The complex clinical and biological manifestations of hepatitis B warrant particular attention. This article discusses the parameters that enable physicians to recognize and assess the disease, as well as counsel, guide and follow-up with patients who are at risk of becoming chronic carriers of viral hepatitis.

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The aim of this article is to review the measures currently available to prevent chronic hepatitis B and its complications. The authors will discuss the epidemiology, clinical signs and symptoms, and virological aspect of this infection, as well as the often unforeseeable consequences of it which can endanger the patient’s life and threaten survival.

Viral hepatitis is defined as a primary disease of the liver, caused by hepatotropic viruses designated by letter names. Other viral agents cause corollary

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hepatic complications, notably the Epstein-Barr virus (the causative agent in infectious mononucleosis), Cytomegalovirus, Coxsackievirus, enteric cytopathogenic human orphan (ECHO) virus, and Flavivirus (leading to yellow fever).

The traditional terminology of viral hepatitis recognizes infections caused by the hepatitis A virus (HAV) and the hepatitis B virus (HBV). Other similar forms of infection caused by unidentified agents were formerly termed non-A, non-B (NANB) hepatitis. These forms of hepatitis, which, in industrialized nations, are essentially linked to post-transfusion or parenteral infections, are now identified as hepatitis C, D and G. Hepatitis E and F are transmitted enterically. The five most common hepatotropic viruses, which have an indisputable impact on public health, are hepatitis A, B, C, D and E. The others are referred to as non A-non E hepatitis. The complex clinical and biological manifestations of hepatitis B warrant particular attention. In light of current knowledge, the authors will attempt to:

• Highlight the parameters that enable the clinician to recognize and assess the disease;
• Counsel, guide and follow-up with patients who are at risk of becoming chronic carriers of viral hepatitis; and
• Prevent potentially serious complications (cirrhosis, hepatoma/carcinoma).

Hepatitis B

The Virus. Hepatitis B (formerly known as serum hepatitis, post-transfusion hepatitis or homologous serum jaundice) is caused by a Hepadnavirus, which belongs to the Hepadnaviridae family. The nucleotide of the virus contains deoxyribonucleic acid (DNA). The hepadnavirus is classified as type 1, and seems to have a replication mechanism that is also typical of retroviruses. It is an enveloped virus that manifests itself by three types of morphologically distinct particles in the serum of infected persons, according to observations under an electronic microscope (Tables 1 and 2).

Epidemiology

Incidence and Prevalence. Viral hepatitis is a major public-health threat. Since HBV was identi-
Preventing Chronic Viral Hepatitis

The Epidemiology of Hepatitis B
Since 1983, the proportion of reported cases (7.7 persons per 100,000) has never dropped below the rate published in 1981 (4.3 persons out of every 100,000) in Canada. Following approval of the first hepatitis B vaccine in 1981, the incidence of HBV infection nevertheless rose by 37% between 1979 and 1990. In certain industrialized nations, only 0.5% of the population are carriers of HBV. However, the prevalence of hepatitis B is at least 10 to 20 times higher for Africa and Asia combined.

Symptoms
In cases of acute infection, most patients present with subclinical hepatitis, which is asymptomatic and without icterus. Symptomatic patients present with various clinical signs, ranging from anticteric hepatitis to fulminant hepatitis, sometimes even resulting in death. In chronic HBV infection, patients most often show signs of fatigue, which may progress towards asthenia, and, in some instances, abdominal pain and icterus.

Preventing Hepatitis B and Potential Complications
Since 1981, there has been a safe, 95%-effective hepatitis B vaccine. Complete primary vaccination usually provides long-term immunization. Since 1984, free vaccines have been systematically administered to fourth-grade students in Quebec. Members of other high-risk groups are also entitled to free vaccination.

Quick Facts

fied in 1965, a certain amount of progress has been made in reducing the frequency of hepatitis B infection in Canada. Nonetheless, since 1983, the proportion of reported cases (7.7 persons per 100,000) has never dropped below the rate published in 1981 (4.3 persons out of every 100,000) in Canada. Following approval of the first hepatitis B vaccine in 1981, the incidence of HBV infection nevertheless rose by 37% between 1979 and 1990. In certain industrialized nations, only 0.5% of the population are carriers of HBV. However, the prevalence of hepatitis B is at least 10 to 20 times higher for Africa and Asia combined.

In certain industrialized nations, only 0.5% of the population are carriers of HBV. The prevalence of hepatitis B, however, is at least 10 to 20 times higher for Africa and Asia combined. It is estimated that more than 2 billion people are infected with HBV worldwide. Of that number, nearly 400 million individuals (75% of whom are in Asia) are chronic carriers of the disease—a prevalence of 5% of chronic HBV carriers in the global population. Regions with a high prevalence of HBV are the Far East and Africa, as well as parts of South America, the Caribbean and the Arctic. The regions with the highest proportion of chronic HBV carriers are Southeast Asia and sub-Saharan Africa. In these areas, the rates of HBV infection vary between 10% and 25%. On a worldwide scale, between 1 million and 1.5 million persons die from HBV infection, which makes the virus one of the 10 leading causes of mortality and morbidity in the world. Liver cancer linked to HBV infection results in 1,500 to 3,000 deaths per day, and HBV-linked cirrhosis results in 3,000 to 5,000 deaths per day.
**Table 1**

Morphology of HBV and serological considerations

**Hepatitis B surface antigen (HBsAg)**
Most virus particles measure 22 nm (20 +/- 5 nm) in diameter and are spherical or threadlike in shape. From an antigenic perspective, they are identical to the outer surface (coat) of the hepatitis B virus (HBV). A glycosylated lipoprotein is found there: the hepatitis B surface antigen (HBsAg), also known as the Australia antigen, discovered by chance in the blood of an Australian aborigine in 1965.1

**The Dane particle and the hepatitis B core antigen**
More complex structures, whose common feature is surface antigens transported by 20 nm particles, are occasionally found in the serum of HBsAg carriers. They are large spherical particles, 42 nm (between 40 nm and 50 nm) in diameter, consisting of a capsid and a core. They are the intact hepatitis B virion—what would seem to be the complete virus, known as the Dane particle. The capsid is the external coat that surrounds the core (the core is an internal icosahedric nucleocapsid that measures between 27 nm and 28 nm in diameter). The core contains a round DNA genome, predominantly double-stranded, with a molecular weight of 1.6 to 2.1 x 106 daltons, activated by a DNA polymerase. Single-stranded DNA is found in a region of the genome that varies in length. The virion’s DNA polymerase is, nevertheless, capable of repairing and completing the single DNA strand and transforming the single-stranded region into a double-stranded one along the entire length of the 3,200 nucleotides (3,200 base pairs). The core of the Dane particle contains the hepatitis B core antigen (HBcAg) on the surface. The antigen, which is present in the core of the hepatocytes, is not found in the serum of carriers. However, the HBcAg antibody (anti-HBc) is present in the serum of infected persons during the acute phase of the infection and for some time afterwards.

**Subdeterminants of the hepatitis B surface antigen**
On the surface of the spherical HBsAg particles is a complex antigen structure marked by various HBsAg subdeterminants. Among them, there is a reactive heterogenetic group-a antigen, which is shared by all types of HBsAg found integrally in the serum of HVB carriers. Moreover, on certain particles, there are two specific determinants of a subtype called either d or y, or w or r. The determinants d and y (d/y) are mutually exclusive as are w and r (w/r). They characterize four combinations of specific virus subtypes (HBsAg, a, d/w; HBsAg a, d/r; HBsAg a, y/w; and HBsAg a, y/r), which can serve as epidemiological markers, but have no clinical or prognostic significance.

**The hepatitis B e-antigen**
The hepatitis B e-antigen (HBeAg), a third antigen associated with HBV, is an internal component of the nucleocapsid. It is a nonparticulate solid protein, totally distinct from HBsAg and HBcAg, which could be the result of HBV degradation. HBeAg is found exclusively in the serum of HBsAg carriers. It constitutes an increased contagion and virulence factor, which correlates with the infectious stage, marked by the presence of intact virus particles.

Table 2

The Pathogenesis and Kinetic Serological Evolution of HBV Infection

Serological detection of the hepatitis B surface antigen

After a 30- to 180-day incubation period (60 to 90 days, on average), the primary infection appears as viremia, which may either last temporarily for four to eight weeks or become chronic. During the transitional period, the first virological marker that can be detected serologically (HBsAg) appears. It comes before the appearance of clinical and biological signs, and is detectable during the entire acute, or symptomatic phase. While antigenemia generally disappears one to two months after the icteric phase, it can last up to 24 weeks following the initial infection.

HBsAg is found in almost all bodily fluids of infected subjects. Serum, semen and saliva are considered the most common sources of infection through both mucocutaneous and non-percutaneous contact. HBV and HCV are transmitted primarily through contaminated blood and body fluids. The most common mode of transmission is direct percutaneous exposure to infected blood.1 HBV and HCV penetrate tissues more easily through the parenteral route, thus shortening the incubation period. A dense inoculum also shortens the HBV incubation period. Conversely, the incubation period becomes longer in the presence of concomitant HCV infection.2 Among the non-percutaneous means of HBV transmission, intimate contact (especially sexual) and perinatal transmission predominate (Table 3). Iatrogenic immunosuppression concomitant with liver or kidney transplants and hemodialysis may constitute an additional risk factor.3

HBsAg and HBcAg

When HBsAg disappears, HBsAg antibodies (anti-HBs) appear in the serum of persons exposed previously and remain detectable indefinitely and virtually. Anti-HBs may neutralize HBV and are thus protective antibodies that prevent infection. HBcAg antibodies (anti-HBc) are detected in serum in the initial weeks after HBsAg first becomes apparent and precede the appearance of anti-HBs by several weeks or even months. Anti-HBc immunoglobulin M (IgM) appears approximately two weeks after HBsAg, followed by immunoglobulin G (IgG) anti-HBc, which appear once HBsAg disappear. In certain cases, there is a “window period” between the disappearance of HBsAg and the detection of anti-HBs. During this period, anti-HBc is the only serological indicator of recent HBV infection. Under certain circumstances, anti-HBc may persist after the disappearance of anti-HBs, even several years after initial HBV infection. In such cases, determining the category of anti-HBc immunoglobulin (i.e., IgM versus IgG) provides a means of differentiating a recent infection from an earlier one. The repeated presence of IgG anti-HBc in the absence of HBsAg and anti-HBs may indicate the presence of chronic hepatitis B in persons with a low HBsAg level.

Hepatitis B e-antigen and its antibody

Hepatitis B e-antigen (HBeAg) appears virtually at the same time as HBsAg. It disappears much earlier than HBsAg, however, giving way to the HBeAg antibody (anti-HBe). The presence of anti-HBe in the absence of HBeAg in a patient with chronic HBV infection results in diminished contagiousness and fewer consequences.

Transmission

In North America, the infection is more prevalent among men who engage in homosexual relations and among injection drug users (IDUs) (Table 3). Moreover, it is spreading among persons with sexually transmitted diseases (STDs). In the US, perinatal transmission accounts for 20% to 30% of the cases of chronic HBV infection. In Western nations, HBV is most often transmitted through sexual contact, however, in high-prevalence areas, vertical (i.e., mother-to-child) transmission and horizontal transmission (i.e., among young children) are most frequent. Newborns who contract the infection from mothers who are active carriers (hepatitis B e-antigen positive [HBeAg-positive]) when they give birth will become chronic asymptomatic carriers in 90% of cases. Of those, 25% will die as a result of HBV infection. Since 1971, direct transmission through the parenteral route has diminished significantly thanks to the systematic screening of blood donors for HBV. Parenteral transmission is frequent among drug users, however. The long-term risk of HBV transmission through blood transfusions, estimated at 1:300,000, could be reduced through polymerase chain reaction (PCR) testing.

Nonrepresentative data on the prevalence of the antibody against hepatitis B surface antigen (anti-HBs) in the U.S. indicate an infection rate of between 10% and 18% for surgeons, as compared with a rate of between 13% and 49% for anesthesiologists.

In the U.S., between 140,000 and 320,000 HBV infections—half of which are asymptomatic—are reported each year. Between 5% and 10% of infected individuals generally become chronic carriers of the virus. In adults alone, this figure is between 2% and 5%. The prevalence of chronic HBV infection in the U.S. is, in fact, approximately 5.5%. The disease affects 1.25 million people and is responsible for 17,000 hospitalizations and 5,500 deaths each year. So-called carriers have a high risk of contracting a chronic hepatic disease. HBV is the virus that causes the highest incidence of chronic viral hepatitis in Montreal (and perhaps even in Quebec as a whole). The risk of chronic infection seems higher for HBV than for HCV in both Canada and the U.S. It is interesting to note that in Europe, the risk of chronic HBV infection is 10 to 14 times greater than that of chronic HCV infection.

Chronic Carriers

It is estimated that more than 100,000 Canadians are chronic HBV carriers. Between 20% and 25% of chronic carriers suffer from cirrhosis, since active viral replication damages the hepatocytes, as HB-eAg testing reveals. A high percentage of these cirrhotic patients also present with hepato-

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**Table 3**

**High-risk Situations for HBV Infection**

- Intravenous drug use with sharing of needles.
- Originating in a region where HBV is highly endemic (i.e., certain parts of Asia, Africa, Southern and Eastern Europe, and the Pacific Islands).
- Sexual promiscuity with unprotected sexual contact, whether homosexual or heterosexual.
- Sexual relations with partners in high-risk groups.
- Visit to or employment in an institution (e.g., an orphanage or institution for the mentally handicapped) in which the residents have not been vaccinated.
- Transfusion of blood products or hemodialysis prior to 1970.
cellular carcinoma. Therefore, in Africa and Asia, patients with hepatitis B are at a 40 to 100 times greater risk of developing hepatocellular carcinoma than the noninfected population. It is interesting to note that this form of neoplasia is currently on the rise in Sweden.11

In the US, where the incidence of hepatocellular carcinoma remained fairly stable (2.1 to 2.5 persons per 100,000) from 1970 to 1986, there seems to have been a rise in the death rate as a result of primary liver cancer.3,12 Hepatocellular carcinoma is currently thought to be the second-most common form of cancer worldwide, next to skin cancer.2

In 1987, a system for assessing diseases according to importance was established in the context of nation-wide monitoring throughout Canada. At that time, hepatitis B ranked fourth among notable diseases.13 In 1997, Quebec had the second-largest number of declared cases of hepatitis B, ranking after Ontario and before British Columbia.

Prevalence of Carriers

In Canada, hepatitis B especially affects young adults (between the ages of 15 and 29)—primarily sexually promiscuous, intravenous drug users. Among the Canadian population, there were 1,591 cases reported in 1997 (5.3 per 100,000).13 In the same year in Quebec, the incidence reached 6.1 per 100,000 (690 ± 82 cases), with a preponderance of individuals aged between 25 and 29 years of age (13.1 for every 100,000) and male predominance (17.5 males per 100,000, as opposed to 8.1 females per 100,000). Each year, hepatitis B affects between 5,000 and 6,000 Quebecers, a population comprised predominantly of young adults. While the prevalence of carriers of the infection (i.e., HBsAg-positive individuals) in Quebec is unknown, it is considered low. For Canada as a whole, it is estimated to be at between 0.3% and 0.9%, and at 10% for IDUs, 6% for male homosexuals, and 10% to 15% among immigrants from endemic regions.14

The prevalence varies according to ethnic group and tends to be moderate or high for certain population segments, such as Canada’s native population (Inuit and other native peoples). For the native population, the HBV-positive rate is estimated at between 2% and 12%—a concentration of cases that is 10 times higher than that found among Caucasians in Southern Canada. In comparison with the human immunodeficiency virus (HIV) and HCV, HBV is the virus most frequently transmitted by accidental puncture among health-care professionals (Table 4). Within this group, viral infection among non-immunized individuals ranges from 6%
to 30% (with an average of 20%), depending on whether the source of infection is HBeAg-negative (2% to 6%) or HBeAg-positive (30% to 40%).

**Clinical Signs**

Hepatitis B remains the most common form of hepatitis. It accounts for 40% to 45% of acute viral hepatitis cases. The clinical signs of hepatitis B are quite variable. The disease is most often acute, insidious and asymptomatic in 90% of patients. In Quebec, 5% to 6% of the population will contract HBV in their lifetime. However, more than 90% of infected persons develop protective antibodies and fight off the infection within two to 12 months. In 1% of HBV cases, acute liver failure occurs, which can be accompanied by coagulopathy, encephalopathy and cerebral edema. The prognosis for elderly patients is poor.

Symptoms

In cases of acute infection, most patients present with subclinical hepatitis, which is asymptomatic and without icterus. Symptomatic patients present with various clinical signs, ranging from anticteric hepatitis to fulminant hepatitis, sometimes even resulting in mortality (in 1% of cases). Icteric hepatitis occurs in 25% to 35% of symptomatic cases.

Symptoms range from mild and transient to debilitating and prolonged. In icteric patients, the mortality rate is below 1% to 2%. In less severe forms of the disease, the patient may gradually recover fully, or enter the chronic phase. The prodromic (or pre-icteric) phase of hepatitis B is longer and more insidious than that of hepatitis A. It lasts from one to two weeks in 80% of cases. At this stage, fever is uncommon and temperature remains below 39.5°C. The patient’s general condition is affected, with headaches, asthenia, myalgia, loss of appetite as a result of a diminished sense of taste and smell, anorexia, nausea, vomiting, weight loss (1 kg to 5 kg), tenderness in the right upper quadrant and hepatomegaly.

The icteric phase of acute hepatitis B is manifested by yellow-brown pigmentation of urine prior to the appearance of clinical signs of icterus. This phase, which lasts approximately one month, is accompanied by improvement in the signs and symptoms of hepatitis. In 10% to 20% of cases, extrahepatic signs are present, likely as a result of immune-complex lesions that are viral in origin, simulating the signs and symptoms of a serum disease with transient arthropathy, leukocytoclastic angiitis, polyarteritis nodosa, membranous glomerulonephritis, or Guillain-Barré syndrome.

Chronic hepatitis is defined as a relatively serious disease that affects the liver tissue, has evolved for at least six months and becomes apparent by an increase in liver enzymes—especially alanine aminotransferase (ALT)—and an abnormal liver biopsy. The diagnosis is confirmed by at least a doubling of normal ALT values. In the case of chronic active hepatitis, there is also an increase in gammaglobulin.

In chronic HBV infection, patients most often show signs of fatigue, which may progress towards asthenia and, in some instances, abdominal pain.
and icterus. In advanced forms of the disease, the clinical and biological signs vary according to the severity of visceral disease.

**Hepatitis B and HIV**

Cirrhosis progresses more rapidly in advanced cases of HIV-positive patients, particularly those with AIDS, than in HIV-negative patients, probably due to a mechanism of mutual facilitation between HBV and HIV. Moreover, HCV can suppress the expression and replication of HBV.

### Prevention of Hepatitis B and Potential Complications

Since 1981, there has been a safe, 95%-effective hepatitis B vaccine. Complete primary vaccination usually provides long-term immunization.

Since 1984, free vaccines have been systematically administered to fourth-grade students in Quebec. Members of other high-risk groups are also entitled to free vaccination (Table 5).

The Direction de la santé publique de Montréal-Centre (the public health office for Montreal-Centre), which distributes the Quebec
Immunization Protocol (Ministère de la Santé et des Services sociaux [MSSS], Gouvernement du Québec, November 1999) and subsequent updates, is preparing to incorporate other groups into its free vaccination program, including patients undergoing hemodialysis or peritoneal dialysis, cirrhotic patients and hemophiliacs. Cirrhotic patients, as well as hemophiliacs who are given coagulation factors derived from plasma, should be immunized with the combined hepatitis A and B vaccine. A free vaccination program instituted by the MSSS in the fall of 1999 targets all adolescents 18 years of age or under, both within the school context (in the last year of secondary school) and outside of the academic environment.

Vaccination against hepatitis A and B is also recommended for the following groups:

- Individuals travelling to certain regions of Africa, Asia and the Americas, where hepatitis A and B are endemic;
- Populations and communities in which hepatitis A and B are endemic;
- Individuals who have already been vaccinated against hepatitis A and B and require booster doses; and
- Individuals suffering from a chronic liver disease with significant clinical signs, including chronic hepatitis C.17

Chronic HCV carriers, especially those with chronic hepatopathy, are more likely to experience serious complications if they contract HAV or HBV, as well.
cinating newborns. Before this measure is implemented, however, and until the government program targeting pre-adolescents is completed, anti-HBV hyperimmune globulin should be used in conjunction with vaccines on all newborns of carrier mothers and on all other persons at risk.

**Risk Groups**

Certain individuals should be contacted and encouraged to be vaccinated, especially those who belong to non-immunized risk groups (Table 4). Another category of persons at risk are adults between the ages of 35 and 40 who are without protective antibodies, either because they have not had access to vaccination or because they have not developed post-exposure immunity. In such cases, it is important to ensure that the target patients are not already HBV carriers. Vaccination is also recommended for patients who have undergone multiple transfusions, as well as those awaiting an organ transplant who have not been immunized. Two other groups, long-term prisoners and individuals who have their bodies tattooed or pierced, are also at risk are contracting HVB infection.

**Immunization and Prevention Programs**

Hospital staff and patients at risk (especially those undergoing hemodialysis) must be encouraged to receive immunization. Anyone accidentally exposed to hepatitis in a hospital setting also should be encouraged to participate in an HBV-prevention program.18 Quebec-based health-care personnel who suffer a workplace accident are covered by the Commission de la Santé et de la Sécurité du Travail du Québec (CSST) programs. Prevention measures also apply to persons in other work environments, such as dentists’ offices, as well as to intravenous drug users in shooting galleries and anyone who has engaged in unsafe sexual practices. It should be noted that the HBV vaccine also provides protection against hepatitis delta virus (HDV).

**Preventing Carcinogenesis**

For the prevention of hepatic carcinogenesis, two new strategies—aside from universal vaccination to reduce the number of HBV carriers—are currently...
being promoted: the eradication of HCV with interferon-alpha in the case of chronic active hepatitis, and the use of acyclic retinoids in patients who have undergone a partial hepatectomy to treat a primary hepatoma in selected cases. The rationale behind the eradication of HCV is based on the fact that occult HBV infection often occurs in patients suffering from chronic hepatitis C.

Conclusion
There are currently various therapeutic combinations for minimizing the danger and consequences of chronic HBV infection. Yet prevention is invaluable and is an indispensable tool in controlling hepatitis B. Alongside preventative measures, pre- or post-exposure counselling that explains the nature of the disease and emphasizes prevalence and the means of transmission can contribute to successful HBV prevention. Educating the public, raising awareness of the risks and providing information will continue to be key factors in preventing hepatitis. N Engl J Med 2000; 342(10):744.

References