

Foreword

Viruses cause more than a fourth of all human cancers. Virus-induced cancers, like all viral diseases, present special challenges and raise specific hopes. The challenges are in understanding the molecular mechanism of the disease, knowing the mode of virus transmission, and obtaining global epidemiological data. The hope is for the development of effective vaccines, antiviral therapies and, ultimately, for the control and eradication of the pathogenic virus.

This book presents a comprehensive survey of human cancer viruses. They include five viral families, the papillomaviruses, herpesviruses, hepadnaviruses, flaviviruses and retroviruses. For most of these cancer viruses, there is a good understanding of transmission, and epidemiological data are extensive. Indeed, epidemiological data have traditionally been essential for establishing the oncogenicity of a virus in humans. The viruses considered here have widely differing impacts on public health. The hepatitis viruses cause acute and chronic infections with significant morbidity and affect millions of people. Infection with oncogenic papillomaviruses is similarly widespread. Papilloma and hepatitis viruses have therefore been the focus of vaccine efforts. These efforts have succeeded for hepatitis B virus and for papillomaviruses; they are still in progress for hepatitis C virus. Kaposi sarcoma herpes virus and human T cell leukemia virus affect much smaller groups of people that are well defined by risk factors and geography.

Our understanding of the molecular mechanisms of viral carcinogenesis in humans shows notable gaps. For some viruses, like the oncogenic papilloma and herpesviruses and for human T cell leukemia

virus, specific proteins have been identified that interact with the growth-regulatory machinery of the cell and that play key roles in the oncogenic transformation process. For other viruses, like hepatitis B and hepatitis C viruses, such relationships between viral gene products and cellular regulation are less definitive. The molecular as well as epidemiological insights into human cancer viruses can be summarized in a single conclusion: These viruses are essential, causative components of the oncogenic process, yet they do not act alone. They are necessary, but not sufficient. Other factors play important roles, and many remain to be defined.

Human cancer virology is now a mature field of science, and most of the groundbreaking discoveries have been made. This state of cancer virology invites historical reflection. The initial events that linked viruses to cancer were the discoveries of Ellermann and Bang and of Rous. It took several decades before this basic link was extended to human medicine. The association of the Epstein Barr herpes virus with Burkitt lymphoma and with nasopharyngeal carcinoma was an early signal. Shortly thereafter, hepatitis B virus, human T cell leukemia virus and carcinogenic human papillomaviruses all appeared on the scene. Kaposi sarcoma herpes virus and hepatitis C virus joined the ranks of human tumor viruses later. True discoveries are always unexpected and surprising; each of the critical events that shaped human tumor virology has these attributes. Ingenuity, hard work, instinct, perseverance and serendipity all played a role. The list of groundbreaking discoveries, all under the intellectual ancestry of Ellermann and Bang and of Rous, is short: Epstein and Barr and the Epstein-Barr herpes virus; Beasley and the connection between hepatocellular carcinoma and hepatitis B virus; zur Hausen and the causation of cervical cancer by papillomaviruses; Yoshida and Gallo and human T cell leukemia virus; and Chang and Moore and Kaposi sarcoma herpes virus. The connection between hepatitis C virus and hepatocellular carcinoma emerged more gradually from clinical and epidemiological observations, and credit for this insight is more widely distributed. Most of these openings were achieved by young scientists. Chang and Moore discovered Kaposi sarcoma herpes virus when they were in their middle thirties. Zur Hausen, Beasley,

Epstein and Barr, Yoshida and Gallo were still in their forties when they achieved their breakthroughs. And not all of these discoveries came from established virology labs. Chang and Moore worked outside the virology mainstream and did not even have grant support when they made their spectacular discovery. Beasley's perspective appropriately focused on public health and epidemiology; a molecular approach toward hepatitis B virus and cancer would not have been successful at the time. The igniting spark for the discovery of human T cell leukemia virus came from epidemiological studies that had revealed a unique, geographically confined T cell leukemia in southern Japan.

Government support for medical research has sharply tightened over the past few years. In the US, the structure of funding and the allocation of resources have changed significantly. There has been a shift away from investigator-initiated projects that have been the source of most innovations and breakthroughs. The emphasis is now on larger conglomerate structures. With this collectivization of research funds has come extreme risk avoidance and support of the predictable and the mundane. Few of the research projects that have led to paradigm shifts in cancer virology would be fundable today. The consequences of these developments have been especially severe for young investigators. There is deep concern in the scientific community that much young talent is turned away and lost to science. However, there are now also some encouraging signs that the mechanism for public support of research has become flexible again. Scientists have a great stake in the restoration of individual initiative, prudent risk taking and the spirit of discovery in science funding, and there is hope that this will be possible.

Reading this book and reflecting on the history and the challenges of the cancer virus field will inspire the insight, wisdom and excitement that are needed to advance science.

Peter V. Vogt, PhD
The Scripps Research Institute
La Jolla, California
March 24, 2009