International Journal of Radiation Oncology biology • physics

www.redjournal.org

HISTORY

Research-Driven Radiation Oncology: A Narrative on the Ongoing Legacy of Henry S. Kaplan

Eli J. Glatstein, MD,*,[1] C. Norman Coleman, MD,[†] David A. Pistenmaa, MD, PhD,[‡] Richard T. Hoppe, MD,[§] Stephen Hahn, MD,[‖] James Metz, MD,[¶] W. Gillies McKenna, MD, PhD,[#] and Eric Bernhard, PhD*,[†,#]

*University of Pennsylvania, Emeritus, Philadelphia, Pennsylvania; [†]National Cancer Institute, Bethesda, Maryland; [‡]International Cancer Expert Corps, Washington, DC; [§]Stanford University, Stanford, California; [‖]University of Texas, MD Anderson Cancer Center, Houston, Texas; [¶]Perelman Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania; and [#]Oxford Institute for Radiation Oncology, Oxford University, Oxford, United Kingdom

Received Sep 12, 2019. Accepted for publication Oct 7, 2020.

In this rapidly evolving time of precision medicine and scientifically based cancer care, how radiation oncology became a strong research-based scientific discipline in the United States after its separation from diagnostic radiology might be lost. The importance of generational mentorship, "family trees," and interpersonal relationships can be difficult or impossible to trace absent personal narrative recollections of those involved. Henry S. Kaplan is a central figure and the focal point for 3 generations of research-based academic department chairs. This report establishes a first draft of a living record of the radiation oncology history of the Kaplan legacy to serve as an example of how knowledge networks grow and flourish and as an impetus for others to trace the legacy of other radiation oncology academic "trees." Published by Elsevier Inc.

Foreword

In that radiation oncology (radiation therapy) as an independent medical specialty is approximately 50 years old, the opportunity to capture aspects of its origination depends on oral histories. The ASTRO History Committee has the wisdom to capture some oral histories. Drs Glatstein and Coleman with the assistance of Dr Eric Bernhard, who transcribed a dictated history from Dr Glatstein, worked together on this project, which is in large measure a narrative from Eli Glatstein. It is an 80th birthday project of Dr Glatstein and his colleagues that is a follow-up from a 70th birthday project.[1] The coauthors who are mentees of Drs Kaplan and Glatstein filled in historical details. This narrative emphasizes the mentorship of the trainees influenced by Dr Henry S. Kaplan in his pursuit of radiation oncology as a rigorous research-based discipline, along with the art of being a physician first and a radiation oncologist second. Recognizing that this is a "first draft" mentorship tree that will grow, it is presented for its own information and to encourage other "schools" of radiation oncology to consider constructing their mentorship trees.

Corresponding author: C. Norman Coleman, MD; E-mail: ccoleman@mail.nih.gov

[1] Deceased.

Disclosures: None. This publication is the personal opinion of the authors and does not represent policy or opinion of the institutions for which they work or have previously worked.

Eli J. Glatstein, C. Norman Coleman, and Eric Bernhard made equal contributions to this study.

Introduction

Radiation oncologists have a long history as pioneers in clinical care of cancer. Soon after the discovery of x-rays in 1895 by Wilhelm Conrad Roentgen, the practice of treating cancer patients with x-rays was started by Europeans and subsequently was established in the United States as a component of diagnostic radiology.

By the mid-20th century, radiation oncology was fundamentally a European specialty. In the United States, the majority of radiologists, including radiation oncologists, made a living by interpreting x-ray films of one type or another because there was no radiation oncology specialty at that time. There were two schools of thought about having a specialty of radiation oncology. One school was led by Henry S. Kaplan, of Stanford University, who was very much in favor of a split between diagnosis and therapy within the field of radiology. The other school, led by Juan del Regato, was very much in favor of maintaining both together. Nonetheless, they both believed that to be a good radiation therapist (later changed to radiation oncologist), one had to know diagnostic radiology to locate and target the tumor accurately.

The influx of European specialists to this country was led by Simon Kramer from Great Britain and Gilbert Fletcher from France, who was the last student of Baclesse, known for his pioneering work on fractionation. It is important to understand that Baclesse believed in protracted fractionation as a way of maximizing radiation dose to the target. Although the acute side effects of radiation therapy were being noted by Europeans and fractionation was demonstrated to increase normal tissue tolerance[2] in the midcentury, the field was not fully aware of the normal tissue injury potential of radiation, particularly the potential for lethal complications. As these European radiation oncologists came to this country, they impressed much of the leadership of radiology at the time, particularly Henry Kaplan and Morton Kligerman. Kaplan and Kligerman were very impressed with the European's knowledge of cancer as a disease process spread through the hematogenous and lymphatic systems.

In the mid-1960s the American Board of Radiology (ABR) agreed to allow 3 individuals to train exclusively in radiation oncology and become certified by the ABR: Sam Hellman at Yale University under Kligerman,[3] Ted Phillips under Franz Buschke at the University of California, San Francisco (UCSF), and Gerry Hanks under Henry Kaplan at Stanford. When it came time for the oral board examinations, all 3 impressed the board of examiners to the degree that they allowed therapy training to become a specialty in its own right. Thus, in around 1967 the ABR approved therapeutic radiology as an acceptable specialty. ABR diplomates in general radiology (issued between 1934 and 1989) were certified in both diagnostic radiology and radiation oncology. Therapeutic roentgenology was an ABR-recognized specialty beginning in 1935. In 1987, the ABR changed the name of therapeutic radiology to radiation oncology.

It is important to understand that Kaplan and Kligerman brought to the table certain traits that the Europeans did not really have at the time. The first of these was that Kaplan and Kligerman both understood the US patient, who was much less docile than the European patient. Second, they understood the US trainee, who was much less accepting of the concept that "Herr Professor" must be right. Kaplan and Kligerman both had a strong affinity for laboratory research and basic science. Both believed that laboratory research in fundamental radiation biology was essential to a strong training program. Both felt the need to build a strong laboratory program to support the clinical training program in radiation oncology. Kaplan and Kligerman were accomplished diagnostic radiologists as well as students of therapy.

The point of this presentation is to show that the impact of strong leadership and strong personality were essential to the development of radiation oncology as a research-based US specialty. This narrative focuses on the contributions of Dr Henry S. Kaplan through recollections of Dr Eli Glatstein and his colleagues and trainees.

Tracing the Kaplan Legacy and the Importance of Basic Research

By the time radiation oncology became a separate specialty with the creation of separate departments of radiology and radiation oncology in the early 1970s, there were a number of pioneers whose trainees carried forth the approach of their teachers, thereby creating a number of legacies over the 5 decades that logically have become entwined as the specialty flourished. This focus in no way diminishes the contributions of the pioneers and leaders in our specialty and may encourage similar narratives of other "schools" as the field of oncology has now evolved into the era(s) of "precision medicine" and "big data," both of which do not minimize the importance of defining the problem to be solved using insight, intuition, objective observation of results, methods, and potential flaws and understanding the pitfalls in terms of progress and potential harm caused by "group-think."

A good point of reference is that the first 3 gold medal winners of the American Society of Therapeutic Radiology, now the American Society of Radiation Oncology (ASTRO), were Drs Juan A. Del Regato, Gilbert H. Fletcher, and Henry S. Kaplan in 1977.[4] All were outstanding teachers, thinkers, and clinicians. Henry S. Kaplan was a laboratory-based researcher-clinician who now would be known as both a basic scientist and a translational researcher. His accomplishments and life have been documented since his death in 1984.[5,6] His work included the discovery of the mouse leukemia virus, the development of clinically applicable monoclonal antibody therapy, the pioneering randomized trials for the treatment

of Hodgkin disease and malignant lymphomas with Dr Saul Rosenberg at Stanford, and his intense interest in the discovery of basic mechanisms of cancer etiology and progression, including the origin of the Reed Sternberg cell. The current tools of molecular biology, including the ability to study RNA from a single cell, would make the question of the cell of origin of Hodgkin disease a much more straightforward study today, but in the 1960s and 1970s painstaking work and years were required to isolate even a single gene and discover its mechanism of action. The complex interaction of the cancer cell and the stroma remains a leading-edge question today, making Kaplan's observations of the importance of inflammation within the tumor 5 decades ago quite extraordinary.

There were a few departments in addition to the one at Stanford that focused on cancer and radiation biology laboratory research. One of these was that of Dr Mort Kligerman of Yale, whose more well-known trainee, Sam Hellman, became a generational leader at Harvard, Memorial Sloan-Kettering Cancer Center, and the University of Chicago. Others were headed by Ted Phillips at UCSF, who trained under Franz Buschke, and Herman Suit at Harvard, who trained under Dr J. Robert Andrews at the National Cancer Institute. Dr Herman Suit was another major force for radiobiology-based cancer treatment at MD Anderson and the Massachusetts General Hospital with an ongoing impact on tumor biology and physiology.

Pions, Personalities

Narrative histories have the opportunity to present observations not found in the study of CVs and publications. The interest in particle radiation therapy was built from research done in physics laboratories, with the Lawrence Berkeley National Laboratory (LBNL) and Massachusetts Institute of Technology (MIT) being examples: LBNL exploring a range of hadrons that exploit both the spatial and geographic advantage of the Bragg peak as well as the biological advantage and MIT exploring proton therapy, which was considered to have a largely physical advantage previously and with the biological properties now being better appreciated.[7] A part of the history that may now be somewhat forgotten was that of negative pi-mesons (pions), pioneered at Stanford and Los Alamos. Stanford had produced a biological rationale and a clinical device for the use of pions and had a grant under review in 1975 to 1976. This grant involved Dr David Pistenmaa, MD, PhD, a pioneering thinker in the linkage between basic physics and clinical medicine. Clinical pion therapy was conducted at Los Alamos directly by Kligerman and Dr Malcolm Bagshaw (who had taken a sabbatical there). Bagshaw succeeded Kaplan as chair of radiology at Stanford and led Stanford to the independent department of radiation oncology.

The pion research illustrates the strength and importance of personalities—always relevant in academics and life but particularly so in nascent specialties and opportunities. Pions were a particle of interest for both their spatial and geographic advantage of the Bragg peak and for their biological advantage. When Kaplan applied for a pion grant at Stanford, Kligerman was on the review committee, and the committee turned him down. Kaplan thought that Kligerman had "submarined" the application, and they never spoke for the last 10 years of Kaplan's life.

The Kaplan-Kligerman intersection occurred over Eli's career path. Kligerman came to Stanford for 6 months when Glatstein was in his last year of residency. Kaplan told Glatstein that Kligerman wanted him in New Haven at Yale, but Glatstein said, "Dr Kaplan, you never tell me to do anything, you ask me. And I'd go through fire for you, but Dr Kligerman only knows one kind of sentence—that's the imperative. And I could never work for him [because of that]." Kaplan asked Glatstein where he wanted to go, and Glatstein said that he wanted to go to London and work with Dr Jack Fowler. Kaplan asked Glatstein if he had done anything in that regard, and Glatstein said that he had written and sent a proposal to study blood flow in normal tissues that get radiation. Kaplan said if Fowler was willing to support him with animals and a radiation facility, he would write to get him a Picker Foundation award. Glatstein was the first Picker fellow in radiation biology in the history of that award. Fowler was a terrific mentor and a wonderful guy. He was a physicist who taught himself radiobiology and is an example of how much of radiation biology research came from medical physics, explaining in part the utility of mathematical models in radiobiology and clinical radiation therapy.

Pion therapy came to an end when federal support was lost at Los Alamos. Kligerman left New Mexico to return to Philadelphia, which was his home. (He had trained at Temple University as an undergraduate and in medical school). He and Dr John Yuhas were recruited independently and both showed up at Penn at the same time, which was a great shock to Yuhas, who had left Los Alamos because of Kligerman. The Kligerman science-based legacy at Yale continued under Dr Jim Fischer and now Dr Peter Glazer.

Tracing the Kaplan Family Tree

With the aging of early generations and the transformation of cancer care from descriptive to mechanism based, this paper aims to provide a marker for historians regarding the legacy of Henry S. Kaplan through the department chairs who are in the Kaplan family tree. The recent retirement of Dr Glatstein, one of the earliest Kaplan "disciples" from Stanford, served as an impetus to capture this information.

Because there are no formal records of which we were aware that traced individual trainees, the co-authors assembled a tree based on oral history. The "tree" was created, recognizing that an individual may fall within more than 1 of the branches, but we selected 1 each for simplicity. The criterion used is who headed departments

that trained residents. Interim chairs, of whom we are aware, are not included in this draft, but this is a living document and can updated periodically, possibly as a letter to the Journal.

There are a number of caveats to this paper in that many members of the Kaplan legacy who have made outstanding contributions were not department chairs. It is possible that some names have been omitted, for which we pre-emptively apologize. For this reason, and for the obvious reason that this tree continues to grow, the chart is labeled "Draft, October 2020."

Included in the tracing of the legacy are radiation oncology trainees at Stanford who worked with Dr Kaplan. Notably, many people from around the world who visited and spent months or years at Stanford were influenced by his drive for laboratory-based radiation oncology and the basic understanding of cancer. These people are not included in this list, but their contributions to oncology would meet the criteria of one of Dr Glatstein's favorite Kaplan quotes: "If you want to cure Hodgkin's disease you have to *think* like a Reed Sternberg cell." Kaplan had a way of wording things so that you would remember, and for many it defined a career commitment to discovery. Kaplan reminds us in a plaque at the University of Pennsylvania Department of Radiation Oncology that although we are specialists, scientists, technologists, and oncologists, "The most essential element of being a radiation oncologist is the judgement that goes with being a good physician."

For the organization of this draft chart, we distinguish the people who became chairs as their first step after leaving Stanford and those who went to another institution and then became a chair, all of whom were at Stanford before 1984 and were directly influenced by the Kaplan model of laboratory and clinical inquiry. These chairs have produced further chairs who are included in the Kaplan Legacy Tree.

Discussion

Figure 1 is the Draft, updated October, 2020: Henry S. Kaplan Tree of Radiation Oncology Department Chairs.

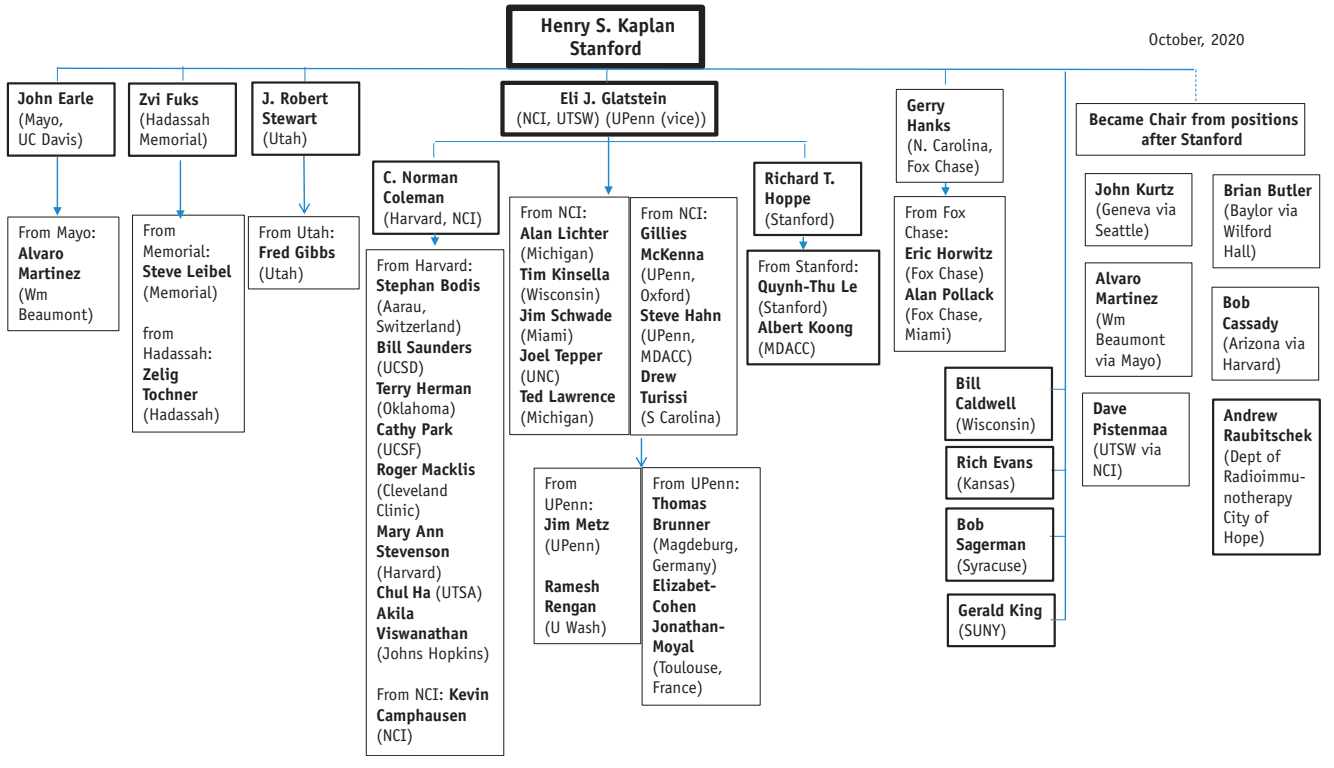

Fig. 1. Henry S. Kaplan tree of radiation oncology academic department chairs. For the sake of organizing the tree and not for a difference in the importance of their contributions to the legacy, the boxes connected to the top bar include those who became department chairs as their initial job after training and/or their initial academic appointment in radiation oncology at Stanford as of Dr Kaplan's death in 1984. Those who also trained at Stanford simultaneously under Kaplan and Glatstein are noted. A separate column "Became chair from positions after Stanford" includes those who became chiefs after another academic position. Within each of the "legacies" the names are more or less listed temporally. The names are those who headed departments that trained residents. We again emphasize that others in the Kaplan legacy have made substantial contributions as heads of research programs, national organizations, research groups, or practices but are not included in this figure. An example is Dr Sarah Donaldson, who has remained on the Stanford faculty, influencing radiation oncology through professional society leadership.

The more complete background to the Kaplan legacy is previously noted.[3,4] Dr Kaplan's successor and chair at the time of his death was Malcolm A. Bagshaw, whose lineage includes training under Isadore Lampe at the University of Michigan, along with fellow trainees Dr Phillip Rubin and Dr Robert Parker. Rubin is another pioneer of biology-based clinical care who did much of the pioneering work in normal tissue biology. Rubin is the creator of many educational tools and the founder of the Red Journal, the first issue of which was published at the American Society of Therapeutic Radiology (ASTRO) meeting when the initial gold medals were awarded. Notably, it was the second meeting in which there was the need for parallel sessions.

The importance of the theme of conducting multimodality, randomized clinical trials as pioneered at Stanford by Drs Henry Kaplan and Saul Rosenberg runs through the Kaplan legacy. Perhaps not so well recognized is the 6-month sabbatical that Dr Vince DeVita took at Stanford (1972) before he became the director of the National Cancer Institute. Kaplan was a terrific teacher and mentor, but he personalized a lot of stuff, as did and still do many others. His personalization included strong loyalty toward honesty, integrity, and action. Vince DeVita liked Kaplan because, although they disagreed on a number of points, DeVita recognized that Kaplan was willing to serve at the National Institutes of Health on various committees. He was a very good committee man because he was able to get committees to function and reach conclusions even when they did not want to; he was very adept at getting committees to make decisions they did not want to make. This affected the presence of radiation therapy at the National Cancer Institute with DeVita's recruitment of Glatstein in 1977. It was also where Dr Norman Coleman became the second board-certified dual medical and radiation oncology specialist in the United States, with Dr Steve Seagren at the University of California, San Diego, being the first (or simultaneous first). Notably, the dual training remained in Europe as the "clinical oncologist."

This paper focuses on radiation oncologists. However, the Kaplan legacy at Stanford is also recognized through the radiation biology division, led by Drs Kendric Smith and Robert Kalman, with their outstanding colleagues Drs George Hahn and J. Martin Brown and numerous trainees from around the world, including US leaders such as Dr Ted Phillips of UCSF and global leaders Drs Yosh Maruyama and Harry Bartelink. Kaplan also collaborated with laboratory-based medical oncologists and early immune oncologists, particularly Drs Ron Levy and Irving Weissman, who were conducting early work in lymphoma biology in the 1970s and 1980s. The physics contributions by Kaplan and colleagues are legendary, with the development of the linear accelerator in the United States in collaboration with Ed Ginzton and Varian and his interest in particle therapy with pi mesons.[2]

The contribution to the science of and clinical care in oncology is often traceable to "schools" and "legacies" of outstanding individuals whose ability to formulate and explore complex problems and influence the careers of others provides an interesting part of the history of a field. Henry S. Kaplan was such an individual. It has been 35 years since his untimely death at the age of 66.[3,4] A number of his first-order trainees who became chairs of academic departments are now or may soon retire or move to a variety of senior positions in the field of academic radiation oncology.

This paper intended to trace the science-based radiation oncology legacy of Henry S. Kaplan from Stanford University Medical Center. Corrections from readers to this October 2020 draft are welcome. The tree will continue to grow to include second, third, and fourth generations (and more, of course). Such legacy trees help those entering a field to understand its history and complexity and, we hope, to recognize the importance of teaching and mentorship that transcends time, distance, and evolutionary thinking upon which advances in cancer care depend. Henry S. Kaplan remains a huge influence, but because names fade into the past over time, names such as his are often unrecognized by new entrants to a field. Even though such evolution is a natural phenomenon, we hope that current science-oriented radiation oncologists appreciate their background from the Stanford program developed by Henry S. Kaplan, how the various schools have evolved, and how their legacies have intertwined over the decades. This paper may encourage other disciples of the early leaders[2] to develop such legacy trees.

References

1. Coleman CN, Glatstein E. The road not taken and choices in radiation oncology. *Oncologist* 2010;15:332-337.
2. Chamberlain WE, Young BR. Should the method of Coutard be applied in all cases of cancer treated by Roentgen rays? Available at: https://doi.org/10.1148/29.2.186. Accessed August 18, 2019.
3. Yale School of Medicine. Radiology and biomedical imaging. Available at: https://medicine.yale.edu/diagnosticradiology/about/history/. Accessed October 22, 2020.
4. Recipients of the ASTRO Gold Medal. Available at: https://www.redjournal.org/article/S0360-3016(02)03763-X/pdf. Accessed August 18, 2019.
5. Henry Seymour Kaplan. Available at: https://www.redjournal.org/article/0360-3016(85)90356-6/pdf. Accessed August 18, 2019.
6. Charlotte DeCroes Jacobs. *Henry Kaplan and the Story of Hodgkin's Disease*. Palo Alto, CA: Stanford University Press; 2010.
7. Mohan R, Held KD, Story MD, et al. Proceedings of the National Cancer Institute Workshop on Charged Particle Radiobiology. *Int J Radiat Oncol Biol Phys* 2018;100:816-831. Erratum in: *Int J Radiat Oncol Biol Phys* 2018;101:1004.