Hepatitis B
Discovery of Hepatitis B virus

- In 1965, Dr. Baruch S. Blumberg at Fox Chase Cancer Center discovered an antigen in the blood of Australian Aborigine and named Australia antigen which was found to be HBsAg
- Made the first HBV vaccine (plasma vaccine Heptavax B), The First “Anti-Cancer Vaccine”
- Received the Nobel Prize in Medicine in 1976

Courtesy of Dr. HW Hann
How Old Is HBV?

- HBV associated with humans for > 1,000 years but no definitive evidence
- Recent evidence establishes ≥ 500 years
- Naturally mummified body of a Korean child found virtually intact
- Laparoscopy: Large organ in RUQ and biopsies sent for pathology and HBV DNA testing
- HBV DNA genotype C isolated from the liver
- Pathology: appeared to be normal liver
Structure of HBV

- HBsAg
- DNA
- HBcAg (HBeAg)
Hepatitis B Virus
Pathogenesis and Pathology

• The most efficient route of transmission is the percutaneous route.

• Transmission across mucous membranes is less efficient requiring higher concentrations of virus.

• Although HBV does not usually cross the placenta, the infants of viremic mothers have a very high risk of infections at time of birth

• Vaccination at birth is 70% protective but when combined with the administration of HBIG it is 90% protective.
• HBV starts to replicate within 3 days of its acquisition but symptoms are not seen before 45 days depending on infectious dose, route of infection and the person.

• Hepatic and extrahepatic lesions of the disease are likely produced by host immune response.

• A direct cytopathic effect of the virus is unlikely.
- Extra hepatic Replication: PBMC, bile duct, smooth muscle, pancreas, spleen, thyroid and kidneys.

- Viral clearance and liver cell injury are mediated by CTLs reactive against HBcAg and HBeAg

- Persistent infection is most common after maternal-neonatal transmission and in immunosuppressed individuals.

- Men are nearly twice as likely as women to become chronically infected.
• Pathology of acute HBV is characterized by extensive parenchymal inflammation, especially near the terminal hepatic vein.

• Chronic HBV infection has undergone extensive revision to make it more useful clinically based on:
  - The necroinflammatory process (minimal to severe)
  - Fibrosis (none to severe) and cirrhosis.
• Minimal to mild chronic hepatitis shows an intact limiting plate and lobular architecture.

• Moderate to severe chronic hepatitis is distinguished by the involvement of the portal periportal areas of the liver.

• The limiting plate is extensively eroded with the formation of active fibrous septa.
FIG. 3. Classification of chronic hepatitis. PZ, portal zone; LP, limiting plate; THV, terminal hepatic vein; SN, spotty necrosis; PN, piecemeal necrosis; BN, bridging necrosis or fibrosis; R, rosettes of hepatocytes. Modified from Sherlock et al. (704); see text for further discussion of these histologic categories.
• The continuing hepatocellular injury accompanied by collapse and fibrosis increase the potential for progression to macronodular cirrhosis.

• The relative abundance of plasma cells differentiates chronic from acute hepatitis.

• HBsAg accumulates in chronically infected cells in the smooth endoplasmic reticulum giving rise to ground glass appearance of hepatocytes.
FIG. 4. Ground-glass hepatocytes in an HBsAg carrier. Hema-
toxylin and eosin, original magnification ×300. AFIP Neg. No.
75-6600. From Ishak (364), with permission.
• Chronic HBV carriage is associated with > 100-fold increase in risk for HCC development relative to non carriers.

• The majority (>80%) of such tumors harbor integrated viral DNA, often multiple copies per cell.

• The HBV integrants are usually highly rearranged with deletions, inversions and sequence reiterations.

• Alterations of host DNA often accompany these integrants (deletions, repeats, translocations).
HBV predisposes to malignancy be either:

- Direct model: viral DNA provides cis-acting sequences or trans-acting factors (protein X).

- Indirect model: Liver cell injury triggers a series of changes and liver cell regeneration with the associated risk of mutation.
Clinical Picture

- The incubation period is 45-120 days followed by a short prodrome

- The majority of cases are anicteric

- Extrahepatic manifestations of HBV infection are seen in 10-20% of cases and include:
  - transient serum sickness-like syndrome
  - acute necrotizing vasculitis
  - membranous glomerulonephritis
  - papular acrodermatitis of childhood (Gianotti-Crosti syndrome)
The vast majority of chronic HBV infections remain asymptomatic for many years.

Patients with moderate to severe chronic hepatitis may be significantly incapacitated.

Easy fatigability, anxiety, anorexia and malaise are prominent complaints.

Ascites develop in about 20% of cases.
Acute Hepatitis B

Complete Recovery 90%
Chronicity 9%
Fulminant Hepatitis 1%

Recovery 50%
Asymptomatic Carrier 10%
Mild chronic Hepatitis 10%
Moderate to Severe Chronic Hepatitis 30%

Extra Hepatic Disease
Cirrhosis
PHCC
The Consequence
Outcome of Hepatitis B Virus Infection by Age at Infection

- **Symptomatic Infection (%):**
  - Birth: 100
  - 1-6 months: 80
  - 7-12 months: 60
  - 1-4 years: 40
  - Older Children and Adults: 20

- **Chronic Infection (%):**
  - Birth: 80
  - 1-6 months: 60
  - 7-12 months: 40
  - 1-4 years: 20
  - Older Children and Adults: 0
Spectrum of Chronic Hepatitis B Diseases

1. Chronic Persistent Hepatitis – asymptomatic

2. Chronic Active Hepatitis – symptomatic
   exacerbations of hepatitis

3. Liver cirrhosis

4. Hepatocellular Carcinoma
FIG. 5. Estimated overall 5-year survival rates from HBV-infected patients with chronic persistent hepatitis, chronic active hepatitis, and chronic active hepatitis with cirrhosis. From Weissberg et al. (833), with permission.
Diagnosis

- Although HBV has been successfully grown in primary cultures of normal adult or fetal human hepatocytes, susceptibility wanes as the cells differentiate and serial propagation over a prolonged period of time is limited by availability of human liver tissue.

- Diagnostic method of choice is serology.
A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection.

- HBsAg - used as a general marker of infection.
- Anti-HBsAg - used to document recovery and/or immunity to HBV infection.
- anti-HBcAg IgM - marker of acute infection.
- anti-HBcAg IgG - past or chronic infection.
• HBeAg - indicates active replication of virus and therefore infectiveness.

• Anti-HBeAg - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.

• HBV-DNA - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.
Sequence of HBV Markers

Incubation  Acute Viremia  Convalescence

SYMPTOMS

HBsAg

Weeks  Weeks  Weeks
Sequence of HBV Markers

- Incubation
- Acute Viremia
- Convalescence

**SYMPTOMS**

- HBsAg
- HBeAg
- anti-HBc
- IgM
Sequence of HBV Markers

- Acute Viremia
- Convalescence
- Recovery

**SYMPTOMS**

- anti-HBc (total IgG)
- anti-HBc IgM

**Markers**
- HBsAg
- HBeAg

**Concentration**

- Weeks
- Weeks
- Years
Sequence of HBV Markers

- **Acute Viremia**
  - Symptoms
  - HBsAg
  - HBeAg

- **Convalescence**
  - anti-HBc (total IgG)
  - anti-HBc IgM

- **Recovery**
  - anti-HBe

Time:
- Weeks
- Weeks
- Years
Sequence of HBV Markers

- Acute Viremia
- Convalescence
- Recovery

- HBsAg
- HBeAg
- anti-HBc (total IgG)
- anti-HBC IgM
- anti-HBe
- anti-HBs

Symptoms

Weeks

Weeks

Years
Acute Hepatitis B Virus Infection with Recovery: Typical Serologic Course

Weeks after Exposure

Symptoms

- HBsAg
- IgM anti-HBc
- Total anti-HBc
- anti-HBs
- HBeAg
- anti-HBe

Titer

0 4 8 12 16 20 24 28 32 36 // 52 // 100
## Phases of acute hepatitis B

<table>
<thead>
<tr>
<th></th>
<th>HBeAg</th>
<th>HBeAg</th>
<th>anti-HBc</th>
<th>anti-HBe</th>
<th>anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>very early:</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Viremia start</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>&gt;14 days:</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Late:</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Noninfectious recovery stage

HBsAg  HBeAg  anti-HBc  anti-HBe  anti-HBs
-     -     -       +       +

IgM  IgG
-     +
Patients with immunization to HBV

HBsAg  |  HBeAg  |  anti-HBc IgM |  anti-HBc IgG  |  anti-HBe  |  anti-HBs
--- | --- | --- | --- | --- | ---
- | - | - | - | - | +
B core window stage

HBsAg | HBeAg | anti-HBc | anti-HBe | anti-HBs

- | - | + | - | -
Hepatitis B chronic carrier serologic profile.
No seroconversion to anti-HBs
Hepatitis B chronic carrier serologic profile.
Late seroconversion to anti-HBe

<table>
<thead>
<tr>
<th>Stages</th>
<th>Incubation</th>
<th>Acute Viremia</th>
<th>Chronic Viremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Weeks</td>
<td>Months</td>
<td>Years</td>
</tr>
<tr>
<td>Markers</td>
<td>HBsAg, HBeAg, anti-HBC, anti-HBe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCENTRATION

Weeks

Months

Years
Chronic carrier state of hepatitis B

- Definition: hepatitis B surface antigen detectable in the blood >6 months
- Influencing factors: — Severity of acute disease  
  — Age at infection  
  — Immunological status
Progression to Chronic Hepatitis B Virus Infection: Typical Serologic Course

**Acute (6 months)**
- HBsAg
- IgM anti-HBc

**Chronic (Years)**
- HBsAg
- Total anti-HBc
- anti-HBe
- HBeAg

**Weeks after Exposure**

**Years**

*Titre Progression to Chronic Hepatitis B Virus Infection: Typical Serologic Course*
Epidemiology

• It is estimated that 1/3 of the world population has been infected with HBV and there are 300-400 million carriers in the world.

• The prevalence of HBV infection varies widely in different parts of the world.

• Transmission occurs by sexual contact, parenterally and perinatally. Congenital infection is believed to be unlikely.
Global Impact of Hepatitis B

2 billion with past/present HBV infection

World population 6 billion

15-40% develop cirrhosis, liver failure or HCC

350–400 million with chronic hepatitis B

~1 million/year die from HBV-associated liver disease
HBV induced mortality

2,000,000 deaths per year

- Fulminant hepatitis: 100,000
- Acute hepatitis: 500,000
- Chronic hepatitis: 400,000
- Cirrhosis: 700,000
- P.H.C.: 300,000
## Concentration of Hepatitis B Virus in Various Body Fluids

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low/Not Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
<td>semen</td>
<td>urine</td>
</tr>
<tr>
<td>serum</td>
<td>vaginal fluid</td>
<td>feces</td>
</tr>
<tr>
<td>wound exudates</td>
<td>saliva</td>
<td>sweat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>breastmilk</td>
</tr>
</tbody>
</table>
Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- Red: ≥8% - High
- Yellow: 2-7% - Intermediate
- Green: <2% - Low
Endemicity

- **High** (HBsAg > 8%, anti HBsAg 70-90%) in South-East Asia, China, equatorial Africa, Oceania and South America.

- **Intermediate** (HBsAg 2-7%, Anti HBsAg 30-40%) in Eastern Europe, Mediterranean region, south America and the Middle East.

- **Low** (HBsAg < 2%, anti HBsAg <5%) Western Europe, North America and Australia.
Global Patterns of Chronic HBV Infections

- **High (>8%)**: 45% of global population
  - lifetime risk of infection >60%
  - early childhood infections common
- **Intermediate (2%-7%)**: 43% of global population
  - lifetime risk of infection 20%-60%
  - infections occur in all age groups
- **Low (<2%)**: 12% of global population
  - lifetime risk of infection <20%
  - most infections occur in adult risk groups
Risk Groups

• Iv drug abusers
• Homosexual men
• Sexual contacts of antigen positive persons
• Residents in long-stay homes of mentally handicapped people
• Renal dialysis patients
• Recipients of multiple blood donors
• Surgeons, dentists and morticians
• Infants of e antigen-positive mothers
Treatment

- **Interferon** - for HBeAg +ve carriers with chronic active hepatitis. Response rate is 30 to 40%.

- **Lamivudine** - a nucleoside analogue reverse transcriptase inhibitor. Well tolerated, most patients will respond favorably. However, tendency to relapse on cessation of treatment. Another problem is the rapid emergence of drug resistance.

- **Adefovir dipivoxil** (Hepsera)

- **Successful response to treatment** will result in the disappearance of HBsAg, HBV-DNA, and seroconversion to HBeAg.
Nucleotide Analogues

- **Lamivudine** (dCTP)
  - Inhibits viral reverse transcriptase (RT) activity
  - HBV DNA reduced 3-4 logs
  - Decreases viremia in acute and chronic patients
  - 10-15% patients have resistant variants 1 year after treatment
    - 2 years: 40%
    - 4 years: 67%

- **Adefovir** (dATP)
  - Inhibits priming of RT
  - 3-4 log reduction of viremia
  - Effective against Lamivudine resistant strains
Vaccination

- Seroconversion rate is influenced by age and sex of the vaccinee as well as the immune status.

- Rates in excess of 95% are seen in young women whereas the rates may drop to 80% in older men.

- It is difficult to define a minimum protective level of anti-HBS but levels should be greater than 100 IU/L.
• The duration of the response to vaccine is variable and depends on the titer of anti HBS and completion of the course:

- Usually > 500 Iu /L titers for > 4-5 years
- If titer 100-500 Iu /L a boaster at 3 years is indicated
- If < 100 Iu /L a boaster should be given

• Low or non-responders need to be identified and passively immunized if they suffer accidental exposure.
Hepatitis D virus (Delta virus)

- HDV is not a true virus but a defective virus or a natural satellite of HBV

- Delta antigen is present in two forms, small (short) with 24 kd and large (long) with 27 kd.

- The short form which is more abundant is required for RNA replication whereas the long form suppresses viral RNA replication and is required for packaging of the HDV genome by HBsAg.
Hepatitis D (Delta)

δ antigen

Virus

HBsAg

RNA
• HDV replicates only in HBV-infected cells and direct pathologic changes are limited to the liver, the only organ in which HDV has been shown to replicate.

• HDV itself seems to be cytopathic and HDV antigen (delta) may be directly cytotoxic.
Hepatitis D Virus Modes of Transmission

- Percutanous exposures
  - injecting drug use

- Permucosal exposures
  - sexual contact
Pathologic Picture

- It is that of acute or chronic hepatitis and consists of hepatocellular necrosis and inflammation.

- Coinfection produces a pathologic picture of acute or chronic hepatitis whereas superinfection produces elements of both acute and chronic hepatitis.
Clinical Picture

- The incubation period is 3 to 7 weeks followed by the onset of the preicteric manifestations.

- The course is variable but it is usually more severe than other viral hepatides.

- Fulminant hepatitis is more common (ten times than any other type) and 60-70% of patients with chronic HDV infection develop cirrhosis (3 times more common than HBV or HCV). It develops in 10% of cases of coinfection and in 20% of superinfection.
• **Coinfection**
  - It leads to acute HBV and acute HDV
  - severe acute disease but low risk of chronic infection.

• **Superinfection**
  - It leads to severe acute hepatitis of relatively short incubation period that results in chronic hepatitis in more than 70% of cases.
  
  - It is often associated with fluminant hepatitis and moderate to severe chronic hepatitis (chronic active) that is often associated with cirrhosis.
• Delta hepatitis is common in some areas of the world with a high prevalence of HBV infection particularly the Mediterranean region, parts of Eastern Europe, the Middle East Africa and South America.

• Currently, approximately 10% of all HBV chronic carriers (about 30 millions) are coinfected with HDV.
<table>
<thead>
<tr>
<th></th>
<th>Co-Infection</th>
<th>Super-Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB virus</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>Delta virus</td>
<td>Acute</td>
<td>Acute or chronic</td>
</tr>
<tr>
<td>Level of delta antibody</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
HBV – HDV Coinfection

Typical Serologic Course

- Symptoms
- ALT Elevated

- IgM anti-HDV
- HDV RNA
- HBsAg

anti-HBs

Time after Exposure
Hepatitis D – Prevention

- HBV-HDV Coinfection
  Pre or postexposure prophylaxis to prevent HBV infection.

- HBV-HDV Superinfection
  Education to reduce risk behaviors among persons with chronic HBV infection.