HEPATITIS B

Hepatitis B in Children

Every year, between 10 and 30 million people worldwide are infected with the hepatitis B virus (HBV). Many are children and teens.

An estimated one-third of the world's population—about 2 billion—have been exposed to the hepatitis B virus (HBV) through contact with infected blood or body fluids, according to the World Health Organization (WHO). Such infections may occur during the birthing process, while sharing contaminated needles, or during transfusions with infected blood.

When teens and adults with healthy immune systems are exposed to the virus, more than 90 percent will successfully fight off the infection and clear the virus. These acute and short-lived brushes with HBV infection typically cause only minor, flu-like symptoms—if any symptoms at all.

But when newborns and very young children are infected, their immune systems often fail to recognize and vanquish the virus. As a result, about 90 percent of babies will develop a chronic or long-term infection.

The virus begins by silently replicating in their livers, undeterred by the young immune systems. Over years and even decades, the infection can cause extensive damage before their immune systems finally recognize the virus and attack the liver cells where the virus resides, possibly resulting in cirrhosis or even liver cancer.

Worldwide, close to 400 million people are chronically infected with the hepatitis B virus. About 80 percent live in Asia or are of Asian descent. Most live in developing countries and were infected at birth. Those babies that escape infection at birth remain susceptible to infection spread from family members infected with HBV, unsafe injections from reused, contaminated needles and syringes and ritual practices (such as scarification) and unscreened blood transfusions. In Europe and North America, most adolescents and adults are infected through sexual contact or injecting drug use.

There are about 1.25 million Americans chronically infected with HBV—20 to 30

percent of whom were infected during childhood.

Of those infected during childhood, between 20 and 35 percent will develop serious liver disease, most during adulthood, according to the National Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

According to the WHO estimates, hepatitis B kills 1.3 to 1.5 million children and adults worldwide each year.

Identification of the Hepatitis B Virus

Some form of viral hepatitis has been infecting humans and harming their livers since 2000 B.C. Until World War II, doctors did not even know that several types of viral hepatitis existed, nor did they know how the infections were transmitted.

A British physician who specialized in liver disorders, Dr. F.O. MacCallum, identified the HBV when he was researching a yellow fever vaccine during the 1940s.

Dr. MacCallum discovered that many British soldiers who received the yellow fever vaccine developed hepatitis, (inflammation of the liver, from hepa: the Latin for liver and 'itis' meaning inflammation) a few months later.

At the time, the yellow fever vaccine was made from human blood (serum). He deduced that a form of viral hepatitis was transmitted by blood after he tracked hepatitis outbreaks in patients who were subject to reused syringes. He called the disease transmitted by contaminated blood "hepatitis B" or "serum" hepatitis.

In 1963, Dr. Baruch Blumberg, who was studying hemophilia at the National Institutes of Health (NIH), discovered a common antibody (produced by the immune system to fight a foreign virus or antigen) in two American hemophilia patients. He found the antibody "reacted" or "attacked" an antigen (a foreign substance that the body identifies as potentially harmful) from an Australian Aborigine.

The antigen, identified as the hepatitis B surface antigen, was found in patients who suffered from hepatitis and was initially called the Australia Antigen. Research eventually found the antigen to be the protein surface coating that encapsulates or surrounds the hepatitis B virus.

Dr. Blumberg, a biochemist, and Irving Millman, a microbiologist, developed a test that identified hepatitis B viruses in blood samples. In 1971, the test became the first

method for screening blood donations for the virus. Together, Blumberg and Millman developed a vaccine against hepatitis B and won a Nobel Prize for medicine in 1976 in recognition of their achievement.

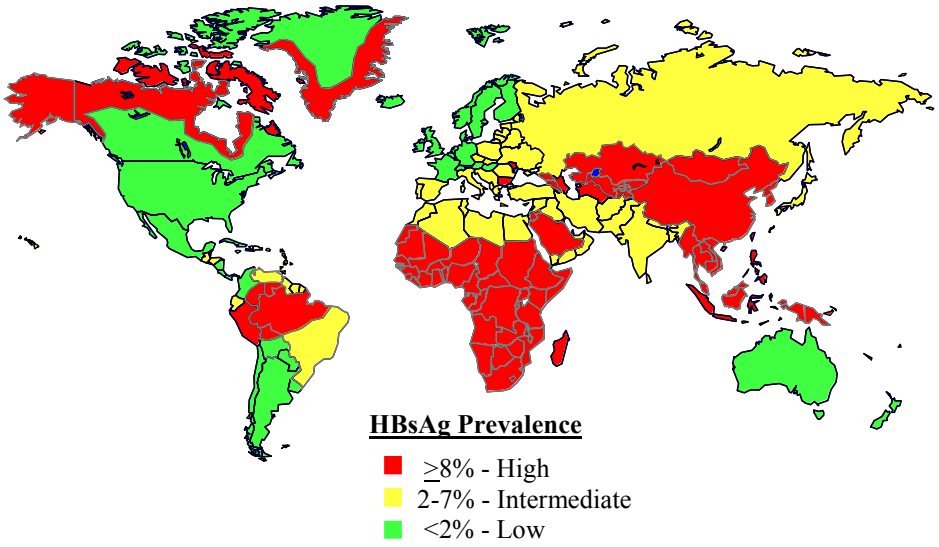
Where Hepatitis B Occurs Worldwide

Around the world, HBV infection has a stronghold in Asia, where it is endemic. China, Southeast Asia, Taiwan and many Pacific islands have chronic infection rates ranging between 5 to 20 percent of their population due to infections at birth or during early childhood. Estimates from the National Centers for Disease Control and Prevention (CDC) for some regions of Asia indicate that between one-third to one-half of entire populations have been infected with HBV.

Sub-Saharan Africa and the Amazon Basin have chronic infection rates exceeding 8 percent, and the HBV infection rate may exceed 5 percent in countries that border the Mediterranean. Eastern Europe and Alaskan and Western Canadian native people also have high rates of infection.

The incidence of HBV infection varies greatly around the world, and it remains an elusive disease to track. The infection and its symptoms can remain "silent"—

Geographic Distribution of Chronic HBV Infection



CDC 2001

especially in children—and cause no pain or discomfort for years. Consequently, the disease often is not diagnosed and/or never reported to public health authorities until symptoms appear, usually years or decades after the initial infection.

Even in European and North American countries with modern health care services, often the only HBV infections reported to government agencies are the new, "acute" cases that have the characteristic of causing symptoms that prompt patients to seek medical care—but this is the tip of the iceberg.

These symptoms, which can range from mild, flu-like symptoms to more serious abdominal pain and jaundice, occur in only 5 to 15 percent of children ages 1 to 5 years, and in 30 to 50 percent of older children and adults acutely infected with HBV, according to CDC's surveillance reports.

Often, those symptoms can resemble other illnesses and many doctors may not test for HBV infection unless the patient is at high risk for hepatitis because of country of origin, injecting drug use or high-risk sexual activities. As a result, the number of hepatitis B infections reported to health departments is far lower than the actual number that occur, epidemiologists report.

For example, in the United States in 2001, there were 7,844 acute clinical cases of HBV infection reported to the CDC. But the CDC estimates that there were actually 78,000 new HBV infections nationwide that year. The vast majority of new HBV infections produce no symptoms and escape the notice of the infected, their doctors and epidemiologists who track infectious diseases.

In Canada, officials estimate the incidence rate of clinically recognized acute hepatitis B is 2.3 per 100,000, resulting in about 700 reported cases a year, according to a 2001 study. The chronic infection rate, reported in 2001, was between 0.5 to 1 percent.

"These figures represent a large under-estimation," reported Dr. Morris Sherman, a Toronto hepatologist, "because only patients with symptomatic infections would present to a physician for testing in the first place. It has been estimated that acute hepatitis case reporting underestimates the incidence of new infections by as much as 50 percent or more."

It is estimated that about 5 percent of Americans have been infected at some time with the hepatitis B virus.

Here is a snapshot of the status of HBV infections around the world:

Asia

In Asia, where 80 percent of the world's HBV infections occur, the prevalence is primarily due to infection passed from mother to child and injections with contaminated, reused needles and syringes administered to infants and young children.

In a recent Chinese study conducted in Guangxi Province, researchers tested 1,882 people from 12 communities ranging in age from 1 to 59 and found that 76.2 percent of them had a past or current hepatitis B infection.

The chronic HBV infection rate was higher in males (23.4 percent) than females (13.8 percent). Researchers hypothesized that young boys, who are favored in Chinese culture, were given access to better medical care than were females and subjected to more injections during infancy and early childhood. As a result, they show a higher chronic HBV infection rate.

The researchers concluded that HBV transmission in Guangxi Province resulted from the following sources:

- At least 12.2 percent from unsafe injections
- 35 percent from perinatal exposure
- 13.9 percent from household personal contact exposure
- 3.3 percent from exposure to infected people outside their homes

Nationwide in China, WHO officials have estimated that one in four HBV infections resulted from unsafe injections.

In 2002, the Global Alliance for Vaccines and Immunization (GAVI), The Vaccine Fund and the Chinese Government signed an agreement to spend $75 million USD over the next five years to vaccinate as many newborns as possible in China against hepatitis B, with a special focus on the country's 12 poorest provinces.

A similar universal immunization program in Taiwan that focused on vaccinating all newborns against hepatitis B has been very successful.

The number of Taiwanese children who showed symptoms of past or present HBV infection was 26 percent before mass immunizations began in 1984 and 4 percent one decade later, according to a report published in the *Journal of the American Medical*

Association. After a decade of mass vaccination, the rate of chronic infections in children dropped from 9.8 to 1.3 percent.

The incidence of childhood liver cancer, linked to HBV infection, has also been cut in half over this time period in Taiwan, according to a report by Dr. Anna S. F. Lok, Director of Clinical Hepatology and Liver Transplant Program, University of Michigan.

The infection rate in India, Pakistan, Afghanistan and Iran is reportedly lower than in Eastern Asia, with chronic rates that range from 2 to 8 percent.

Middle East

While Saudi Arabia has a high endemic rate exceeding 8 percent, most of the Arab countries around the Mediterranean have an intermediate rate between 2 to 8 percent, according to CDC, resulting from perinatal and early childhood infections and from the reuse of improperly sterilized medical equipment.

Africa

The North African countries along the Mediterranean, including Egypt, Libya, Tunisia, Algeria and Morocco, have an intermediate rate of hepatitis B infection that ranges between 2 to 8 percent, according to CDC. As in Asia, many more than 8 percent of the population has been exposed to the virus.

In Sub-Saharan Africa, the rate of current hepatitis B infections catapults to 8 to 20 percent. The main transmission modes, as in Asia, are perinatal and/or early childhood exposure from close contact with infected friends and family members, sexual transmission and contaminated medical equipment.

Australia and New Zealand

In Australia and New Zealand, the prevalence of current infection is less than 2 percent, and infection occurs in adolescents and adults through sexual transmission or injecting drug use.

Among the Maori people of New Zealand and the Aborigines of Australia and those of Asian descent, the rate is much higher, estimated to be between 2 to 7 percent.

The Pacific Islands, including Polynesia, Melanesia and Micronesia, have far higher rates, exceeding 8 percent.

South and Central America and the Caribbean

HBV infection rates are high, exceeding 8 percent, in the Amazon Basin of Brazil and interior regions of Peru, Colombia and Venezuela as well as in Haiti and the Dominican Republic.

The rate of current infections is considered intermediate, ranging from 2 to 7 percent, in Guatemala, Honduras and Cuba and low, i.e., less than 2 percent, elsewhere in the region, including Mexico.

Europe

In Scandinavia and France, the current infection rate is the lowest in Europe, according to CDC, ranging between 0.1 and 0.4 percent.

In the rest of Europe, the rate ranges from 2 to 7 percent, with higher pockets of infection reported in eastern and southern Europe, the Balkan region and some former Soviet Union countries. Romania and regions that once made up Yugoslavia have rates that reportedly exceed 5 percent. Greece, Crete, Cyprus and Italy have higher rates of current infections that fluctuate around 5 percent.

Many Eastern European countries report high rates (i.e., 8 percent or more), primarily due to injecting drug use, sexual transmission and improperly sterilized medical equipment.

Canada and the United States

In Canada and the United States, the percentage of people who have chronic or current HBV infections is low, averaging 0.1 to 0.5 percent, according to CDC. However, within both countries, there have been high infection rates among Asian émigrés, native Eskimos, Inuits and other native people who live along the northern tier of both countries and in nearby Greenland. Routine immunizations are beginning to decrease the spread of the infection among tribal people.

In the United States, one out of 20 people has been infected in the past with HBV, a rate of about 5 percent of the entire population, according to the National Health and Nutrition Surveys. Many live in urban areas. The vast majority of these people—about 90 to 95 percent—have healthy adult or adolescent immune systems that were able to clear the virus.

Today, CDC estimates that 1.25 million Americans have chronic HBV infection, and about one-fourth to one-third of these infections were acquired during early childhood. Many pediatric chronic infections occurred in children whose mothers were not infected.

CDC says the number of new HBV infections has declined from an average of 260,000 per year during the 1980s to about 78,000 in 2001. CDC estimates that every year about 19,000 women with chronic HBV infection give birth in the United States.

Each year in the United States, HBV infections cause 8,400 to 19,000 hospitalizations, according to CDC, and 5,000 deaths from liver disease or cancer related to HBV.

According to reports on the epidemiology of HBV infection in the United States presented at the 2000 National Institutes of Health Workshop on the Management of Hepatitis B, sexual transmission continues to cause 45 percent of new HBV infections each year. The Planned Parenthood Federation states that teens and young adults are the ones most commonly infected through sexual transmission.

According to a June 2000, report in the *American Journal of Public Health*, nearly one-fifth of young gay and bisexual men may be infected with HBV by the time they reach age 22. Meanwhile, only 9 percent of the study group of 3,432 young men between the ages of 15 and 22 had been immunized against the virus—despite availability of a vaccine since 1982.

Injection drug use is credited with causing 21 percent of new HBV infections in the United States. The remaining new cases result from transmission of the virus from mothers to their newborns either during childbirth or soon after. Many of these women come from countries with high rates of HBV infection.

According to CDC, studies of immigrants in the United States conducted during the mid-1990s revealed a high rate of active HBV infection. Between 14 to 15 percent of Vietnamese and Cambodians, between 6 to 14 percent of Koreans and about 8 percent of immigrants from the Philippines had active HBV infections.

According to a report published in the November 1998 issue of the U.S. Department of Health and Human Services (*Closing the Gap: A Newsletter of the Office of Minority Health, U.S. Department of Health and Human Services),* Vietnamese-born men in the United States have the highest rate of liver cancer in the country.

Among these immigrant groups in the United States, the vertical transmission of HBV is

usually halted after the first generation due to the universal policy of immunizing newborns against hepatitis B.

What Is the Hepatitis B Virus?

Hepatitis B is a disease of the liver caused by one of the smallest microorganisms that can infect humans—a virus.

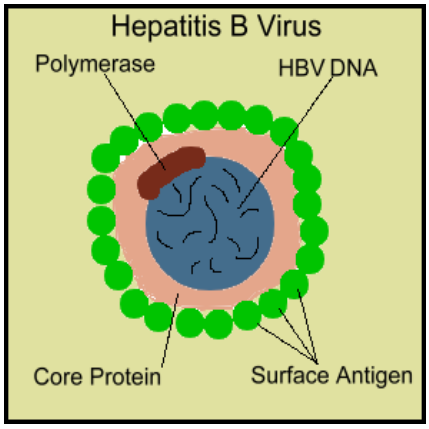
Viruses are much smaller than a human cell. The hepatitis B virus is a spherical particle with a diameter of 42 nanometers (1 nm = 0.000000001 meter).

Hepatitis B is a DNA virus of the hepadnaviridae family of viruses. Once inside a host cell, it takes over the cell's normal functions and uses the cell's resources to produce more viruses, a process called replication.

The hepatitis B virus primarily infects liver cells. However, other cells of the body, including white blood cells and other tissues, can harbor the HBV.

The virus is composed of an outer coat or surface protein, called the surface antigen (HBsAg, previously known as the Australia Antigen). The surface protein coats or surrounds the inner core (machinery) of the virus that contains the genetic material (genes made of DNA) of the virus and some enzymes that are essential for the reproductive process of the HBV. This surface coat is made in abundance and is shed into the blood—this is the marker for the surface antigen test.

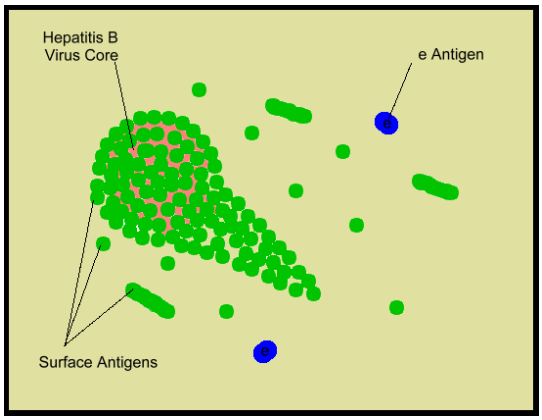
The virus infects a person when blood or certain body fluids—such as semen—carrying the virus enter a person. Infection can occur through a break or abrasion in the skin or when the bloodborne virus comes into contact with a mucous membrane, such as the thin lining inside the mouth, around the eyeballs or inside the nose.



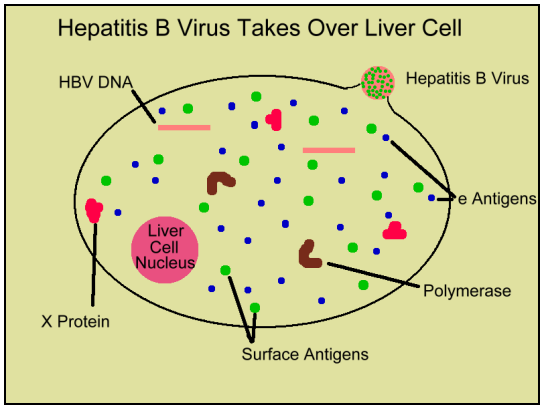
Once in the bloodstream, it is easy for the virus to come into contact with the liver, the largest internal organ in the body. If the hepatitis virus makes it past the body's immune system and encounters a liver cell (known as an hepatocyte), the virus's outer coat sticks to the liver cell's surface, and the virus's core genetic material inserts itself into the liver cell.

The viral core releases its DNA and DNA polymerase enzymes into the liver cell. The HBV uses the cell's resources to begin manufacturing or replicating the components needed to construct new hepatitis B viruses. These include:

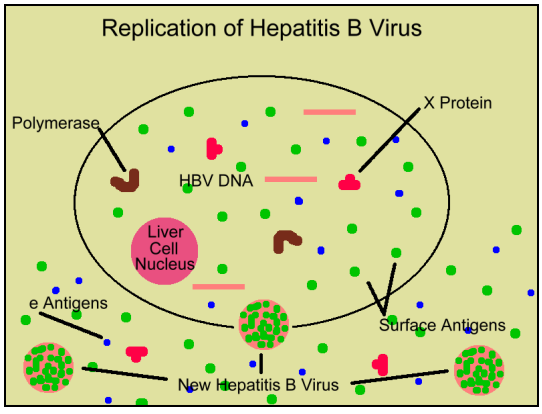
- The virus's outer surface proteins
- Its two core proteins, which include the core and precore protein called the HBcAg and HBeAg
- The genetic instructions carried in the DNA polymerase
- The X protein and other as-yet undetected proteins and enzymes



The DNA polymerase enzyme is instrumental in causing the liver cell to create copies of the hepatitis B DNA, and hence, more viruses. Once these components are produced within the liver cell, they are assembled into complete viruses and these virus copies are released into the bloodstream. There are "leftovers" remaining after the assembly process, including surface proteins that are released into the bloodstream.



The new hepatitis viruses go on to infect other liver cells and repeat this efficient and rapid reproduction process. In fact, thousands of new viruses can be produced in just one day from each liver cell.



However, during this viral reproduction process, mistakes can occur in the way the virus's genetic code is read, producing mutations of hepatitis B viruses. Some of these mutated hepatitis B viruses appear to be able to escape from the body's immune system more efficiently that the original (native or wild) strains of HBV.

The longer the hepatitis B virus replicates in the liver, especially in those infected as children, the more entrenched the virus becomes within the structure of the liver cells. Researchers suspect that over a period of years or decades, the hepatitis B DNA locks itself into the genetic material (DNA) of the liver cell—a process called integration—which makes it harder for the immune system to target and fight the infected cells. Integration may make the liver cells more prone to becoming cancerous.

Life Cycle of the Hepatitis Virus

The hepatitis B virus can take a liver cell's energy and resources away from producing the substances it needs to survive and use them instead to generate more viruses. As a result, the liver cell's life span is much shorter than average. Before it dies, the infected liver cell may have produced thousands of viruses.

This process, from the moment the virus attaches to the cell and begins replicating until the host cell dies, can span a few hours. Because there are so many liver cells, this infection process happens billions of times over an average of several months or years before a person may feel any symptoms.

Estimates vary, but the average incubation period (from time of infection until symptoms appear, if they do) of the hepatitis B virus ranges from 30 to 180 days, with an average of 60 to 90 days. In most children infected during birth or early childhood, there will be no symptoms or outward signs of HBV infection because their immune systems typically do not recognize the presence of this viral invader, and therefore do not put up a fight. Before symptoms appear, there are numerous biochemical changes in the liver cells and elsewhere in the body that occur following the initial infection.

When the body's immune system recognizes the presence of the hepatitis B virus, it doesn't attack the virus itself, but instead, tends to attack the liver cells that have become infected and now "host" the virus's replication machine. In those infected as infants or children, years or decades may pass before the immune system finally recognizes the virus as a foreigner and goes on the attack—or it may never do so.

The typical human liver has units called lobules (around 50,000 to 100,000 lobules in an adult and perhaps 50,000 in a child, as a child's liver is smaller than an adult's) that consist of a central hepatic vein surrounded by individual, tiny liver cells (hepatocytes). The border of each lobule contains the hepatic artery and portal vein, which delivers food components from the intestine to the liver lobule. The liver cells purify the blood, remove wastes and poisons, and store healthy nutrients for the body to use when needed. The purified blood passes into the hepatic vein in the center of each lobule, where it is

conveyed away from the liver to the heart to be pumped around the body.

As the virus takes over more and more liver cells in its replication campaign, liver cells are damaged and the surrounding cells (called fibroblasts) that form the supporting structure for the delicate liver cells are turned on (activated) to form scar tissue in a process called fibrosis.

Meanwhile, the liver tries to compensate for its scarred or malfunctioning areas by generating new liver cells—so called liver nodules. This constant scarring and regeneration causes the liver to become distorted in its structure (liver architecture) in a fashion that impairs blood flow.

Although the liver can lose more than 80 percent of its mass and still regenerate itself, if the scarring becomes extensive, then cirrhosis develops. And, as the hepatitis B viruses integrate themselves into the cells' nuclei and alter the genetic code, the chance of liver cancer increases.

Among children and adults chronically infected with HBV, 15 to 30 percent subsequently develop liver complications or cirrhosis, and about 20 to 25 percent of those patients with cirrhosis will develop liver cancer, according to CDC reports. However, according to the National Institutes of Health (NIH), about 15 to 25 percent of liver tumors develop in patients without cirrhosis.

The progress and severity of liver disease in people with hepatitis B varies depending on gender, consumption of alcohol, any coinfections and the regional strain of the virus and any viral mutations.

The Make-up of the Hepatitis B Virus

The hepatitis B virus is made up of antigens (protein components that the immune system identifies as foreign) and DNA.

As the body fights this virus, it creates a series of antibodies to counter (neutralize) each of the antigen proteins produced by the virus.

The outer coating or surface envelope of the virus is composed of several proteins known collectively as the hepatitis B surface antigen (HBsAg). It surrounds an inner protein shell or nucleocapsid, consisting of a core of nucleic acid that has two parts, the core antigen (HBcAg) and the precore antigen, which is commonly referred to as the e antigen (HBeAg). The core substance surrounds the virus's DNA genetic material and

the DNA polymerase enzyme, which contains the key replication instructions.

When doctors test for hepatitis B infections, they take a blood sample and look for surface antigen, e antigen and core antibodies, and they look at the levels of virus in the blood (the HBV DNA) to track the natural history of the HBV infection in the individual.

There are also a number of accessory proteins that play a critical role in how the virus behaves and progresses in a person. Researchers are still working to understand what role these other proteins play in the natural history of the disease.

Hepatitis B Surface Antigen (HBsAg)

The virus's surface protein is called the hepatitis B surface antigen, and it is commonly referred to as HBsAg. The presence of the surface antigen in a blood test indicates a current HBV infection (either acute or chronic) and that the person may be capable of transmitting the infection to others.

When a virus replicates in a liver cell, these surface proteins are produced in much larger quantities than any other component of the hepatitis B virus. These excess surface proteins clump together into rods and spheres in the bloodstream. In completely formed viruses capable of infecting liver cells, the surface protein encapsulates the core proteins and DNA particles.

The excess spheres and rods of the surface antigen enter the bloodstream in large numbers and, when present, they indicate an active HBV infection that can be either acute (short-lived; the body is actively fighting it) or chronic (long-term; the body cannot quickly eradicate it).

While only a small portion of surface antigen combines with the viral core products to form a complete virus, anyone with the surface antigen in his or her bloodstream should be considered infectious to others.

Laboratory tests can usually find the surface antigen about four weeks after infection with the virus, but detection in some may range from one to twelve weeks after infection. Detection of the surface antigen can precede the onset of symptoms such as jaundice and elevation of liver enzymes (which indicates liver cells are injured) by one to seven weeks.

This surface antigen goes away when a person's immune system overcomes the virus.

However, there can be a small window of time when the surface antigen becomes undetectable but the antibodies to the surface antigen (immunity to the virus) have not yet developed.

Some studies suggest that in some people, the surface antigen may never completely go away. The surface antigen and hepatitis B virus DNA may simply decline to very low levels that are not detectable by most laboratory tests.

According to an article on persistent HBV infection after clearance of the surface antigen in a 1998 issue of *Hepatology*, hepatitis B viruses were found to continue to replicate at low levels years after the surface antigen became undetectable in some patients. This may be why the virus reappears in people who become ill from another disease and why some people who receive transplanted livers from people who test negative for the surface antigen may later develop HBV infections. The transplanted organ may in fact house minute levels of surface antigen that went undetected in the laboratory tests.

"Moreover, it is possible that this low-level hepatitis B virus replication may be another cofactor for the development of hepatocellular carcinoma in (surface antigen negative) patients, in addition to cirrhosis and the integration of HBV DNA into the host's genome," wrote the study's authors.

Hepatitis B Surface Antibodies (Anti-HBs, anti-HBsAg or HBsAb)

The hepatitis B surface antibody (HBsAb) is an antibody formed by the body in response to the presence of the surface antigens, or proteins, of the hepatitis B virus. This antibody provides immunity against future HBV infections and is generally considered the hallmark of a cure. The antibody is detected through blood tests.

The HBsAb is the antibody (immunity) produced by responders to the hepatitis B vaccine.

These antibodies are the last antibodies to appear when a person recovers from hepatitis B and are usually detectable about eight weeks after clearance of the surface antigen. The antibodies remain present for many years after hepatitis B infection clears. The presence of this antibody indicates clinical recovery and development of immunity to hepatitis B and suggests that the person is no longer infectious.

However, the presence of these antibodies is not an absolute indication of a resolved case of hepatitis B, nor do they always guarantee protection from future infection.

Because there are different strains and mutations of hepatitis B, it is possible for a patient to have an antibody to one surface antigen type and to be acutely infected with a strain or mutation of a different HBV genotype or viral strain, though this is very rare.

While extremely rare, in areas where HBV infection is endemic, hepatitis B infection has occurred in vaccinated people. Researchers believe these vaccinated people may have contracted a mutant strain of HBV that produces different surface proteins than those used in genetically-engineered hepatitis B vaccines.

Hepatitis B Core Proteins

The hepatitis B core gene protein is divided into two regions, the pre-core and the core. The names used for these two different proteins are the hepatitis B core antigen (HBcAg) and the hepatitis B e antigen (HBeAg).

Hepatitis B Core Antigen (HBcAg)

The hepatitis B core antigen (HBcAg) forms the inner core of the virus and is produced by the infected liver cells during viral replication. The core proteins link together to form the hepatitis B core that encapsulates or coats the hepatitis B DNA and DNA polymerase enzyme.

The core antigen is not found in the bloodstream at any time. This antigen can only be found by analyzing an infected liver cell obtained during a liver biopsy, in which a needle retrieves a small sample of liver tissue.

Hepatitis B Core Antibodies (anti-HBc or HBcAb)

These are the first detectable antibodies to appear around eight weeks after infection. These antibodies do not completely neutralize the virus and are generally present in people with chronic HBV infection.

There are two types of antibodies that appear in response to the core antigen. The IgM (Immune Globulin Class M) antibodies appear to fight this virus. The level of IgM antibodies declines quickly during recovery of acute infection, so doctors look for them as an indication of a recent or acute infection.

Also responding to the invading viruses are IgG (Immune Globulin Class G) antibodies. They are the most abundant of circulating antibodies and can cross the walls of blood vessels and enter tissue fluids to fight an antigen.

The core antibodies, especially the IgG antibodies, persist in the bloodstream after an HBV infection has been resolved. Testing for this antibody has been used to detect previous exposure to the live virus. These core antibodies do not appear in someone who has been vaccinated against hepatitis B, only in those who have been infected in the past.

Hepatitis B e Antigen (HBeAg)

The hepatitis B e antigen is a protein secreted by infected liver cells into the blood-stream. When the e antigen is present in the blood, it means the HBV is replicating. A person with detectable e antigens is more infectious than a person without them.

People with this antigen are considered at greater risk of progressing to liver disease than those who have developed an antibody to this antigen because it indicates on-going infection and viral replication within the liver.

The e antigen is a little-understood component of the hepatitis B virus. There are strains of hepatitis B where the e antigen is not present at all, and in some mutated versions of the virus, viral replication occurs without the presence of the e antigen.

When the hepatitis B virus DNA (HBV DNA) is able to integrate or incorporate itself into the DNA of a liver cell, often the e antigen disappears, though no one is sure exactly why this happens. Once integration occurs, the "integrated" liver cells are far more vulnerable to becoming cancerous as a result of their genetic alteration.

Researchers have suggested the e antigen may be influential in suppressing the immune system's response to HBV infection, especially in children, or hiding the virus from the immune system.

In the natural history of the disease, the e antigen usually appears in the blood very shortly after the surface antigen appears and disappears before the surface antigen becomes undetectable.

In acute cases of hepatitis B, when the body's immune system successfully and quickly eradicates the infection, the e antigen is only transiently present. It disappears as viral replication declines in the face of an effective immune response.

Hepatitis B e Antibodies (anti-HBe or HBeAb)

Hepatitis B e antibodies appear as the e antigen disappears and usually persist for one or

more years after resolution of hepatitis B. Seroconversion, or production of the e antibodies, generally represents a reduction in infectivity—a decreased ability to infect others.

Note, however, that a person who has antibodies to the e antigen still may have HBV and be infected and infectious to others.

There is now evidence of "flip-floppers"—those whose e antigen and e antibody status may in fact flip-flop back and forth throughout their lives. This is also called spontaneous reactivation.

In this scenario, researchers suspect the e antigen levels are low and that the e antibodies keep them in check. However, at times the e antigen may flare—perhaps because the immune system is weakened by a different infection—and become visible in lab tests.

Hepatitis B Virus DNA (HBV DNA)

Hepatitis B virus DNA (HBV DNA) is the genetic material that carries the replication blueprint of the virus. The presence of HBV DNA in a person's bloodstream is the most specific indication of the presence of the virus. The virus's DNA is one of the first things that can be detected in the bloodstream after a person is infected. It can be detected as soon as one week after infection, if sensitive tests are used to detect the genetic material.

Measuring HBV DNA "has led to the recognition of low-level viremia (HBV DNA) in many patients who have no apparent liver injury," noted the authors of the National Academy of Clinical Biochemistry's *Laboratory Medicine Practice Guidelines* for screening, diagnosis and monitoring of liver disease.

Generally, HBV DNA levels indicate how fast the virus is replicating. High levels indicate ongoing replication of the virus. Low or undetectable levels indicate the infection is in a less active phase.

HBV DNA is detected by genetic engineering using a technique called the Polymerase Chain Reaction (PCR) test. This is the most sensitive testing method or assay for measuring DNA levels. The PCR creates copies of specific DNA fragments to detect and measure the HBV DNA. The test for HBV DNA measures the "copies" or number of viruses in a blood sample.

Patients with active HBV infection may have up to several billion virus particles per milliliter. Patients with inactive or dormant HBV infections will have very few particles per milliliter.

A hybridization method (assay) that tests for DNA produces results that are far less sensitive than the PCR test. The hybridization test reveals DNA only when there is a certain quantity of HBV DNA copies in the blood.

Unlike detection of the surface antigen, tests for HBV DNA are not performed as a standard test and many insurance companies do not cover the cost unless they are used to monitor disease progression during medical treatment.

The World Health Organization has created an international standard for measuring HBV DNA in serum. It established the HBV DNA international unit (IU or viral copies) per milliliter (mL). As a result, every HBV DNA test (assay) should be reported in IU/mL.

While there is a global standard for measurement, the types of tests used to measure HBV DNA vary widely. There are a variety of technologies used by labs around the world to measure viral load in serum. For example, some labs use a "branched DNA" and others use a polymerase chain reaction (PCR) test. Laboratories are supposed to offer test results with a conversion factor so all HBV DNA results can be compared using the global IU/mL standard no matter what testing technology was used.

NIH reports have suggested that viral loads that exceed 10^5 copies/mL be considered 'clinically significant' viral loads, while lower viral loads represent an inactive carrier state.

"However, there are problems with this definition," wrote Drs. Anna Lok and Brian McMahon in the American Association for the Study of Liver Diseases Practice Guidelines published in October 2002. "First, assays for HBV DNA are not well standardized. Second, some patients with chronic hepatitis B have fluctuating HBV DNA levels that may at times fall below 10^5 copies/mL. Third, the threshold HBV DNA level that is associated with progressive liver disease is unknown."

Hepatitis B Virus DNA Polymerase (HBV DNA Polymerase, DNAp)

The HBV DNA polymerase, an enzyme, instructs the liver cell to make copies of HBV DNA. This enzyme can be detected in the bloodstream about one week after infection, at about the same time as the HBV DNA. The DNA polymerase test is no longer

performed as a standard test to monitor infection.

Hepatitis B x Protein (HBx Protein)

The function of the hepatitis B x protein is not clear, but some researches believe the X gene (HBx) plays a critical role in the development of liver cancer in those with chronic hepatitis B infections.

Researchers believe this protein contributes to the persistence of HBV infection in liver cells and sets up cellular responses in infected liver cells that promote development of cancerous cells.

Interpreting Hepatitis B Tests

When these tests are performed, doctors will receive a report from the laboratory that details the results. Once a doctor has this report, he or she will sit down with the patient and/or parents and review the results and what a suitable next step should be.

Hepatitis B Surface Antigen (HBsAg)	• It is used to diagnose an acute or chronic infection. • It is the first antigen to appear in the bloodstream during an acute infection. • Its disappearance indicates recovery from infection. • Persistence for more than six months indicates chronic infection. • Individuals tested within two weeks after receiving the vaccine may test positive, but this result is transient; they are not infectious.
Hepatitis B Surface Antibody (Anti-HBs or HBsAb)	• This is the only test that determines whether there is protective immunity following immunization with a hepatitis B vaccine. • These antibody levels may decline with time. • Positive results in individuals with recent acute hepatitis B infection indicate that recovery is complete. • This antibody is usually not detected when the surface antigen is also present. • In rare cases of chronic hepatitis B infection, both the surface antigens and surface antibodies can be present and detectable at the same time. When both are present, the antibodies cannot be relied upon. The person should be considered infectious to others.
Hepatitis B Core IgM Antibody (Anti-HBc IgM or HBc IgM Ab)	• This test is expensive and should primarily be used if there is a chance that the patient is in the early convalescence "window period" (two to 16 weeks after infection) when the surface antigen has disappeared and surface antibodies are not yet detectable. • A positive result in patients who are also surface antigen positive usually indicates acute infection. • This antibody is usually detectable for about six months. • Depending on the sensitivity of the test, a low level may be detected in patients with chronic infection who are experiencing a reactivation of viral replication.

Hepatitis B e Antigen (HBeAg)	• This indicates active hepatitis B replication in liver cells. • This also indicates a high degree of infectivity. However, *the absence* of the e antigen in a person who is positive for the surface antigen does not mean the individual is not infectious. Anyone with the surface antigen is always infectious. • This is often measured to monitor the success of therapy of patients with chronic hepatitis B infection.
Hepatitis B e Antibody (Anti-HBe or HBeAb)	• The e antibody appears as the e antigen disappears. • In chronic hepatitis B infections, this can indicate the end of the immune tolerant stage and the beginning of the immune clearance stage. • People who have the e antibody but still have the surface antigen must still be considered infectious and capable of transmitting the disease.
Hepatitis B Core Antibody (Anti-HBc or HBcAb)	• A positive result indicates past infection. • This antibody usually persists for life after infection. • This antibody is absent in individuals who are immune because they have been vaccinated.
Hepatitis B Virus DNA (HBV DNA)	• This is a costly test available by special request. This is not used in any initial diagnosis of a hepatitis B infection. • This is used to determine the presence of HBV DNA circulating in the blood, which indicates how much viral replication is occurring in the liver. • This test is used primarily during treatment to ascertain the success of therapy.

The Stages of HBV Infection

Medical experts view an HBV infection as having three stages. When an infection develops into a chronic or long-term infection, especially in newborns or young children, these stages span several years or decades. However, sometimes these stages are accelerated, depending on:

- An individual's immune response,
- How old they were at the time of infection,
- And with what strain or genotype of hepatitis B virus they were infected.

Phase 1: The Immune Tolerant Stage

In this phase, which can last the first two decades of life when children are infected during infancy, the virus is actively reproducing in the liver, but only mild liver disease may be present and liver enzymes are often normal. Frequently, there are no symptoms of hepatitis.

HBV DNA levels usually are high, and the e antigen (HBeAg) is generally present.

When infected at an early age, this phase of immune tolerance generally lasts until tolerance to the virus breaks down, generally after the age of 15 to 20.

In this first phase, because the immune system basically ignores the HBV infection or only recognizes it at a low level, only minimal liver damage occurs. When adults are infected, this phase can be very short.

Phase II: Immune Clearance Stage

During this stage, the immune system finally recognizes the virus as not belonging and attacks the liver cells infected with the virus. HBV DNA is present, but generally in lower levels than during the immune tolerant phase and the e antigen is generally also present. Liver enzymes, which are released when liver cells are damaged or die, are often elevated as the immune system attacks infected liver cells.

During this phase, HBV replication decreases and spontaneous seroconversion from e antigen to e antibody can occur, often preceded by a "flare" or sudden increase in liver enzymes.

Transition from this phase to the non-replicative phase may occur quickly or be a prolonged process. There may also be fluctuations of activity, with spikes in liver enzymes as the immune system attempts to clear the virus from the liver.

It is during the immune clearance phase that most liver damage occurs. The longer this phase lasts, the greater the risk of liver disease.

Ironically, a flare can be a good sign as it can signal seroconversion and creation of the e antibody and transition into the non-replicative phase. However, when seroconversion does not occur, the repeated flares often indicate continued liver damage.

Phase III: Non-Replicative Stage

This stage begins once the majority of infected liver cells have been destroyed and few if any viruses are replicating in the liver. The surface antigen (HBsAg) is still present, but the e antigen (HBeAg) has disappeared, the e antibody has appeared and liver enzymes have normalized. HBV DNA in the bloodstream has become undetectable or remains at very low levels.

A person in this state is still a chronic carrier and remains capable of infecting others. While there is normally no new liver damage occurring during this phase, there may be

liver damage present from the previous phase when the immune system was attacking infected liver cells.

The transition from one stage to another is rarely linear. There can be relapses, such as a return to the immune tolerant stage followed by immune clearance. Or, an individual can experience flares and return to the immune clearance state after being in the non-replicative stage for several years.

Viral mutations can also develop during the immune clearance stage—especially if it is prolonged—as the viruses that are able to evade the immune system emerge through natural selection and become the dominant hepatitis B virus.

Acute vs. Chronic Hepatitis B Infection

When healthy older children, teens and adults are infected with HBV, their immune systems swing into action. The immune system responds by unleashing a two-fold punch with the release of IgM and IgG antibodies that zero in on the virus's core antigen.

The irony is, when there is a strong response, there is usually some liver damage (which is later repaired) as the immune system targets the infected liver cells during its eradication campaign. This is the period when symptoms, such as nausea, abdominal pain and jaundice, appear in 5 to 15 percent of children ages 1 to 5, and 30 to 50 percent of older children and adults, according to the CDC's Viral Hepatitis Surveillance Report.

As the immune system responds, the HBV DNA, the surface antigen and e antigen disappear from the bloodstream as the e antibodies and core antibodies appear over a two- to 16-week period. After this eradication phase concludes and the infected cells are targeted and cleared from the liver, surface antibodies begin to appear, heralding the end of the acute infection and immunity from future HBV infections in most cases.

Who will develop chronic hepatitis B following contact with the virus?

According to the CDC:

- 90 percent of those born to infected mothers
- 30 percent of children infected between the age of 1 and 5 years
- 6 percent of people infected after age 5

In children under the age of 10 and in older children, teens or in adults who receive immune-suppressing medication or have another illness or infection, the immune system's response is not so vigorous or effective. The virus and infected liver cells are masked in a way that allows them to elude the immune system's sensors.

Scientists writing on the clinical relevance of hepatitis B viral mutations in the May 2000 issue of *Hepatology* suggest that certain mutated viruses found in regions with high rates of perinatal transmission, especially Asia, may excel at cloaking themselves from a person's immune system for up to 30 years until a biochemical change or a new viral mutation finally catches the attention of the immune system.

Doctors consider anyone to have a chronic HBV infection if HBV DNA and the surface antigen persist at detectable levels in their bloodstream for longer than six months.

Variations in Hepatitis B e Antigen and Antibody Status

Historically, doctors assumed that anyone who had developed e antibodies was in remission and even on the road to recovery from the disease. However, there is now evidence of "flip-floppers"—those whose e antigen and e antibody status may in fact flip-flop back and forth throughout their lives.

These flip-floppers appear to have cleared or eradicated the e antigen particles from their bloodstream and produced e antibodies. However, tests conducted months or years later may reveal the presence of the e antigen again and HBV DNA. This is also called spontaneous reactivation.

During this re-emergence of the e antigen and HBV DNA, there is usually a significant spike in liver enzymes, which liver cells release when injured, and hepatitis B symptoms may appear, including jaundice, nausea, flu-like illness and fever.

Researchers suggest that a person's immune system may become weakened from an illness and may not be able to keep the trace levels of HBV in check. As a result, rapid viral replication begins again in the liver and HBV DNA and e antigens are once again produced and circulate in the bloodstream.

When specialists evaluate patients with flip-flopping e antigens/antibodies, they suggest that if the e and surface antigens are present, as well as their respective antibodies, then the antigen takes precedence when making a diagnosis and a doctor must assume the infection is active.

Or, if the e antigen is present (even with antibodies) then a doctor should assume the

virus is still replicating. A test for the presence of HBV DNA would confirm this.

Hepatitis B e Antigen Negative Chronic Hepatitis B

When the immune system goes on the attack against infected liver cells, some viruses that happen to have a different molecular make-up are able to evade the attacking immune system better than the naturally-occurring or "wild" viruses.

During the immune clearance phase, the wild viruses without mutations are eradicated, while the mutated viruses avoid the immune system's attack and eventually become the dominant type of hepatitis B virus in the body.

One of the more common mutations in hepatitis B viruses occurs in the precore or core promoter regions. This precore mutation stops the virus from producing or secreting the e antigen. Despite its inability to secrete this protein, these mutated viruses are able to live and replicate without it.

Patients with the precore mutation have the surface antigen and no e antigen, but they can have the e antibody. They often have elevated liver enzyme levels, which indicates liver cell damage is occurring.

Unfortunately, people with this e antigen-negative (but not necessarily with e antibody) hepatitis often have active liver disease that resists treatment with medications such as interferon and lamivudine.

The prevalence of these mutations ranges from 20 to 90 percent among patients from Europe and the Mediterranean region, 10 to 38 percent among those from Asia and the South Pacific region and about 10 percent of those in the United States.

One study that followed 365 children in Taiwan for 10 years suggests that this viral mutation or strain is rare in children, and it may evolve during the viral clearance phase of infection.

Hepatitis B Surface Antigen Negative Hepatitis

Though extremely rare, there have been some HBV infections that failed to produce detectable hepatitis B (HBsAg) surface antigen. These patients had HBV DNA in their bloodstream, but showed no other antigens normally associated with HBV infection.

The Genotypes or Strains of the Hepatitis B Virus

In the past decade, researchers have discovered there are different strains or genotypes of hepatitis B viruses around the world.

HBV genotypes are identified by the genes that define (encode) the protein that covers the outer surface of the virus—called the surface antigen.

In fact, epidemiologists can trace the origin of various viruses and how they spread through a particular community by looking at the distribution of dominant genotypes in one community and then tracking when they appear in other communities.

Currently, researchers have identified seven main genotypes for HBV and most have specific geographic distributions.

- Genotype A is found mainly in North America, Northwest Europe and Central Africa.
- Genotype B is found primarily in Southeast Asia, China and Japan.
- Genotype C is found primarily in Southeast Asia, China and Japan.
- Genotype D is found in Southern Europe, in the Middle East and India.
- Genotype E is found predominantly in Africa.
- Genotype F is found predominantly in Native Americans of North America and in Polynesia and Central and South America.
- Genotype G, the most recent HBV genotype to be identified, has been found in the United States and in France.

There is also a strong correlation between race/ethnicity and HBV genotype:

- Caucasian patients are almost exclusively infected with genotype A or D.
- Asian patients typically are almost exclusively infected with genotype B or C.
- Patients of African descent typically are infected with genotype A, D, or E.

Within each of these major genotypes can be up to four different subgroups, called "serotypes" because they can be identified by testing blood (serum). Researchers believe some viruses belonging to certain serotypes are more prone to mutations, especially during treatment with lamivudine—an antiviral medicine that stops the virus from replicating.

They have found that the precore mutation that does not produce the e antigen is found most commonly in genotypes B, C and D, but not genotype A.

Researchers in Taiwan were among the first to investigate the association between

certain HBV genotypes and severity of liver disease. They studied 100 people with chronic hepatitis B who had no symptoms of liver damage and 170 chronically infected patients with obvious liver disease and liver cancer. They found that ethnicity, as well as genotype, played a role in the development of liver disease from hepatitis B.

All genotypes except genotype E were identified in the patients in Taiwan and genotypes B and C were the most common, according to their report published in 2000. Researchers found genotype C was most common among patients with cirrhosis (liver scarring) and those with liver cancer who were aged 50 years or older. Genotype B was significantly more common in patients who experienced liver cancer under the age of 50.

In contrast, patients with genotype B who lived in Japan and China had a relatively good prognosis, and they had only a rare occurrence of liver cancer—unlike their counterparts in Taiwan.

Other researchers examining the seriousness of liver disease in India found patients with HBV genotype D had more severe liver disease at a younger age than those with genotype A.

A study of 64 German patients found that the rate of interferon-induced HBeAg seroconversion (creation of the e antibody) was higher among patients with genotype A than in those with genotype D (37 percent vs. 6 percent).

Another study in Taiwan found patients with genotype B had a significantly higher rate of losing the e antigen and developing the e antibody when treated with interferon, compared to patients with genotype C.

In an editorial in *Hepatology* magazine, published in May 2002, Drs. Anna S.F. Lok and Chi-Jen Chu of the University of Michigan Medical Center's Division of Gastroenterology wrote, "…there is growing evidence that HBV genotypes may influence HBeAg seroconversion rates, mutational patterns… and severity of liver disease."

Currently, genotyping of the hepatitis B virus is done only in research settings.

Mutations Within the Hepatitis B Virus

Like all living things, viruses can undergo genetic mutations or changes within their cellular structure as they reproduce millions of times. While the hepatitis B virus is a DNA virus, its replication instructions come from the polymerase enzyme, which is an

RNA compound.

Its replication process (which is similar to the HIV virus) lacks a "proofreading function" that is common in other cells. As a result, hepatitis B viruses have a mutation rate that is ten-fold higher than other DNA viruses, according to a report published in *Hepatology* in May, 2000. The mutations scientists have identified to date occur in the hepatitis B virus's core region (precore gene or core promoter region) and also in the surface antigen.

Some of the mutant strains with mutations in the core region are called precore mutant strains. Hepatitis B viruses that have no mutations at all are called "wild type" viruses.

In some children and adults, the precore mutant becomes the dominant form of the hepatitis B virus in their bodies over a period of years. But some individuals are clearly infected from the start with virus in which the precore mutant is the dominant viral form.

The precore mutations, which have missing or altered components in their genetic blueprint, may make the virus difficult for a child's immune system to target and fight. These mutations may also make the virus resistant to certain anti-viral drugs, such as interferon, according to the report in *Hepatology*.

These viral mutations may also dictate how quickly a child or adult is able to develop the e antibody. Another mutant strain allows the virus to replicate without producing or secreting the e antigen. This tends to occur more in people from Asia and the Mediterranean region, but it may predispose people to chronic or long-term HBV infections.

A study of the Canadian Inuit population showed 70 percent of chronic carriers had precore mutant infections, according to a Canadian Hepatitis Education Council article by Dr. Samuel S. Lee.

A study reported in the *Annnals of Internal Medicine* in 1995 focused on 43 patients in Japan with serious fulminant (life-threatening) hepatitis B. The study found that 37 of the patients had a version of hepatitis B that did not produce the e antigen.

The second group of mutations, mentioned earlier, occurs in the surface antigen. These mutated viruses, originally called vaccine escape mutants, are of concern because the current blood screening process fails to detect this altered surface antigen. To date, these mutations are rare and occur primarily in Asia.

How the Immune System Fights the Virus

The body's immune response to the hepatitis B virus dictates whether the body successfully eradicates the virus during an acute episode, or becomes its long-term host as is the case with many childhood infections.

To successfully combat the virus, the body must mount a broad-based immune response to the hepatitis B virus, according to Dr. Jack R. Wands, director of the Molecular Hepatology Laboratory at Massachusetts General Hospital. This battle requires the presence of antibodies to the virus's core, e, and surface antigens, and the assistance of T-cells. T-cells are lymphocytes or white blood cells that fight infection.

There are two types of T-cells that play a role in fighting hepatitis B: Helper T-cells and Killer T-cells.

Helper T-Cells (HTLs) boost the body's immune response by releasing chemicals that stimulate Killer T-cell (CTL) response as well as antibody response.

Cytotoxic T Lymphocyte (CTLs) or Killer T-cells kill foreign cells that have been marked for destruction by the cellular immune system. When activated, they multiply in number and kill diseased cells.

Both HTLs and CTLs are activated by the presence of specific epitopes on infected cells or antigens. An epitope is a chemical group recognized by the immune system. It is a small fragment (peptide) from an antigen. The cellular immune response by CTLs and HTLs against hepatitis B viruses hinges on their ability to recognize the epitopes on infected cells.

When the immune system works well, as in healthy adults with acute hepatitis B, the CTLs and HTLs bind to their individually-targeted epitopes on the infected cells or antigens and successfully kill the diseased cells.

In some people, these CTLs remain detectable in their systems for years after recovery from HBV infection, leading some to believe that even after recovery, some traces of HBV DNA may remain in the body for years, causing the CTLs to remain active to keep the virus in check.

But if a child's T-cells are not able to recognize the epitopes and fight the infected liver cells for some reason, then hepatitis B becomes chronic. This may occur if the child has a precore mutation or genotype of the virus that is able to effectively cloak itself and

escape T-cell recognition.

A study by the Department of Molecular and Experimental Medicine at Scripps Research Institute, looked at CTL response to multiple epitopes in the hepatitis B virus. Their research shows the CTL response to those epitopes was barely detectable in the majority of adult patients with chronic hepatitis B.

The period when the virus silently escapes recognition by the immune system is called the immune tolerant stage. This period usually begins at the time of infection in infants and children and can last up to 30 years.

During this period, the liver appears undamaged and often does not release any enzymes that indicate liver cell damage even though the viruses are replicating, often at high rates.

An article in the May 2000 issue of *Hepatology* on the "Clinical Relevance of Hepatitis B Viral Mutations," suggests that in perinatally-acquired hepatitis B, the virus could have a mutation in its core region that somehow alters core proteins and manages to block recognition of the virus by the Helper and Killer T-cells.

"In patients with perinatally-acquired chronic hepatitis B, a prolonged immune tolerant phase with minimal-to-absent hepatic necroinflammatory activity (liver damage) is typically seen for the first 20 to 30 years of hepatitis B infection; this quiescence may be related to the acquisition of core deletions (mutations in the virus core region)," the researchers explained. They suggest that this genetic core structure may remain intact or "highly conserved" for more than 20 years.

It is only when the core mutates or changes its genetic structure, and possibly undergoes a change in its proteins or amino acids, that those infected as children pass from the immune tolerant stage and enter an active liver disease period during which the immune system finally recognizes and targets the infected liver cells.

During the immune clearance phase, the immune system attempts to clear or eliminate the virus by attacking and injuring the infected liver cells. Unfortunately, the liver may be damaged during this active disease-fighting period. During this phase, doctors test for certain enzymes that liver cells release when they are damaged.

The severity of cell destruction and the duration of this immune clearance phase will determine whether an individual develops significant liver disease and extensive liver scarring, which is called cirrhosis.

Once the immune clearance phase is completed, the levels of HBV DNA become extremely low and liver enzymes become normal. If liver scarring has not been extensive, the liver begins to regenerate and repair itself. However, in many chronic cases of hepatitis B, the surface antigen will persist even though the immune system has minimized the volume of virus in the bloodstream and the person has developed the e antibody. This phase is also called the quiescent phase.

Occasionally during this quiescent period, the virus can become active again if the immune system is compromised by another disease or infection. The virus will re-activate or flare, and once again cause liver scarring as the immune system struggles to clear away the infected liver cells. Men of Asian descent over the age of 40 are particularly vulnerable to these flares.

The Chronic Hepatitis B Cycle – Mother to Child

Infants who are infected by their mothers are at the highest risk of developing chronic hepatitis B infection because their immune systems usually fail to identify the virus and fight the infection.

But whether or not they become chronically infected depends to a certain degree on their mothers' viral status.

According to a report issued by the Advisory Committee on Immunization Practices in the *Morbidity and Mortality Weekly Report*, infants born to mothers who tested positive for both the hepatitis B surface and e antigens faced a 70 to 90 percent risk of infection, with 85 to 90 percent of those infected infants becoming *chronically* infected. Infants born to mothers with the surface antigen and e antibody faced a 31 percent risk of infection.

However, children born to surface antigen positive mothers who were not infected at birth faced a 30 to 60 percent risk for acquiring the infection during their first five years of life, depending on the e antigen status of the mother.

Infections acquired during infancy, while estimated to represent only 1 to 3 percent of hepatitis B cases in the United States, account for 20 to 30 percent of chronic infections, according to the U.S. Preventive Services Task Force.

Historically, it was thought that a fetus did not contract HBV infection in the womb. Doctors believed the placenta prevented the virus from reaching the fetus. Doctors believed transmission occurred through the placenta in only about 6 percent of the cases.

However, according to Dr. Elizabeth Ann Fagan, writing in *Viral Hepatitis: A Handbook for Clinicians and Scientists*, transmission of the virus through the placenta may be more frequent than previously thought. HBV DNA was detected in 44 percent of livers of fetuses from Chinese mothers who tested positive for the surface antigen. This may explain why in some cases infants of mothers with surface antigens become infected despite immediate administration of hepatitis B immune globulin and immediate administration of a hepatitis B immunization after birth.

During delivery, upon entering the birth canal, the baby also encounters the mother's blood, which is infected with HBV DNA. Viruses in the blood, vaginal fluids and amniotic fluid readily expose the baby to infection when they are ingested or come into contact with the child's nose or eyes or enter through the mucous membranes.

However, according to Dr. Fagan, Caesarean delivery does little to cut down on the perinatal transmission of hepatitis B. Following birth, close contact with the mother exposes the baby to viruses in the mother's body fluids, including saliva and blood.

Despite the documented presence of hepatitis B virus in breast milk, infected mothers are not discouraged from breast-feeding. According to Dr. Harold Margolis of CDC, "Studies done before the hepatitis B vaccine was available showed that breast-fed infants born to infected mothers did not have an increased risk of perinatal or early childhood hepatitis B infection. Among infants receiving postexposure prophylaxis to prevent perinatal hepatitis B infection, studies have shown that there is no increased risk of infection among breast-fed infants."

Breaking the Perinatal Transmission Cycle

Fortunately, a combination of passive and active immunization is highly effective in preventing vertical (mother-to-child) transmission of the HBV.

When a baby is born to an infected mother who has the surface antigen and the e antigen, if hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccine are administered to the newborn within 12 hours of birth, the combined regimen is 85 to 95 percent effective in preventing HBV infection.

In a study in Thailand, 97 babies born to infected women with the e antigen were immunized against hepatitis B at birth. Despite the absence of HBIG treatment, between 82 to 86 percent of the immunized infants remained free of HBV infection. Without the vaccine, between 70 to 90 percent of them would have been infected.

In the United States, infants born to all HBV infected mothers should receive HBIG and the first shot of the hepatitis B vaccination series within 12 hours of birth.

Obstetricians should screen all patients for hepatitis B at some point during pregnancy. If doctors decide to screen pregnant women based only on the women's acknowledged risk factors, they will fail to identify 30 to 50 percent of infected women, according to CDC and others.

Regular prenatal testing of all pregnant women is now recommended. According to CDC, such screening would identify an estimated 22,000 hepatitis B positive mothers and could prevent at least 6,000 chronic hepatitis B infections in children each year.

According to a recent report by Dr. Anna S. F. Lok, the various genotypes or variants of the hepatitis B virus can impact the effectiveness of the vaccine in breaking the cycle of hepatitis B transmission from infected mother to child.

She found that mothers with the precore mutation that failed to produce e antigens, or who had both the e antigen and e antibody, or who had a mutation in the virus's surface antigen, gave birth to children who were resistant to the hepatitis B vaccine. These cases are very rare and occur primarily in Asia.

How Chronic Hepatitis B Acts in Children

Infants and very young children who are infected with HBV at birth or within the first few years are more prone to become chronic carriers of the disease.

The first 10 to 20 years of their lives may pass without any symptoms or signs of liver disease. Because their immune systems do not recognize the virus as foreign, they do not attack the infected liver cells or appear to cause any liver damage.

But even during this asymptomatic period, liver disease can develop. Doctors have discovered that despite an absence of symptoms or abnormal liver enzyme tests, liver scarring and even cirrhosis can quietly and subtly develop over a period of two to 10 years, according to Dr. Phil Rosenthal, medical director of the Pediatric Liver Transplant Program at the University of California, San Francisco.

In adults with chronic hepatitis B, 15 to 25 percent of those who develop liver cancer have no visible signs of cirrhosis, according to the NIH Workshop on the Management of Hepatitis B 2000.

In a best case scenario, children with chronic infections will develop the e antibody, which indicates a decline in viral replication. Unless the child has the rare hepatitis B strain that allows replication without the e antigen, this seroconversion (development of the e antibody) may be the first indication that the child/adult's immune system is beginning to recognize the epitopes on the infected liver cells.

It has been found that the age at infection, the e or surface antigen status of the mother and the genotype of hepatitis B all contribute to the course (and severity) of the infection in children—and whether they develop the e antibody and fight off the virus successfully, or lose the battle and develop cirrhosis and liver disease.

"The cumulative rate of spontaneous HBeAg (e antigen) clearance is estimated to be approximately 2 percent during the first three years and only 15 percent after 20 years of infection," wrote Dr. Anna Lok in "Clinical Manifestations and Natural History of Hepatitis B Virus Infection," published in *UpToDate.* "The low rate of viral clearance in adolescence and early adulthood accounts for the high frequency of maternal-infant transmission in Asian countries."

The advent of the development of the e antibody signals the end of the immune tolerant stage and the beginning of the immune clearance stage. The clearance stage can begin during the second or third decade of life, according to Dr. Lok.

The e antigen seroconversion can be accompanied by biochemical exacerbations or sudden increases in the level of the alanine aminotransferase (ALT) liver enzyme. Liver cells produce the ALT enzyme and ALT levels increase when liver cells are damaged or die.

An elevated ALT level can indicate that the immune system is attacking the infected liver cells. But ALT levels can remain normal even when there is liver damage occurring during a child's immune tolerant stage. This is why many pediatric gastroenterologists and hepatologists test alpha fetoprotein levels in immune tolerant children annually to identify advanced cirrhosis or cancer.

These ALT exacerbations are more commonly observed in men than in women. The reason for the gender difference is not clear, writes Dr. Lok, but it may account for the higher rate of extensive liver scarring or cirrhosis and liver cancer in men than women. With time, patients who have developed the e antibody will slowly stop replicating the virus and in the best of all possible worlds develop the surface antibody. But this total clearance of the disease happens rarely in people with chronic infections who contract the virus early in life.

If there are no coinfections, alcohol or injecting drug abuse, the person who was infected at birth may never develop progressive liver disease. Their viral replication rate will probably decline but they will remain infectious, though relatively asymptomatic for liver disease, through life.

How Hepatitis B Progresses to Liver Cancer

When a child has chronic hepatitis B, the disease may remain "silent" for years, but these people, especially when they reach adulthood, are still at risk of liver disease and liver cancer, even after they seroconvert and develop e antibodies.

Fifty-two Japanese children between infancy and 15 years of age, who tested positive for both the hepatitis B surface and e antigens, were followed for more than a decade by researchers at the National Defense Medical College in Japan. During the study period, during which many children entered adulthood, half of them seroconverted and developed the e antibody. However, one patient developed liver cancer at age 21, more than 16 years after he seroconverted, even though his liver enzymes remained normal.

The other 26 children in the study remained e antigen positive. Of these 26, 16 were treated with interferon alpha. Eleven of them developed the e antibody within 12 months of ending therapy. However, liver cancer developed in one of these children at age 16, six years after the child received interferon therapy and developed the e antibody.

The researchers, writing in the February, 2000, issue of the *Journal of Pediatric Gastroenterology and Nutrition*, recommend that all children with the hepatitis B surface antigen should be monitored for liver cancer, even after they develop the e antibody or receive interferon treatment.

The Importance of Hepatitis A Vaccines for People with Hepatitis B

Hepatitis A is spread through close, intimate contact with infected people and by food or water contaminated by the feces of infected people. Unlike the bloodborne hepatitis B virus, the hepatitis A virus is transmitted through the feces or stool of infected people.

Those most commonly infected by the hepatitis A virus (HAV) in the United States and around the world are children. Researchers now estimate that one-third of the United States population has been infected with HAV, most during childhood. According to the researchers, between 35 to 65 percent of HAV infections occur in children age 4 years or younger. Daycare centers are believed to be places where HAV is frequently transmitted.

Like all forms of viral hepatitis, HAV causes acute inflammation of the liver. If people with hepatitis B are infected with HAV, they face serious liver damage due to the "double whammy" of an additional virus infecting their already diseased livers. Anyone infected with hepatitis B needs to speak with their physician about receiving the hepatitis A vaccine.

Hepatitis B Transmission

The hepatitis B virus is transmitted by sexual contact or by ingesting the blood or body fluids of an infected person. Transmission can even occur if personal household items such as razor blades or toothbrushes that are contaminated with infected blood are shared.

Injecting drug users and men who have sex with men are at especially high risk of HBV infection, but the virus can also be easily transmitted during heterosexual activity.

The virus is not spread through food or water or by casual contact. However, it is a resilient virus. The hepatitis B virus can live for more than seven days on a dry surface. The virus may survive in dried blood for up to seven days at 25 degrees C. Hand contact with blood-contaminated surfaces such as tables, refrigerator handles and other items in the environment may transfer the virus to skin or mucous membranes.

Hepatitis B viruses appear to be more easily spread than hepatitis C viruses through semen, vaginal secretions and saliva. Saliva can contain hepatitis B viruses, but in very low concentrations, compared to blood. Injections of infected saliva can transmit the virus, so deep bites could transmit the infection, though this is extremely rare. There are no reports of people getting hepatitis B from mouth-to-mouth contact with infected CPR manikins or mouthpieces of musical instruments. However, some researchers suspect vigorous or deep kissing could cause abrasions and exposure to blood.

The highest concentration of hepatitis B viruses is in blood and in fluids that come from open sores or abrasions. There are lower concentrations of viral DNA in semen, vaginal fluid and saliva. Therefore, blood exposure and sexual contact are relatively efficient modes of transmission.

Anal sex is also an efficient way to transmit the virus—abrasions can occur and increase exposure to semen. The virus can enter the body through a break in the skin. The lining of the nose, mouth, eyeballs (mucous membranes), vagina and anus are areas where the skin is likely to get tiny breaks or small sores that cannot be seen, and the virus can sneak in through these breaks.

Unprotected sexual activity continues to be an established route for HBV transmission. Among young adults in the United States and Canada, transmission is most frequent through sexual activity, according to the findings of the National Health and Nutrition Evaluation Study (NHANES). These findings spurred calls for nationwide vaccination of pre-adolescents in the United States.

Risk of sexual transmission of HBV increases with the number of partners one has had. Several studies have demonstrated in different groups that the prevalence of HBV infection increases dramatically in those who have more than three partners over a six-month period.

Hepatitis B is 100 times more infectious than HIV, according to CDC. There is a far greater concentration of hepatitis B viruses in a given blood sample than of HIV particles.

The number of reported hepatitis B infections in healthcare workers has declined significantly over the years, from 12,000 cases in 1990 to 5,100 cases in 1995, according to the CDC's Advisory Committee on Immunization Practices. This decline occurred because of widespread adoption of preventive immunization, increased adherence to standard precautions and use of personal protective equipment by healthcare workers.

The risk of developing hepatitis B after a "needle stick" and exposure to someone's contaminated blood ranges from 2 percent if the patient is negative for the hepatitis B e antigen to 30 percent if the e antigen is present.

Risk of Hepatitis B Infection in Daycare Centers

While transmission of the virus is well-documented between children in developing countries, primarily through exposure to open sores, in developed countries transmission in daycare centers has been nearly non-existent.

Urine and feces are not vehicles of HBV transmission unless blood is present. Most licensed daycare centers require employees to wear gloves and practice standard precautions with all children.

Oral transmission of the hepatitis B viris is almost non-existent. Several studies have failed to document transmission between people exposed only to saliva from those with chronic hepatitis B when, for instance, they shared resuscitation dummies in CPR training.

According to a 1990 study by Drs. Craig Shapiro and Stephen Hadler published in *Seminars in Pediatric Infectious Diseases*, only a handful of studies on transmission in daycare centers have been conducted in the United States and abroad. They found one case in Washington D.C. of hepatitis B transmission by a 4-year-old carrier to another child. The carrier child had a history of aggressive behavior, including biting and scratching, but did not transmit disease to other children or staff at the center.

In a study in Rome, an 18-month-old child developed acute hepatitis B, and it was discovered that a 2-year-old at her daycare center was a carrier and may have been a possible source.

"Review of surveillance data of hepatitis B cases to the CDC does not show daycare center attendance to be a significant risk factor for acquiring acute hepatitis B infection," Drs. Shapiro and Hadler wrote. Unless a chronically infected child exhibits highly aggressive behavior, children with HBV infection should not be excluded from daycare centers, according to their report.

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