Current Cancer Research

Erle S. Robertson *Editor*

Cancer Associated Viruses

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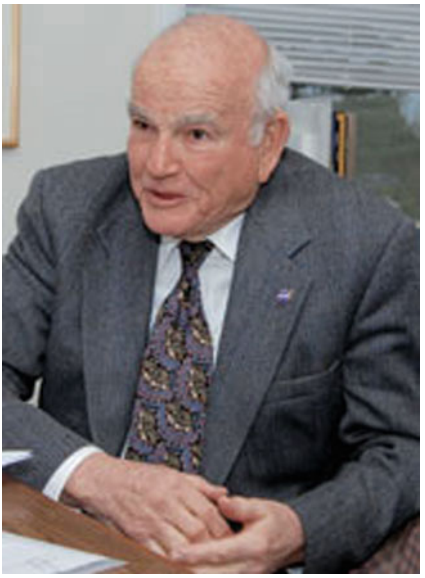
In Memoriam



Baruch S. Blumberg, M.D., D.Phil.

Baruch Samuel (Barry) Blumberg died suddenly on April 5, 2011 shortly after giving a presentation on "citizen science" at the NASA Lunar Science Institute in Ames, California. Barry's talk concerned making spacecraft data available to the public so that ordinary people could contribute to its interpretation. That final talk reflected his deep belief that anyone who was willing to invest time and thought could have ideas that would lead to new understandings of research information.

This volume is about viruses and cancer, but Barry was neither a virologist nor an oncologist. However, he contributed fundamentally to both. Barry began his research career as a medical student at Columbia University when he took an elective in

Tropical Medicine in Suriname. There, he observed that filariasis was rampant, but that only some of the many infected people showed signs of disease. Suriname had many different ethnic groups and some of the diversity in responses was associated with ethnicity. That led him to wonder for the rest of his life why humans living in the same environment responded so differently to infectious agents.

After an internship and assistant residency in medicine at Bellevue Hospital in New York City and a fellowship in rheumatology, Barry went to Oxford University to study biochemistry with Alexander Ogston. He was in the lab at the same time as Oliver Smithies who also went on to win a Nobel Prize. In England, he was exposed to the history of scientific discovery and began formulating his scientific ideas. It was there that he found his scientific inspiration in the lives and work of the nineteenth-century naturalists Charles Darwin and Alfred Russell Wallace. He began to apply the principles of evolution to his research.

After receiving a doctorate, Barry went to an obscure unit called Geographic Medicine and Genetics of the National Institute of Arthritis and Metabolic Disease (NIAMD) in Bethesda, Maryland. He chose this hidden corner because he thought it would allow him to pursue his own ideas and travel wherever he pleased. He began a lifelong pattern of collecting blood samples everywhere he went, making observations about the people from whom they were drawn and often collecting samples of vegetation from their environments. It was at the NIH that Barry honed his interest in genetic polymorphisms in human blood, inherited variants of proteins or blood groups, which he believed were likely to be associated with human diseases. As a believer in the central importance of natural selection, he thought all such variants had to be important. Otherwise, they would not have persisted in human populations.

In 1964, the Director of the Institute for Cancer Research (ICR, precursor to the Fox Chase Cancer Center) recruited Barry to become the head of a new Division of Clinical Research. The lure was that Barry was promised he could do whatever he wanted as long as his research ultimately had consequences for disease in humans. Barry was intrigued and immediately began assembling a small group of physicians to staff this new enterprise. He had complete faith that his approach: identifying variants in human blood and then finding out what they meant, would be much more informative than starting with a disease and trying to identify its causes. It was this approach that first resulted in identifying an antigen on a lipoprotein in serum, and subsequently to a different antigen, the "Australia antigen."

Barry focused the efforts of his new division on understanding the biological significance of Australia antigen. In a series of studies of diseases associated with the antigen, the group found that Australia antigen was closely associated with one form of viral hepatitis, later called hepatitis B. At the same time, they observed that Australia antigen was a particle similar in appearance to a virus. That was enough information for Barry to begin to develop a unique vaccine, one that was prepared from antigenic particles in human blood. The patent for the vaccine was submitted in 1969 and granted in 1971. By 1975, before the vaccine had even been tried in humans, Barry predicted in print that the vaccine would not only prevent infection

with the hepatitis B virus but that it would also prevent liver cancer. Therefore, it would be the first cancer vaccine.

In 1976, Barry was awarded the Nobel Prize in Physiology or Medicine for "discoveries concerning new mechanisms for the origin and dissemination of infectious diseases." Very few people are privileged to win a Nobel Prize. Barry made his success a celebration for everyone in his group. He took as many of his colleagues and staff in the division to the ceremony as he was permitted, and least 15 and their spouses.

In 1989, he returned to Oxford to become the Master of Balliol College serving until 1994. Balliol was founded in 1263 and Barry was its first American Master. From 1999 to 2002, he was director of the NASA Astrobiology Institute. He continued his affiliation with NASA and in 2008 became a Senior Scientist at the NASA Lunar Science Institute. In 2005, he became the President of the American Philosophical Society, founded by Benjamin Franklin, and the oldest learned society in the Americas.

Barry was always a happy person. He celebrated his own life by living it to the fullest. He cycled, hiked, ran, rock-climbed, canoed, and kayaked until the end of his life. Barry had a long and happy marriage. He was always proud of the accomplishments of his wife, Jean, his four children and nine grandchildren. He left a legacy of accomplishments that saved an enormous number of lives and prevented hundreds of millions of people from becoming ill with the hepatitis B virus. On every continent, his many friends and colleagues mourn his loss.

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Preface

For almost 30 years, there has been no comprehensive text covering the many viral agents and their contributions to cancers or cell proliferation. The goal was to provide a relatively up-to-date tome, which would be a wonderful resource for the many investigators in the field of viral oncology. The chapters are meant to be a thorough review of the literature, which covers specific viruses as well as provide some synthesis of what we now know about viruses, cell proliferation and the genes that target specific cellular pathways. The previous works are outdated, and as this book is put to press, we would still have additional works to be published that will certainly be missed. We have tried to be as comprehensive as possible within the guidelines of the text without sacrificing the science and we have allowed authors much flexibility that would only be fitting if one takes on a job to complete a chapter that is as comprehensive and current as we have attempted in this book.

The primary goal here was to provide the most comprehensive version of chapters covering the majority of viruses and cancers, which will be a major resource for all trainees in the field of viral oncology from undergraduates and graduate students to post-doctoral fellows in basic science and translational or clinical studies, as well as investigators related to viral oncology. This approach was certainly limited as we will, without a doubt, be missing some of the detail and intricate nuances of each viral system. That said, we certainly tried to encourage a general theme throughout and so the experienced readers in the field may find some aspects of it less inviting. Nevertheless, I think that overall, we have attained a level of scientific sophistication for each of the chapters that it would be worth the time of experts in the field to read and it would be a solid contribution enjoyed by all including novices, as well as the experts. Thus, I take full responsibility for any omission that may have occurred, unintentionally. I also want to say that each contributor has done a fantastic job in completing his or her chapter, and that one would have to give them all a tremendous thank-you for their efforts in making this project happen even with the burdensome task of meeting deadlines and responding to my many emails in nudging them along.

The book begins with a chapter that introduces the father of viral oncology Professor Peyton Rous with some of his many interesting findings and his training,

as well as his international interactions with many scientists across the world. This year would be the 100th anniversary of the initial discovery of the Rous Sarcoma Virus. This is followed by a chapter contributed by Baruch Bloomberg, one of the many Nobel laureates whose contributions to the field has made a huge impact in saving lives throughout the world. He was passionate about pushing for the development of the hepatitis B vaccine and in doing so, led to the vaccination of millions throughout the world who would have been infected and would have a higher probability of developing hepatocellular carcinoma. He presents a historical perspective on viruses and cancer. The chapters by Drs. Jae Jung, Blossom Damania and Robin Weiss present a broad outline of how viruses can contribute or drive the oncogenic process and the potential for cancer transmission. Dr. Alwine wrote the introductory chapter for the DNA tumor viruses and suggests that while some large DNA viruses may not be able to directly transform a cell, they can certainly alter signaling and metabolism in ways that can certainly drive the transformation and possible immortalization of the infected cells. The chapter by Dr. Bala Chandran brings together the many contributions by the large DNA herpesviruses and their ability to induce the oncogenic process. Further on this theme, we also cover specific chapters on viruses in herpesviridae with my group looking at the Lymphocryptoviruses; Dr. Schultz on the Rhadinoviruses; Dr. Rose on the contribution of the retroperitoneal fibromatosis herpesvirus to retroperitoneal fibromatosis, a Kaposi's sarcoma-like disease in macaques with simian AIDS; Dr. Wong exploring the viruses in nonhuman primates; Dr. Speck presenting the murine herpesvirus model of tumorigenesis; and Drs. Parcells and Morgan who describe the Marek's disease virus and its contribution to T-cell lymphomas in chickens. These chapters provide an in-depth analysis of these viral agents and their similarities and differences in driving the oncogenic process.

We have had a great deal of success in bringing in a number of talented investigators looking at the small DNA tumor viruses, in particular the Polyoma and Papilloma viruses as well as the Adenoviruses. Dr. Gjoerup did a fantastic job in describing the many facets of the Polyomas and their contribution to cancer and this was followed by chapters from Drs. Butel, Hirsch, Khalili and Becker who provided a thorough review of the SV40 as a model system, the BK virus, the JC virus and the new Merkel cell Polyoma virus, respectively. I should also mention at this stage, that more recently in July 2010, there was a report of another virus, which belongs to the Polyoma virus family now called Trichodysplasia Spinulosa-associated Polyoma virus (TSV), which was identified in a rare skin disease called Trichodysplasia Spinulosa, exclusively seen in immunocompromised patients. It is yet to be seen if this is a ubiquitous virus in the population, which becomes opportunistic in these group of patients. A review of the Papilloma viruses covering the HPV and BPV systems was completed by Drs Jianxin You and Suzannne Wells. Adenoviruses, another group of oncogenic DNA viruses, were also included, although to date there has been no direct association with Adenoviruses and human cancers. However, there has been a wealth of information over more than 30 years showing that Adenoviruses are fully capable of meeting the major criteria for driving the oncogenic process using in vitro studies and also inducing tumors in an animal model.

The Hepadnaviruses have also been addressed in the compendium, where we take a closer look at the contributions of the hepatitis viruses B and C. Professor Tim Block has done a marvelous job of reviewing the many general attributes of the hepatitis viruses and the cancers they are associated with from a virological to a more molecular perspective. This is followed by chapters on hepatitis B virus by Dr. Mason from the Fox Chase Cancer Center, where Barry Bloomberg spent a great many of his years as a scientist working on the hepatitis virus. Dr. Mason did a fantastic job in getting us up to date on the causes of chronic liver disease, cirrhosis and many years later HBV-induced hepatocellular carcinoma, which takes at times as long as 40 years. Dr. Bret Lindenbach explores the contributions of hepatitis C virus to the development of hepatocellular carcinoma and summarizes the clinical and molecular virology links between the HCV virus and HCC. Dr. Kathleen Boris-Lawrie finds an interesting angle to explore further the role of HIV-1 as a risk factor for the development of malignancies in AIDS patients by describing why Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical carcinomas can function as prognostic indicators of AIDS and begins to suggest the relationship of coinfection and how this may contribute to the oncogenic process. We also cover the HTLV-1 and HTLV-2 where their contributions to cell proliferation were well described. Dr. Chou-Zen Giam focuses on the role of HTLV-1 in causing adult T-cell leukemia paying attention to the role of two viral proteins Tax and HBZ in viral replication and leukemogenesis. Dr. Patrick Green focuses on the biology and pathogenesis of HTLV-2 and further dissects the various cellular processes utilized by the virus in contributing to cell proliferation. The chapter on avian and murine retroviruses was skillfully put together by Drs. Karen Beemon and Naomi Rosenberg. This chapter provides information on viral oncogenes and the cooperation between these viral oncogenes as a major step in the development of cancer. They also describe the potential role of these viruses as vector systems. Dr. Leslie Parent goes into further detail in contributing the chapter on the Rous Sarcoma Virus which takes the reader from the provirus concept and how the integrated provirus, which certainly has transforming activities, led to the identification of the a cellular gene highly homologous to the viral transforming gene. Dr. Susan Ross thoroughly presents the mouse mammary tumor viruses (MMTV), which can cause breast cancer in mice by causing insertional activation of mutation of cellular oncogenes and provides an extremely useful model for understanding human breast cancer. Another very interesting virus is the Jaagsiekte Sheep retrovirus, which is associated with lung cancer. This virus causes ovine pulmonary adenocarcinoma which is derived from the secretory lung epithelial cells. Dr. Hung Fan describes here how the pathology of the virus is directly linked to the envelope protein (Env) and that JSRV is mostly pathogenic in the lung as the viral LTR is transcriptionally active only in differentiated airway epithelial cells. Drs. Renne and Swaminathan now contributed a chapter on the small RNAs and their role in viral-mediated cancers. The final chapter was a wonderful contribution by Dr. Charles Wood, who explores the role of immunodeficiency and opportunistic infections and their cooperation in driving the oncogenic process.

Finally, I wanted to personally thank all the authors for their patience and their hard work in getting their contributions to me as timely as can be expected. Even the folks who were somewhat tardy in their delivery have made it worthwhile, and I can say overall that I am personally happy with the final product. I hope this project provides a renewed vigor to our community of scientists to explore the contributions of viruses to cancer. In my many discussions with investigators in the cancer field it is still amazing and a bit puzzling to me that a great many are still hesitant to acknowledge that viruses or infectious agents on a whole have much to do with cancer, even though it is well known that about 20% of all known cancers are associated with infectious agents. I hope this renewed thrust will minimize these concerns and provide new support for the many investigators who have spent their entire lives working towards understanding how viruses contribute to the oncogenic process. Happy reading.

Cheers

Philadelphia, PA, USA Erle S. Robertson

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Chapter 1
Peyton Rous: A Centennial Tribute to the Founding Father of Cancer Virology

Volker Wunderlich and Peter Kunze

Introduction

On December 10, 1966, the American pathologist and cancer researcher Francis Peyton Rous (1879–1970) (Fig. 1.1), professor emeritus at the Rockefeller Institute for Medical Research, New York, was awarded the Nobel Prize for Physiology or Medicine "for his discovery of tumor-inducing viruses." He received the award in Stockholm from the hands of the Swedish King Gustav VI Adolf (1882–1973). Fifty-five years after his discovery (Rous 1911a, b) and forty years after his first nomination by Karl Landsteiner (1868–1943) (Nomination Database 1901–1951), one of the great scientists of the twentieth century was awarded this long-deserved honor. His work launched a new era of medicine (Vogt 1996). Amazingly, however, up to now, science historians have not written a biography of Rous.

Just a few months before the Nobel ceremony, Rous had received the prestigious Paul Ehrlich and Ludwig Darmstaedter Prize (Germany's supreme medical accolade) in St. Paul's Church in Frankfurt am Main on March 14, 1966. There, he began his award acceptance speech with the words:

> The joy that moves me on this festive occasion is particularly great because it brings to mind some personal memories. When I studied at The Johns Hopkins School of Medicine at the beginning of this century, all young physicians looked to Germany as a model. The dean of the school, Professor William Welch, an eminent pathologist, had many years earlier worked with Paul Ehrlich in Breslau (today Wroclaw) [both under the supervision of the pathologist Julius Cohnheim (1839–1884)], and upon his return to the United States had informed the American medical community of the major progress made in Germany during this time. (Rous 1966: 20) [German in original]

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Fig. 1.1 Photograph of Peyton Rous, 1959 in Israel, courtesy of Dr. Inge Graffi, Berlin. Photo credit: Weizmann Institute of Science, Rehovot, Israel

In fact, during those years, German science (and in a broader sense European science) was a world leader in many fields within and outside of medicine, not only in the inner circle of Paul Ehrlich. As a result, it was extremely attractive for young scientists from other countries to come to Germany to work here temporarily. For a future career in the USA, proof of European experience could be quite helpful, not unlike as it is today with many appointments of professors in Germany, where a previous work stay in the USA is regarded a *conditio sine qua non.*

If the young Rous, while still a student, dreamed of a sojourn in Germany, this dream was soon to become reality. In the official Nobel biography, which is based on Rous's own autobiographical notes, an additional personal recollection of the laureate is recorded:

> [At The Johns Hopkins Medical School] he graduated in 1905 [Doctor of Medicine] and became an intern in its hospital. Then, finding himself unfit to be a "real doctor," he turned to medical research instead, and for this purpose became an instructor in pathology at the University of Michigan on a beggarly salary. His work in the laboratory turned out to be mainly that of a technician because the University had small funds only, but with noble generosity Professor Alfred [sic] Warthin, head of the Department, came to his rescue, actually offering to "teach summer school" in his stead, and give Peyton the sum thus earned, if he would study German hard and use the money to go for the summer to a certain hospital in Dresden where morbid anatomy was taught. Dresden in 1907! Exquisite city in an exquisite land, with no hint of war in the air! (Anonymous 1966)

Rous, who in 1966 was well along in years, could still remember Dresden, although he seemed to have forgotten the names of the host institution (the specific hospital) and his Dresden mentor. Thus, these details remained largely unclear and

were mentioned only very briefly in the Biographical Memoirs (Andrewes 1971; Dulbecco 1976) dedicated to Rous. However, his sojourn in Dresden was the only one abroad before Rous began his exceptionally successful career as independent research scientist at the Rockefeller Institute, and apparently – even in retrospect – the time spent in Dresden was very important to him. In this paper, we report on new research inquiries concerning Warthin, Schmorl, and Rous. But first, we shall briefly present some of the pathologists who influenced Rous before his stay in Dresden. In subsequent sections, we shall briefly present several aspects of Rous' work in the years immediately following his Dresden stay that were crucial for tumor virology.

A Fresh Age of Medical Endeavor in America: William Henry Welch

Welch and Warthin influenced the career of the young Rous in different ways. He studied at the School of Medicine at The Johns Hopkins University, America's first research university, which opened in 1892. Apparently, William Henry Welch (1850–1934) (Fig. 1.2), the founding dean and professor of pathology at the medical school and at that time academic teacher, was able to spark Rous' interest in experimental medicine in general and in pathology in particular. In Baltimore, Welch established the first pathology teaching laboratory in the USA. In general, Welch dedicated himself to an extraordinary degree to the modernization of American medicine in teaching and research ["a fresh age of medical endeavor came in – an

Fig. 1.2 Photograph of William H. Welch. Photo credit: Courtesy of the Rockefeller Archive Center

age in which experiment largely took over from observation," Rous wrote, in retrospect (Rous 1948: 611)], whereby the experience gained during his research stays in Europe helped him (1875–1878, 1884) (MacCallum 1936; Flexner and Flexner 1941; Flexner 1943; Brieger 1970). As first president of the Board of Scientific Directors at the Rockefeller Institute for Medical Research in New York (1901–1933), Welch took a keen interest in Rous' subsequent rise to become a distinguished scientist. Just a few years after his death, Rous had the honor of presenting a *William Henry Welch Lecture* (Rous 1941). On another occasion, Rous noted: "It is not too much to say that modern scientific medicine reached America through William Henry Welch" (Rous 1949: 411). The *Journal of Experimental Medicine* was launched in 1896 by Welch as founding editor of a new type of medical publication, which was then developed into a highly prestigious journal by Rous during his extremely long tenure (1922–1970, until 1945 together with Simon Flexner).

Aldred Scott Warthin: A Consummate Pathologist

As a young, freshly graduated medical doctor, Rous came to Aldred Scott Warthin (1866–1931) (Fig. 1.3) at the University of Michigan with the aim of doing experimental work and obtaining training in pathology. He could not have made a better choice.

Warthin was initially trained as church musician before turning to the study of medicine. He received his MD in 1891 and his PhD in 1893. He worked temporarily in the Department of Internal Medicine at the University of Michigan before he

Fig. 1.3 Photograph of Aldred S. Warthin. Photo credit: A.S. Warthin Papers, Bentley Historical Library, University of Michigan

started his academic career there as pathologist. Following various positions from 1896 on (among them as instructor, a position Rous later held under him), he was appointed professor and director of the Pathological Laboratories at the University of Michigan in Ann Arbor in 1903. Between 1893 and 1900, Warthin regularly traveled to Europe during the summer months in order to work at the institutes of pathology in Vienna, Freiburg, and Dresden and at the same time to pursue his multifaceted interests (music, art history, collection of old books, particularly of medical incunabula). While doing so, he in no way neglected his extensive pathological research. A number of eponyms are today associated with the name Warthin: Warthin's sign (exaggeration of pulmonary sounds in acute pericarditis), Warthin's tumor (benign salivary gland tumor with lymphoid tissue covered by epithelium), and Warthin–Finkeldey giant cells (multinucleated giant cells seen in the lymphoid tissues of patients with measles). Moreover, he translated Ernst Ziegler's (1849–1905) *Lehrbuch der allgemeinen und speziellen pathologischen Anatomie und Pathogenese* [Text-Book of Pathological Anatomy and Pathogenesis] (two volumes; Jena, 1881–1882) from German into English. Warthin was, as one would say today, very well-networked and held important posts in numerous medical societies.

> In person and manner, Warthin was a model of virile fastidiousness. […] Warthin's approach to pathology was based upon a familiarity with and keen interest in internal medicine. He had a full appreciation of the biological significance of pathology, but to him, study in this field represented a particular opportunity for advancement of medicine as a science. (Anonymous 1932: 134–35) [And Rous later noted]: Warthin was bright-eyed and fresh-colored, quick and strong. He was drastic yet kind, earnest yet cheerful, and most sensitive to beauty. He loved music, gardens, books, and friends. (Rous 1936: 494)

Warthin's research on the familial incidence of cancer had a particularly lasting impact. In 1895, he initiated one of the most thoroughly documented and longest family histories ever recorded (Warthin 1913, 1925). Recently, a new update of this family, originally referred to as Warthin's family G and subsequently described as Lynch syndrome family, has been published (Douglas et al. 2005). "He [Warthin] can properly be called the father of cancer genetics," Henry T. Lynch affirmed, 90 years after the beginning of this study (Lynch 1985).

In his later years, Rous drew attention to some forgotten, yet at their time very far-sighted, works of his teacher.

> In 1904 and again in 1906 Professor Aldred Warthin of the University of Michigan, a consummate pathologist whose abilities I came to know through serving under him as instructor, reported facts making plain that human leukemia is a neoplastic disease; and in 1907 he published a study showing that this held true of a leukemia he came upon in a chicken [Warthin 1907. At the end of this paper he stated: "The problem of leukemia, then, becomes identical with that of malignant neoplasms in general." Not bad for 1907]. No causative agent was then perceptible within the neoplastic tissue, but in 1908 two Dutch [sic, correct would be Danish] workers, Ellermann and Bang, reported on a virus as causing a chicken leukemia [Ellermann and Bang 1908]. Soon after, they procured another agent from a leukemia of a differing sort, and by means of these agents they transferred the two diseases in fowl after fowl. Their findings were wholly convincing yet were written off because leukemia was not generally realized then to be a neoplastic disease. Indeed, this did not come about until the 1930s. Warthin's papers had been completely overlooked. He and the [Danish] workers were more than 20 years ahead of their time. (Rous 1967a: 844)