Hepatitis B and Delta Hepatitis

Tens of millions of persons are infected by hepatitis viruses annually, which produces a significant impact on health. Hepatitis occurs in three forms: A, B, and non-A/non-B. The Delta agent, a defective virus that requires hepatitis B virus as a helper for its replication, can aggravate hepatitis B infections, particularly when superinfection occurs.

Hepatitis B

Hepatitis B (HB) infection may lead to chronic infection and the development of long-term sequelae such as cirrhosis, chronic active hepatitis, and hepatocellular carcinoma, particularly when infection occurs early in life. There are at present an estimated 200 million persistent HB carriers worldwide. At least 250,000 cases of liver cancer occur each year, most of which are attributable to hepatitis B virus (HBV). Most HB infections occur in childhood, and it is unlikely that improvements in the environment and personal hygiene will significantly impact their transmission. HB is most effectively controlled by large-scale immunization. Several effective and safe vaccines have been developed and have been shown to provide adequate protection in both children and adults.

Hepatitis infection usually results in an acute self-limiting infection, which may be inapparent or symptomatic. The serological course of a typical uncomplicated HB infection with recovery appears in Figure 1. A proportion of infected persons, however, becomes persistent virus carriers. The development of

Figure 1. Serologic course of uncomplicated acute hepatitis B with recovery.

Abnormal biochemical tests

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the carrier state is inversely related to the age of infection, ranging from approximately 90% in newborns to 10% or less in adults. An HBV carrier is defined as one whose blood contains surface antigen (HBsAg), detected at an interval of at least six months. The occurrence of HBsAg in high titers during the acute phase of the disease, with persistence for more than six weeks, is often followed by the development of chronic hepatitis.

Likewise, presence of hepatitis B e antigen (HBeAg) in high titers (>1,000 in radioimmuno- or enzyme immunooassays) indicates the possible development of chronic disease, particularly if it persists for more than six to eight weeks after the acute phase. In most patients, however, HBeAg disappears early during convalescence, usually before HBsAg becomes undetectable. Presence of HBeAg in the serum indicates persistent, active viral replication, and most sera with a medium to high HBeAg titer also contain measurable HBV polymerase activity and complete Dane particles demonstrable by electron microscopy. Blood of such patients must be considered highly infectious. The disappearance of HBeAg and development of antibody to HBeAg (anti-HBe) are in general good prognostic markers, but do not guarantee complete clearance of HBV. Anti-HBs appears late, sometimes only several months to a year after the disappearance of HBsAg, and indicates immunity.

Antibody to HB core antigen (anti-HBc), especially of the IgM class, is almost without exception present in the early acute phase of the illness or even precedes the onset of symptoms. Anti-HBc IgM usually disappears within six months to two years, but may stay longer in persistent or chronic active hepatitis B. Anti-HBc IgG remains detectable for many years and perhaps for life.

Viral DNA polymerase activity in the serum indicates that viral replication in the liver is continuing. Sequential determinations of this enzymatic activity are the most sensitive measurement of a therapeutic effect during treatment of chronic hepatitis with interferon or other chemotherapeutics, but they do not add substantially to the diagnostic evaluation of the disease.

Most recently, highly specific techniques (more than 100 times that of conventional methods), have been developed to identify HBV-DNA in liver tissue and serum, which are of importance for molecular and pathogenetic studies.

The significance of HBV markers for the diagnosis of the status of HBV infection is presented on Table 1. It should be noted that the patient's history and data obtained by clinical examinations, clinical chemistry, and, when possible, liver biopsy may also be needed to arrive at an accurate diagnosis in some cases.

### Epidemiology

Hepatitis B is a major public health problem in practically all parts of the world. Acute HBV infection is a notifiable disease in many countries; most reporting systems, however, are inadequate to define its epidemiology on a global basis. Deficiencies in the collection of basic information and lack of appropriate laboratory support are primary constraints. In the United States of America, for instance, some 50,000-60,000 cases of hepatitis are reported to the U.S. Centers for Disease Control each year. Approximately half of these appear to be hepatitis B; however, the real incidence may be as high as 150,000 cases per annum.

Chronic infections are now classified as "healthy" carriers, with no detectable or only minimal disease, without infection, or recovered from past hepatitis B infection

### Table 1. Interpretation of the presence of combinations of serologic markers of the hepatitis B virus.

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>Anti-HBe</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
<th>Infectivity of blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Incubation period or early acute period during hepatitis B</td>
<td>high</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Acute hepatitis B or chronic carrier</td>
<td>high</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Late during hepatitis B or chronic state</td>
<td>low</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Convalescent from acute hepatitis B infection</td>
<td>none</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Recovered from past hepatitis B infection</td>
<td>none</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Immune to HBV, repeatedly exposed to HBsAg without infection, or recovered from past hepatitis B infection</td>
<td>none</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Recovered from past hepatitis B infection with undetectable Anti-HBs</td>
<td>questionable</td>
</tr>
</tbody>
</table>

aAll positive for HBsAg are acutely or chronically infected with HBV.
bAll positive for anti-HBs are immune to hepatitis B.

The titre of anti-HBc and/or the immunological class of the anti-HBe may differentiate between the convalescent phase, persistent carrier, or chronic infection.

persistent hepatitis with stable disease, and chronic active hepatitis with progressing disease. Most of the above-mentioned 200 million carriers of HBV in the world (Table 2) are concentrated in Asia and Africa. Figures from the Americas may actually be underestimated; there is clear evidence that in certain areas of the Region the carrier state is higher than 10%.

### Table 2. Estimated number of HBV carriers in the world.

<table>
<thead>
<tr>
<th>Region</th>
<th>Population (millions)</th>
<th>%</th>
<th>Number (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>441</td>
<td>6.0</td>
<td>26.5</td>
</tr>
<tr>
<td>United States of America and Canada</td>
<td>338</td>
<td>0.5</td>
<td>1.8</td>
</tr>
<tr>
<td>South America</td>
<td>234</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Asia</td>
<td>2,437</td>
<td>6.9</td>
<td>168.0</td>
</tr>
<tr>
<td>Europe</td>
<td>480</td>
<td>1.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Oceania</td>
<td>22</td>
<td>2.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Union of Soviet Socialist Republic</td>
<td>320</td>
<td>4.0</td>
<td>12.8</td>
</tr>
</tbody>
</table>


Extreme variations occur in the frequency of persistent infections caused by HBV. In most Anglo-Saxon populations the carrier rate is less than 1 per 1,000, while on the Pacific Island of Rapa, it is one in two. The age of infection is one of the most important risk factors for a person who becomes a long-term HBV carrier. In adults, from 5-10% of infections result in persistent infections, whereas in infants the rate may exceed 80%.

Persons with certain health problems, such as lymphoproliferative disorders, leprosy, Down's syndrome, and patients on immunosuppressive therapy, are more likely to become carriers. Carrier rates are usually higher among males than females. In chronic carriers, the titers of HBsAg usually decline with increasing age, and many of them eventually eliminate the virus from their body and develop anti-HBsAg, believed to be the protective antibody.

### Patterns of Infection

A marked variation in the prevalence of HBV infection is observed in different settings: in general, it is lowest in countries or areas with high standards of living and highest in countries or areas in which the socioeconomic level is lower and where there is overcrowding. Certain population groups such as homosexuals, intravenous drug users, those in institutions for the mentally retarded, patients in hemodialysis units, and certain groups of health workers exhibit high infection rates.

Striking differences may occur in infection rates and carrier rates among different ethnic groups; for example, in New Zealand the carrier rate among the Maoris (an ethnic group of Polynesian-Melanesian origin) is 9.5%, whereas among the Anglo-Saxon population it is only 0.1%. Marked variation in carrier rates may occur even within apparently homogenous populations: among the 3,500 Micronesians who live in Nauru, for instance, the carrier rate oscillates from 5-28% in the different villages of this Pacific Island.

Worldwide patterns of HB infection may be conveniently divided into three categories (Table 3). In areas of low endemicity such as North America, Western Europe, and Australia, prevalence of HBsAg in asymptomatic carriers is 0.2-0.5%. Areas like Eastern Europe, the Mediterranean region, South-West Asia, and certain parts of South America have an intermediate prevalence (2-7%). In high prevalence areas such as China, South-East Asia, and tropical Africa rates of HBsAg may be as high as 20%.

### Table 3. Hepatitis B prevalence patterns.

<table>
<thead>
<tr>
<th>Low endemicity</th>
<th>Intermediate endemicity</th>
<th>High endemicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg, 0.2-0.5%</td>
<td>HBsAg, 2.7%</td>
<td>HBsAg, 8-20%*</td>
</tr>
<tr>
<td>Anti-HBs, 4.6%</td>
<td>Anti-HBs, 20.55%</td>
<td>Anti-HBs, 70.95%</td>
</tr>
<tr>
<td>Childhood infection infrequent</td>
<td>Childhood infection frequent, neonatal infection frequent</td>
<td>Childhood infection highly frequent, neonatal infection highly frequent</td>
</tr>
<tr>
<td>Australia, Western Europe, parts of South America, USSR; possibly parts of some parts of China, South-East Asia, and tropical Africa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prevalences up to 50% have been identified in some isolated Pacific islands.


### Transmission

HBsAg is found in virtually all body secretions and excretions; however, only blood, saliva, and semen have been shown to be infectious. Transmission is often by percutaneous (intravenous, intramuscular, subcutaneous, or intradermal) inoculation of human blood, plasma, serum, thrombin, fibrinogen, and other blood products from an infected person. Immunoglobulin, heat-treated plasma, protein fractions, albumin,
and fibrinolysin are generally considered safe. Contaminated needles and syringes are important vehicles of spread, particularly among drug addicts. The infection may also be disseminated through contamination of wounds and lacerations. Exposure of mucous membranes to infective blood can also result in infection. HBV may be also transmitted by kissing or by sexual contact.

Perinatal transmission of HBV from carrier mothers to their babies appears to be the single most important factor for the high prevalence of HBV infection in some areas. When mothers are HBsAg- and HBeAg-positive, approximately 95% of their newborn children become infected, usually in the perinatal period. Transmission during pregnancy itself is rare. In parts of Asia 30-50% of HBsAg carrier women of childbearing age are HBeAg-positive, and perinatal infections account for about half the carriers in the population. Children of non-carrier mothers can be infected by contact with other children who have been infected by their carrier mothers. Consequently, perinatal transmission appears to be the driving force in maintaining high HBsAg carrier rates in eastern Asia, for example. In contrast, perinatal transmission is uncommon in Caucasian populations, and it has an intermediate frequency in mothers of West-Asian or of Afro-Caribbean origin. In Africa the infection occurs more commonly during early childhood than in the perinatal period because HBeAg in carrier mothers is less frequent than in Asia. Infection of the baby following acute or chronic infection of the mother is usually anicteric and is recognized by the appearance of HBsAg between 60 and 120 days after birth.

It has been suggested that mosquitos and other blood-sucking insects might be important vectors of the disease in tropical areas; however, there is no convincing evidence to support this suggestion.

**Prevention**

Until recently, preventive measures for HB infection consisted in screening blood donors for history of hepatitis and for serologic markers of HBV infection, hygiene measures, and passive immunization. In recent years, however, active immunization has been demonstrated effective in controlling the infection.

**Screening Blood Donors**

Blood banks should reject as donors all individuals who have a history of viral hepatitis or jaundice. High-risk groups such as drug addicts and homosexuals should not donate blood, nor should persons who received a blood transfusion within the preceding six months. The use of paid donors should be discouraged or prohibited, and any person HBsAg-positive should not be accepted as a blood donor.

In areas where such measures have been implemented, there has been a decrease of up to 85-90% in incidence of post-transfusion hepatitis. This decline parallels the use of laboratory tests with augmented sensitivity for detecting HBsAg. Less sensitive methods such as counterimmunoelectrophoresis should be replaced by more sensitive ones like reverse passive hemagglutination, radioimmuno- or enzyme-immuno-assays.

**Hygienic Measures**

Simple environmental precautions when dealing with persons known or presumed to be infectious, or their blood, and contaminated instruments are useful in preventing infection.

Such measures are of great importance for protecting medical and dental personnel and some hospitalized patients who are at increased risk of acquiring HB infection. In renal dialysis units where HB transmission can be very high, hygienic measures can ensure considerable reduction or prevention of transmission. This is accomplished by the careful use of instruments for individual patients and the testing and segregation of susceptible patients from infectious ones.

Disposable syringes and needles should be used. Reusable syringes and needles should be properly sterilized by boiling at 100°C for a minimum of five minutes, or preferably by autoclave at 120°C for 30 minutes. Instruments used for ear piercing or scarification should simply be heated over a flame to eliminate the unnecessary risk of transmission.

**Passive Immunization**

Although use of normal pooled immunoglobulin (IG) has given inconsistent results in preventing hepatitis B, special HB immunoglobulin (HBIG) rich in anti-HBs has been shown to be effective in pre-exposure and postexposure prophylaxis. Long-term use of HBIG is not practical because of its limited availability, high cost, and the potential risk of complications when frequently administered.

Until recently postexposure prophylaxis consisted in the administration of HBIG to protect babies born to carrier mothers and health personnel accidentally exposed to infectious materials during the course of work. Ideally, HBIG should be administered im-
Table 4. Hepatitis B virus postexposure recommendations.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>HBIG</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommended dose and timing</td>
<td>Dose and recommended timing</td>
</tr>
<tr>
<td>Perinatal</td>
<td>0.5 ml IM, within 12 hours of birth</td>
<td>0.5 ml (10 μg) IM, within 7 days; repeat at 1 and 6 months</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>0.06 ml/kg IM or 5 ml for adults, single dose within 24 hours</td>
<td>1.0 ml (20 μg) IM, within 7 days; repeat at 1 and 6 months</td>
</tr>
<tr>
<td>Sexual</td>
<td>0.06 ml/kg IM or 5 ml for adults, within 14 days of sexual contact</td>
<td>See footnote d</td>
</tr>
</tbody>
</table>

*The first dose can be given the same time as the HBIG dose but at a separate site.

*For persons under 10 years of age, use 0.5 ml (10 μg).

*For those who choose to receive HB vaccine.

*Vaccine is recommended for homosexually active males and for regular sexual contacts of chronic HBV carriers.


Immediately after exposure, and preferably no later than 48 hours. If feasible, a rapid test for anti-HBs should precede the decision to give HBIG. For accidental needle stick, a dose of 0.05 ml/kg of HBIG should be given intramuscularly, and repeated after one month. Infants born to HBsAg carrier mothers should receive 0.5 ml, and the same dose should be repeated one or more times 3-6 months later; the efficacy of this procedure for preventing chronic infections oscillates between 70-80%.

Concurrent administration of HBIG and vaccine has been recently recommended in the United States for postexposure prophylaxis of HBV infection (Table 4). Such procedure has a greater efficacy over the use of HBIG alone in preventing infection due to perinatal exposure of HBV.

**Active Immunization**

The most effective means of controlling hepatitis B is likely to be by wide-scale active immunization. Several purified subunit vaccines have been developed from HBsAg existing in the blood of chronic HBsAg carriers. Various controlled trials have shown that HB vaccines are safe and induce antibodies to HBsAg in about 95% of healthy recipients.

Immunogenicity studies have demonstrated that more than 90% of newborns develop HBsAg antibodies by six months of age in response to two doses of vaccines. These findings are unusual since the response of newborn infants to other vaccines is generally poorer than that of older infants and children. The immunization is effective even in the presence of passively acquired antibodies.

Studies have been completed or are now in progress in several countries to evaluate the efficacy of HB vaccine alone or in combination with HBIG for the prevention of perinatally transmitted HBV infections. In Japan, a protection rate against the carrier state of 90-99% was demonstrated after follow-up examinations for at least 12 months. The infants were given an intravenous or intramuscular injection of HBIG at birth followed by repeated intramuscular injections of HBIG and active immunization with vaccine on three occasions. Trials in Taiwan in which HBIG was given immediately after birth to infants of HBeAg-positive mothers, followed by three different schedules of vaccination, demonstrated that all three schedules were efficacious; the combined efficacy was 94% compared with that of HBIG alone (71%) or vaccination alone (75%). Recent trials in China, utilizing vaccine developed by the U.S. National Institutes of Health, showed that immunization of infants born to HBsAg- and HBeAg-positive mothers was 91% efficacious in preventing chronic infection.

While the response to hepatitis B vaccines has been highly satisfactory in healthy persons, this has not been the case with dialysis patients because of their immunodeficiency. In a recently reported study, however, one vaccine induced anti-HBs in 88% of hemodialysis patients; the protective efficacy rate of the vaccine was 78% against all HBV infections in the entire study and 94% against HBsAg-positive hepatitis more than three months after the initial dose of the
vaccine. More studies are needed to evaluate properly the protection conferred by hepatitis B vaccines in these patients.

Large-scale studies should be conducted to measure the effectiveness of immunization in preventing hepatocellular carcinoma before mass vaccination campaigns are carried out. Such studies ought to be undertaken in different areas of the world, because the long-term efficacy of immunization may vary with factors affecting HBV transmission. Each trial would probably involve tens of thousands of individuals and would be useful in assessing the logistic problems associated with establishing and evaluating worldwide mass immunization campaigns.

**Vaccination Strategies**

Strategies for vaccine use must take into consideration different HB prevalence patterns (Table 3). In areas of low prevalence, selected vaccination of groups of individuals known to be at high risk of acquiring the infection appears to be the best strategy. In intermediate and high prevalence areas, large-scale administration of the vaccine could be considered, depending on the availability of vaccine (Table 5). It is unlikely that effective control of HB can be achieved unless entire populations are immunized prior to exposure (i.e., during infancy and early childhood).

Likely candidates for vaccination in areas of low endemicity include health care workers, hospital staff, clients and personnel of institutions for the mentally retarded, hemodialysis patients, recipients of certain blood products, household and sexual contacts of HBV carriers, homosexually active males, users of illicit injectable drugs, and inmates of long-term correctional facilities.

Exposure rates differ among the various units of a hospital. Clearly, staff in liver or renal units handling HBsAg-positive patients and certain others working in a related capacity such as pathologists, dentists, and surgeons are prime candidates for vaccination. Similarly, vaccination is strongly recommended to staff members who run the risk of potential high exposure to infectious HBsAg carriers, including those in genitourinary medicine (particularly in clinics dealing with large numbers of homosexual patients), those running drug addiction clinics, and those treating hemophiliacs or working in institutions for the mentally handicapped. These individuals should be immunized prior to entering high-risk environments.

A cost-benefit evaluation of HB vaccination in a given population should include the estimated attack rate, which determines the net cost of each prevented case; it has been suggested that net cost benefits emerge when the attack rate exceeds 5% or 6% per annum.

Decisions regarding pre-immunization screening will differ from country to country, depending upon the expected immune status of given population groups and the costs and availability of both the reagents and vaccine. In general, screening followed by vaccination of non-immune persons in populations with a high prevalence of HBV markers leads to a significant reduction in medical care costs.

**Hepatitis B Vaccines**

Failure to propagate HBV in the laboratory in vitro has made it impossible to date to prepare a vaccine from virus grown in cell cultures. The demonstration that heat inactivated HBsAg-positive human plasma confers partial protection to inoculated subjects against the disease provided a great stimulus for developing vaccines using HBsAg purified from plasma obtained from antigenaemic asymptomatic carriers.

Several human plasma-derived, inactivated, subunit HB vaccines have now been prepared. The fact that the starting material is human plasma obtained from persons infected with HB requires that extreme caution be exercised to ensure their freedom from all harmful contaminating material, including host components. Different approaches have been used for purifying HBsAg from human plasma and for inactivation. WHO has formulated the requirements for hepatitis vaccine prepared from human plasma\(^1\), and a proposal reformulating these requirements was recently pre-

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pared. Procedures for detecting extraneous viruses include testing in adult and suckling mice, in embryonated eggs, and in cell cultures. Testing for residual HBV infectivity in susceptible chimpanzees should also be included.

**Vaccines for the Future**

Although plasma-derived inactivated subunit HB vaccines have been shown to be safe and effective for preventing infection both in normal children and adults, there are important concerns regarding their costs and availability for mass vaccination programs. Such constraints are associated with several problems. For example, although there are large numbers of persistent HBsAg carriers in the world, it is currently impossible to collect and process sufficient quantities of plasma to conduct mass immunization campaigns. In addition, the production and standardization of vaccines is so expensive that the countries which need them most may not be able to afford them; moreover, availability may be limited by the current requirements for safety testing. Sources of sufficient donor plasma for producing large quantities of vaccine are disproportionately located in countries that have the least capability for efficient vaccine production for their own use. Large-scale shipping of such plasma from developing countries with intermediate-to-high HB prevalence to developed countries for vaccine processing and production may create sociopolitical problems, while the hazards associated with local vaccine manufacture under conditions of inadequate technology and poor control are of equal concern.

In view of the foregoing considerations, attention must be given to preparing vaccines from alternative sources in order to improve safety and reduce costs. Fortunately, work on developing new hepatitis vaccines is in progress at several laboratories. Three approaches are being pursued:

- **Vaccines prepared by recombinant DNA technology.** Vaccine production by molecular cloning is under way. Production of hepatitis surface antigen in different prokaryotic and eukaryotic cells has been reported by several groups. Expression of HBsAg has been obtained in yeast cells, and antigenic material from this source has been recently shown to be safe and immunogenic for man. These developments are potentially important for large-scale in vitro production of vaccines produced by recombinant DNA technology. Scientists were able recently to incorporate the HBV gene that directs production of surface antigen to vaccinia virus DNA. When the hybrid virus was injected into rabbits, it produced a local reaction to vaccinia virus and stimulated significant amounts of antibody to hepatitis antigen. In humans, equivalent levels of antibodies would provide protection against hepatitis B virus.

- **Synthetic hepatitis peptide vaccines.** Synthetic peptides, with the amino acid sequences of HBsAg are being tested for immunogenicity in several laboratories. Synthetic peptides may possibly be employed as vaccines in the future, although mixtures of more than one of the peptides may be required. Many questions remain unanswered; the critical ones are: will antibodies induced by synthetic immunogens be protective and will that protective immunity persist? Studies using such synthetic vaccines in susceptible chimpanzees are under way.

- **Vaccines prepared from antigen "producer" cell lines.** Secretion of HBsAg by heteroploid cells derived from primary hepatocellular carcinoma has been reported. The surface antigen obtained in this way is noninfectious and of relatively simple biochemical composition. Techniques to ensure freedom from contaminating nucleic acid and potent inactivating agents are available. Since the cell lines are transformed and show hetero-transplantability, developments in this area must proceed with caution.

**Delta Hepatitis**

The delta agent, discovered in 1977, is a defective virus that requires HBV as a helper for successful replication. Two models of infection have been identified: acute coinfection with HBV, and superinfection of an HBV carrier. Acute coinfection with HBV, observed experimentally in chimpanzees and directly in humans, appears to cause acute hepatitis which resolves and seldom leads to chronic disease. Superinfection may cause no disease, acute hepatitis which resolves, or chronic hepatitis; however, the latter may be the most common outcome and may have the most severe consequences. It has been estimated that 50-75% of delta superinfections may result in chronic hepatitis.

The delta agent is unique among virus-like agents: it consists of a particle 35-37 nm in diameter that resembles a large HBsAg particle and possesses the HBsAg coat of HBV. It also contains specific antigen and a very small RNA molecule, which presumably is the genome of the agent. Delta antigen can be detected in the nuclei of infected hepatocytes and in the serum during the late incubation period and early acute phase of infection. When infection with the delta agent
occurs, synthesis of HBV components is usually suppressed: serum HBsAg and HBeAg levels and DNA polymerase may fall to low or undetectable levels and intrahepatic markers of HBV synthesis, especially HBCAg, may become undetectable.

On the basis of limited serologic surveys, the delta agent seems to have a worldwide distribution but to be epidemiologically important primarily in southern Italy, where it appears to be highly endemic. A severe epidemic of hepatitis due to superinfection of hepatitis B chronic carriers by delta agent has recently been observed in Venezuela, with an acute case fatality rate of 20% and with 60% progression to chronic illness in survivors. Preliminary observations suggest that delta agent may also be associated with fulminating hepatitis in certain areas of the western Amazon region of Brazil and in northern Colombia. The introduction of this agent into unaffected areas of the world where the frequency of HBV carriage is high could have devastating consequences.

Delta agent is transmitted by contaminated blood and blood products. It is probable that nonpercutaneous modes of transmission also exist and that the agent can be spread by sexual contact. At least one instance of perinatal transmission of the delta agent from mother to infant has been reported.

Since delta infection has only been observed in people who are acutely or chronically infected with HBV, the increasingly widespread use of hepatitis B vaccine is likely to constitute an effective mechanism for preventing delta hepatitis.

The WHO Viral Hepatitis Control Program

For almost 30 years WHO has been actively involved in the field of viral hepatitis. Specially convened groups of experts have regularly reviewed advances in the field with particular emphasis on diagnosis and control, and have prepared pertinent publications. In addition, WHO has promoted training in laboratory techniques for the diagnosis of diseases, supported field research, and established a network of Collaborating and National Reference Centers.

In recent years safe and effective hepatitis B vaccines have been developed, and hepatitis A vaccines are currently under study. Moreover, modern technological approaches are being applied to develop new hepatitis B vaccines, which eventually may be produced large-scale at a lower cost.

In view of the magnitude of the problem and the present and upcoming technological advances toward the control of viral hepatitis, WHO is launching a Viral Hepatitis Program. In July 1983 an Advisory Group on the development of such a program met in Geneva and proposed the following overall objectives:

1) Define the natural history of viral hepatitis in all regions of the world, and in particular determine ways in which the agents are spread and the mechanisms by which they produce disease.

2) Assist in the development and evaluation of safe, effective, and inexpensive means of preventing the disease and treating its long-term sequelae, including hepatocellular carcinoma.

3) Promote and assist in the application of these methods in countries in which viral hepatitis is a public health problem.

In addition, the Group defined targets and activities. Two main targets were envisaged: strengthen diagnostic capabilities, such as epidemiological surveillance, define population groups at special risk of infection, etc.; and reinforce general sanitation and environmental procedures, immunization, treatment, and other control efforts. Six main activities were identified: surveillance and epidemiological studies; information synthesis, exchange, and dissemination; training; reagents production; development of field trials for immunization; and standardization of immunoglobulins and vaccines.

Over the years, PAHO has assisted countries of the Region in promoting some of these activities. However, now is the time to formulate and implement more vigorously such activities. As a first step to accomplishing this, PAHO plans to convene a meeting of experts to discuss the Program and draft sound recommendations and approaches for its implementation.

(Source: Epidemiology Program, Health Programs Development, PAHO.)