Brève Histoire de la découverte des virus des hépatites

Professeur Christian TREPO

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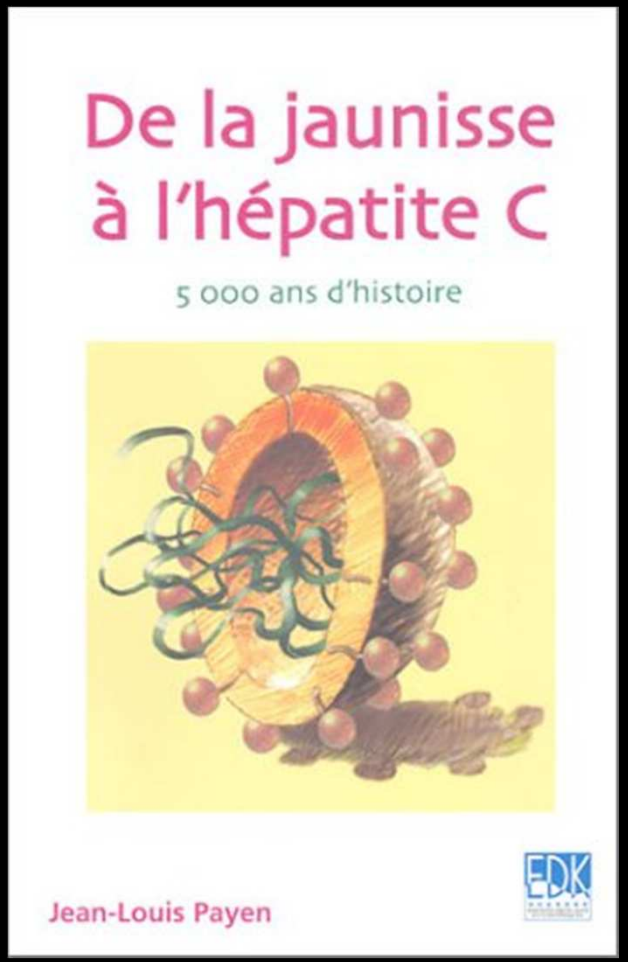
INSERM Unité de Recherche U1052 – Lyon – France

Stephen Hawking – Brief History of time

History of hepatitis – From jaundice to HCV

Hepatoscopy



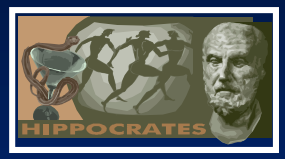
Les étapes

- -3000 à 1900 — le symptôme (jaunisse → ictère)
- 1900-1960 — La maladie
  - Autopsie
  - PBF
  - Transaminases
- 1965-1975 — Le virus et les marqueurs
- 1975-1980 — Le vaccin
- 1975… — Le traitement
  - 75-2005 — Symptôme / maladie
  - >2006 — **L'infection / réplication**
- 2008 — Entecavir
- 2008 — Tenofovir

2020 ?
Mort annoncée du virus de l'hépatite B !

I. L'hépatite épidémique (-3000 à 1900)

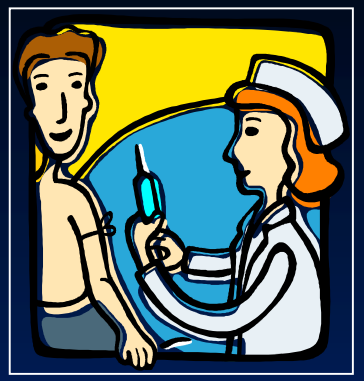
- -3000 Sumériens (Jaunisse…)
- -420 Grecs Hippocrate → « ictère »
- +750 Moyen-âge
  Pape Zacharie St Boniface
  → isolement
- 1800 Jaunisse des camps



Sièges < de St Jean d'Acre (1799)
de Paris (1870)

→ prévention

II. L'hépatite sérique (1880-1945)



Hépatite de la seringue

injections pour syphilis

Hépatite post-vaccinale

1882 : anti-variolique: Lurman (Breme)

1937 : anti-fièvre jaune : Findlay

1942 : 28000 cas US navy

Hépatite sérique et post-transfusionelle

(1945-1975)

Dualité des Hépatites

1947 Mc Callum

- **Hépatite A** **epidémique**
- **Hépatite B** **sérique**

1964 Krugman (Willow Brook School)

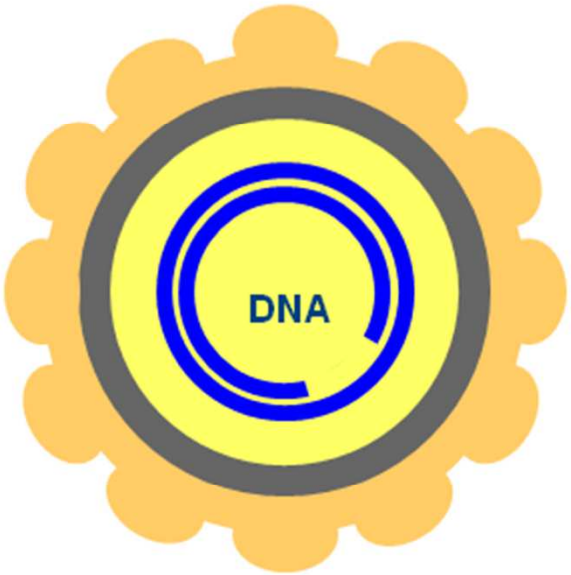
- **Hépatite A → orale (30-45j)** **« MS1 »**
- **Hépatite B → parentérale (60-90j)** **« MS2 »**

HISTORY OF VIRAL HEPATITIS

1963	HBV	Blumberg et al.	Serology
1973	HAV	Feinstone et al.	IEM (stool)
1977	HDV	Rizzetto et al.	Serology, IF (liver)
1983	HEV	Balayan et al.	Serology, IEM (stool)
1989	HCV	Houghton et al.	Cloning (liver)

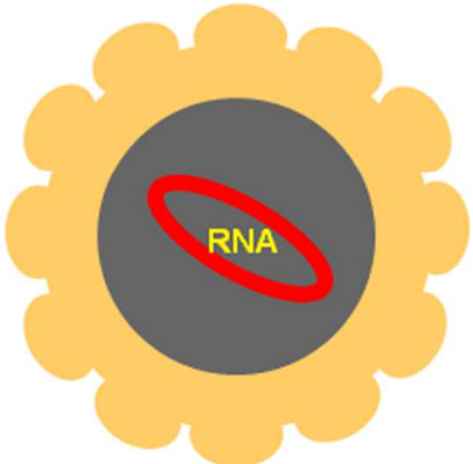
HEPATITIS A - E

HAV



HBV

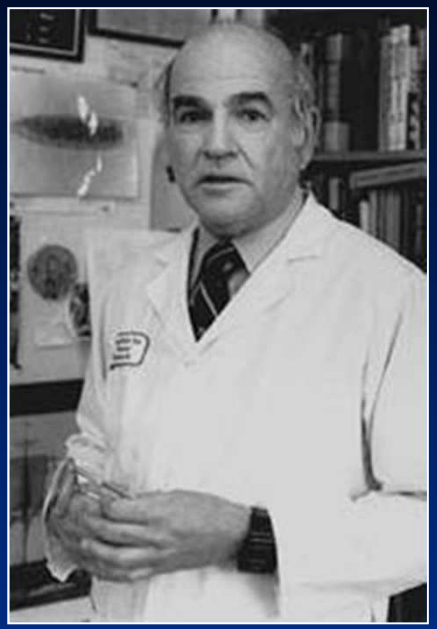
HEV



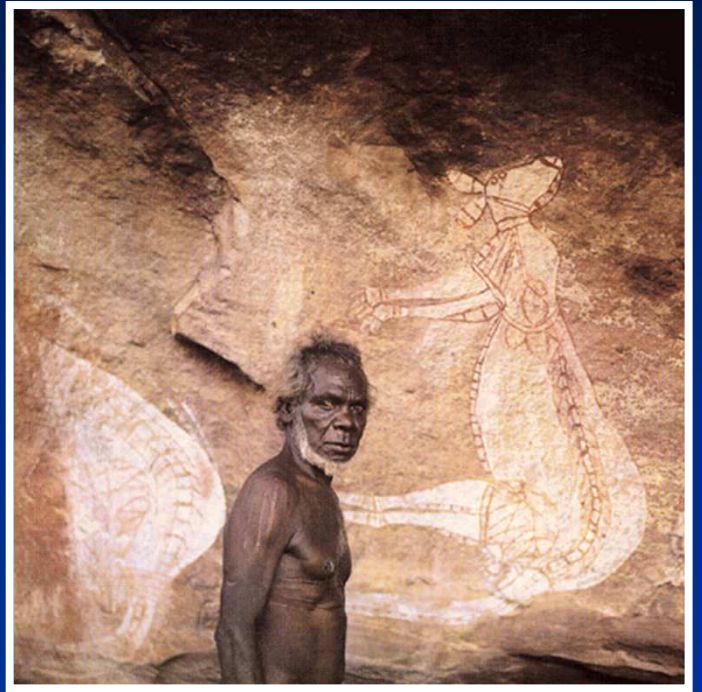
HDV

HCV

Pr BLUMBERG



1964



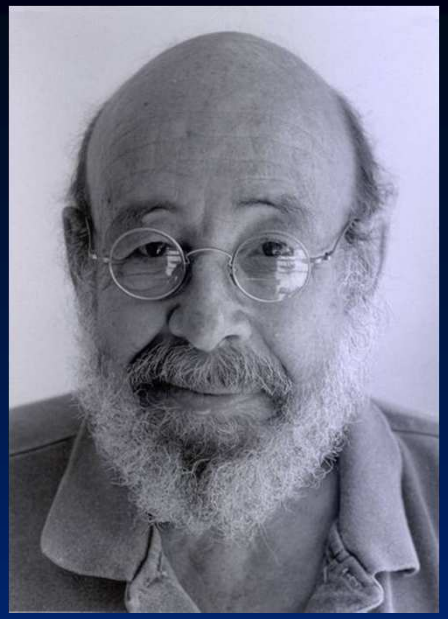
La découverte en 1964 par Blumberg d'un nouvel antigène dans le sérum d'un aborigène d'Australie marque le début d'une ère nouvelle dans l'histoire des hépatites. Blumberg, ethnologue, montra que cet « antigène Australia » était un marqueur de l'hépatite.

Prix Nobel en 1976 pour des découvertes sur de nouveaux mécanismes de dissémination des maladies infectieuses

PRINCE

(New York Blood Center)

1968

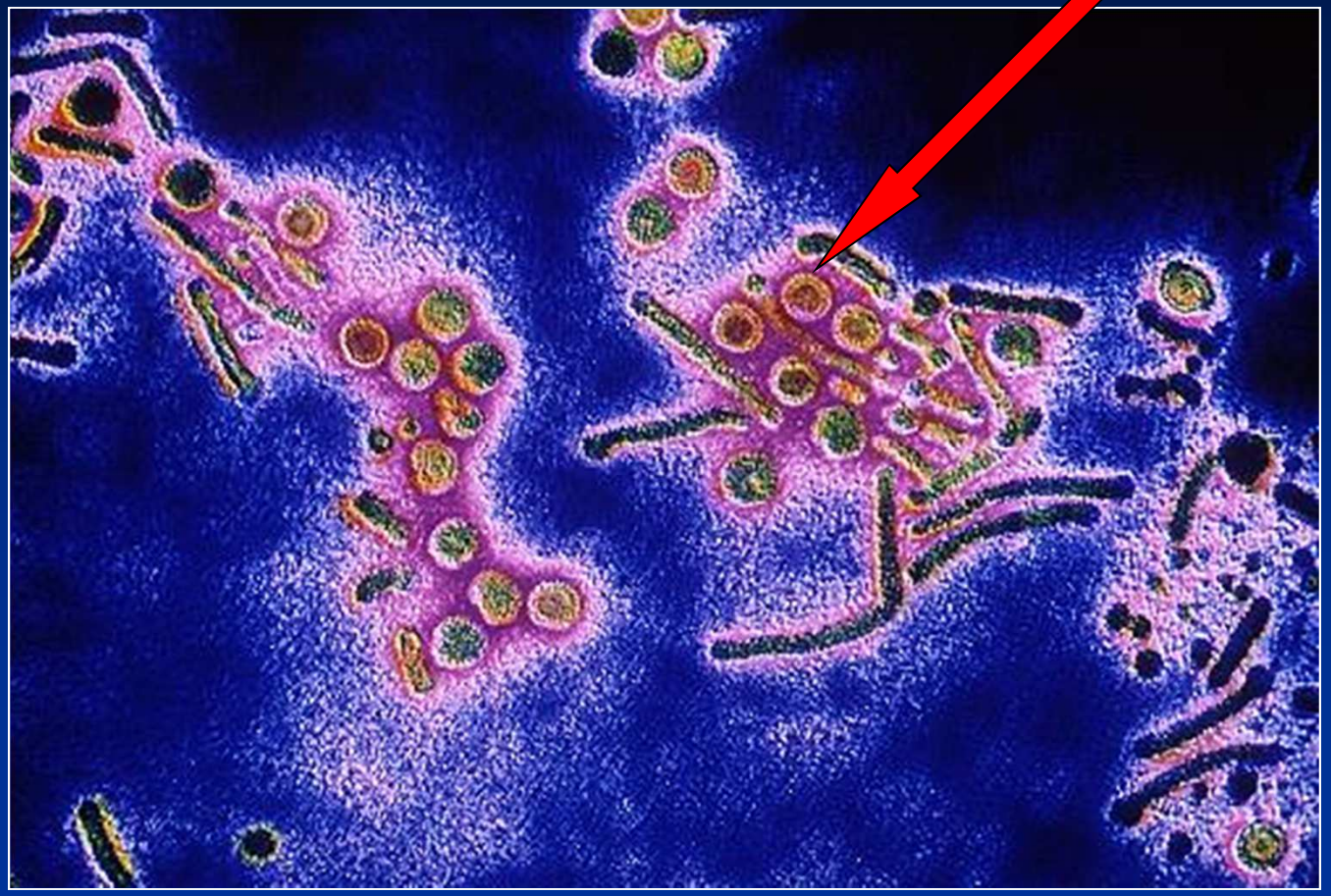


- Décrit l'Ag SH chez les patients qui développent une hépatite post-transfusionnelle
- Confirme
  - La spécificité de cet Ag pour l'hépatite B
  - L'identité avec l'Ag Australia

Le virus

1970

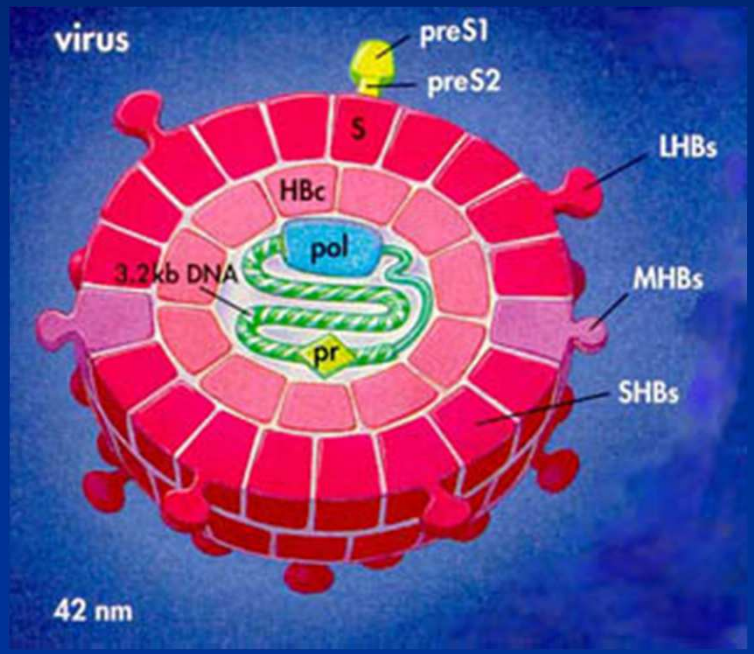
DANE



HBV marqueurs sérologiques

Antigènes

- HBsAg (1965)
- HBeAg (1972)



Anticorps

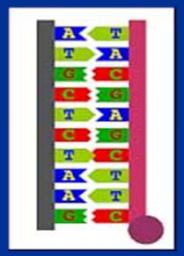
- Anti-HBc total (1971)
- Anti-HBc-IgM
- Anti-HBe
- Anti-HBs

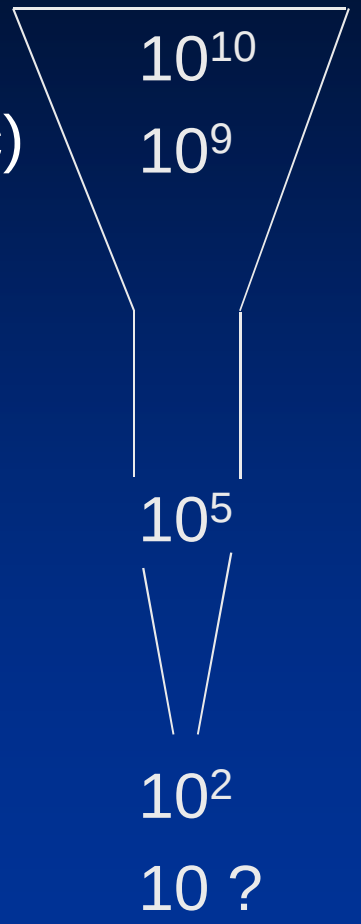
- ADN POL (1972)
- ADN (1974)

Les tests / techniques

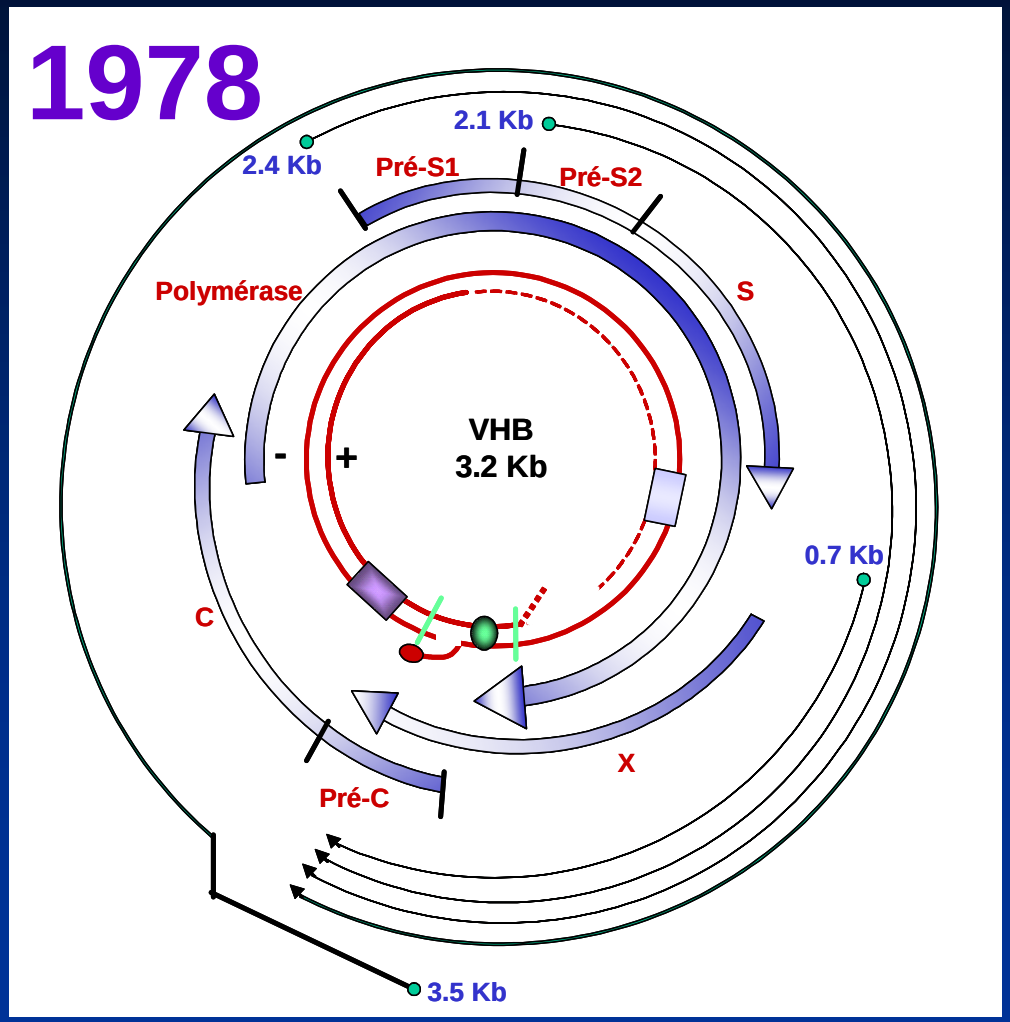
- 1965 Immunodiffusion (AgHBs/e et Ac)
- 1970 Contre électrophorèse (Ag HBs/e et Ac)
- 1970 RIA Ag/Ac
  DBA polymérase (HBV)
- 1975 ELISA (Ag/Ac)
- 1980 DNA hybridization

PCR Real time





Le clonage du VHB



P. TIOLLAIS/ F. GALIBERT

Le vaccin

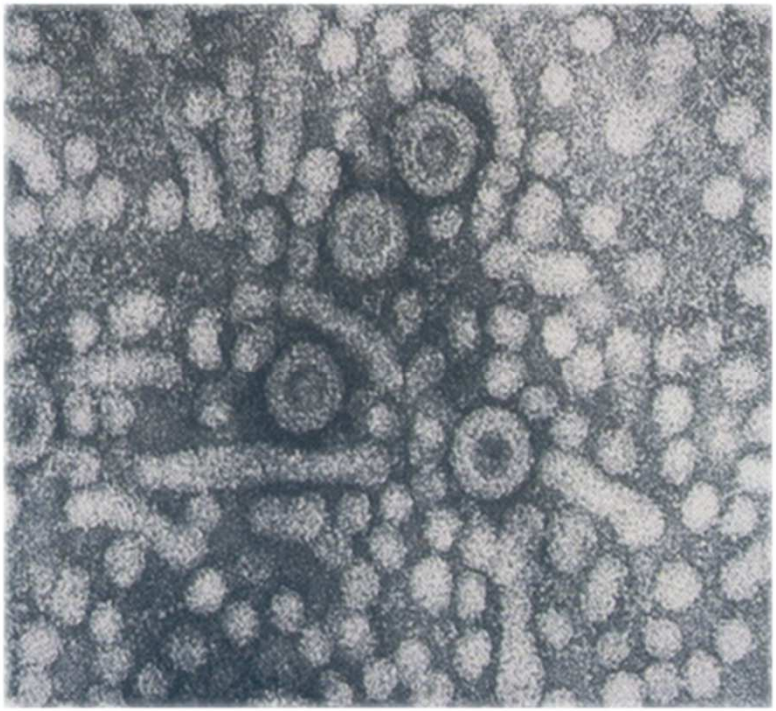
Vaccins plamatiques (1975-76)

- Ph. Maupas / institut Pasteur (F)
- M. Hilleman / MSD (USA)

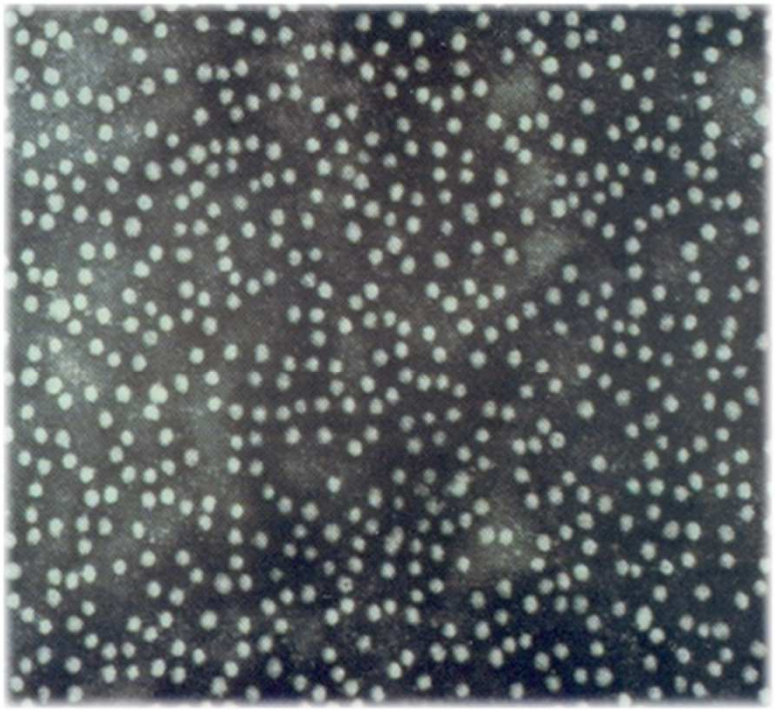
Vaccins recombinants (1981)

- P. Tiollais / institut Pasteur
- W. Rutter/ Chiron/MSD

HBV PARTICLES

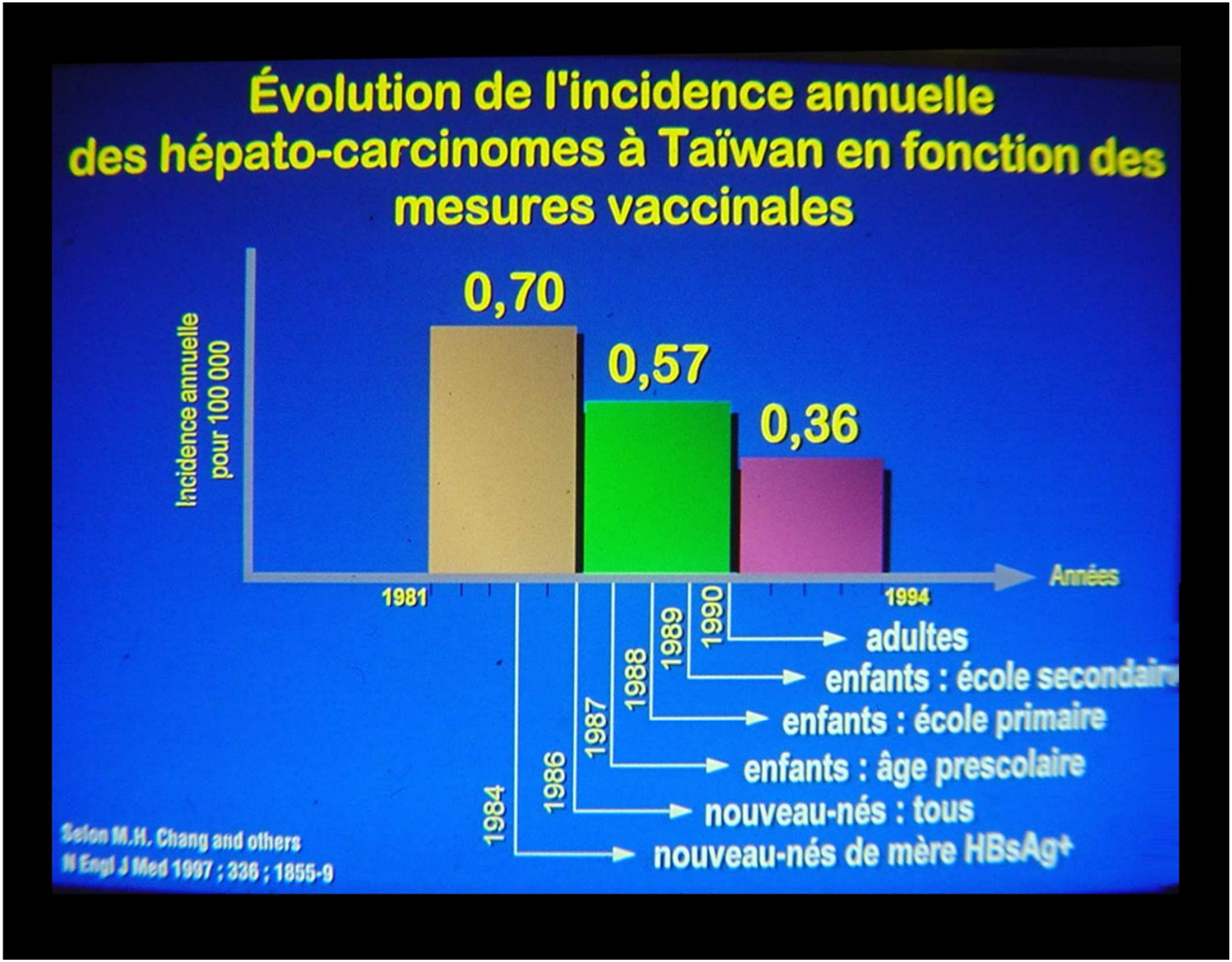


Serum



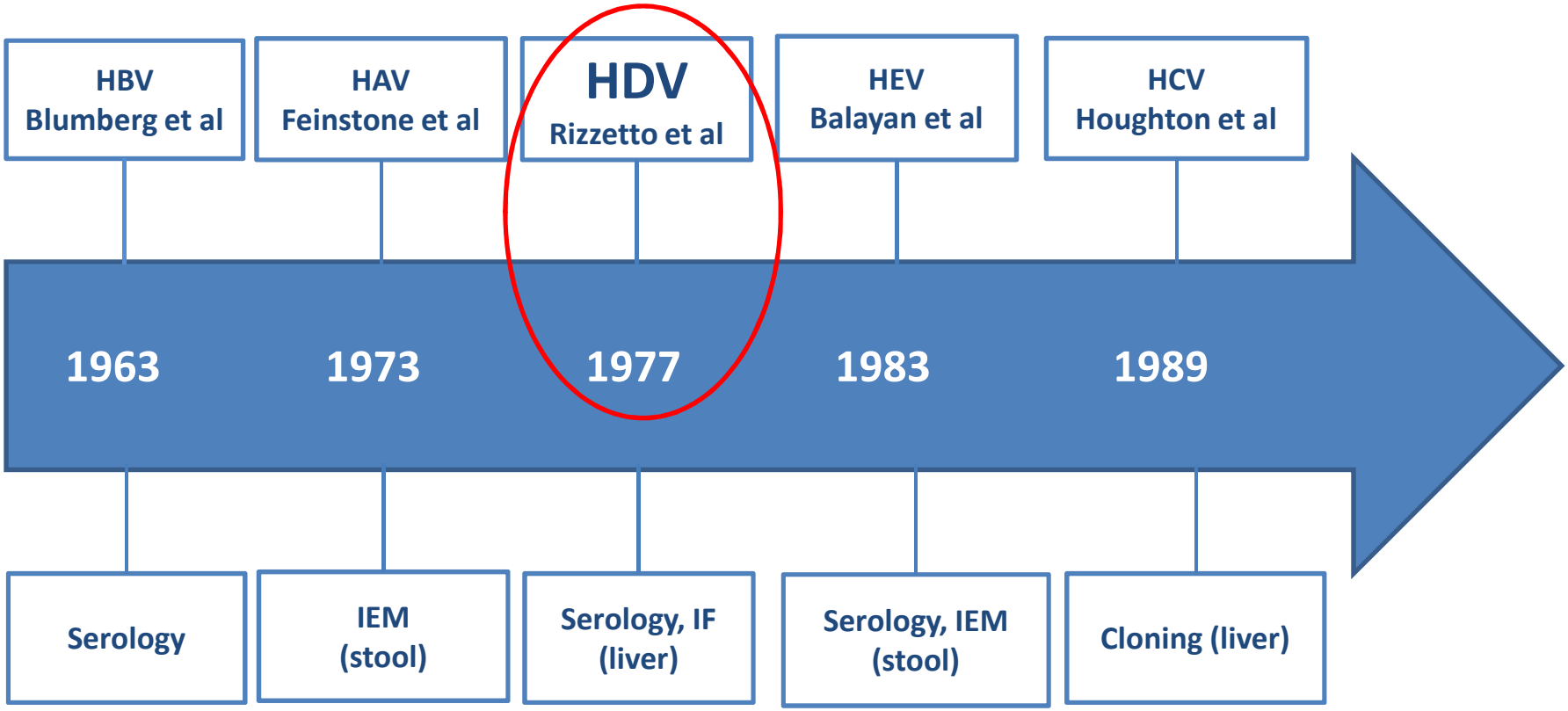
Serum-derived vaccine: Szmuness W et al. N Engl J Med 1980; 303: 833-841

Recombinant vaccine: Valenzuela P et al. Nature 1982; 298:347-350


Évolution de l'incidence annuelle des hépato-carcinomes à Taïwan en fonction des mesures vaccinales
Incidence annuelle pour 100 000
0,70
0,57
0,36
Années
1981
1994
1984
1986
1987
1988
1989
1990
nouveau-nés de mère HBsAg+
nouveau-nés : tous
enfants : âge prescolaire
enfants : école primaire
enfants : école secondaire
adultes
Selon M.H. Chang and others
N Engl J Med 1997 ; 336 ; 1855-9


HEPATITIS
LEGENDS

HEPATITIS VIRUSES DISCOVERY



HDV 37 th Birthday

Gut, 1977, **18**, 997-1003

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,[1] M. G. CANESE, S. ARICÒ, O. CRIVELLI, C. TREPO, F. BONINO, AND G. VERME

From the Department of Gastroenterology, Ospedale Mauriziano Umberto I, Turin, Italy, the Electron Microscopy Centre of the Faculty of Medicine, University of Turin, Italy, and INSERM U45, and Laboratory of Hygiene, University Claude Bernard, Lyon, France

SUMMARY A new antigen-antibody system associated with the hepatitis B virus and immunologically distinct from the HB surface, core, and *e* systems is reported. The new antigen, termed δ, was detected by direct immunofluorescence only in the liver cell nuclei of patients with HBsAg positive chronic liver disease. At present, the intrahepatic expression of HBcAg and δ antigen appears to be mutually exclusive. No ultrastructural aspect corresponding to the δ antigen could be identified under the electron microscope. δ antibody was found in the serum of chronic HBsAg carriers, with a higher prevalence in patients with liver damage. The nuclear fluorescence patterns of HBcAg and δ antigen were similar; it is only possible to discriminate between the two antigens by using the respective specific antisera.

While studying liver biopsies from patients who were seropositive for the hepatitis B surface antigen (HBsAg) in direct immunofluorescence, it was noted that an antiserum against the hepatitis B core antigen (HBcAg), as well as staining specimens in which core particles could be demonstrated by the electron microscope (EM), also reacted with additional biopsies which did not contain core particles (at electron microscopy) and were negative with other reference antisera against HBcAg.

When the EM core positive and core negative specimens were tested with several HBsAg positive sera, it soon became apparent that some sera reacted with either one or the other liver substrate; this suggested that there were two distinct nuclear antigenic specificities.

The identification of this new antigen and of its antibody as an immunological system independent of other known reactions associated with the HB virus is reported in this communication. Provisionally, we propose that it should be called δ.

[1]Address for correspondence: Dr M. Rizzetto, Department of Gastroenterology, Ospedale Mauriziano Umberto I, Cs. Turati 46, 10128 Turin, Italy.

Received for publication 30 May 1977

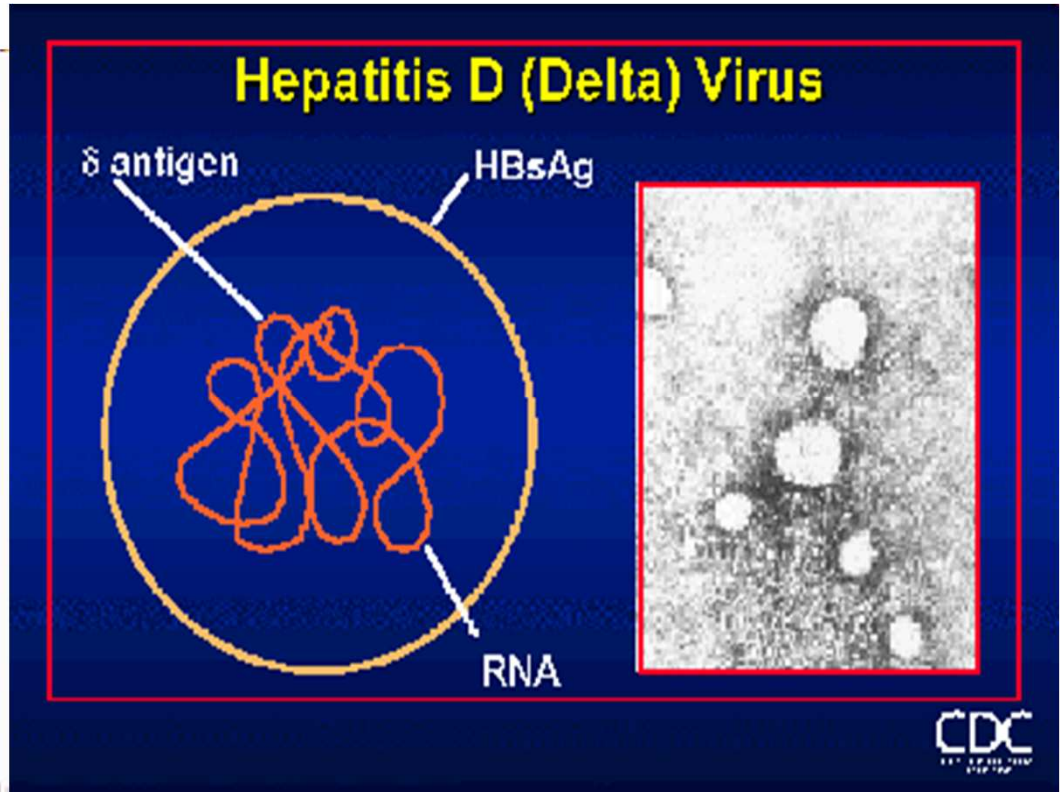
Methods

PREPARATION OF STANDARD FLUORESCENT ANTISERA AGAINST δ ANTIGEN (δ ANTISERUM), AGAINST HBCAG (HBC ANTISERUM), AGAINST HBSAG (HBS ANTISERUM), AND AGAINST *e* ANTIGENS (e_α + e_β ANTISERUM), STANDARD δ ANTIGEN (δ) AND HBCAG POSITIVE LIVER SUBSTRATES

A fluorescein isothyocianate (FITC) conjugated antiserum against HBsAg was prepared from Beheringwerke rabbit precipitating serum RBBO4 (Rizzetto *et al.*, 1976b). A FITC conjugated antiserum against *e* antigens (e_α + e_β) was prepared from a human serum as previously described (Trepo *et al.*, 1976).

A FITC antiserum monospecific against HBcAg and one monospecific against δ were prepared from the blood of two apparently healthy HBsAg carriers; both sera were negative when tested by the Reuma and Waaler-Rose techniques. The gamma globulin fractions, isolated after precipitation with $(NH_4)_2SO_4$, did not contain autoantibodies (in indirect Immunofluorescence (IFL)), antibodies against HBsAg, *e* antigens, or *e* antibodies.

After conjugation with FITC, the HBc antiserum


Hepatitis D (Delta) Virus
δ antigen
HBsAg
RNA
CDC

HDV HBV

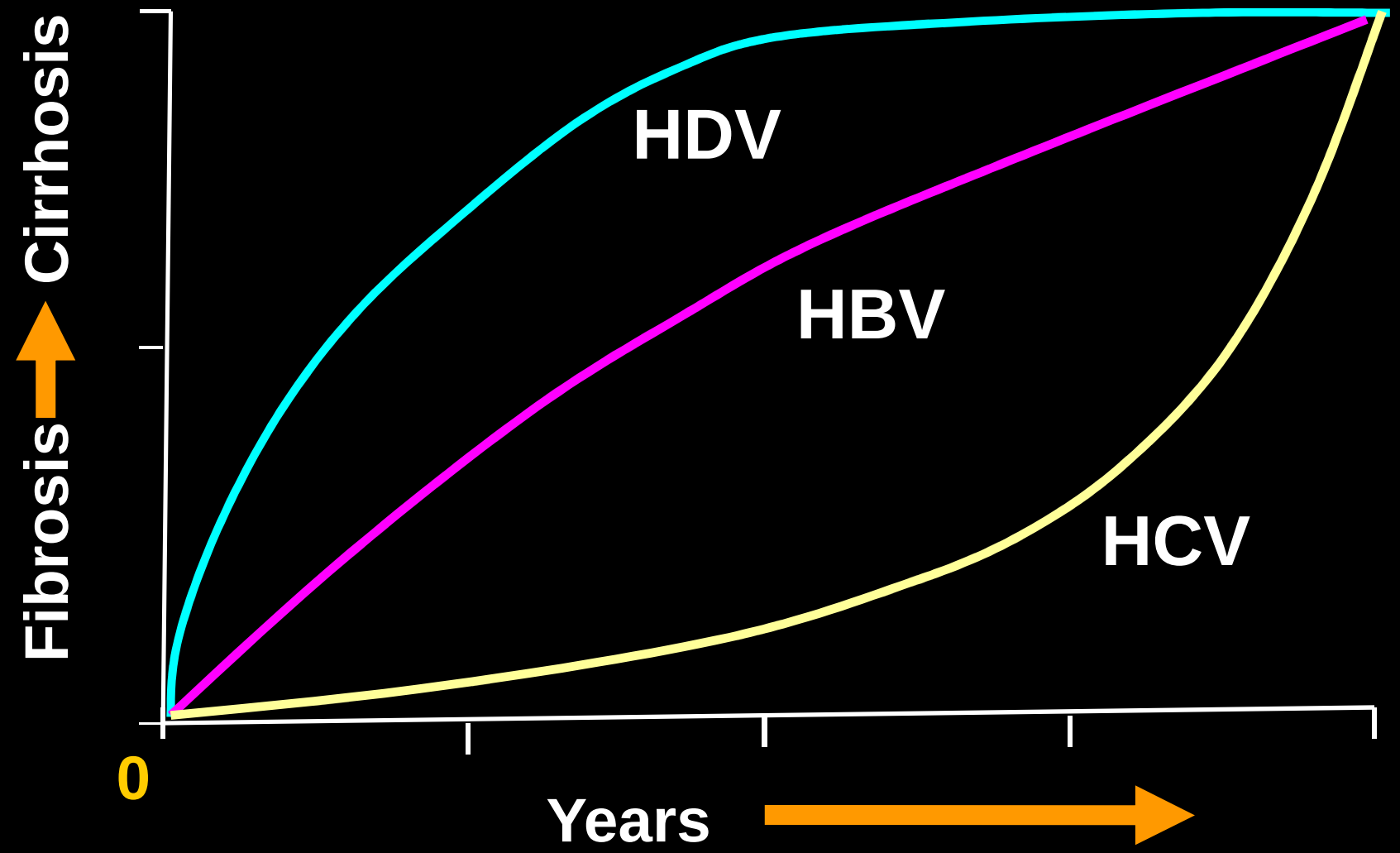
HDV INHIBITS HBV REPLICATION

Anti-transcriptional effec

Competition envelope

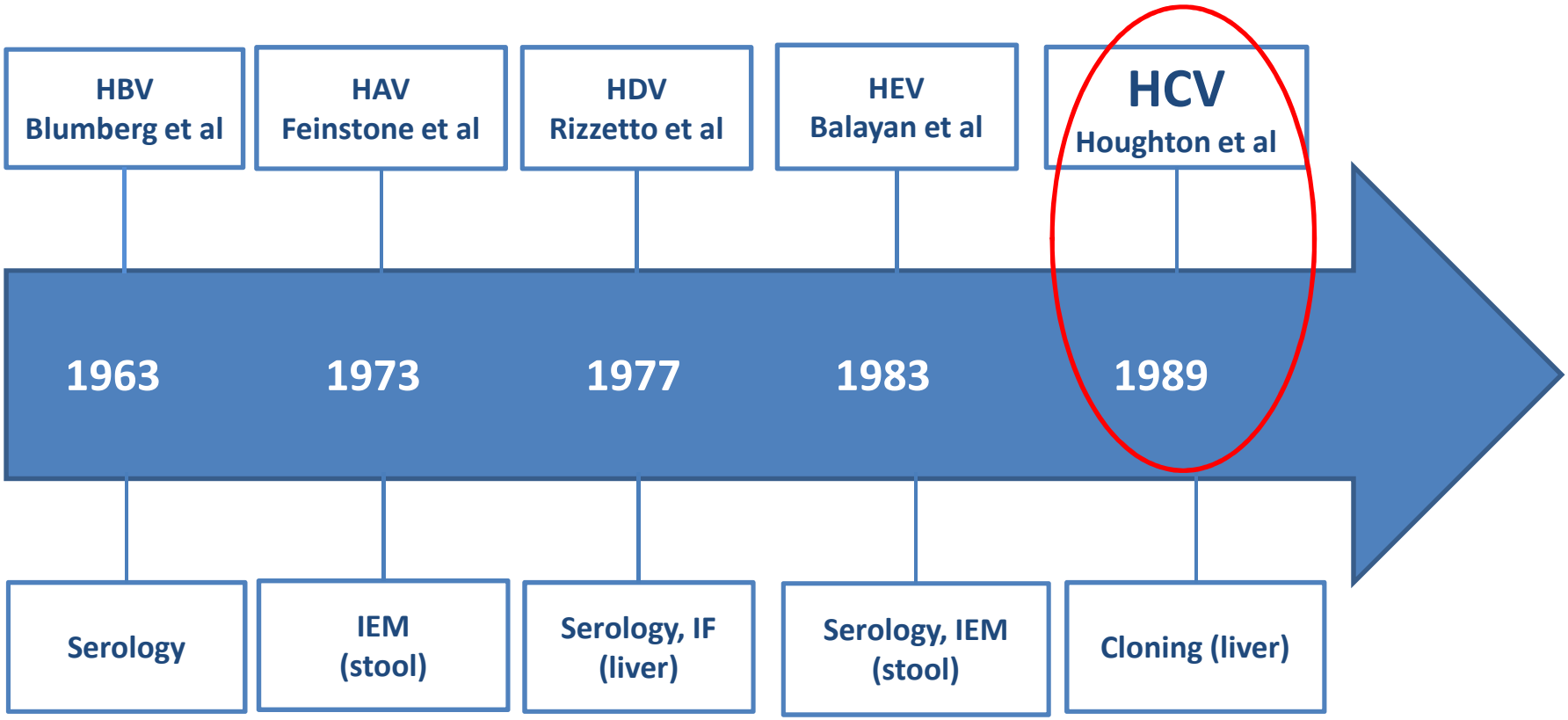
Cytokines (MxA ?)

Evolution of Hepatitis D Compared to Hepatitis B and C



Epidemic of Fulminant Hepatitis Delta In Central African Republic

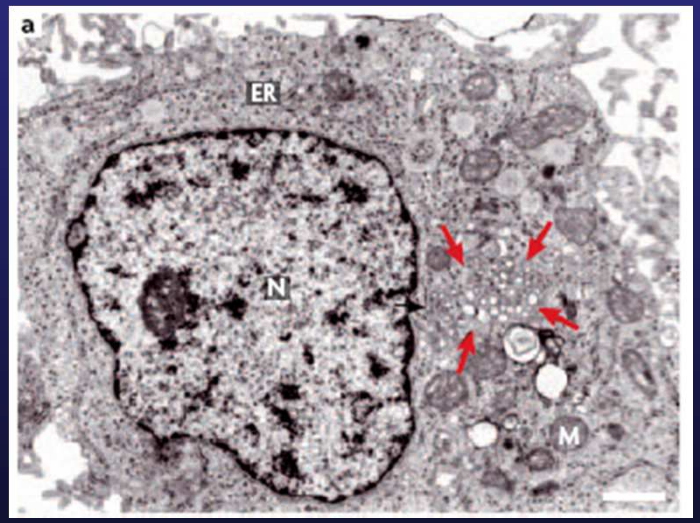
HEPATITIS VIRUSES DISCOVERY

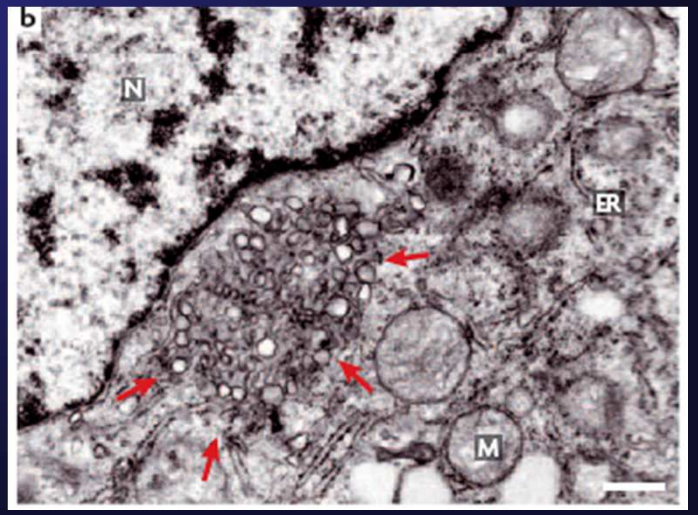


Les marches d'approche (1979-85)

1. **1979** Tubule Forming Agent → Shimizu (NIH)
2. **1985** D. Bradley (CDC)
   - Togavirus
   - Flavivirus
   - HDV
3. **1987** <50nm filter
4. Post-transfusion NANB hepatitis 1980- incidence 7% en France → 10% USA

Tubules double membranes « TFA »





Moradpour, Penin, Rice Nature Rev 2007

Les impasses

- 1983 HDV like → Kamimura/Purcell
- 1984 Retrovirus → Seto/Gerety
- 1984 Spumavirus → Prince
- 1985-9 Non-A, non-B Ag/Ab systems
  Shimizu & many others

L’ascension

- **1er isolement viral**
  - sans culture
  - sans microscopie électronique
  - sans sérologie

Approche moléculaire directe

Depuis

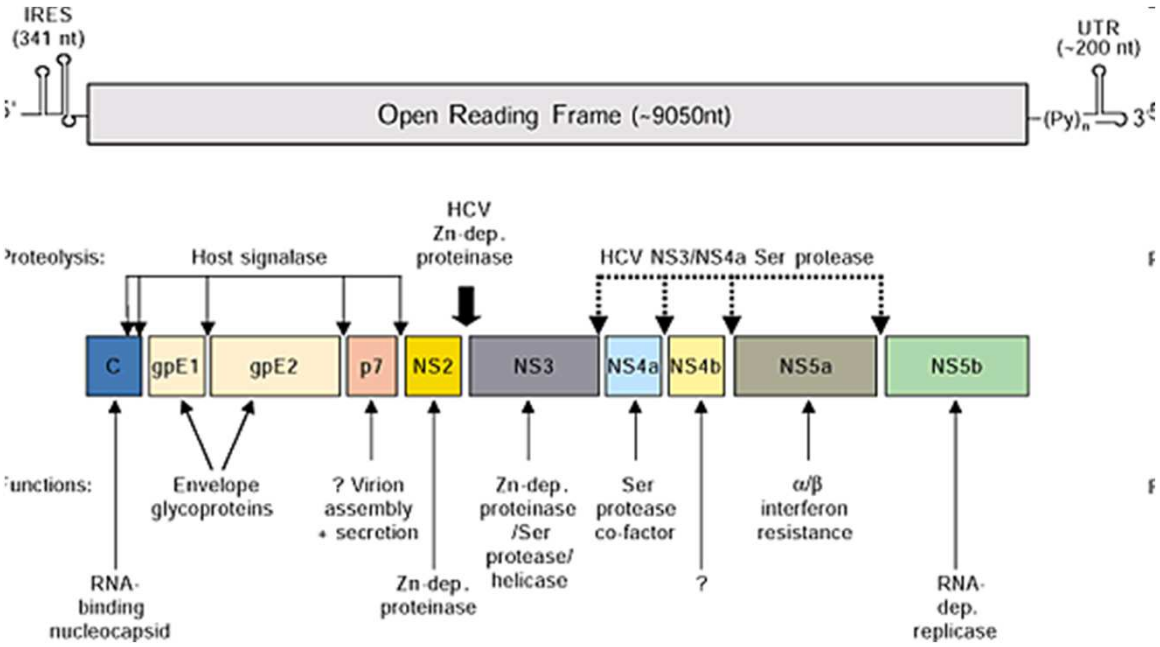
- HEV, HHV8
- TTV
- HGV

1988-89

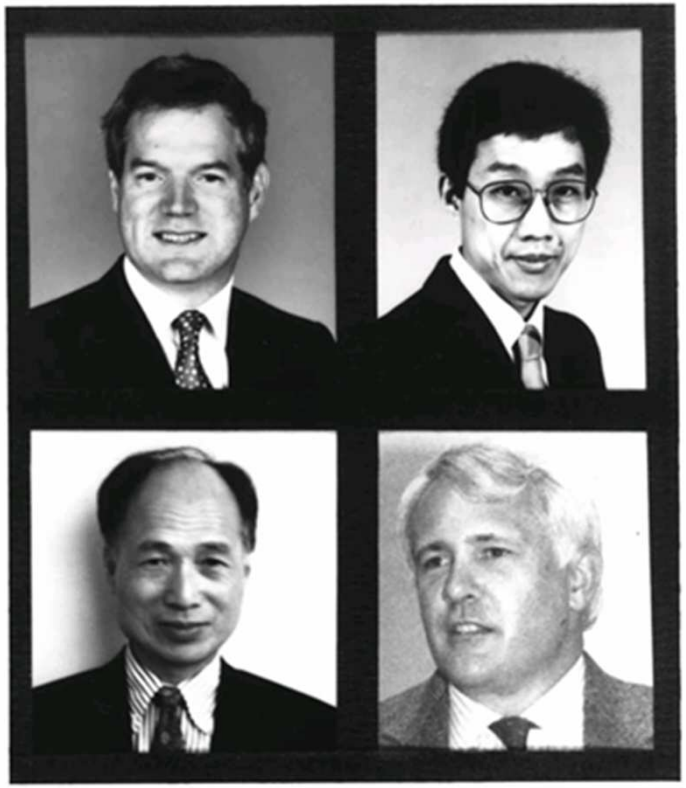
Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

Science, New Series, Vol. 244, No. 4902 (Apr. 21, 1989), pp. 359-362



The HCV discovery team
(from left to right; M. Houghton, Q-L Choo, G. Kuo and D. Bradley



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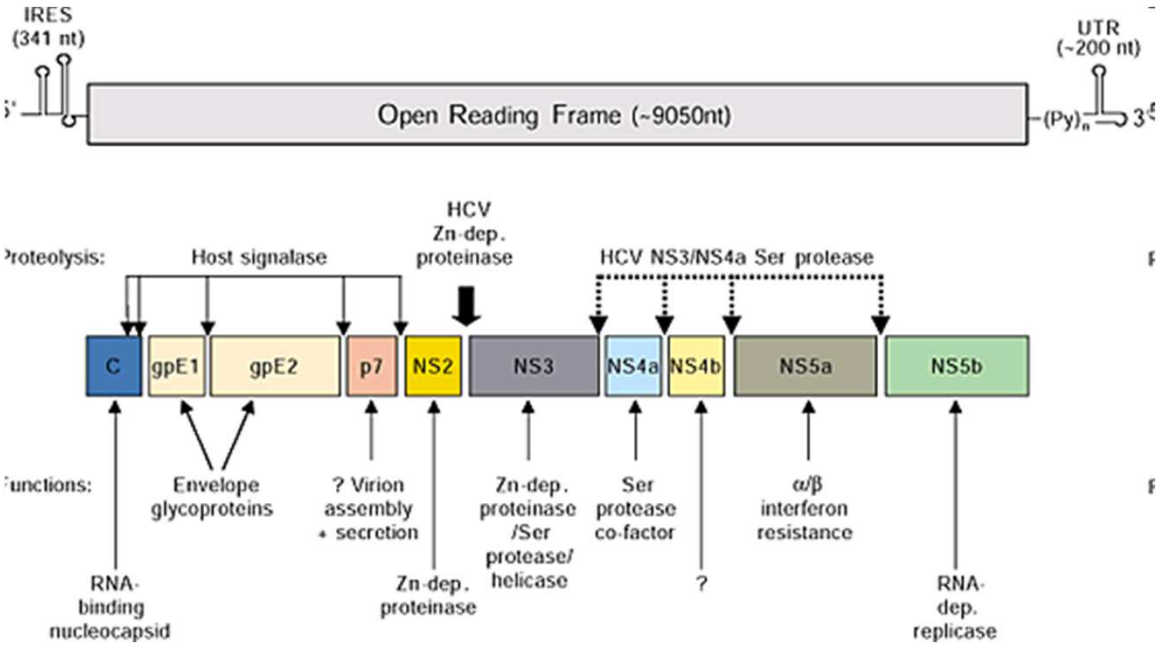
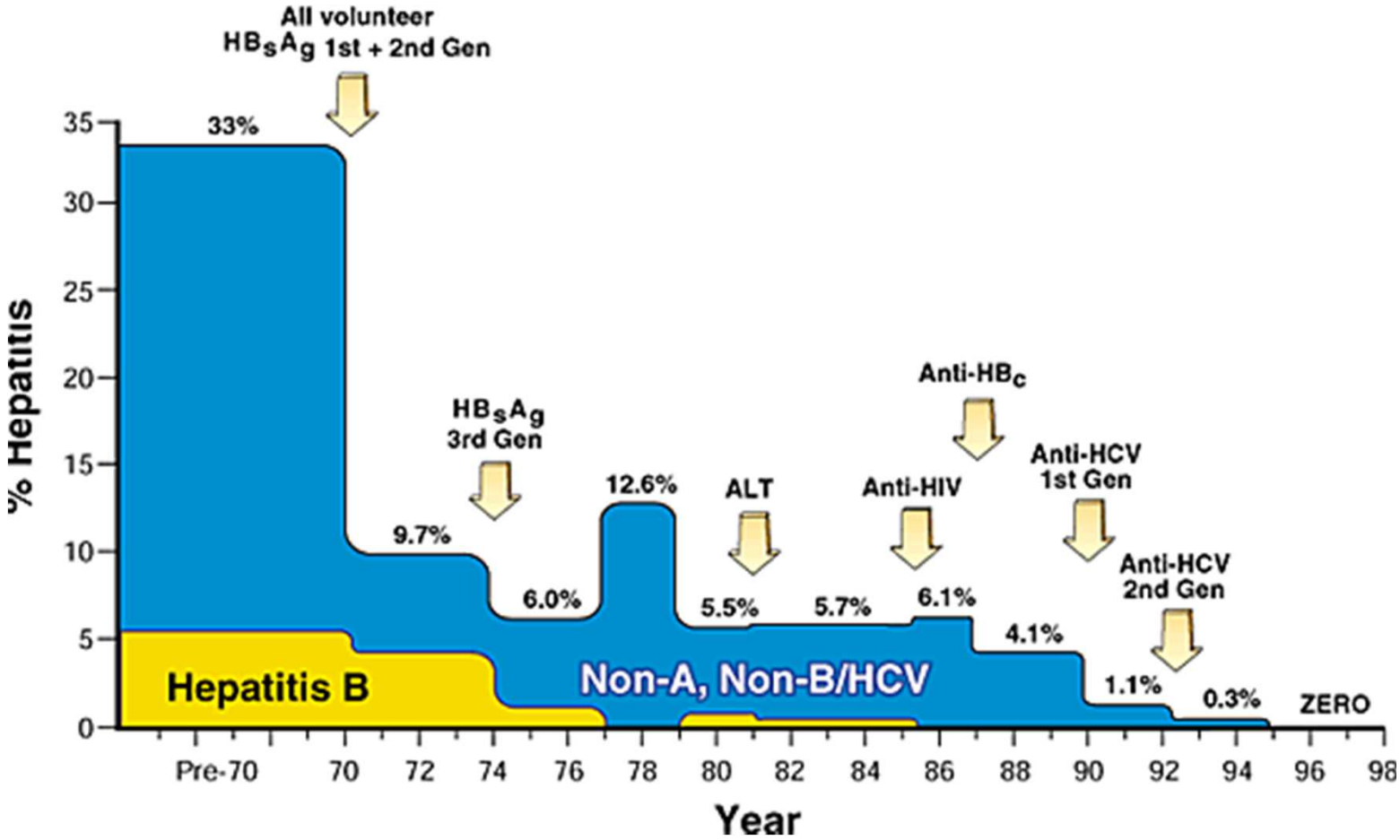


Clinical Medical Research Award

Hepatitis C Virus and eliminating post-transfusion hepatitis

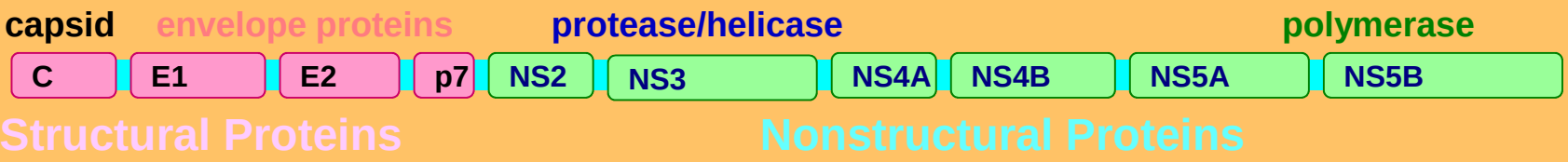
Harvey J. Alter & Michael Houghton

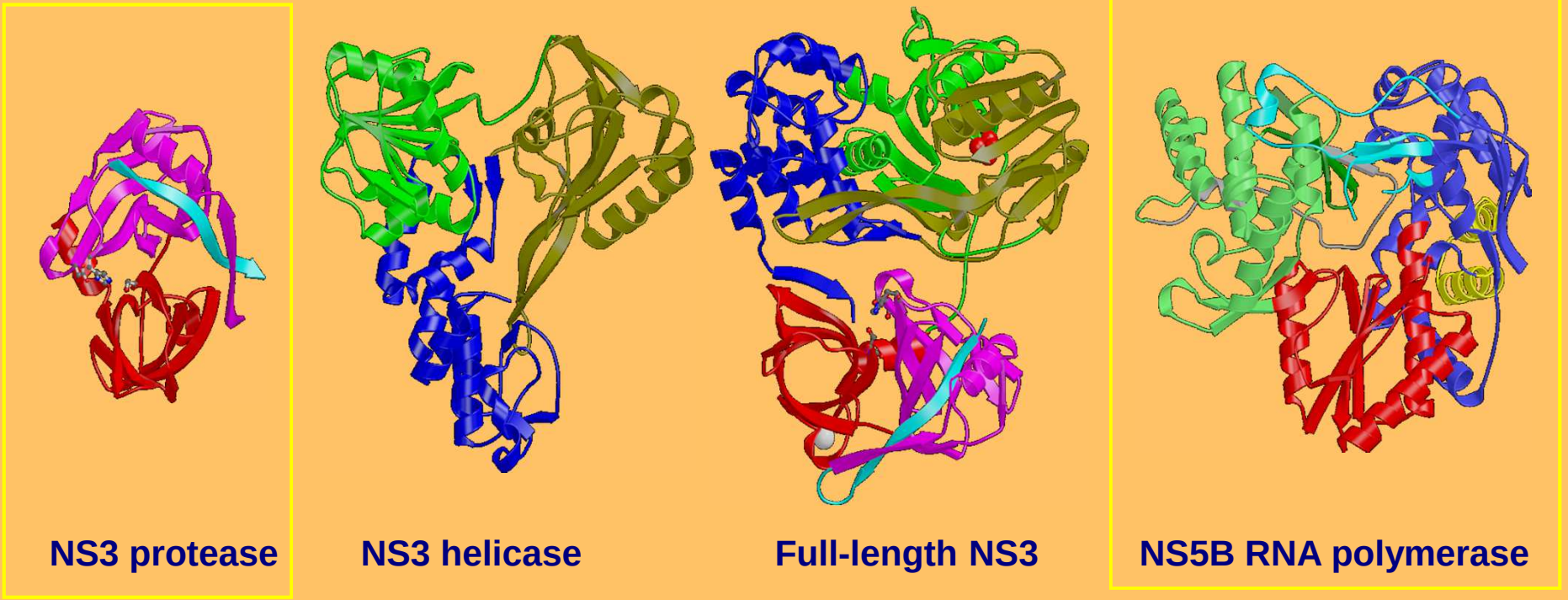
NATURE MEDICINE • VOLUME 6 • NUMBER 10 • OCTOBER 2000



Targets for HCV Antiviral Agents

HCV Polyprotein





NS3 protease | NS3 helicase | Full-length NS3 | NS5B RNA polymerase

NUCLEOSIDES & PIs CURRENTLY DOMINATE THE ANTI-HCV FIELD

Graveyard for HCV Compounds is Filling Up Quickly!

ISIS 14803
(Antisense)

UT-231B
(Imino sugar)

Heptazyme
(Ribozyme)

VX-497
(IMPDH inhibitor)

ANA975
(TLR agonist)

BILN 2061
(Protease)

JTK-003
(Polymerase)

HCV-796
(Polymerase)

NM-283
(Polymerase)

R803
(Polymerase)

CPG 10101
(TLR agonist)

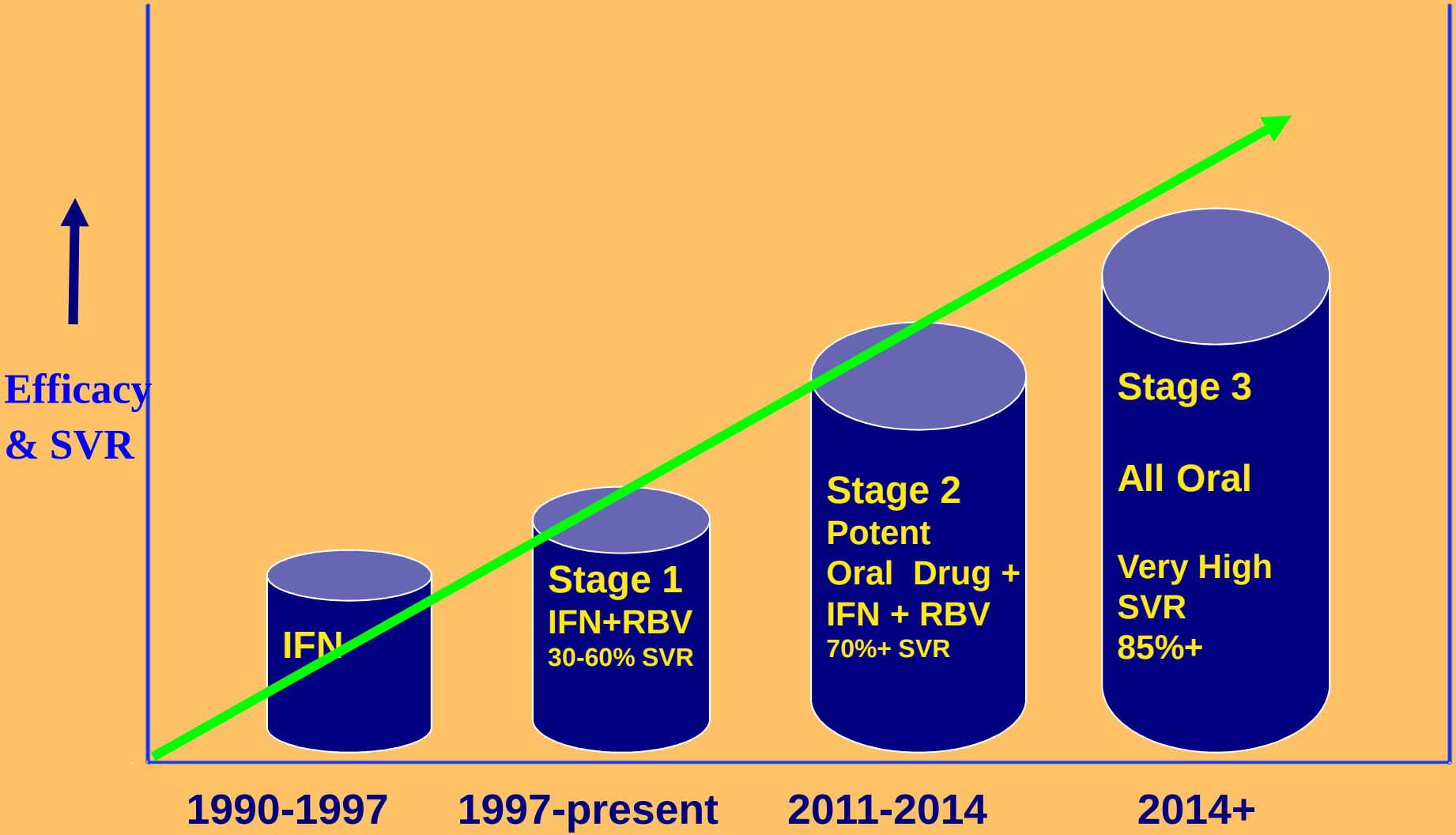
ACH-806/GS-9132
(NS4a)

R7025
(Interferon-alpha)

Data have not been reviewed or approved by FDA.

Courtesy of Nelson D. Adapted from 2008 Roche HCV Symposium.

Positioning HCV Therapeutics



SVR = Sustained Virologic Response

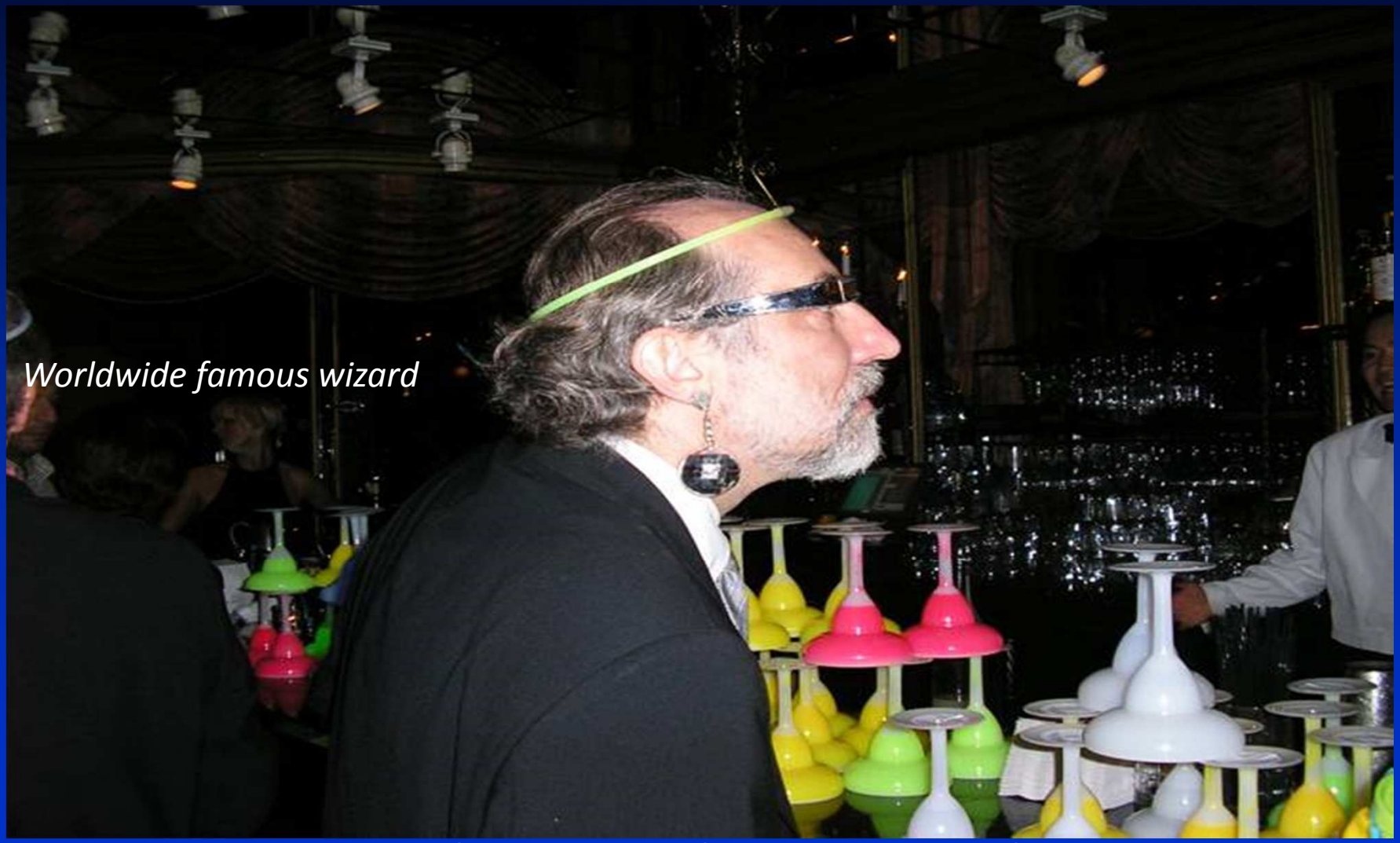
L'hépatite C
une des plus belles histoires de la médecine depuis la variole, la polio et la tuberculose

« Nous assistons à une révolution dans le traitement du virus de l'hépatite C, avec des molécules puissantes, capables de guérir l'infection.

Il n'est pas question que ces traitements, qui peuvent sauver des millions de vie, ne soient pas universellement disponibles à un prix abordable. »

Pr Françoise BARRÉ-SINOUSSI
Prix Nobel de Médecine, 2008

I had a dream



Marcellin P et al. Adefovir dipivoxil for the treatment of B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348:808-16

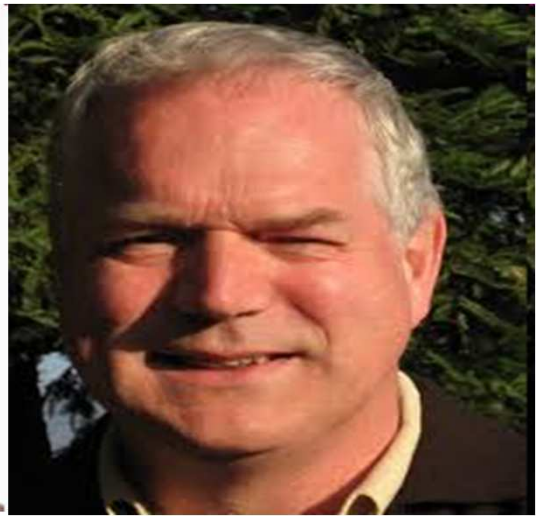
1) **Le traitement de l'hépatite C**

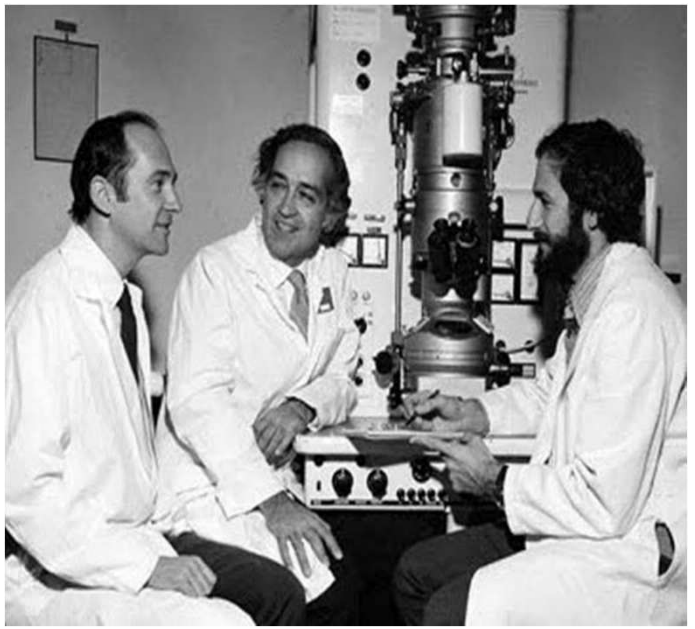
(de 1 à 3 mois) est accessible à tous et la maladie en voie de disparition

2) L'hépatite B est devenue curable et le virus éradicable

3) Les vaccins contre le VHA, VHB, VHE sont universels

They paved the way





Acknowledgements

Hepatitis C virus
Research groups in Lyon

C. Trépo
F. Zoulim

G. Inchauspé

FL. Cosset
JL. Darlix

BioMérieux

V. Lotteau
P. André

F. Penin
G. Deléage

BioSciences Federative Research Institute
(IFR 128 - INSERM, CNRS, UCBL, ENSL, INRA, HCL)

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