

## Preface

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During his 1996 reelection campaign, Bill Clinton's slogan of "Building a Bridge to the 21<sup>st</sup> Century" was lampooned widely and became hackneyed. The need for more and better communication links among medical subspecialties, however, is undeniable as we enter the era of molecular medicine. Prior to the acquired immunodeficiency syndrome (AIDS) epidemic, professional communication between oncologists and infectious disease specialists was limited almost exclusively to consultations for neutropenic fever during cancer chemotherapy. AIDS patients required the broader expertise of oncologists, dermatologists, pathologists, pulmonologists, and infectious disease physicians, with the latter becoming primary caregivers during the decade between the discovery of human immunodeficiency virus (HIV) in 1984 and the development of combination antiviral chemotherapy in the 1990s. The spectacular efficacy of highly active antiretroviral therapy (HAART) against HIV and AIDS is a model likely to be repeated, as drugs are discovered not so much by their efficacy against an overt disease, but rather by their design to block specific molecules in critical pathways underlying the disease. *Infectious Causes of Cancer: Targets for Intervention* reviews neoplasms in which certain viruses, bacteria, and parasites play critical roles, anticipating that they will be likely targets for drugs or vaccines.

Cancers are the most thoroughly studied of a growing list of chronic diseases previously thought to be noninfectious. As such, they provide lessons that are likely to apply more broadly.

**Lesson one** is that the infection must be persistent or chronically active to play a role in a complex disease such as cancer. Putative "hit-and-run" mechanisms are likely an artifact of insensitive methods for detecting the infection. A corollary is that many infectious agents, such as Epstein–Barr virus (EBV), human papillomaviruses (HPVs), and *Helicobacter pylori* (*H. pylori*), much like neoplastic cells, have evolved ways to evade immune recognition. For some infections, the activity of the infection and the risk of the cancer is markedly increased by acquired or, rarely, congenital immune deficiency.

**Lesson two** is that the relationship between infection and cancer, like that between any single host gene and cancer, is never a simple cause-and-effect. Through interactions with the human host, most of the implicated infections are cofactors that indirectly increase the probability of critical genetic mutations. Age at infection and host immunogenetics often have a major influence on susceptibility to EBV-related Burkitt's lymphoma and nasopharyngeal carcinoma and to *H. pylori*-related gastric cancer (Chapters 5, 6, and 21, respectively). Because the odds of the critical genetic mutations are low, the corollary of this lesson is that most infected people do not develop cancer.

**Lesson three** is that the infection may not be necessary for the cancer phenotype. As classical examples, Burkitt's lymphoma and hepatocellular carcinoma do occur without EBV infection and hepatitis B or C virus (HBV, HCV) infections, respectively. This implies

that pathways that affect the occurrence of genetic mutations and the resulting cancer are accessible by noninfectious mechanisms. These include spontaneous *c-myc*/immunoglobulin gene rearrangement of a pre-Burkitt's B lymphocyte; alcoholic hepatitis, cirrhosis, and precancerous clonal regeneration of the liver; and others. The exceptions are noteworthy, since squamous cell carcinoma of the cervix probably does not occur without a "high-risk" HPV infection, nor Kaposi's sarcoma without human herpesvirus type 8 (HHV-8) infection.

**Lesson four** is that a substantial part of the disease process and of the tumor tissue itself results from responses such as inflammation, lymphedema, sclerosis, and neovascularization that are ancillary to the cancer cell. Hodgkin's disease (Chapter 7) is a prototype, in which the cancerous, EBV-infected Reed–Sternberg cells are few and far between.

**Lesson five** is that cancer often can be prevented by preventing the infection or the immune deficiency that allows it to persist or reactivate. Likewise, remissions of the cancer often can be induced by successful early treatment of the infection or the underlying immune deficiency.

**Lesson six** is that "cancer" or "malignancy" can be difficult to define. Two examples resulting from uncontrolled EBV infection, fulminant X-linked lymphoproliferative disease and post-transplant lymphoproliferative disease, present and often must be treated as highly aggressive non-Hodgkin's lymphomas, irrespective of oligo-, poly-, or monoclonality. As nicely reviewed in Chapter 1, difficulties with basic definitions such as "cancer," "infection," "dissemination," and "spread" are not new to infectious disease oncology. The practicing physician already is familiar with "remission" and "cure," which are so difficult to define as to depend more upon consensus than certainty.

*Infectious Causes of Cancer: Targets for Intervention* is intended to serve as an introduction to infectious disease oncology for practitioners. It has only five overview chapters on the major human carcinogenic infections (herpesviruses, retroviruses, papillomaviruses, hepatitis viruses, and *H. pylori*). Most of the other chapters focus on specific neoplasms, often adding perspectives to the six aforementioned lessons. Each of the chapters—including the overviews, the specific neoplasms, and those that are more oriented to research frontiers—reviews the history and current status of its topic and provides a vision of the future in terms of prevention and treatment of the disease, the underlying infection, or both. The goal is to bridge the disciplines and not to present detailed recapitulations of virology, bacteriology, parasitology, and oncology, all of which are available elsewhere.

### **Mechanisms of Neoplasia: Targets of Opportunity**

Oncogenic infections increase the risk of cancer through expression of their genes in the infected cells. Occasionally, these gene products have paracrine effects, leading to neoplasia in neighboring cells. More typically, it is the infected cells that become neoplastic. These viral, bacterial, and parasitic genes and their products are obvious candidates for pharmacologic interruption or immunologic mimicry, promising approaches for drugs or possibly vaccines.

Herpesviruses, especially EBV and, since its discovery in 1994, human herpesvirus 8 (HHV-8, also known as Kaposi's sarcoma-associated herpesvirus), are the most extensively studied and best characterized infections that cause cancer in humans (Chapters 2–10). They are relatively large DNA viruses with an approximately 140,000 basepair genome that codes for more than 80 genes, including those for building daugh-

ter virions during the “lytic” portion of their life cycle, as well as regulatory genes that enable the infection to persist in “latency” for prolonged periods. Several of the regulatory genes have human homologs that apparently were pirated by the virus during mammalian evolution and that probably contribute to its evolutionary survival and to human disease. As a rule, the DNA of EBV and HHV-8 does not integrate into the human genome. Rather, during “latency” the extrachromosomal (“episomal”) herpes DNA is copied during mitosis, yielding progeny cells that are likewise latently infected with episomal herpes DNA. Uncontrolled proliferation of these latently infected progeny cells characterizes EBV- and HHV-8-associated neoplasms. Proliferation of both the EBV-associated lymphoproliferative diseases and of HHV-8-associated Kaposi’s sarcoma seems to be highly sensitive to the severity of the cell-mediated immune deficiency that occurs with AIDS, with pharmacologic suppression of allograft rejection, and with the congenital X-linked lymphoproliferative disease originally described by Purtilo (1) (*see also*, Chapter 3). In other neoplasms, such as endemic (African) Burkitt’s lymphoma and nasopharyngeal carcinoma, EBV is able to evade immune recognition by masking or downregulating critical antigens.

Retroviruses and their lentivirus cousins are RNA viruses with a pathognomonic enzyme, reverse transcriptase, that enables them to make a DNA “provirus” copy of their genome and to integrate it permanently into the genome of the infected host cell. Rare cases of Non-Hodgkin’s lymphoma (NHL) among persons with AIDS appear to result from activation of a protooncogene owing to upstream integration of HIV in macrophages (Chapter 13). However, the overwhelming way that HIV causes cancer is by destroying cellular immunity, thus dysregulating HHV-8 and leading to Kaposi’s sarcoma (Chapter 10), dysregulating EBV, leading to some AIDS NHLs (Chapter 8), and perhaps other indirect and paracrine effects of dysregulated cytokines and growth factors. The effects of HIV on cellular immunity are not a major focus of this book. It should be noted, however, that there is clear, if incomplete, recovery of cellular immunity and reduction in risk of some cancers that occurs with interruption of the replication of HIV through drugs that interfere with reverse transcriptase and especially those specifically designed to interfere with the viral protease enzyme (2). The prototype human retrovirus, human T-lymphotropic virus type I (HTLV-I), causes transformation of T lymphocytes and highly aggressive adult T-cell leukemia/lymphoma (ATL) through poorly characterized mechanisms that probably include transactivation of cellular genes controlling growth by HTLV-I’s *tat* gene and possibly alteration of cellular immunity (Chapters 11 and 12). Anti-HIV drugs have little or no activity against HTLV-I, illustrating the specificity of each virus’s reverse transcriptase and protease.

HPVs encompass more than 100 genotypes of small, related DNA viruses that have a strong tropism for epithelial cells. The major oncogenic agents for humans are HPV-16, HPV-18, and several others that are sexually transmitted and cause cancer of the cervix, penis, and anus (Chapters 14 and 15). HPV-16 and -18 appear to transform infected cells when their episomal circular genome is broken open and integrated into the host genome, allowing marked upregulation and expression of their E6 and E7 proteins. Unlike the E6 and E7 proteins of nononcogenic HPVs (such as type 1, which causes common warts), those of HPV-16 and -18 have strong affinity for the p53 and Rb pathways, respectively. Interference with both the p53 and the Rb pathways allows

unregulated cell cycling and failure to undergo apoptosis (normal cellular senescence), increasing the likelihood of additional mutations. A possible role for HPVs in other squamous cell carcinomas, such as those of the skin and oropharynx, is uncertain, although the mechanisms appear to be the same (Chapter 16). HPV-16 virus-like particle and E6 recombinant protein vaccines are currently in clinical trials in hopes of reducing the major HPV diseases, cervical and anal cancers.

The two oncogenic hepatitis viruses, HBV and HCV, are phylogenetically unrelated but do share the ability to establish chronic active infection, inflammation (hepatitis), cell death, scarring (cirrhosis), and clonal, nodular regeneration of the liver (Chapters 17 and 18). Because this sequence appears to underlie virtually all cases of hepatocellular carcinoma, there should be several opportunities for intervention. Unfortunately, the mechanisms for this sequence of events are largely unknown. HBV, however, has been well studied and has the advantage of two natural animal models, the woodchuck and ground squirrel hepatitis viruses, both of which cause hepatocellular carcinoma in their respective species. HBV is a partially double-stranded DNA virus; it uses an RNA intermediate and a reverse transcriptase for its replication; and it can integrate into the host genome. The integration appears to drive the liver tumor in the animal models and may contribute directly to human hepatocellular carcinoma. HCV, an RNA virus that cannot integrate into the host genome, increases the risk of hepatocellular carcinoma indirectly. These primarily include the sequence of inflammation, cell death, scarring, and nodular regeneration with increased chance of a proneoplastic genetic mutation. The cancer risk increases with all insults to the liver, including HBV, HCV, alcoholism, and other hepatotoxins. Aflatoxin B1, a fungal contaminant of peanuts and other food staples in parts of Africa and China, is associated with a highly specific mutation of the *p53* cancer suppressor gene and greatly increases the risk of hepatocellular carcinoma among people with chronic HBV infection.

A similar sequence of inflammation, scarring, and regeneration, probably contributes to the development of squamous cell bladder cancer. This neoplasm, which is unusual in industrialized societies, is closely tied to heavy, chronic bladder infestation by *Schistosoma haematobium*, a helminthic parasite that infects some 200 million people in endemic regions of Africa (Chapter 24). The same may also be true for the reported association of cholangiocarcinoma with chronic infection by the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, which are summarized in depth elsewhere (3). Risk of cancer with these chronic parasitic infections may be increased or actually depend on vitamin deficiencies, polymorphisms in detoxification or activation enzymes of the human host, superinfection by bacteria, or several of these.

Chronic bacterial infections (and perhaps also chronic helminth and fluke infections) generate reactive oxygen species that, like aflatoxin B1, can be genotoxic and may contribute to the odds of mutation in a gene that increases neoplasia (4). Such a mechanism is postulated specifically for the clear associations between *Salmonella typhi* and gallbladder cancer and between *H. pylori* and gastric cancer (Chapters 23 and 21, respectively). It should be noted that these infections generate relatively little inflammation and scarring and that, instead, they are associated with mucosal atrophy and a high risk of adenocarcinomas rather than squamous cell carcinomas. Identification of the mechanisms for these associations may not be immediately important, since

these bacteria can be eradicated by antibiotics and, for *Salmonella typhi*, by cholecystectomy. However, these mechanisms could have broader implications for understanding and preventing or treating noninfectious adenocarcinomas.

Inability of the immune system to eradicate a chronic infection appears to underlie the association between *H. pylori* and B-cell non-Hodgkin's lymphoma of the mucosa-associated lymphoid tissue (MALT) of the stomach (Chapter 22). It seems that bacterial antigens are passaged and presented by the M cells (specialized epithelial cells) of the gut to Peyer's patches where B lymphocytes are recruited, activated, and circulated back to the mucosa where they are maintained by T-cell signaling. Regression can occur with either eradication of the *H. pylori* or with blockade of the T-cell signaling. A similar continuous feedback-loop mechanism has been postulated for the association of chronic HCV infection with type 2 mixed cryoglobulinemia and other B-cell disorders that may include NHL (Chapter 19).

### The Infectious Disease Universe

The polymerase chain reaction (PCR) revolution led to a rapid discovery of novel viruses, bacteria, and parasites and to a recognition of our ignorance of how these organisms relate to human beings. At least two recently discovered viruses, the DNA transfusion-transmissible virus (TTV) and the RNA GB-virus C (also known as hepatitis G virus), establish chronic, active infections in peripheral blood lymphocytes, but as yet have no known chronic disease (5,6). Perhaps they are symbionts and cause no disease in humans. The discoveries of HCV, HHV-8, *Tropheryma whippelii* (the Whipple's disease bacterium), and *Bartonella henselae* (the agent of cat scratch disease) parallel a growing body of literature supporting the association of chronic viral or bacterial infections with atherosclerosis, Alzheimer's disease, rheumatoid arthritis, type 1 diabetes mellitus, and other nonmalignant chronic diseases.

On the frontiers of this universe are cancers of high incidence, viruses of high prevalence, and novel associations. Investigators are searching for homologs of mouse mammary tumor virus (MMTV) or interactions with endogenous retroviruses in human breast cancer (Chapter 27). One model posits that breast cancer is an MMTV zoonosis acquired from domestic mice (7). Others are investigating simian virus 40 (SV40), which causes mesothelioma, osteosarcoma, and brain tumors when injected into newborn hamsters and which contaminated poliovirus vaccines administered to tens of millions of people from the mid-1950s to the early 1960s (Chapter 26). The human polyomaviruses, BK virus and JC virus, are related to SV40 and cause cystitis and progressive multifocal leukoencephalopathy, respectively, in immune-deficient patients. Discoveries are certain to come from these frontiers. As with explorations of the New World, however, they may not bring back the anticipated gold of definitive disease associations, but instead may provide fundamental insights to be exploited with unforeseen technologies.

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