Observations on Radiation-Induced Lymphoid Tumors of Mice

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See related article by Kaplan, Cancer Research 1947;7:141–7.

Here we highlight Dr. Henry S. Kaplan's article, "Observations On Radiation-Induced Lymphoid Tumors Of Mice," published in the March 1947 issue of *Cancer Research* (1). Dr. Kaplan is recognized as one of the most significant contributors to numerous conceptual advances and discoveries in radiobiology and lymphoid tumors. During Dr. Kaplan's storied career, his untiring devotion to science led to lasting insights into radiation-induced carcinogenesis and his creativity assisted in the development of tools and procedures to cure Hodgkin lymphoma, a disease once thought to be incurable. To fully grasp Dr. Kaplan's ingenuity and contributions to cancer research, we must start with a reflection of the state of scientific thinking at the time when Dr. Kaplan first initiated the studies that led to his landmark article.

Two of the most pressing issues in cancer medicine in the early 1900s were, first, achieving a full understanding of the nature of external cancer-causing agents and, second, detailing the carcinogenesis process itself. Unearthing answers to these related issues was thought to hold promise for preventing cancer at its source and had potential to lead to the design of approaches that could reverse or halt the process of carcinogenesis. To achieve this ambitious mission, cancer research at the start of the 1900s was dominated by the suspected roles of viruses and radiation in causing cancers, both central subjects of Dr. Kaplan's research interest. In addition, during this time, the scientific community began turning to animal models to induce cancers, in an attempt to decipher the principles of latency during carcinogenesis and to understand questions relevant to human cancer.

Since Peyton Rous's discovery in 1911 that a virus can cause cancers in chickens, there has been a strong belief among experts that human cancer may also be caused by viruses. In the ensuing years, the notion that human cancers have a viral origin is also credited for resulting in a whole range of discoveries, such as oncogenes, reverse transcriptase enzyme, and cloning strategies, to name a few, which have collectively influenced the evolution of modern cancer biology. Similarly, the link between radiation and leukemia in humans had long been part of the history of cancer research and can be traced to a well-documented association of increased leukemia in radiologists in the early 1900s, as elegantly summarized by Herman C. March (2). The understanding of radiation as a causative agent for leukemia was experimentally crystallized in mice by Krebs and colleagues in 1930 (3) as well as by Dr. Kaplan's first research article in October 1944 (4). Furthermore, the idea of radiation as an agent in the development of leukemia received additional support from an epidemiologic study of atomic bomb survivors in Hiroshima and Nagasaki by Folley and colleagues in 1952 (5).

Despite these distinct developments in our understanding of the viral and radiation origins in human cancer, it was not until Dr. Kaplan's momentous work that anyone had successfully connected both radiation and viruses to cancer using a single model: mice. Beginning with his first project while attending the University of Minnesota Medical School, Dr. Kaplan started using mice as a model system to investigate whether radiation, one of the suspected cancer-causing agents at that time, could cause tumors in lymphoid tissue (4). This led to the dramatic discovery of radiation induction of leukemia in certain mouse strains and the start of an illustrious scientific journey for Dr. Kaplan.

Dr. Kaplan's pioneering work is credited for advancing basic cancer biology. Specifically, he established links between a cancer-causing agent, the activation of a latent radiation-induced virus, and leukemia. Moreover, Dr. Kaplan also provided the research community with mice as a valid model to study radiation modulation of leukemogenesis. Dr. Kaplan's work also extends to applications for cancer treatment. He coinvented a linear accelerator with Edward Ginzton for treating cancer patients with radiation and transformed Hodgkin lymphoma from a fetal cancer in the early 1950s to a nearly curable disease.

Dr. Kaplan's third research article, published in the March 1947 issue of *Cancer Research* (1), was especially noteworthy and dealt with the "observations on radiation-induced lymphoid tumors of mice." This article served as a guidepost for scientific thinking in mid-1900s and would shape some of the major advances by Dr. Kaplan and others in the coming decades. The study described how, at the time of first exposure to radiation, age was a critical variable for influencing the susceptibility and latency of radiation-induced lymphomas. Dr. Kaplan's work demonstrated that maximum susceptibility occurred during puberty and hypothesized that this correlation was related to the effects of radiation on endocrine functions. The study also established an essential role of the thymus in determining the latency of lymphomas, as the removal of the thymus increased the latency period. This correlation underscored the significance of thymus-derived factors in the development of lymphomas, and the study provided evidence that supported the spleen's role in influencing the incidence but not the latency of radiation induced lymphomas.

Dr. Kaplan's third study also resolved an important prevailing controversy at that time about the multicentric/multifocal versus unicentric nature of lymphoid cancers. The study established that unicentric nature is the correct paradigm, as Dr. Kaplan noticed the appearance of lymphomas in the thymus first before its dissemination to other organ systems (1). These observations were further refined in a follow-up study to establish the importance of the thymus and monofocal nature of lymphomas, which showed that incidents of these tumors were blocked by shielding the thymus from whole body radiation (6). These significant observations provided clues about the possible mode by which cancer spreads in humans and, in turn, opened up the possibility of interfering with the spread of cancer at multiple points.

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doi: 10.1158/0008-5472.CAN-15-3431

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Although Dr. Kaplan's third study convinced him about the origin of radiation-induced leukemia to the thymus in mice, he continued to chase the role of the thymus in radiation-induced leukemia and lymphomas in his follow-up studies. In one such study, Dr. Kaplan decided to directly irradiate the thymus but noticed no signs of radiation-induced lymphomas (7). Faced with these negative results, Dr. Kaplan corrected the theory of radiation-induced leukemia and provided an alternative hypothesis that radiation causes cancer in the thymus through an indirect mechanism. These apparently simple yet powerful observations allowed Dr. Kaplan to redirect his efforts to transplantation experiments involving grafting the thymus from nonirradiated mice to irradiated mice. These transplants again resulted in the development of lymphomas in the thymus (7), allowing Dr. Kaplan to conclude that radiation causes lymphomas by activating a dormant factor and not by directly damaging the thymus cells. The precursor for of all these impactful discoveries can be traced back to the observations reported in Dr. Kaplan's third study (1). These events eventually allowed Dr. Kaplan to discover the presumed radiation-activated factor as an RNA virus, which he named "radiation leukemia virus" (RadLV; ref. 8). Soon after, Dr. Kaplan started inquiring about the viral origin of human cancer and, as described by Dr. Charlotte D. Jacobs, Dr. Kaplan "join[ed] the ranks of pioneers in tumor virology," and "became obsessed with finding a virus that causes human cancer" (9).

Another distinctive feature of this landmark article by Dr. Kaplan was a standalone section on "Incidental Observations," which presented findings that could not be accommodated in the "Results" section but that Dr. Kaplan felt were nonetheless important. The "Incidental Observations" focused on the incidents of increased ovarian tumors, often bilateral in nature, in younger mice and allowed Dr. Kaplan to re-emphasize the influence of age upon radiation-induced ovarian tumors (1). Over time, these simple observations have proven instrumental in raising patient-relevant concerns and research questions about the chances of developing second primary cancers in patients treated with radiotherapy, developing leukemia in patients treated with radiation for other cancers (as was recently shown was the case in a breast cancer study highlighting the development of leukemia among those treated with radiotherapy; ref. 10), the role of genetic susceptibility factors in patients with certain mutations in inherited predispose genes, and raising awareness and knowledge of poorly understood underlying molecular mechanisms.

In contrast with the situation of ovarian cancer in irradiated mice, Dr. Kaplan also made another fascinating observation that radiation had a profound inhibitory effect on the development of mammary gland tumors in mice that were highly susceptible to spontaneous mammary tumors (1). This suggested that the radiation could have two opposing effects on female reproductive organs. As a matter of fact, radiotherapy is now successfully used to prevent invasive cancer including when patients receive conservative surgery. At the time these studies were conducted, it remained unknown if these effects were due to a reduction in the levels of circulating estrogen, to a radiation-induced destruction of ovarian follicles, or both. Dr. Kaplan felt these effects are likely to be associated with the effect of radiation on systemic estrogen (1). It is clear that, even today, the concepts derived from these incidental observations continue to provide answers to unresolved research questions about the nature of molecular interactions between radiation and other leukemia-promoting agents and the basis of selective primary cancers in patients treated with such external agents in various settings.

In addition to the scientific advances and overall progress that stem from this 1947 *Cancer Research* article, it is worthwhile to point out how Dr. Kaplan felt about the very purpose of communicating scientific findings with the research community. Dr. Kaplan begins the article with the stated purpose: "to present certain heterogeneous (implying inconsistency among results) observations recorded during an investigation of leukemogenesis in irradiated mice." He continues by observing that this study should be connected to future studies of induced leukemia and stated that, "[i]n as much as some of this data is a prerequisite to the proper planning of other experiments on induced leukemia, it was felt that this communication may help other investigators in this field to avoid experimental pitfalls." These keen observations underscore Dr. Kaplan's remarkable recognition that his studies are part of the broader, continuous story that is cancer research.

In brief, the third research article of Dr. Kaplan's illustrious career, published in the Journal's illustrious lifetime, will always hold a special place in scientific literature as it generated numerous advances, established the principles of radiation-induced leukemia in mice, and provided precursor observations for some of the major discoveries in the field of radiobiology, lymphoma and leukemia, and, eventually, advanced the field of cancer medicine at the levels of basic science, translational research, and patient care.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received December 16, 2015; accepted December 23, 2015; published online February 1, 2016.

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