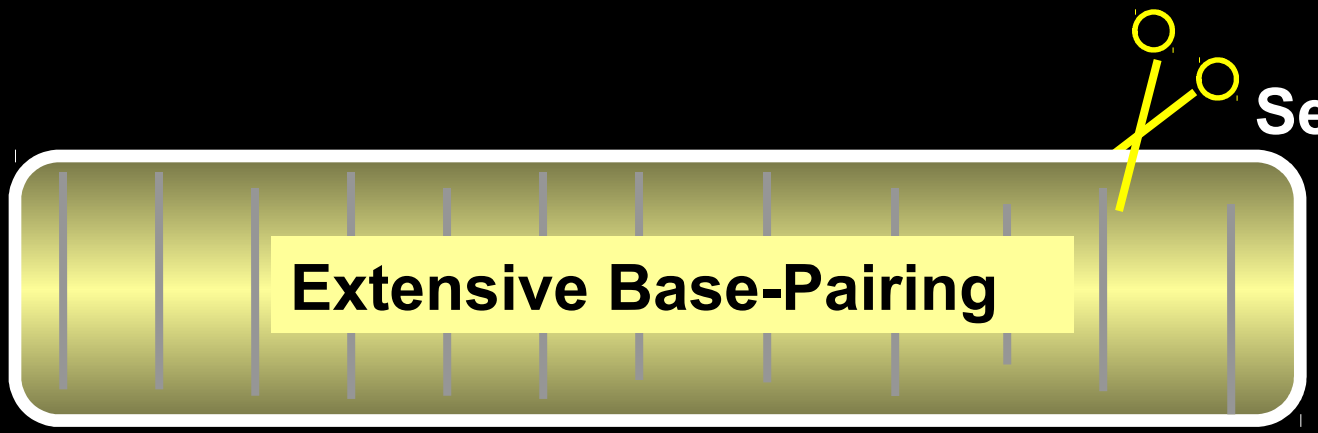
Camille Sureau

John Taylor

HDV-RNA: structure

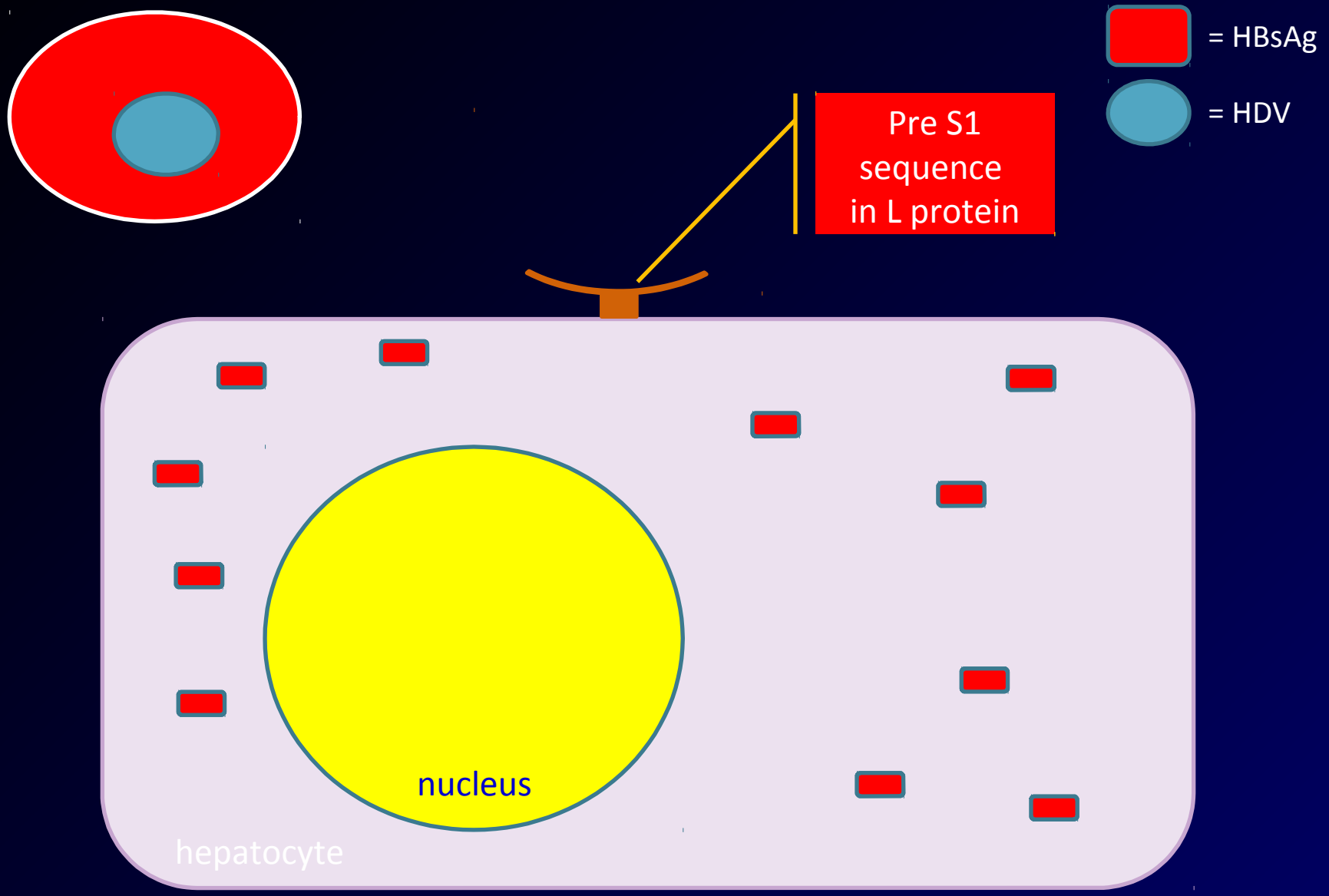


HDV RIBOZYME

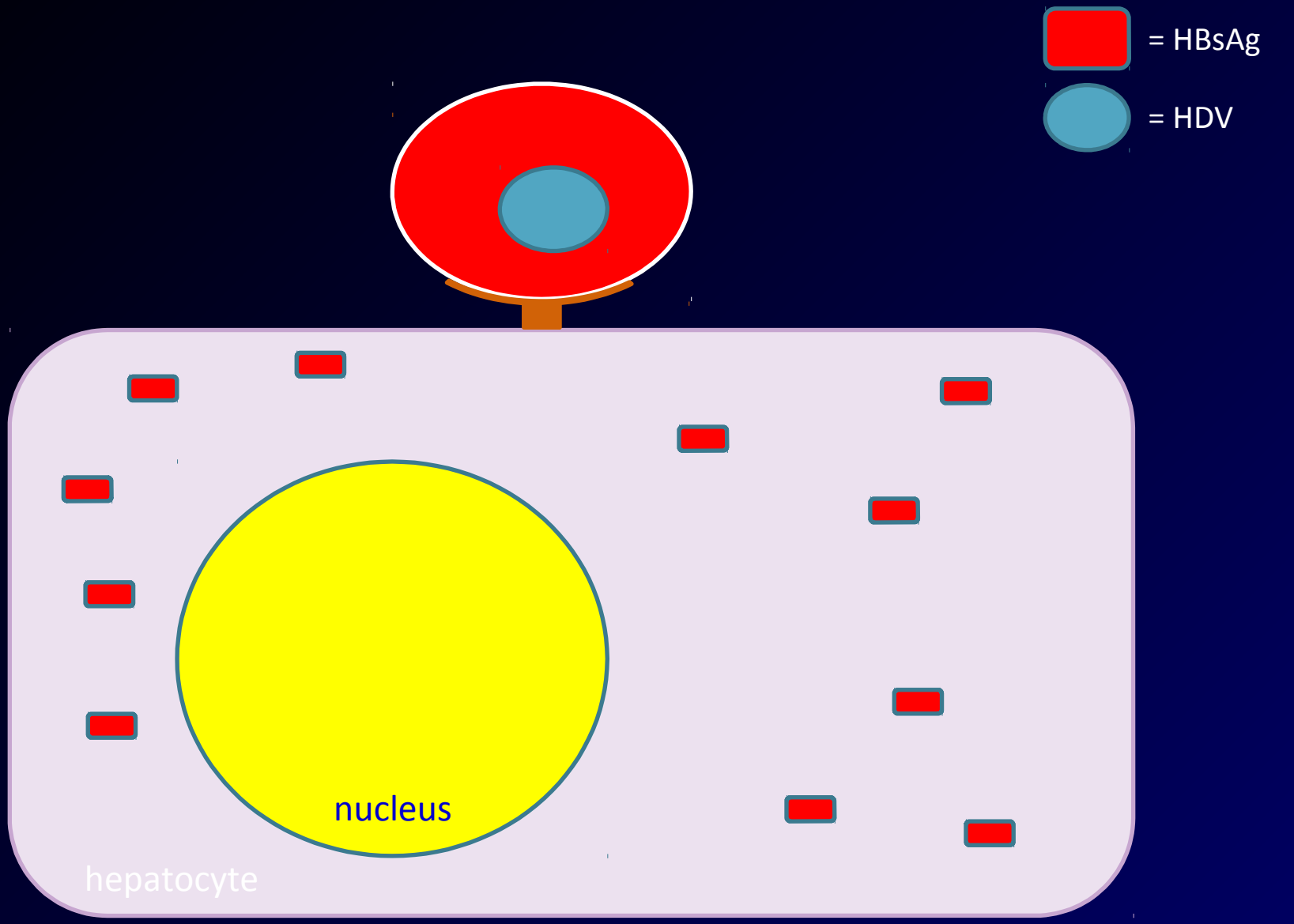


- only ribozyme encoded by a human pathogen
- < 100 nucleotides
- crystallized, complex three-dimensional architecture

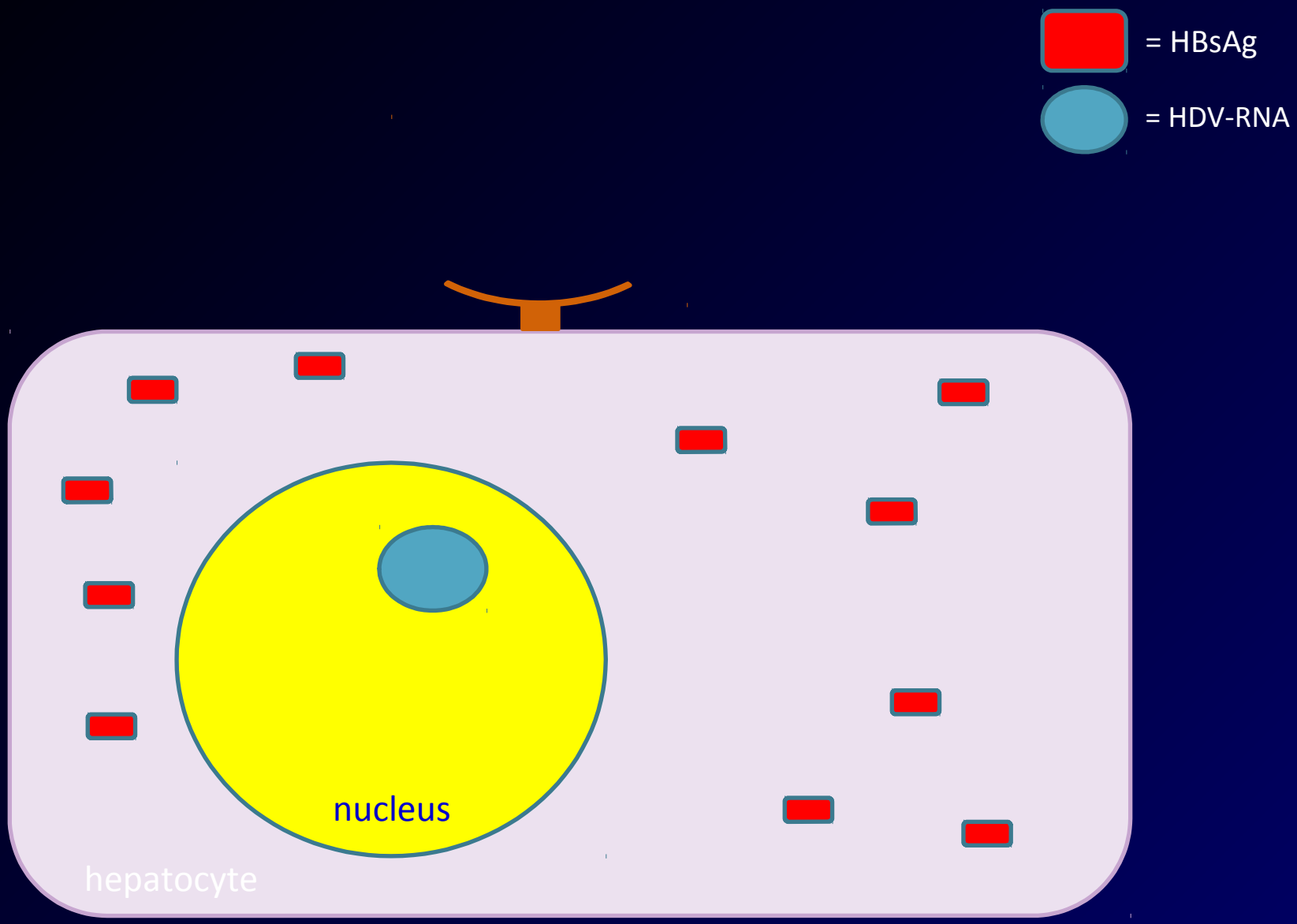
Attachment of HDV through HBsAg



HDV transferred to nucleus

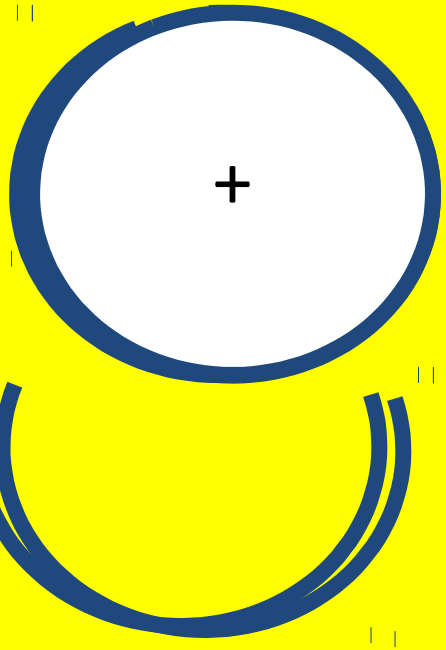


HDV transferred to nucleus



Replication of HDV-RNA

Cell Ligase
HDV Ribozyme?

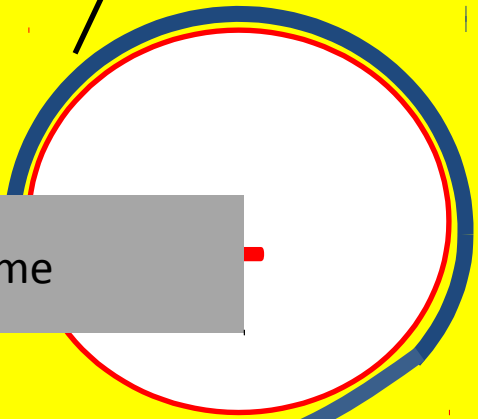


= genomic HDV-RNA

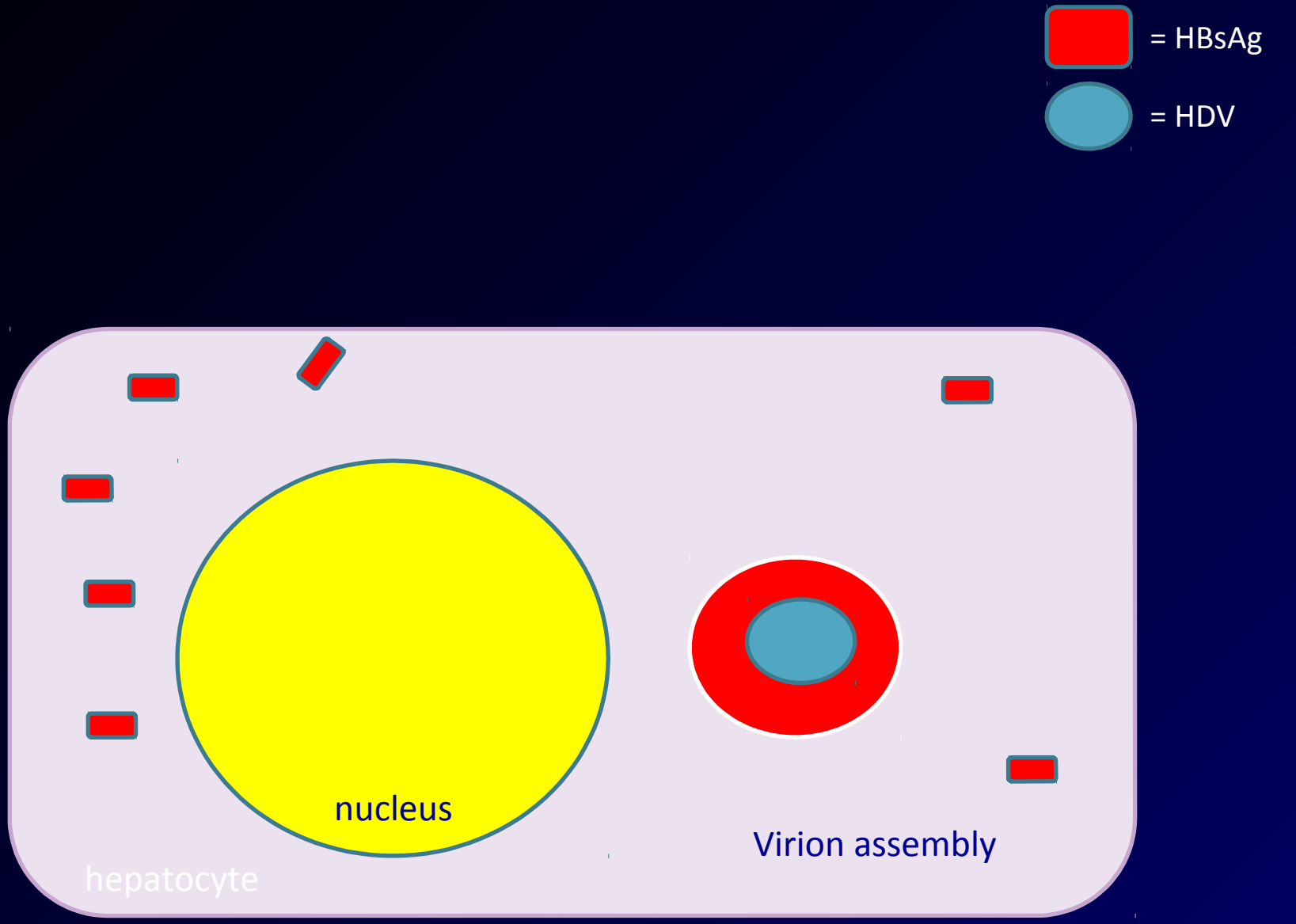
= antigenomic HDV-RNA

HOST
RNA polymerase II, I, III

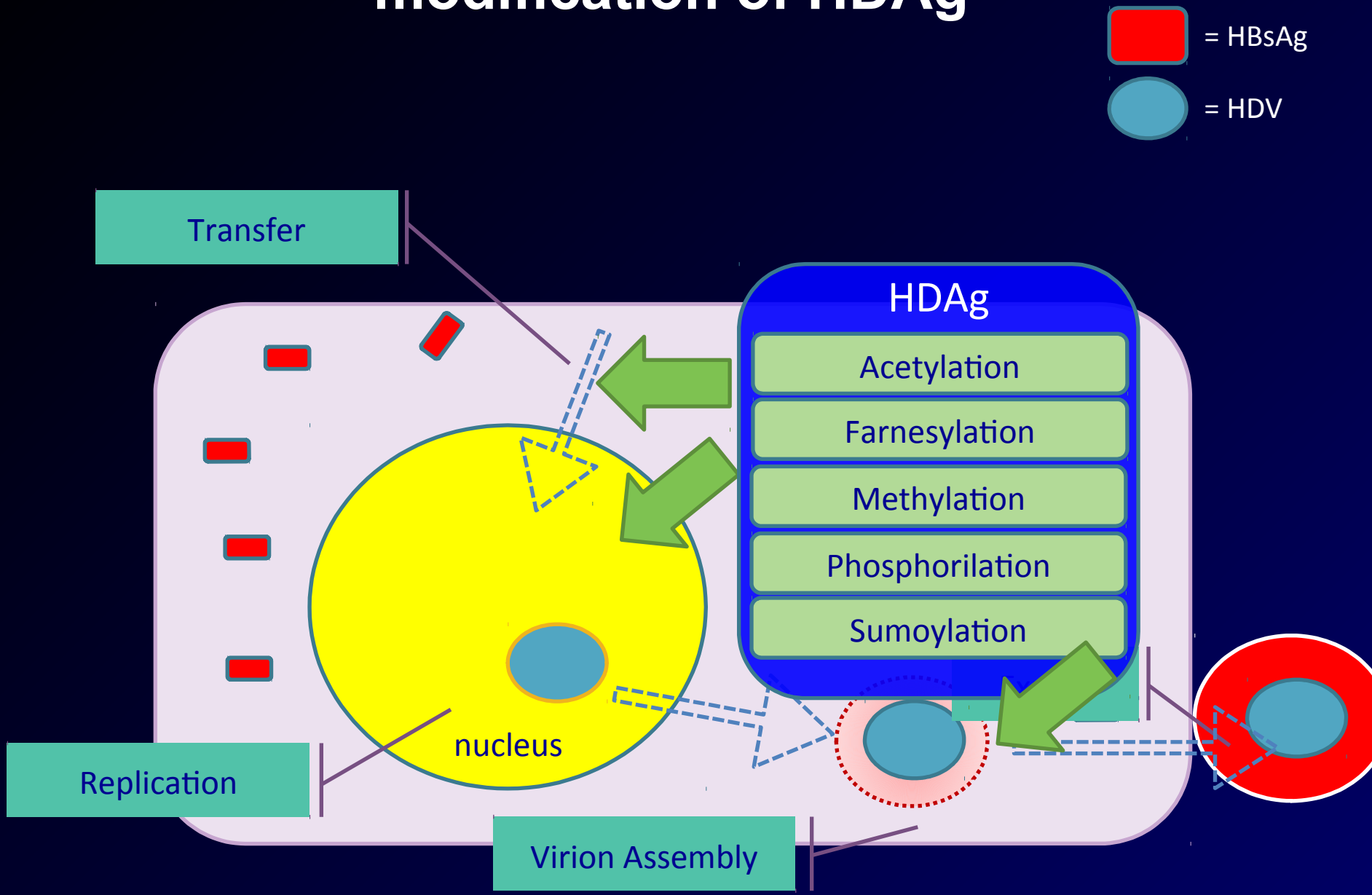
HDV Ribozyme



Assembly of HDV virions



Life cycle of HDV directed by post-translational modification of HDAg



Corollaries

- ✓ HDV latency,

  theoretically HDV may survive in the absence of HBV as helper virus

- ✓ Hepatitis D therapy,

  no replicative target for antivirals

Latency of HDV

- ✓ survival of HDV monoinfection for up to 38 days in woodchucks

Netter HJ, 1994

- ✓ HDV monoinfection persisting in mice for at least 6 weeks before conversion to HBV/HDV infection by HBV rescue

Giersch K, 2014

- ✓ in vitro and in vivo HDV survives liver regeneration, propagates and amplifies among cells, despite absence of HBV

Giersch K, 2015

HDV: unique features

- ✓ Smallest infectious agent in man: 1700 nt
- ✓ Circular, single stranded-negative polarity
- ✓ Infectious at 10-11 serum dilutions in HBsAg +
- ✓ Rolling circle mechanism of replication
- ✓ Self-cleaving ribozyme
- ✓ Transcription by host-RNA polymerases

HDV: BIOLOGICAL ANALOGIES

	PLANTS		MAN	ANIMALS
	VIROIDS	SATELLITE RNAs	HDV	RNA VIRUSES
autonomous	+	-	-	+
Helper dependent	-	+	+	-
Encapsidated	-	+*	+	+
Translation of RNA	-	-	+	+
Rolling circle replication	+	+/-	+	-
Ribozyme	+	+/-	+	-

* in helper virus coat

HDV origin

HDV evolved from a viroid-like RNA that captured the m-RNA encoding the HD-Ag protein

Taylor, 2010

Hammerhead and HDV-like self-cleaving ribozymes ubiquitous, expressed along the tree of life (worms, mosquitos, see urchins, plants…)

Webb C-HT, 2009

Flores R et al, Seminars in liver Disease, 2012

HDV 2016

- ✓ Infection, present and ominous throughout the world
- ✓ Hepatitis D, only viral liver disease in search of a cure
- ✓ HBV vaccination best and cheaper antidote
- ✓ HDV-RNA, a continuing biological surprise

ADVENTURE OF DELTA

"a risky undertaking"

"an unusual and exciting experience"

American Heritage