BOOKS: MEDICINE

Infectious Avenues to Cancer

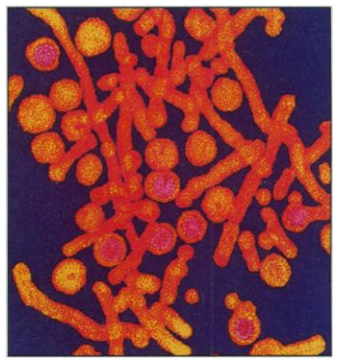
Don Ganem

The idea that infection may cause, or predispose an organism to, malignancy is an old one that has cycled in and out of favor over the years, but dramatic recent advances in epidemiology, microbiology, and cancer biology have greatly renewed interest in the topic. The tendency for certain neoplasms to develop when an organism is immunosuppressed, first recognized in organ transplantation and then very strikingly underscored by the global HIV epidemic, has raised awareness of connections between infections and cancer, both within the scientific community and among the general public. Additionally, the recognition that other diseases once strongly believed to be noninfectious (such as peptic ulcer disease and certain forms of arthritis) are now known to have microbial causes (*Helicobacter pylori* and the Lyme-disease spirochete, *Borrelia burgdorferi*, respectively) has further reduced long-standing resistance to accepting microbial causes of malignancy. So the appearance of a new book on this subject is nothing if not timely.

Microbes and Malignancy
Infection as a Cause of Human Cancers
Julie Parsonnet, Ed.
Oxford University Press, New York, 1999. 477 pp. $79.95, £59.50. ISBN 0-19-510401-3.

Perhaps the most intellectually gratifying aspect of the resurgence of interest in microbial causes of cancer is that it involves the convergence of many previously disparate disciplines. Recent progress in the field owes a particularly strong debt to practitioners of epidemiology and clinical investigation. Microbiologists and molecular geneticists are rarely the first to posit an infectious cause of a given malignancy. Rather, these suspicions typically arise as a result of associations established in various populations between either known or suspected infections and certain cancers. For example, the presence of cirrhosis or chronic hepatitis in biopsies of liver cancer suggested a link between viral hepatitis and liver cancer; this hypothesis was then supported by the striking similarity in the global distributions of hepatitis B virus infection and the tumor. Prospective epidemiologic studies revealed that carrying the virus conferred a 100-fold increase in the risk of liver cancer; these studies eliminated all doubt that this infection was centrally linked to the devastating neoplasm. Now the ball is in the court of virologists and cancer biologists to determine the mechanisms that underlie this association. Similar epidemiologic work laid the foundations for linking human papilloma virus infection to cervical cancer. And it was the peculiar epidemiology of Kaposi's sarcoma that first suggested that a sexually transmitted agent might be responsible for that disease and precipitated the search that led to the discovery of a new human herpesvirus (KSHV), now believed to be required for Kaposi's sarcoma pathogenesis.

So it is appropriate that *Microbes and Malignancy* includes contributions from the full spectrum of investigators in the field: clinicians, epidemiologists, microbiologists, cancer biologists, and pathologists. This is an important feature, because the relationship of carcinogenesis to infection, for many of the diseases considered in the book, is rather indirect. Consider the case of hepatitis B virus, which, as far as can be determined, does not alter the programmed growth of cells in culture and yet is markedly associated with hepatocellular cancer. Most evidence (ably reviewed by Robinson in this volume) suggests that the oncogenic risk cannot be firmly linked to any single viral gene; rather, it is the consequence of immunologically mediated liver injury, hepatocyte regeneration, and the presence of chronic inflammation. Such a complex situation cannot be simply reproduced in culture and challenges the traditional reductionism of molecular virologists. It requires a broader understanding of the relationship between infection and chronic inflammation, the generation of reactive oxygen species, mutation, cell proliferation, and cellular transformation. Five introductory chapters consider these broader pathophysiologic subjects in an attempt to provide this background information. Although most of these contributions are, unfortunately, too superficial to be useful, Bruce Ames and colleagues provide a remarkably substantive chapter on the biochemical consequences of chronic inflammation and their implications for multistep tumorigenesis.



Linked to liver cancer. Hepatitis B virus (shown in this colored transmission electron micrograph) is the most important risk factor for hepatoma.

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The book does a much better job in its consideration of specific malignancies now believed to have infectious causes: cervical and anogenital cancer and human papilloma virus; nasopharyngeal carcinoma and Epstein-Barr virus; Kaposi's sarcoma and KSHV; hepatoma and hepatitis B and C viruses; and T cell lymphoma and human T cell leukemia viruses. These chapters succinctly review what is known in these areas and provide well-referenced overviews of contemporary notions of pathogenesis. They represent useful starting points for outsiders wishing to familiarize themselves with the main currents of thinking on these topics, though professional virologists will find little here that is new.

Microbes and Malignancy concludes with a series of chapters on bacterial and parasitic infections that are also associated with malignancy—schistosomiasis, liver flukes, and, most remarkably, *Helicobacter pylori*. Although these chapters deal with infection-cancer linkages whose mechanisms are poorly understood, in many ways they represent the most interesting part of the book. These extracellular pathogens do not invade the nucleus of the cancer cell and do not contribute new oncogenes to the host's genetic repertoire. Instead, they interact with the host in much more subtle and interesting ways. Certain gastric lymphomas associated with *H. pylori* bacterial infection present a striking example. These monoclonal B cell lymphomas are dependent upon the local presence of the bacterium in the gastric mucosa: antibiotic treatment of *H. pylori* not only eliminates bacterial colonization but also leads to an involution of the lymphoma! Current models envision that this B cell lymphoma is driven by factors supplied by helper T cells, which are themselves specific for bacterial antigens. Examples like this reveal how much we still have to learn at the cellular and molecular level about the roles of infection in triggering cell proliferation—and how likely we are to be surprised by what we learn.

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