EBNA2, and other EBV proteins that drive B-cell growth and immortalization.

Given these observations, how then does EBV contribute to the genesis of endemic Burkitt lymphoma? One possibility is shown in Figure 7-46. In regions of the world where Burkitt lymphoma is endemic, concomitant infections such as malaria impair immune competence, allowing sustained B-cell proliferation. Eventually, T-cell immunity directed against EBV antigens such as EBNA2 and LMP-1 eliminates most of the EBV-infected B cells, but a small number of cells downregulate expression of these immunogenic antigens. These cells persist indefinitely, even in the face of normal immunity. Lymphoma cells may emerge from this population only with the acquisition of specific mutations, most notably translocations that activate the *MYC* oncogene. It should be noted that in nonendemic areas 80% of tumors are unrelated to EBV, but virtually all endemic and sporadic tumors possess the t(8;14) or other translocations that dysregulate *MYC*. Thus, although sporadic Burkitt lymphomas are triggered by mechanisms other than EBV, they appear to develop through similar oncogenic pathways.

In summary, **in the case of Burkitt lymphoma, it seems that EBV is not directly oncogenic, but by acting as a polyclonal B-cell mitogen, it sets the stage for the acquisition of the (8;14) translocation and other mutations that ultimately produce a full-blown cancer.** In most individuals, EBV infection is readily controlled by effective immune responses, and virtually all infected individuals remain asymptomatic or develop self-limited infectious mononucleosis. In regions of Africa where Burkitt lymphoma is endemic, poorly understood cofactors (e.g., chronic malaria) may favor the acquisition of additional genetic events (e.g., the t(8;14)) that lead to transformation.

The role played by EBV is more direct in EBV-positive B-cell lymphomas in immunosuppressed patients. Some persons with AIDS or who receive immunosuppressive therapy for preventing allograft rejection develop EBV-positive B-cell tumors, often at multiple sites and within extranodal tissues such as the gut or the central nervous system. These proliferations are polyclonal at the outset but can evolve into monoclonal neoplasms. In contrast to Burkitt lymphoma, the tumors in immunosuppressed patients uniformly express LMP-1 and EBNA2, which are antigenic and can be recognized by cytotoxic T cells. Also, in contrast to Burkitt lymphoma, they usually lack *MYC* translocations. These potentially lethal proliferations can be subdued if the immunological status of the host improves, as may occur with withdrawal of immunosuppressive drugs in transplant recipients.

Nasopharyngeal carcinoma is also associated with EBV infection. This tumor is endemic in southern China, in some parts of Africa, and in the Inuit population of the Arctic. In contrast to Burkitt lymphoma, 100% of nasopharyngeal carcinomas obtained from all parts of the world contain EBV. The structure of the viral genome is identical (clonal) in all of the tumor cells within individual tumors, excluding the possibility that EBV infection occurred after tumor development. Antibody titers to viral capsid antigens are greatly elevated, and in endemic areas patients develop IgA antibodies before the appearance of the tumor. The uniform association of EBV with nasopharyngeal carcinoma suggests that EBV has a central role in the genesis of the tumor, but (as with Burkitt lymphoma) the restricted geographic distribution indicates that genetic or environmental cofactors, or both, also contribute to tumor development. Unlike Burkitt lymphoma, LMP-1 is expressed in nasopharyngeal carcinoma cells and, as in B cells, activates the NF-κB pathway. NF-κB in turn upregulates the expression of factors such as VEGF, FGF-2, MMP9, and COX2 that may contribute to oncogenesis.

The relationship of EBV to the pathogenesis of Hodgkin lymphoma, yet another EBV-associated tumor, is discussed in Chapter 13.

Hepatitis B and C Viruses. Epidemiologic studies strongly suggest a close association between hepatitis B and C virus infection and the occurrence of liver cancer (Chapter 18). It is estimated that 70% to 85% of hepatocellular carcinomas worldwide are caused by infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). HBV is endemic in countries of the Far East and Africa; correspondingly, these areas have the highest incidence of hepatocellular carcinoma. Despite compelling epidemiologic and experimental evidence incriminating HBV and HCV, the mode of action of these viruses in liver tumorigenesis is not fully elucidated. The HBV and HCV genomes do not encode any viral oncoproteins, and although the HBV DNA is integrated within the human genome, there is no consistent pattern of integration in liver cells. Indeed, **while the oncogenic effects of HBV and HCV are multifactorial, the dominant effect seems to be immunologically mediated chronic inflammation and hepatocyte death leading to regeneration and, over time, genomic damage.** It is also suspected that in the setting of unresolved chronic inflammation, as occurs in viral hepatitis or chronic gastritis caused by *H. pylori* (see later), the immune response may become maladaptive, promoting rather than preventing tumorigenesis.

As with any cause of hepatocellular injury, chronic viral infection leads to the compensatory proliferation of hepatocytes. This regenerative process is aided and abetted by a plethora of growth factors, cytokines, chemokines, and other bioactive substances. These are produced by activated immune cells and promote cell survival, tissue remodeling, and angiogenesis (Chapter 3). The activated immune cells also produce other mediators, such as reactive oxygen species, that are genotoxic and mutagenic. One key molecular step seems to be activation of the NF-κB pathway in hepatocytes in response to mediators derived from the activated immune cells. Activation of the NF-κB pathway within hepatocytes blocks apoptosis, allowing the dividing hepatocytes to incur genotoxic stress and to accumulate mutations. Although this seems to be the dominant mechanism in the pathogenesis of virus-induced hepatocellular carcinoma, the HBV genome also contains genes that may directly promote the development of cancer. For example, an HBV gene known as *HBx* can activate a variety of transcription factors and several signal transduction pathways. In addition, viral integration can cause structural changes in chromosomes that dysregulate oncogenes and tumor suppressor genes.

Although not a DNA virus, HCV is also strongly linked to the pathogenesis of liver cancer. The molecular mechanisms used by HCV are less well defined than are those of HBV. In addition to chronic liver cell injury and