

THE INAUGURAL UNITED THERAPEUTICS
DISTINGUISHED LECTURE IN VIROLOGY PROGRAM

HEPATITIS B

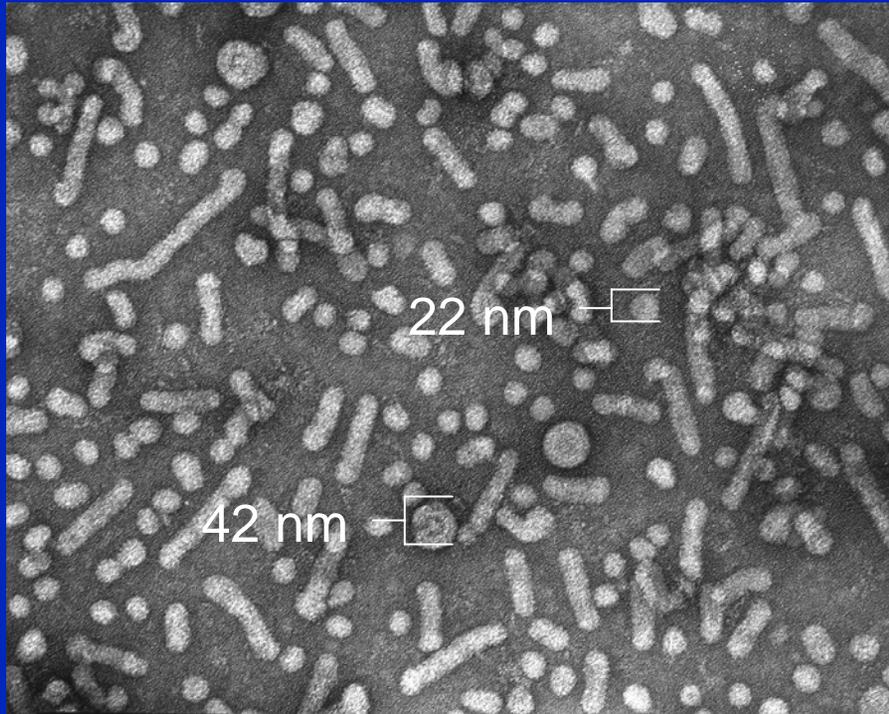
THE FIRST CANCER VACCINE

30 November 2006
Oxford University
Museum of Natural History

OUTLINE OF PRESENTATION

1. HBV is a common infection
2. It is a causative agent of HCC worldwide (estimate 80%)
3. The vaccine is highly effective and in wide use
4. HBV carrier rates have been dramatically reduced by vaccination
5. The vaccination program decreases the incidence of HCC
6. There are many cancers whose cause is attributed to infectious agents
7. There are probably others in which viruses contribute to pathogenesis
8. The pathogenesis and etiology of cancer is complex with multiple "causes"
9. A program for the identification and prevention of virus related diseases should be a priority in the cancer program

HEPATITIS B VIRUS MORPHOLOGY



Characteristics

Nucleic acid: DNA

Classification:

hepadnavirus type 1

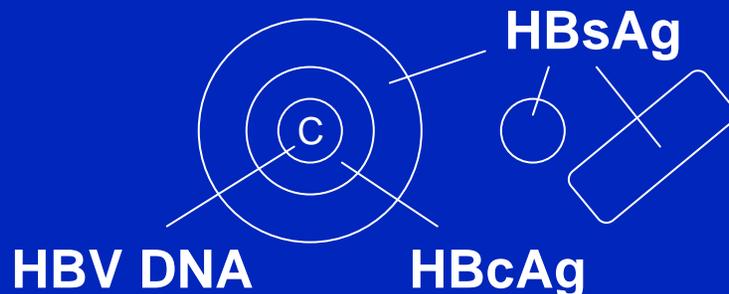
Serotypes: multiple

In vivo replication:

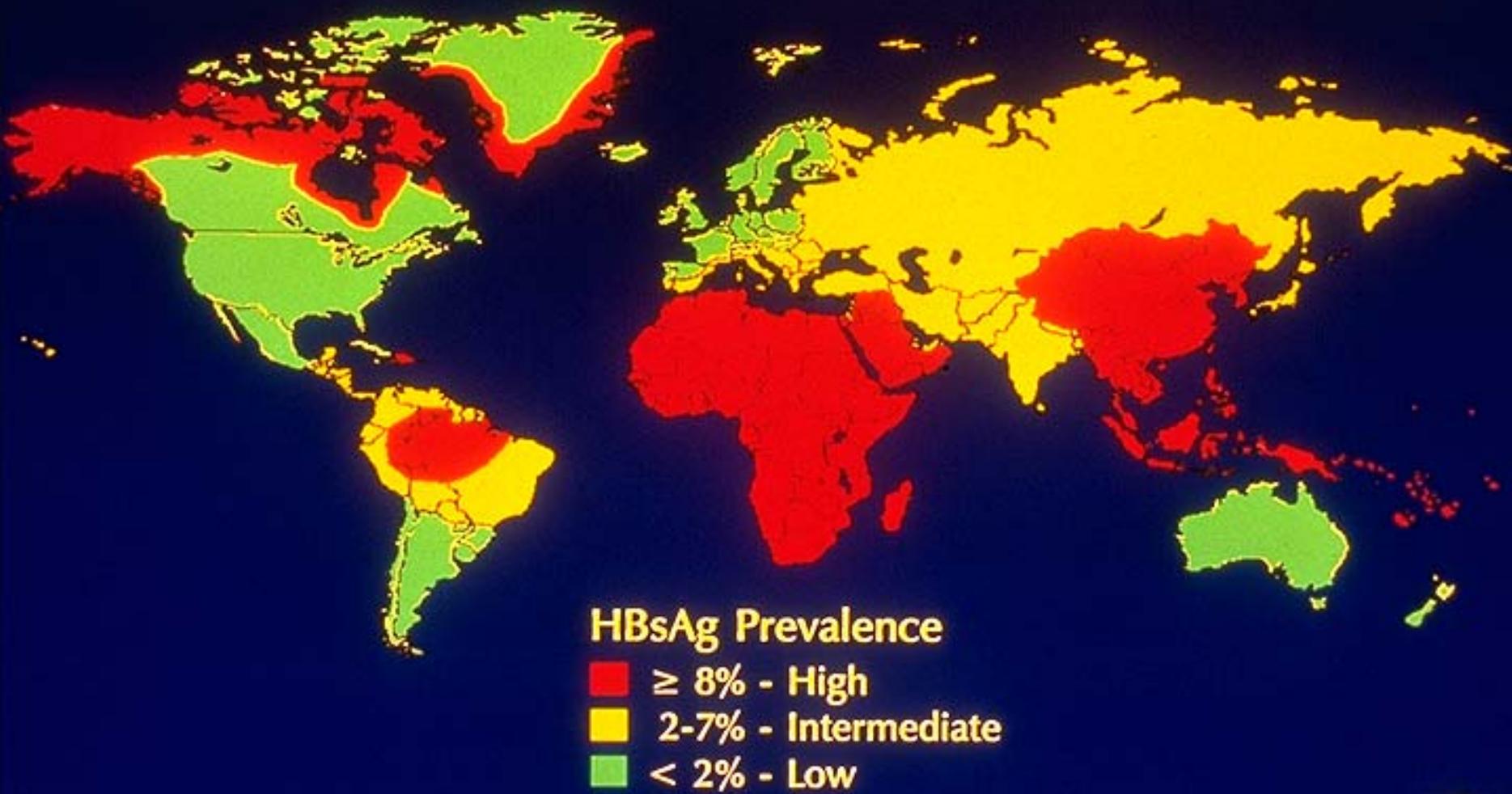
reverse transcription in
liver and other tissues

In vitro propagation:

primary hepatocyte
culture and transfection
by cloned HBV DNA



Global Distribution of Chronic HBV Infection



“Hepatitis B is a viral infection of the liver. More than two thousand million (2 billion) people alive today have been infected with the hepatitis B virus. Approximately 350 million are chronically infected and are at high risk of serious illness and death from cirrhosis of the liver and primary liver cancer.

Hepatitis B is preventable with a safe and effective vaccine — **the first vaccine against cancer.**”

WHO website, 2004

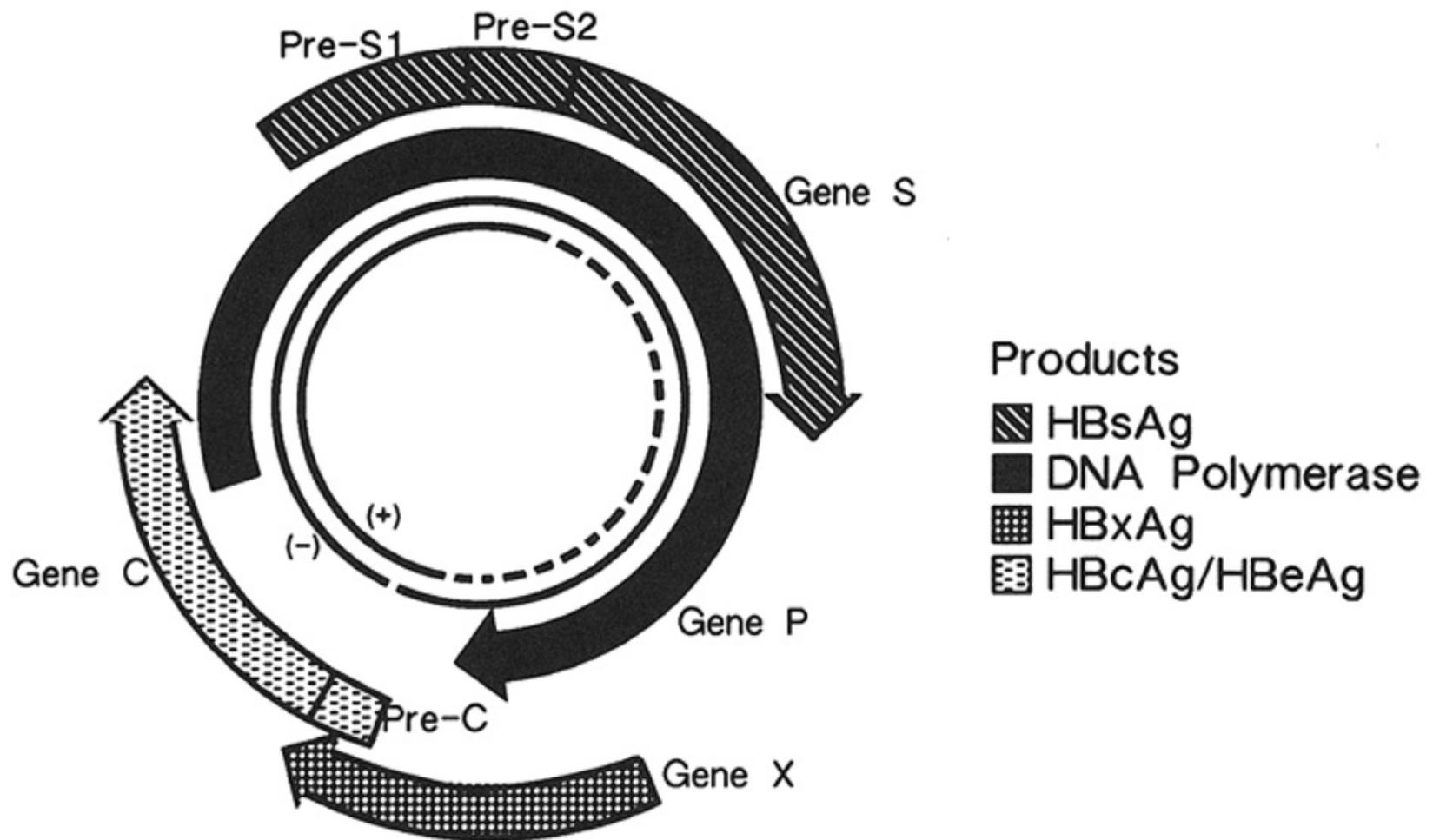
Primary Cancer of the Liver

– Worldwide:

- Third most common cause of death from cancer in males
- Seventh most common cause of death from cancer in females
- More than a million deaths per year
- Hepatitis B virus (about 85%) and hepatitis C virus account for most of these cancers
- Many other factors involved in the pathogenesis

HBV

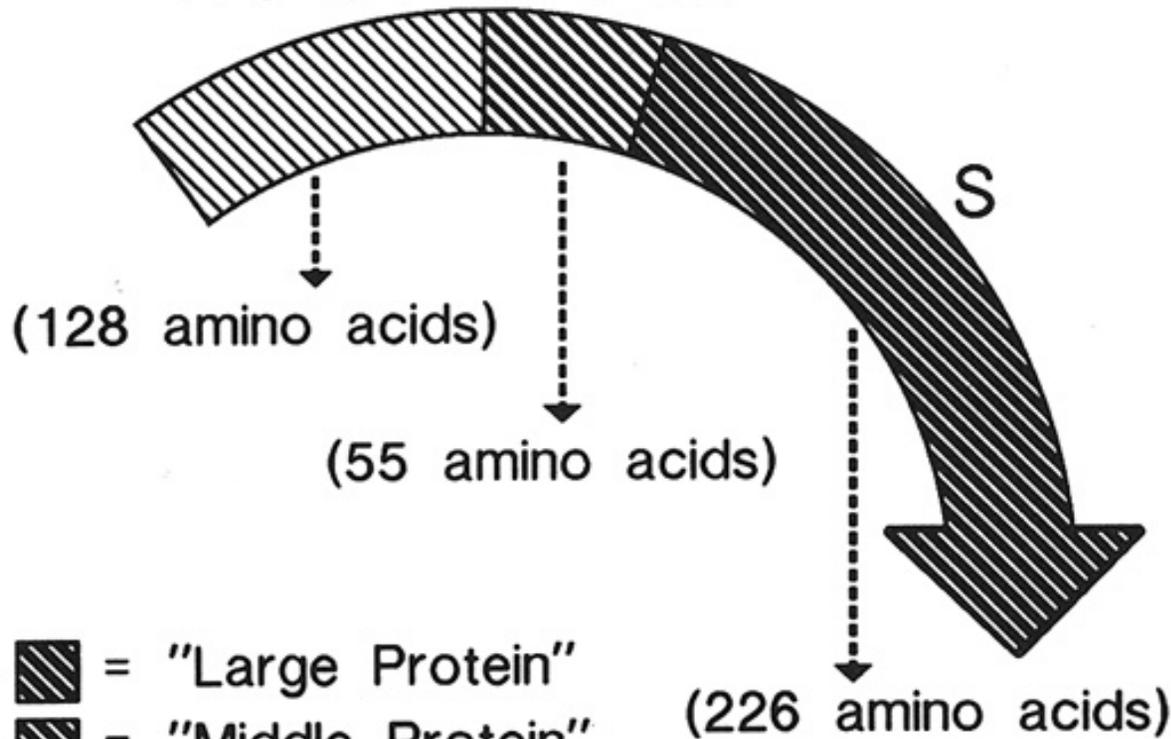
Genes and Gene Products



HBV

S Gene and Pre-S Region

Pre-S1 Pre-S2



 +  +  = "Large Protein"
 +  = "Middle Protein"
 = "Major Protein"

HBV INFECTION BEFORE AND AFTER VACCINATION PROGRAMS

| LOCATION | BEFORE | AFTER | NOTES |
|-----------------------|---------------|------------|---|
| China, regional study | 16.0% | 1.4% | HBV Carriers |
| USA, CDC | 260,000 | 78,000 | Total HBV cases |
| USA, Alaska | 215 | 7-14; 1993 | Native Americans. Acute cases per 100,000 |
| | | 0; 1995 | |
| Gambia, W. Africa | 10.0% | 0.6% | Carriers |
| Afragola, Italy | 10.5% | 0.8% | Males <12 y. Carriers |
| “ | 52.6% | 1.2% | Males <12 y. Anti-HBc |
| Afragola, no vaccine | 18.0% | 5.5% | M. 13–60. Carriers |
| Southern Italy * | 48% | 18% | Liver disease due to HBV |
| Catalonia, Spain | 9.3% | 0.9% | 15-24 ages |
| Catalonia | | | 80% reduction HBV in Liver disease |
| Saudi Arabia** | 6.7%; 1989 | 0.3%; 1997 | Carriers |
| “ | 4.2% anti-HBc | 0.5% | Anti-HBc |
| Japan | 2.7% | 0.9% | General population. Carriers |
| “ | ~4.0% | 0.04% | Children <6 y. Carriers |

* “If coverage rates are maintained at the present levels, elimination of HBV transmission in Italy may be envisaged in a few years”.

** “The ultimate goal of preventing HBV-related chronic liver disease and hepatocellular carcinoma in Saudi Arabia is foreseeable in the near future”.

THE INCIDENCE OF HEPATOCELLULAR CARCINOMA PER 100,000 POPULATION BEFORE AND AFTER HBV VACCINATION.

| LOCATION | BEFORE | AFTER | NOTES |
|-----------------|---------------|---|--|
| Taiwan | 0.70 | 0.36 | Ages 6-14 |
| “ | 0.52 | 0.13 | Ages 6-9 |
| Korea | 18.1 | 1) Vaccinated 0.58 2) “natural” anti-HBs 0.34 | Cohort 370,285 m. 30+. 35,934, vaccinated |

VIRUSES AND CANCER

| <i>Virus Family</i> | <i>Type</i> | <i>Human Tumor</i> | <i>Cofactors</i> |
|---------------------|----------------|---|-----------------------------|
| Adenoviruses | Types 2, 5, 12 | ?None ?Mesothelioma ?Other | ?Asbestos ?Other |
| Flaviviruses | HCV | Hepatocellular carcinoma | - |
| Hepadnavirus | HBV | Hepatocellular carcinoma (? Cancer of the pancreas) | Aflatoxin, alcohol, smoking |
| Herpesviruses | EBV | Burkitt's lymphoma | Malaria |
| | | Immunoblastic lymphoma | Immunodeficiency |
| | | Nasopharyngeal carcinoma | Nitrosamines, HLA Genotype |
| | | Hodgkin's disease | — |
| | HHV-8 | Leiomyosarcomas | — |
| | | Gastric cancers | — |
| | | Kaposi's sarcoma | HIV Infection |
| | | Body cavity-based lymphoma | HIV Infection |
| | | Castleman's disease | HIV Infection |

EBV, Epstein-Barr virus; EV, epidermodysplasia verruciformis; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HTLV, human T-cell leukemia virus; SV40, simian vacuolating virus 40.

From: *Cancer: Principles & Practice of Oncology* (7th Edition)

Editors: DeVita, Vincent T., Hellman, Samuel, Rosenberg, Steven A.

Publisher: Lippincott Williams & Wilkins, 2005

Chapter: SECTION 2: DNA Viruses

VIRUSES AND CANCER

| <i>Virus Family</i> | <i>Type</i> | <i>Human Tumor</i> | <i>Cofactors</i> |
|---------------------|-----------------------|--|----------------------------------|
| Papillomaviruses | HPV-16, -18, -33, -39 | Anogenital cancers and some upper airway cancers | Smoking, ? other Factors |
| | HPV-5, -8, -17 | Skin cancer | EV, sunlight, immune suppression |
| Polyomaviruses | SV40, JC, BK | ? Brain tumors | — |
| | | ? Insulinomas | — |
| | | ? Mesotheliomas | — |
| Retroviruses | HTLV-I | Adult T-cell leukemia/lymphoma | Uncertain |
| | HTLV-II | Hairy cell leukemia | Unknown |

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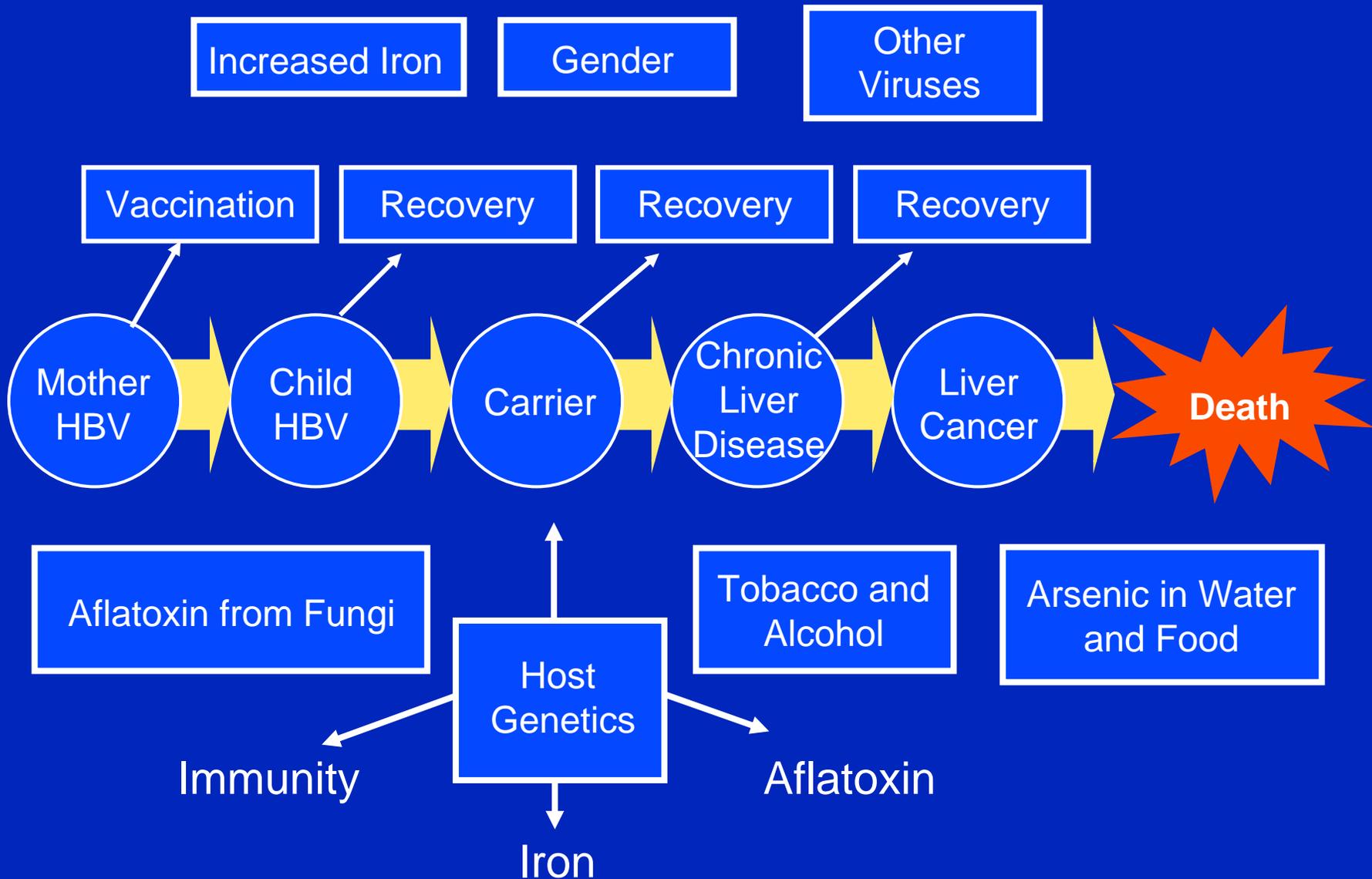
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Progression from HBV infection to cancer.

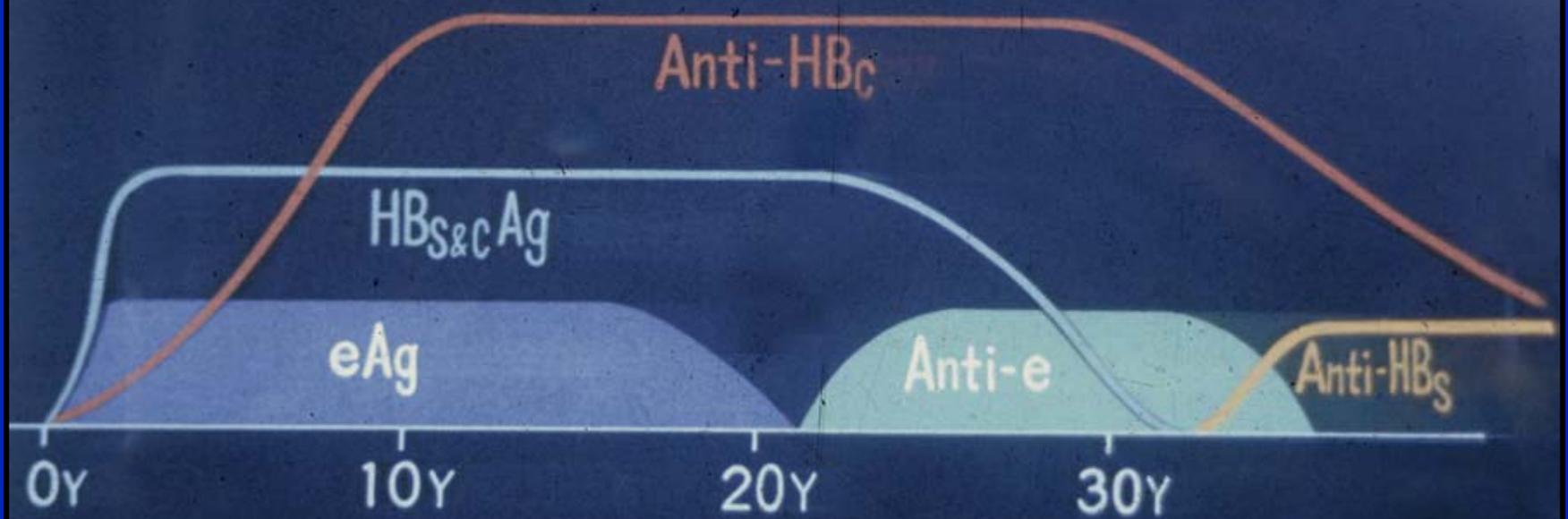
Factors which effect outcome



| HBsAg | Aflatoxin | |
|----------|-----------------|--------------------|
| | Negative | Positive |
| Negative | 1.0 | 3.4 (1.1, 10.0) |
| Positive | 7.3 (2.2, 24.4) | 59.4 (16.6, 212.0) |

Risk ratios (95% CI) for hepatocellular carcinoma.
Urinary aflatoxin biomarkers and HBsAg carrier
status in populations from Shanghai
(Qian. *et al* 1994)

CLINICAL COURSE OF CHRONIC CARRIER OF HBV



PREVENTION BY DELAY

- Many individuals infected at birth remain carriers for decades. Only some of these go on to chronic liver disease and hepatocellular carcinoma (HCC)
- A goal of treatment is to prolong the asymptomatic period so that carriers die of other causes before they develop symptomatic chronic liver disease or cancer
- There is a strong correlation between titers of HBV in carriers and the probability of developing hepatocellular carcinoma (HCC)
- Antivirals that decrease the titers of virus can decrease the probability of HCC. The elimination of the virus is not essential for prevention. Hence, drugs that are only moderately effective may be satisfactory. Therefore they can be used in doses that decrease the probability of toxicity.
- This is cancer therapy that is not dependent on the killing of cancer cells but on the treatment of viral infection

S Pfeffer and O Voinnet, *Viruses, microRNAs and cancer, Oncogene (2006) 25, 6211-6219*

Viruses represent one of the main factors that cause normal cells to proliferate and to become malignant: **up to 15% of all human cancers are associated with single or multiple virus infections**, and several viruses have been recognized as causal agents of specific types of cancer. Viruses have evolved many strategies to prevent infected cells from becoming apoptotic and to evade the innate and adaptive immune responses of their hosts. **The recent discovery that Epstein-Barr virus and other herpesviruses produce their own sets of micro (mi)RNAs brings an additional layer of complexity in this ongoing host—virus arms race** and changes our initial views of the antiviral roles of RNA silencing in plants and insects. It seems that, rather than being inhibited by this process, **many mammalian viruses can usurp or divert the host RNA silencing machinery to their advantage. Viral-encoded miRNAs can act both in *cis*, to ensure accurate expression of viral genomes, and in *trans*, to modify the expression of host transcripts.** Here, we review the current knowledge on viral miRNAs and discuss how mammalian viruses can also perturb host miRNA expression. **Those recent findings provide new insights into the role of viruses and miRNAs in cancer development.**

- 15% of all human cancers are caused by viruses. In others viruses are involved in pathogenesis
- Prevention by vaccination, or “Treatment by Delay” of infected but asymptomatic individuals can prevent the development of cancer or chronic disease
- There is an imperative to focus on this rich possibility for cancer control