

# Infection and Chronic Disease

## *The Divide Blurs as Mounting Evidence Shows Links*

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As technological advances have expanded our understanding of disease causation, the divide between infectious diseases and chronic, apparently noninfectious conditions has begun to dissolve. An infectious component is suspected, or in some cases proven, in some well-established chronic diseases (Table 1). Liver cancer is strongly associated with chronic infection with hepatitis virus B or C. Most stomach ulcer cases can be linked to infection with *Helicobacter pylori*. Now it appears that coronary artery disease has an association with *Chlamydia pneumoniae*. These findings have drawn wide attention from the press, as witnessed by a recent article in *Forbes* magazine, a general business publication. These three diseases share common features: long incubation periods, interaction of multiple risk factors, and occurrence of disease among only a fraction of all those with the infection. What are the implications for public health prevention measures?

### Natural History

#### Liver Cancer and Hepatitis

Liver cancer (hepatocellular carcinoma, hepatoma) has a high prevalence in southeastern Asia, Taiwan, and sub-Saharan Africa, with annual incidence rates as high as 5 per 1000.

In contrast, liver cancer is rare in the United States and northern Europe. This disparity across countries prompted many studies postulating a relationship between diet (focusing on aflatoxins) and the prevalence of liver cancer.

Development of diagnostic tests for hepatitis B infections in the 1970s led to the observation that areas with high prevalence of hepatitis B infections also had high prevalence of liver cancer. In a prospective study in Taiwan, Beasley found that chronic carriers of hepatitis B were at least 250 times more likely to develop liver cancer than were people who had not been infected or who had been infected but were now immune. This relative risk was one of the largest ever measured. In Taiwan, a 40-year-old male hepatitis B carrier had a 50% lifetime risk of developing liver cancer. Figure 1 depicts the hepatitis B virus.

In some countries, the incidence of liver cancer did not always parallel hepatitis B infection; in Italy, for example, liver cancer showed only a small association with hepatitis B positivity. The discovery of hepatitis C in 1989 and development of serological tests in the 1990s expanded views on the causes of liver cancer. Studies showed that chronic carriers of hepatitis C developed liver cancer in the absence of hepatitis B, again after a long incubation period. The relatively high prevalence of hepatitis C infection explains the high liver cancer rate in Italy.

Carrier factors, including age at infection, affect the progression from infection to liver cancer. It is widely thought that chronic destruction and regrowth of liver cells is the prime mechanism in the multistep derivation of cancer cells from normal liver cells. This slow progression would explain the long and variable incubation period between infection and cancer (Figure 2). It also explains why only chronic carriers are at risk. Age at infection influences manifestation of hepatitis B; infected infants rarely show symptoms whereas most adults are symptomatic. Age

Table 1: *Microbial agents associated with chronic diseases, hepatitis B and C liver cirrhosis, and liver cancer*

Hepatitis virus B and C	Liver cirrhosis and liver cancer
<i>Helicobacter pylori</i>	Stomach ulcers, stomach cancer
<i>Chlamydia pneumoniae</i>	Coronary heart disease, stroke
Human papilloma virus	Cervical cancer
Epstein-Barr virus	Burkitt's lymphoma
	B-cell lymphoma
	Nasopharyngeal cancer
Human herpes virus 8	Kaposi's sarcoma
Human T-cell leukemia virus	T-cell leukemia
Mouse mammary tumor-like virus	Breast cancer?
Borna virus	Schizophrenia?

also influences carriage; infected infants nearly always become chronic carriers compared to only 20% of newly infected adults.

Less is known in hepatitis C, but it appears that 80% or more of those infected become chronic carriers. The time from development of the carrier state to cirrhosis, liver cancer, or chronic liver disease ranges from years to many decades. Many carriers die from other causes before their liver disease becomes critical. What might be the role of other factors? Alcoholism has long been associated with liver cirrhosis and liver cancer. Alcoholics who are hepatitis C carriers are far more prone to develop cirrhosis and liver cancer than are those who have one factor but not both. Aflatoxins may have a similar role in liver cancer. Hepatitis C is becoming a major problem in the United States among persons who share needles; 80% or more of such persons are positive in Seattle.

Figure 2: Possible outcomes of infection with hepatitis B or C virus. (1) The incubation period from infection to symptoms is 2–4 months. (2) Carriage can last for decades. A small percentage of hepatitis B carriers convert to noncarrier status each year. (3) The incubation period to serious liver disease is highly variable, taking decades. Many carriers die from other causes before their liver disease becomes critical. (4) Cirrhosis usually but not always precedes liver cancer.

### *Helicobacter and Stomach Ulcers*

The stomach is an organ that gets little respect except when it fails to function properly. The lining of the stomach secretes a high concentration of hydrochloric acid. This acidity promotes digestion and protects the digestive tract from infections with many bacteria and viruses. The wall of the stomach is protected from acid attack by a mucous layer. When this barrier is breached, ulcerations of the stomach wall develop. The lifetime prevalence of stomach ulcers is 10%

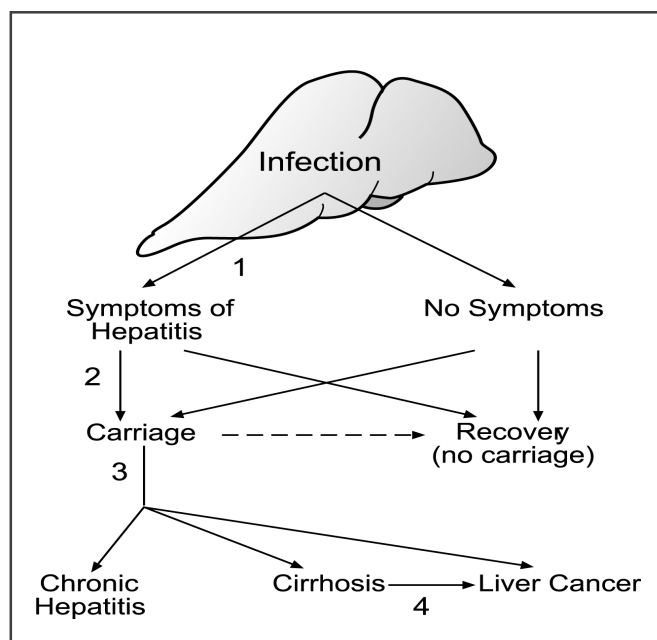
in Western countries. Several blockbuster drugs that inhibit acid production in the stomach have come on the market in recent years. These drugs do not cure ulcers but alleviate the symptoms if they are taken often for many years. Consequently, these agents have been major contributors to pharmaceutical company profits since the 1970s.

Numerous etiologic factors have been implicated in ulcers including stress, smoking, coffee, diet, anxiety, and attitudinal behaviors that essentially put the blame on the patient. In the 1980s, Warren discovered *Helicobacter pylori* growing in the stomach and proposed the radical hypothesis that stomach ulcers resulted from infection with this organism. This hypothesis was not well received by physicians accustomed to conventional treatment. It also posed a major threat to profits of some drug houses. Not till the mid-1990s did the medical profession generally accept that *Helicobacter* infections had a major role in stomach ulcers, convinced by studies showing that eliminating the organisms with chemotherapy cured ulcers, and reinfection frequently led to reoccurrence.

*Helicobacter* infections also have been associated with stomach cancer, but the association is weaker than that for ulcers. In the United States, the incidence of stomach cancer dropped markedly from 1900 until the present, while incidence in the developing world has remained high. Decreased incidence in the United States could be related to older age at infection, whereas infection still occurs at an early age in the developing world. This finding has led to the hypothesis that infection in childhood is a risk factor for stomach cancer whereas infection in adolescence and early adulthood is a risk factor for stomach ulcers. Interestingly, the U.S. Environmental Protection Agency has classified *H. pylori* as a major carcinogen.

### *Chlamydia pneumoniae and Coronary Artery Disease*

*Chlamydia pneumoniae* is an obligate intracellular pathogenic bacterium (Figure 3). It causes pneumonia, bronchitis, and sinusitis, but two-thirds of infections are asymptomatic or limited to the upper respiratory tract. The prevalence of antibodies rises from 50% in young adults to 70% in old age, which suggests that most people are infected and



reinfected throughout life. The possibility that *C. pneumoniae* might have a role in cardiovascular disease was first described by Saikku et al. (1988), who demonstrated a correlation of antibodies against *C. pneumoniae* and acute myocardial infarction. Several other studies have confirmed these findings with relative risk factors of two.

More strikingly, the organism has been detected in the foam cells in the lesion in atheromatous plaques. In some 50 studies, the organism has been detected in an average of 50% of atherosclerotic lesions from persons with coronary heart disease, carotid artery stenosis, aortic aneurysm, and occlusion of the lower extremity arteries (claudication), but not in normal arteries from healthy persons.

It has been most difficult to isolate the organism from lesions, which is not surprising because the organism is difficult to isolate from any site.

How will we be able to separate the effects of infection from the other known risk factors such as smoking, high cholesterol, and hypertension and other less well-defined factors such as diabetes and family history? In rabbit and mouse models of hypercholesterolemia, infected macrophages spread from the lungs to the aortic atherosclerotic lesions, and infection appears to accelerate development of disease. Three of four pilot studies reported a favorable effect of short-term treatment with macrolides or tetracycline. Two multicenter studies in the United States are using azithromycin for long-term therapy in persons at risk for coronary heart disease.

## Prevention and Public Health Implications

In these long-term infections, prevention has three major aspects. The best approach is to prevent initial infections. Preventing disease in carriers depends upon our ability to devise therapies to terminate carriage. Finally, treatments can be devised for those who have disease.

The blood supply is screened for both hepatitis B and hepatitis C to eliminate transmission by that route. Needle exchange programs would be useful to prevent spread of these viruses. Hepatitis B infections can be controlled or even eliminated because we have an effective vaccine and no apparent animal reservoir. A vaccine for hepatitis C may be difficult to devise because nearly all infected persons become carriers.

Early detection is critical in liver cancer. By the time clinical symptoms develop, the prognosis is poor. Early diagnosis can be accomplished by population screening to detect those who are antigen positive and at risk for liver damage and cancer. Persons who are positive for hepatitis B antigen are monitored for development of increased alpha-fetoprotein levels, an early marker for liver cancer. Those with elevated levels are then monitored by acoustic scan to detect small excisable tumors. This approach for early detection of tumors in hepatitis B infection has enhanced survival. Similar data are not available for hepatitis C carriers. Progress has

occurred in using interferon and ribavirin to terminate carriage of hepatitis C, but toxicity of treatment is a problem.

The high prevalence of *Helicobacter* infections in children in developing countries indicates that infection control is clearly related to sanitation and crowding. The infection route is oral but the source of infecting material is unknown because the organism apparently does not survive its trip to the colon. *Helicobacters* have contaminated local well water supplies. Animals also carry *Helicobacter* species, but those characterized so far are distinct from the human strains. A major public health goal would be to find the mode of transmission of these infections.

Treatment is critical to patients with ulcers because some 70% of ulcers appear to be caused by *Helicobacter*. Vaccines may be difficult to develop given the chronic character of the infection. Variability in pathogenicity of *H. pylori* strains might explain the relatively high ratio of infection to disease. Control of ulcer disease itself could be accomplished by the detection and treatment of infections. A major campaign to eliminate carriage nationwide or worldwide by antibiotic treatment is an interesting possibility. However, antibiotic resistance is already being observed in *Helicobacters*.

The situation for *C. pneumoniae* in coronary artery disease is much more complex. We need carefully defined studies of respiratory disease to determine the incidence of infection by age and the prevalence of chronic infection. Large etiologic studies of respiratory disease have been largely unfeasible in the past decade. Eliminating infection by treatment is probably impossible because infection is asymptomatic. Development of a vaccine is important but most likely will be difficult if we find that *C. pneumoniae* infections are frequently chronic. If such a vaccine becomes available, it should be administered before five years of age when infection is rare. In the meantime, control measures may require the screening of persons at high risk for chronic chlamydial infection, and their subsequent treatment might be a reasonable method for preventing some coronary artery disease.

The immediate practical goal is to investigate whether antibiotic therapy is beneficial for persons at risk for coronary artery disease. On a more fundamental level, we need to know the natural history of chlamydial infections to determine when they begin and if persistent infection is typical of *C. pneumoniae*. To achieve this goal, a marker (or a laboratory test) is needed to detect persistent infections in atherosclerotic lesions.

Advances in medicine have gradually enhanced understanding of the links between infectious and chronic disease. Interestingly, as early as the 1920s, spiral-shaped organisms (probably *H. pylori*) were detected in the stomach, and technology available at the beginning of the twentieth century could have allowed culture of this organism on agar. For each of the diseases reviewed, investigators used classic epidemiologic approaches to establish relationships. Molecular technologies (immunocytochemistry, polymerase chain reaction, or recombi-

nant DNA) were critical to detection of agents for hepatitis C and *C. pneumoniae*. They were not needed for detecting hepatitis B, but were necessary to develop the vaccine. A mid-century advance, the development of antibiotics, permitted the recent treatment studies.

### *Recommended Reading*

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