I. Bernard Weinstein
September 9, 1930–November 3, 2008

The sudden death of Dr. I. Bernard Weinstein on November 3, 2008, left all who knew him shocked and saddened. He had spoken to colleagues just days earlier, as usual discussing the latest results from his lab and new ideas. The community has lost a most dear colleague and mentor, and a leader who paved major roads in cancer research.

Bernie was born in Madison, Wisconsin, the youngest of four sons of Russian immigrants who inspired in him a lifelong dedication to learning and intellectual pursuit. He completed his bachelor's and medical degrees at the University of Wisconsin and his residency at Montefiore Hospital in New York. Early in his career, Bernie discovered a passion for research, initially as a clinical associate at the National Cancer Institute (NCI) and later as a fellow at Harvard Medical School and MIT. Bernie was recruited to Columbia University in 1961 and was an active member of the Columbia faculty as a Professor and Attending Physician until his death. Bernie's passion for research distinguished him throughout his career, even as he assumed major administrative roles, including Director of the Environmental Health Sciences Division at the Columbia School of Public Health, Director of the Columbia-Presbyterian Comprehensive Cancer Center, and President of the American Association for Cancer Research (AACR). Bernie's contributions to cancer research broke new ground in our understanding of the mechanisms of multistage carcinogenesis and laid the foundation for additional discoveries based on the concepts he first articulated. Here we summarize some of his major accomplishments.

Beginning in the 1970s, Bernie (often in collaboration with his close friend Dezider Grunberger) identified the structures of covalent adducts formed by chemical carcinogens on DNA and how such modifications altered the conformation of the DNA helix. In the case of BPDE, the reactive metabolite of the polycyclic aromatic hydrocarbon benzo(a)pyrene, the bulky carcinogen residue binds the N2 position of guanine and lies in the minor groove of the double helix. In contrast, the activated form of the carcinogenic aromatic amine *N*-2-acetylaminofluorene binds the C8 position of guanine, causing the modified base to be displaced from the helix and inducing a major distortion of DNA structure. Bernie's research identified conformational changes elicited by carcinogens bound to DNA and provided insight into the mutagenicity of such compounds. As a result, today it is well recognized that such changes underlie some of the mutations observed in oncogenes and tumor suppressor genes. Furthermore, the discovery that DNA conformation is altered due to adduct formation led to the idea that it could be possible to monitor DNA adducts as an approach to assessing exposure to, and biologically effective doses of, carcinogens. In collaboration with the groups of Stuart Yuspa and Curtis Harris at NCI, Bernie developed immunoassays to detect carcinogen-DNA adduct formation in human tissues following carcinogen exposure. These studies blazed a trail to a new field in cancer research, termed molecular epidemiology, and set the foundation for the ability to identify populations at increased risk of cancer by analyzing specific markers associated with environmental exposures.

Bernie also pioneered studies of the molecular actions of tumor promoters, compounds that lack carcinogenic capacity on their own but promote tumor formation from cells initiated by subthreshold doses of carcinogens. His group was the first to define molecular responses in cells treated with the phorbol ester tumor promoter TPA. He also showed that transformation of rodent cells by oncogenes is enhanced by treatment with TPA. Following the identification of protein kinase C (PKC) as a phorbol ester receptor by Castagna and Nishizuka, Bernie's lab characterized biochemical interactions between TPA and PKC and demonstrated that PKC binding and activation are common properties of diverse, structurally unrelated tumor promoters. His group was one of several to clone cDNAs encoding PKC and show that PKC constitutes a family of related enzymes. Importantly, Bernie's lab showed that enhanced expression of specific PKC isoforms mimics the effects of TPA, providing evidence that PKC is the key mediator of phorbol ester-induced tumor promotion.

Finally, following studies in his and other labs on deregulated expression of cell-cycle control proteins in cancer cells, Bernie proposed concepts about homeostatic feedback mechanisms in tumor cells that have worn well with time, gaining wide attention. In 2000, he proposed that multiple oncoproteins and tumor suppressors interact in complex networks analogous to electronic circuits and that accumulation of multiple mutations in cancer cells leads to disordered, or even "bizarre," types of circuitry not present in the normal parental cells. Bernie thus postulated that specific key proteins in cancer cells function within contexts not found in normal cells. Accordingly, he suggested that the regulatory circuitry operating in evolving tumor cell populations must adapt to the stochastic occurrence of additional mutations, possibly through homeostatic feedback mechanisms. In 2002, Bernie coined the term "oncogene addiction" and elaborated on the concept that even though cancer cells harbor numerous genetic and epigenetic alterations, many are dependent on a single

oncogenic pathway or protein to maintain their malignant phenotype and, often, their survival; by contrast, normal cells do not exhibit such dependency. He suggested that the phenomenon of oncogene addiction reflects the notion that the multistage process of carcinogenesis involves disordered regulatory circuitry, which arises in tumors as a consequence of oncogene activation and tumor suppressor gene inactivation events. Bernie's concept of oncogene addiction could in fact serve as an "Achilles' heel" for cancer cells and suggests therapies targeted at single pathways, which spare normal cells. Recent clinical successes with chronic myelogenous leukemia and with a subset of non-small cell lung cancers that harbor specific mutations of the EGF receptor augur well for this approach.

Bernie authored more than 600 publications, and his accomplishments were recognized by numerous honors, among them the Clowes Award from the AACR, the Anthony Dipple Carcinogenesis Award, the Distinguished Achievement Award of the American Society of Preventive Oncology, the AACR-American Cancer Society Award for Excellence in Cancer Epidemiology and Prevention, the Charles Heidelberger Award for Cancer Research, and an honorary degree from his alma mater, the University of Wisconsin. He was a member of the Institute of Medicine and a fellow of the American Association for the Advancement of Science and the American Academy of Arts and Sciences.

Bernie is survived by his wife of 56 years, Joan; their three children; two grandchildren; and a large extended family. He is also survived by a large group of students, postdocs, and other trainees whom he—and we—considered his second family. When referring to those who inspired him, Bernie often cited the 12th-century Hebrew scholar and physician Maimonides, who said "Honor your teachers, because they have brought you into the world of the future." Bernie inspired those he taught to emulate not only his qualities of creativity and excellence in science but also his personal qualities of warmth, generosity, and integrity. He will be sorely missed.

Robert S. Krauss[1,*] and Ze'ev A. Ronai[2,*]
[1]Department of Developmental and Regenerative Biology, Mount Sinai School of Medicine, New York, NY 10029, USA
[2]Signal Transduction Program, Burnham Institute for Medical Research, La Jolla, CA 92037, USA
*Correspondence: robert.krauss@mssm.edu (R.S.K.), ronai@burnham.org (Z.A.R.)
DOI 10.1016/j.ccr.2008.11.007