CHAPTER II

REVIEW OF LITERATURE
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Hepatitis B Virus infection is associated with a wide spectrum of clinical manifestations in humans. Knowledge of the intricacies of viral infection and of the molecular biology of this fascinating virus has led to the successful development of a vaccine and to treatment sometimes capable of eradicating chronic infection.

Historical Background

Serendipity led to the identification of the Australia antigen, which we now know as hepatitis B surface antigen (HBsAg). An immunodiffusion precipitin line between the HBsAg present in the serum of an Australian aborigine and the antibody to HBsAg in a patient with hemophilia who had received multiple transfusions provided the first clue. The subsequent development of acute hepatitis in a laboratory technician provided the essential link to the clinical illness. This discovery fostered an explosion of knowledge about the hepatitis B virus.

Dr. Baruch Blumberg received the Nobel Prize in Physiology and Medicine in 1976 for the landmark discovery of Australia antigen, subsequently renamed hepatitis B surface antigen (HBsAg) in 1965.23,24
EPIDEMIOLOGY

In developed countries

The distribution of hepatitis B infection varies greatly throughout the world. According to WHO there are three zones of prevalence of HBV chronic carriers. (Figure. 1a) The area with high prevalence (> 8 %) include Southeast Asia, China, and Africa where more than half the population is infected at some time in their lives, and more than 8 percent are chronic carriers of the virus, the result of either neonatal transmission (vertical) or transmission from one child to another (horizontal).

Areas with low levels (< 2 % chronic HBsAg carriers) of endemicity include North America, Western Europe, and Australia where only a minority of people come into contact with the virus, as a result of horizontal transmission among young adults.4

Areas with intermediate prevalence (2% - 7%) include Eastern Europe, and Middle East.

Chronic HBV infection afflicts 1.25 million people in the United States. Of the 22,000 infants born each year to HBsAg-positive mothers in the United States, more than 98 percent receive immunoprophylaxis (hyperimmune globulin and vaccine) and are protected from infection.25 A vaccination program aimed at all newborn infants and adolescents is under way in this country. 26,27

Most HBV infections in developed countries result from sexual activity, injection-drug use, or occupational exposure. Other, less
Figure 1a Prevalence of HBV Chronic Carriers | WHO Data

Legend:
- <1.2% - Low
- 1.2% to 7% - Intermediate
- 7% - High

Percentage HBsAg Chronic Carriers
frequent causes of infection include household contact, hemodialysis, and transmission from a surgeon, and receipt of organs or blood products. No clear risk factors are found in 20 to 30 percent of patients, perhaps because of a reluctance to report high-risk behavior or possibly mucosal or other unrecognized routes of infection. Because HBV is present in serum in large quantities (10^8 to 10^{10} virions per milliliter), it is not surprising that HBV can also be detected in semen, saliva, cervical secretions, and leukocytes. Respiratory, water-borne, or insect-related infections have not been documented.

In India

In a vast country like India, in the absence of nation wide epidemiological infrastructure, reports published periodically regarding community loads of chronic hepatitis B among Indian population, suggest ubiquitous presence of hepatitis B virus related disorders in India.

Reports from various places in India such as

- Patnaik SK et al studied prevalence of HBsAg in under-five children, in Banglore & Rajamundry, of chronic carriers was 3% to 5%, which is in good agreement with the data published by NIV [National Institute of Virology], Pune in 1997.29
- Saha M.K. et al have reported that 100 % of intravenous drug users (n=77) in Manipur were positive for HBsAg.30
- Chowdhary et al evaluated burden HBV infection in the entire population of a village in district Birbhum, Prevalence of HBsAg
carrier state was 5.3% and young [age < 20 Years] male, injection drug users were at increased risk.\textsuperscript{31}

- Hazra BR et al investigated HBV in cases of acute hepatitis in calcuta. 30.5% of acute hepatitis were due to HBV, transmission routes were parenteral in 52% cases, Sexual in 24% and remained unknown in the rest. 45.5% of health care workers [medical/paramedical/support staff] have at least one or more disease markers indicative of HBV disease.\textsuperscript{32}

- Katiyar S et al reported that extremely high frequency of HBV infection (> 90%) was found in cases of hepatocellular carcinoma (HCC).\textsuperscript{5}

indicate that the prevalence is more or less in the range of 5 to 7% although large studies representative for the vast country are yet to be conducted. Blood transfusion, vertical transmission and sexual transmission appear to be the major routes of spread. India contributes to 10% - 15% of the global pool of HBV infected people. It is estimated that India has 35 - 45 million chronic HBV infected people.\textsuperscript{33}

**Virologic Features**

**Classification and Structure**

HBV belongs to a family of closely related DNA viruses called the hepadnaviruses. Included in this family are the woodchuck hepatitis virus, the duck hepatitis B virus, and several other avian and mammalian variants.
Figure 1  Morphology of Hepatitis B Virus.
Legend Figure I

Illustrated in this figure is the structure of Hepatitis B Virus. It is a double-shelled particle, 40 to 42 nm in diameter with an envelope that contains three related envelope glycoproteins (or surface antigens), an outer lipoprotein. Within the envelope is the viral nucleocapsid, or core and the core contains the viral genome, a relaxed-circular, partially duplex DNA of 3.2 kb, and a polymerase.
HBV virions are double-shelled particles, 40 to 42 nm in diameter (Figure I) with an outer lipoprotein envelope that contains three related envelope glycoproteins (or surface antigens). Within the envelope is the viral nucleocapsid, or core. The core contains the viral genome, a relaxed-circular, partially duplex DNA of 3.2 kb, and a polymerase that is responsible for the synthesis of viral DNA in infected cells. DNA sequencing of many isolates of HBV has confirmed the existence of multiple viral genotypes, each with a characteristic geographic distribution.

The whole virion, or Dane particle, is a 42-nm sphere that contains a core, or nucleocapsid, enclosing the DNA. One peculiar feature of HBV is the great excess of envelope material found in the circulation, consisting of both small spheres and rods with an average width of 22 nm. Figure II is the electron micrograph illustrating the three Forms of Hepatitis B Surface Antigen, with details of the surface-protein structure.

Virologic Characteristics

All the hepadnaviruses have similar hepatotropism and life cycles in their hosts. Chronic hepatitis and hepatocellular carcinoma, for example, are commonly observed in woodchucks and less frequently observed in ground squirrels and ducks.

The viral genome of HBV is a partially double-stranded circular DNA of approximately 3200 base pairs that encodes four overlapping open reading frames: $S$, for the surface, or envelope, gene; $C$, for the core
Figure II  Structure of Hepatitis B Virus

Complete particle

Capsid

Cutaway view of
Complete viral particle

Major envelope
protein

Large envelope
protein

Middle
envelope
protein
Legend Figure II

Illustrated in this figure are the three Forms of Hepatitis B Surface Antigen. The electron micrograph shows a serum pellet containing whole virions, rods, and small spheres with details of the surface-protein structure, including the three envelope proteins.
gene; X, for the X gene; and P, for the polymerase gene (Figure III). The S and C genes have upstream regions termed preS and preC.\textsuperscript{41}

The viral DNA is partially double-stranded (red circle). The long strand of fixed length (blue circle) encodes seven proteins from four overlapping reading frames (surface [S], core [C], polymerase [P], and the X gene [X]), shown as large arrows, and three upstream regions (preC, preS1, and preS2). A protein is covalently linked to the 5' end of the long strand (hatched blue oval) and a short oligoribonucleotide at the 5' end of the short strand (red zigzag). The EcoRI restriction-enzyme binding site is included as a reference point. The size of each segment is shown in parentheses; aa denotes amino acids. The diagram is adapted from Wei et al.\textsuperscript{40}

The viral envelope encoded by the S gene contains three distinct configurations synthesized in all persons, termed the large, middle, and major proteins, which are produced by beginning transcription with, respectively, preS1, preS2, or the S gene alone. The preS1 and preS2 represent two of the more immunogenic portions of HBsAg. Several specific antigenic determinants, including the a determinant, common to all HBsAg, and the d, y, w, and r determinants, are mainly of epidemiologic importance. The development of cellular and humoral immunity to HBsAg is protective, and recombinant HBsAg provides the basis for the HBV vaccines currently available.

Hepatitis B core antigen (HBcAg) is the nucleocapsid that encloses the viral DNA. When HBcAg-derived peptides are expressed on the surface of hepatocytes, they induce a cellular immune response that is crucial for killing infected cells.
Figure III  Genome of Hepatitis B Virus.
Legend Figure III

The figure III depicts Genomes of Hepatitis B Virus. It shows the viral DNA is partially double-stranded (red circle), four overlapping reading frames (surface $S$, core $C$, polymerase $P$, and the $X$ gene $X$), shown as large arrows, and three upstream regions ($preC$, $preS1$, and $preS2$). aa denotes amino acid.
Hepatitis B e antigen (HBeAg), a circulating peptide derived from the core gene and then modified and exported from liver cells, serves as a marker of active viral replication. HBeAg may act as a tolerogen, since its presence in the circulation has been associated with a diminished immune response because of its close resemblance to HBcAg, the putative target of the immune response. With few exceptions, HBeAg is present only in persons who have circulating serum HBV DNA.

The long P gene encodes the DNA polymerase, which also serves a reverse-transcriptase function, since replication requires RNA intermediates. The X gene encodes two proteins that serve as transcriptional transactivators, aiding viral replication. These proteins may also play a part in the development of hepatocellular carcinoma. Several additional enhancer and promoter elements have also been identified within the HBV genome.

The presence of HBV DNA in serum, the best indication of active viral replication, is detected by hybridization methods or by the more sensitive polymerase-chain-reaction (PCR) technique.

Antibody to HBsAg, produced in response to exposure to the envelope antigen, confers protective immunity. The antibody is detectable in patients who have recovered from acute hepatitis B and in those immunized with HBV vaccine, but it may become undetectable in patients who have recovered fully from infection. Antibody to HBcAg is detected in virtually all patients who have ever
been exposed to HBV. Unlike antibody to HBsAg, this antibody is not protective; its presence alone cannot be used to distinguish acute from chronic infection. Patients who have persistent HBV infection are positive for antibody to HBcAg, as are those who have recovered from HBV infection. The IgM subtype of antibody to HBcAg is associated with acute infection and is therefore helpful in distinguishing acute from chronic infection. IgM antibody usually disappears within four to eight months after acute infection. Since some patients with chronic hepatitis B become positive for IgM antibody during flares in their disease, its presence is not an absolutely reliable marker of acute illness. Antibody to HBeAg appears once the antigen has been cleared and the virus is no longer replicating.

Life Cycle of HBV in the Human Host

Viral Replication Cycle

Figure IV shows the main features of the hepadnavirus replication cycle, the cardinal feature of which is the replication of the DNA genome by reverse transcription of an RNA intermediate. Incoming HBV virions are bound by cell-surface receptors, the identity of which remains unknown. After membrane fusion, cores are presented to the cytosol and transported to the nucleus. There, their DNA genomes are converted to a covalently closed circular (ccc) form, which serve as the transcriptional template for host RNA polymerase II. This enzyme generates a series of genomic and subgenomic transcripts.
Figure IV  The Replication Cycle of HBV.

- **Entry of HBV into cell**
- **Vesicular transport**
- **Core synthesis and RNA packaging**
- **Translation**
- **Transcription**
- **Budding into Endoplasmic reticulum**
- **Repair**
- **ccc DNA**
Legend Figure IV

The figure depicts The Replication Cycle of HBV.

The replication cycle includes Viral entry into hepatocyte by binding to surface receptors, migration of core particles to the hepatocyte nucleus, repairing genomes to form a covalently closed circular DNA (cccDNA), transcription of viral messenger RNA (mRNA), translation of viral mRNA in the cytoplasm to produce the viral surface, core, polymerase, and X proteins, packaging of viral RNA, reverse-transcription into viral DNA and the exit of virion from the hepatocyte or recycle of genomes into the nucleus for conversion to cccDNA.
All viral RNA is transported to the cytoplasm, where its translation yields the viral envelope, core, and polymerase proteins, as well as the X and preC polypeptides. Next, nucleocapsids are assembled in the cytosol, and during this process a single molecule of genomic RNA is incorporated into the assembling viral core. Once the viral RNA is encapsidated, reverse transcription begins. The synthesis of the two viral DNA strands is sequential. The first DNA strand is made from the encapsidated RNA template; during or after the synthesis of this strand, the RNA template is degraded and the synthesis of the second DNA strand proceeds, with the use of the newly made first DNA strand as a template. Some cores bearing the mature genome are transported back to the nucleus, where their newly minted DNA genomes can be converted to cccDNA to maintain a stable intranuclear pool of transcriptional templates. Most cores, however, bud into regions of intracellular membranes bearing the viral envelope proteins. In so doing, they acquire lipoprotein envelopes containing the viral L, M, and S surface antigens and are then exported from the cell.

**Pathogenesis of Hepatitis B**

The HBV replication cycle is not directly cytotoxic to cells. This fact accords well with the observation that many HBV carriers are asymptomatic and have minimal liver injury, despite extensive and ongoing intrahepatic replication of the virus. It is now thought that host immune responses to viral antigens displayed on infected hepatocytes are the principal determinants of hepatocellular injury. This notion is consistent with the clinical observation that patients
Figure V  Cellular Immune Responses To HBV Infection.
Legend Figure V.
The figure shows cellular immune responses to HBV infection. The role of Antigen-presenting cells, CD4+ T cells and Virus-specific CD8+ cytotoxic T cells in recognition reaction of viral antigens that can result into either direct lysis of the infected hepatocyte or the release of interferon-γ and TNF-α, which can down-regulate viral replication in surrounding hepatocytes without direct cell killing.
with immune defects who are infected with HBV often have mild acute liver injury but high rates of chronic carriage.\textsuperscript{50}

The immune responses to HBV and their role in the pathogenesis of hepatitis B are incompletely understood. Correlative clinical studies show that in acute, self-limited hepatitis B, strong T-cell responses to many HBV antigens are readily demonstrable in the peripheral blood.\textsuperscript{51} These responses involve both major-histocompatibility-complex (MHC) class II-restricted, CD4+ helper T cells and MHC class I-restricted, CD8+ cytotoxic T lymphocytes. The antiviral cytotoxic T-lymphocyte response is directed against multiple epitopes within the HBV core, polymerase, and envelope proteins; strong helper T-cell responses to C and P proteins have also been demonstrated in acute infection. By contrast, in chronic carriers of HBV, such virus-specific T-cell responses are greatly attenuated, at least as assayed in cells from the peripheral blood. However, antibody responses are vigorous and sustained in both situations (although free antibodies against HBsAg [anti-HBs antibodies] are not detectable in carriers because of the excess of circulating HBsAg). This pattern strongly suggests that T-cell responses, especially the responses of cytotoxic T lymphocytes, play a central role in viral clearance. Figure V summarizes the major types of cellular immune response to HBV.

The mechanisms by which cytotoxic T lymphocytes kill liver cells and cause viral clearance have been incisively investigated in transgenic mice that express viral antigens or contain replication-competent viral genomes in the liver.\textsuperscript{51,52} Because these mice harbor HBV genes in
their germ-line DNA, they are largely tolerant to HBV proteins, and accordingly, clinically significant liver injury does not develop. However, if antiviral cytotoxic T lymphocytes of syngeneic animals are transferred into such mice, acute liver injury with many of the features of clinical hepatitis B develops.\textsuperscript{53} It is striking that, in this model, the number of hepatocytes killed by direct engagement between cytotoxic T lymphocytes and their targets is very small and clearly insufficient to account for most of the liver damage. This suggests that much of the injury is due to secondary antigen-nonspecific inflammatory responses that are set in motion by the response of the cytotoxic T lymphocytes. Presumably, much of the damage occurring in this context is due to cytotoxic by-products of the inflammatory response, such as tumor necrosis factor (TNF), free radicals, and proteases. Other immune-cell populations, notably natural killer T cells,\textsuperscript{54} probably also contribute to liver injury.

**Natural History**

Primary HBV infection in susceptible (nonimmune) hosts can be either symptomatic or asymptomatic. The latter is more common than the former, especially in young children. Most primary infections in adults, whether symptomatic or not, are self-limited, with clearance of virus from blood and liver and the development of lasting immunity to reinfection.\textsuperscript{55, 56} However, some primary infections in healthy adults (generally less than 5 percent) do not resolve but develop into persistent infections. In such cases, viral replication continues in the liver and there is continual viremia, although the titers of virus in the liver and blood are variable. Persistent HBV infection may be
symptomatic or asymptomatic. People with subclinical persistent infection, normal serum aminotransferase levels, and normal or nearly normal findings on liver biopsy are termed asymptomatic chronic HBV carriers; those with abnormal liver function and histologic features are classified as having chronic hepatitis B. Cirrhosis, a condition in which regenerative nodules and fibrosis coexist with severe liver injury, develops in about 20 percent of people with chronic hepatitis B. The resulting hepatic insufficiency and portal hypertension make this process one of the most feared consequences of chronic HBV infection.

**Primary Infection**

**Figure VI**

In primary infection, HBsAg becomes detectable in the blood after an incubation period of 4 to 10 weeks, followed shortly by antibodies against the HBV core antigen (anti-HBc antibodies), which early in infection are mainly of the IgM isotype. Viremia is well established by the time HBsAg is detected, and titers of virus in acute infection are very high — frequently $10^9$ to $10^{10}$ virions per milliliter. Circulating HBeAg becomes detectable in most cases, and studies of chimpanzees and other animals with primary hepadnaviral infection show that 75 to 100 percent of hepatocytes are infected when this antigen is evident. Thus, it is not surprising that epidemiologic studies consistently show high rates of both vertical and horizontal transmissibility during acute HBV infection.
Figure VI  Acute Self-limited HBV Infection.

- HBV DNA
- HBeAg
- Anti HBs
- Anti HBe
- HBsAg
- Anti HBe
- ALT

Anti-HBV level vs. Weeks and Years since exposure.
Legend Figure VI.

The figure shows a Patterns of Serologic and Molecular Markers in HBV Infection. The intensity of the responses, as a function of time after infection, is indicated schematically.

Typical levels of Alanine aminotransferase (ALT), HBV DNA, Hepatitis B s and e antigens (HBsAg and HBeAg), and anti-HBc, anti-HBe, and anti-HBs antibodies are shown in acute self-limited HBV infection.
When liver injury does occur in primary infection, alanine aminotransferase levels do not increase until after viral infection is well established, reflecting the time required to generate the T-cell-mediated immune response that triggers liver injury. Once this response is under way, titers of virus in blood and liver begin to drop. The fact that infection can be cleared from virtually all hepatocytes without massive hepatic destruction (in most cases) is a testament to the extraordinary power of the noncytolytic clearance mechanisms described above. With clearance of the infection, the viral antigens HBsAg and HBeAg disappear from the circulation, and free anti-HBs antibodies become detectable.

Surprisingly, in self-limited infection, as defined by the disappearance of the viral antigens and the appearance of anti-HBs antibodies, low levels of HBV DNA in the blood may persist for many years, if not for life. It is not known whether this DNA contains the entire HBV genome, or even whether it is contained in virions. However, inoculation of serum from three subjects with persistent HBV DNA into chimpanzees has not led to documented infectivity.

Persistent Infection

Figure VII

In persistent HBV infection, the early events unfold as in self-limited infection, but HBsAg remains in the blood and virus production continues, often for life. However, levels of viremia in chronic infection are generally substantially lower than during primary
infection, although they can vary considerably from person to person. High titers of HBV in the blood are often indicated by the continued presence of HBeAg. Typically, there are $10^7$ to $10^9$ virions per milliliter in the blood in such cases, which are highly infectious. But most people with persistent infection, especially those with anti-HBe antibodies, have somewhat lower levels of viremia.

One feature of chronic HBV infection that is not widely appreciated is its dynamic natural history. Even though, in most cases, HBsAg remains detectable for life, titers of viral DNA tend to decline over time. With the passage of time, there is also a tendency for HBeAg to disappear from the blood, along with seroconversion to positivity for anti-HBe antibodies — a progression that occurs at a rate of 5 to 10 percent per year in persistently infected people. Often, the disappearance of HBeAg is preceded or accompanied by a transient rise in alanine aminotransferase levels, known as a flare, which suggests that the process reflects immune-mediated destruction of infected hepatocytes. Reductions in the level of viremia as great as five orders of magnitude may accompany seroconversion to anti-HBe antibodies. Thus, the natural history of HBV persistence suggests that there is an ongoing immune attack on infected cells in the liver — an attack that is usually inadequate to eradicate infection altogether, but that does reduce the number of infected cells and thereby lowers the circulating viral load. Figure VI & VII shows typical patterns of serologic and molecular markers in both acute self-limited and chronic HBV infection.
Figure VII  Chronic HBV Infection.

Weeks since exposure  Years since exposure

Antigen or Antibody Level

- HBV DNA
- HBeAg
- Anti HBs
- Anti HBc
- HBsAg
- Anti Hbc
- ALT
Legend Figure VII.

The figure shows pattern of serologic and Molecular Markers in chronic HBV Infection. The intensity of the responses, as a function of time after infection, is indicated schematically.

Typical levels of Alanine aminotransferase (ALT), HBV DNA, Hepatitis B s and e antigens (HBsAg and HBeAg), and anti-HBc, anti-HBe, and anti-HBs antibodies are shown in chronic HBV infection.
The widely held view that circulating viral DNA disappears when anti-HBe antibodies appear is incorrect; this idea reflects the fact that, for many years, HBV DNA was measured by relatively insensitive hybridization methods with a detection limit of $10^5$ to $10^6$ virions per milliliter. Thanks to the advent of the polymerase-chain-reaction (PCR) method, we now know that at least 70 to 85 percent of people with anti-HBe antibodies have detectable viral DNA in the circulation, typically in the range of $10^3$ to $10^5$ molecules per milliliter, and sometimes higher. Although these levels of HBV DNA are relatively low, they are hardly negligible. (For reference, they are similar to levels of human immunodeficiency virus [HIV] and HCV DNA in many patients with symptomatic acquired immunodeficiency syndrome or hepatitis C.) Given the short half-life of HBV virions (approximately one day) such levels can be sustained only by ongoing viral replication; therefore, the claim that HBV enters a so-called nonreplicative phase later in its course is not correct. For this reason, anyone who has a positive test for HBsAg should be presumed to have some level of ongoing viremia. For example, when a decision must be made about immunoprophylaxis after a needle stick involving blood from an HBsAg-positive patient, prophylaxis should be offered irrespective of that patient's HBeAg status.

HBeAg-negative carriers are a heterogeneous group. Most such carriers have low levels of viral DNA, relatively normal levels of alanine aminotransferase, and a good prognosis. However, particularly in southern Europe and in Asia, at least 15 to 20 percent of such carriers have elevated levels of alanine aminotransferase and
viral DNA in the blood. The virus in many such carriers harbors mutations in the preC region that prevent the production of HbeAg. It has been suggested that persistently abnormal levels of alanine aminotransferase and elevated levels of viral DNA may denote a subgroup of HBeAg-negative carriers who should receive active antiviral therapy.

**Hepatocellular Carcinoma**

Another feature of the natural history of HBV infection is its link to primary hepatocellular carcinoma. Chronically infected subjects have a risk of hepatocellular carcinoma that is 100 times as high as that for noncarriers; within the HBsAg-positive group, HBeAg-positive carriers have the highest risk of hepatocellular carcinoma, but even carriers with anti-HBe antibodies have a substantial risk of cancer (Although the role of HBV in provoking hepatocellular carcinoma is undisputed, its cellular and molecular mechanisms remain incompletely understood. Given these facts, twice-a-year screening of chronically infected patients with measurements of serum alpha fetoprotein or hepatic ultrasonography, or both, is warranted. However, there is debate as to when such screening should begin. Furthermore, screening is imperfect — alpha fetoprotein screening, for example, has an excellent negative predictive value, but its positive predictive value ranges from 9 to 30 percent.
Associated Clinical Syndromes

Hepatitis D
The remarkable discovery in 1977 of a passenger virus termed delta, or hepatitis D virus (HDV), added to our understanding of HBV. HDV is a defective, RNA-containing passenger virus requiring the helper functions provided by HBV, including nucleocapsid assembly and provision of an HBsAg-derived envelope. In virtually all circumstances, HDV cannot replicate in the absence of HBV, because whole virions cannot be formed. HDV resembles certain plant viruses; there are no other known passenger viruses in the animal kingdom. HDV infection occurs either as a simultaneous coinfection with HBV (acute HBV and HDV infections), which is usually self-limited because of the eradication of HBV, or as a super infection in an HBV carrier, typically an injection-drug user. HDV infection is an important consideration when the condition of a patient with chronic HBV infection worsens or when a test for HBeAg is negative but active liver disease persists.

Hepatitis C
Many injection-drug users have detectable antibody to HBeAg and hepatitis C virus (HCV), indicating exposure to both parenteral hepatotrophic viruses. Although HBV is cleared in most adults, approximately 90 percent have active hepatitis C, and a smaller fraction (approximately 5 percent) have dual infections, with very active liver disease.
Human Immunodeficiency Virus Infection [HIV]

Patients with both human immunodeficiency virus (HIV) infection and HBV infection do not seem to have altered outcomes as a result of the combined infections. That is, HBV infection does not alter the outcome of HIV infection, nor does HIV infection alter the evolution of HBV infection, despite the recognized effects of HIV on the immune system. Until recently, HBV infection was not treated in HIV-positive persons because of their limited life expectancy; improvements in survival and new agents that are effective against one or both of the viruses have made treatment possible.

Infection with Mutant Viruses

A small but important group of patients have no detectable HBeAg in serum because of a viral mutation that does not affect replication, underlining the value of testing for both HBeAg and HBV DNA. HBeAg-negative mutants have been associated with fulminant hepatitis B and have caused more severe chronic hepatitis B and more rapid graft loss after transplantation than nonmutant HBV. The most common mutation is a single nucleotide change at position 1896 (G to A), resulting in a stop codon (TGG to TAG) at the end of the precore region, preventing HBeAg synthesis. Since only the precore region is deleted, HBcAg synthesis remains intact. Lack of circulating HBeAg, the immune tolerogen, may contribute to the more aggressive disease frequently observed. Other core-related mutations yielding similar results have been noted. A variety of mutant forms occurring...
in the same patient (similar to hepatitis C quasispecies) have also been described.\textsuperscript{83}

A few patients have been identified who have mutations in the S gene sufficient to prevent normal production of HBsAg despite detectable viral DNA levels.\textsuperscript{84} These mutations are extremely rare, as are "vaccine escape" mutants, viral subtypes that can cause HBV infection in vaccinated persons.\textsuperscript{85}

**Extrahepatic Diseases**

Hepatitis B is frequently detected in patients with polyarteritis nodosa and less commonly in those with membranous or membranoproliferative glomerulonephritis or leukocytoclastic vasculitis, all immune-complex mediated diseases.\textsuperscript{86,87} A previously noted association with mixed cryoglobulinemia now seems less likely, since, in retrospect, many of the patients had hepatitis C, and hepatitis B represented an innocent coinfection.\textsuperscript{88} Treatment of the underlying HBV infection generally improves the associated disease, particularly in the case of glomerulonephritis.\textsuperscript{89} In contrast, immunosuppressive treatment (e.g., for polyarteritis nodosa) results in a remission of the disease but perpetuates the HBV infection.\textsuperscript{90}

**Hepatitis B Vaccine**

Even though a vaccine for hepatitis B has been available since 1982, almost no inroads have been made in eradicating this ubiquitous infection. The lack of progress is largely the result of the failure of the initial vaccination program (which targeted only high-risk groups) to affect the overall carrier rate. In 1991, the American Council on
Immunization Practices proposed universal vaccination of newborns and adolescents in order to eliminate the transmission of hepatitis B in the United States. This approach has been approved by the American Academy of Pediatrics. Concern has been expressed, however, that physicians are not enthusiastic about the eradication of HBV, despite the obvious benefits in terms of preventing end-stage liver disease and liver cancer, both nationally and worldwide.91,92,93

**Hemodialysis and HBV: Prevalence and Transmission**

Chronic hemodialysis patients are at high risk for infection because the process of hemodialysis requires vascular access for prolonged periods. In an environment where multiple patients receive dialysis concurrently, repeated opportunities exist for person-to-person transmission of infectious agents, directly or indirectly via contaminated devices, equipment and supplies, environmental surfaces, or hands of personnel. Furthermore, hemodialysis patients are immunosuppressed94, which increases their susceptibility to infection, and they require frequent hospitalizations and surgery, which increases their opportunities for exposure to nosocomial infections.

Transmission. HBV is transmitted by percutaneous (i.e., puncture through the skin) or permucosal (i.e., direct contact with mucous membranes) exposure to infectious blood or to body fluids that contain blood, and the chronically infected person is central to the epidemiology of HBV transmission. HBV is relatively stable in the environment and remains viable for at least 7 days on environmental surfaces at room temperature.95 HBsAg has been detected in dialysis
centers on clamps, scissors, dialysis machine control knobs, and doorknobs. 96 Thus, blood-contaminated surfaces that are not routinely cleaned and disinfected represent a reservoir for HBV transmission. Dialysis staff members can transfer virus to patients from contaminated surfaces by their hands or gloves or through use of contaminated equipment and supplies. 96

Recommendations for the control of hepatitis B in hemodialysis centers were first published in 1977 97, and by 1980, their widespread implementation was associated with a sharp reduction in incidence of HBV infection among both patients and staff members. 98 In 1982, hepatitis B vaccination was recommended for all susceptible patients and staff members. 18 However, outbreaks of both HBV and hepatitis C virus (HCV) infections continue to occur among chronic hemodialysis patients.

A large survey of HD centers, in United States, in 1974 found HBV incidence rates of 6.2% among patients and 5.2% among staff. 99 As a result of segregation, universal precautions, vaccination, reduced blood transfusions, and screening of organs before transplantation, the incidence of HBV infection decreased to 0.08% for patients and 0.05% for staff within dialysis units by 1996 99 These achievements were also supported by better blood-bank screening-measures, the introduction of which dramatically decreased the risk of transfusion-associated HBV infection. The current risk in the United States of transfusion-related infection with HBV is 1 in 63,000 transfused units.
In spite of the reduction of HBV spread within dialysis centers, some isolated outbreaks of HBV infection continue to be reported among HD patients in developed countries. On the other hand, the little data available from less developed countries show that prevalence and incidence rates of HBV infection among patients undergoing long-term HD remain very high. The prevalence of chronic HBsAg positivity was 17% and 21.6% in HD patients from Moldavia and Romania, respectively; the frequency of HBsAg chronic carriers on HD was 15.1% in San Paulo City, Brazil, 7.6% in Lucknow, India and 10% in Izmir, Turkey.

Several cases of hepatitis B, some of them fatal, were reported within dialysis units during the years 1960-1970. In the general population, the association between chronic HBV infection and HCC is very strong. A recent multicenter survey has demonstrated that the risk of liver cancer is significantly higher in patients with ESRD treated by dialysis, compared to the general population: this is likely related to the greater exposure to hepatitis B and C viruses.

Indian data in this regard appear scanty and are complicated by the fact that there has been enormous variation in the data from various centers. The data in Indian studies has ranged from 3.4% to 42% and Mani et al have reported the prevalence to be as high as 77%. Shreeprakash et al observed HBsAg prevalence of 7.5% in Central India.
Hemodialysis and HCV: Prevalence and transmission.

Worldwide data of HCV infections in dialysis patients varies from 5% to 69% in CRF\textsuperscript{19,20}. Indian reports indicate 12 – 45% range of HCV infection in CRF patients\textsuperscript{21,22}. The study done by Shreeprakash et al reported 30% patients reactive for Anti HCV antibodies in CRF patients in Central India\textsuperscript{17}.

Transmission. HCV is most efficiently transmitted by direct percutaneous exposure to infectious blood, and like HBV, the chronically infected person is central to the epidemiology of HCV transmission. Risk factors associated with HCV infection among hemodialysis patients include history of blood transfusions, the volume of blood transfused, and years on dialysis\textsuperscript{111}.