



Henry S. Kaplan

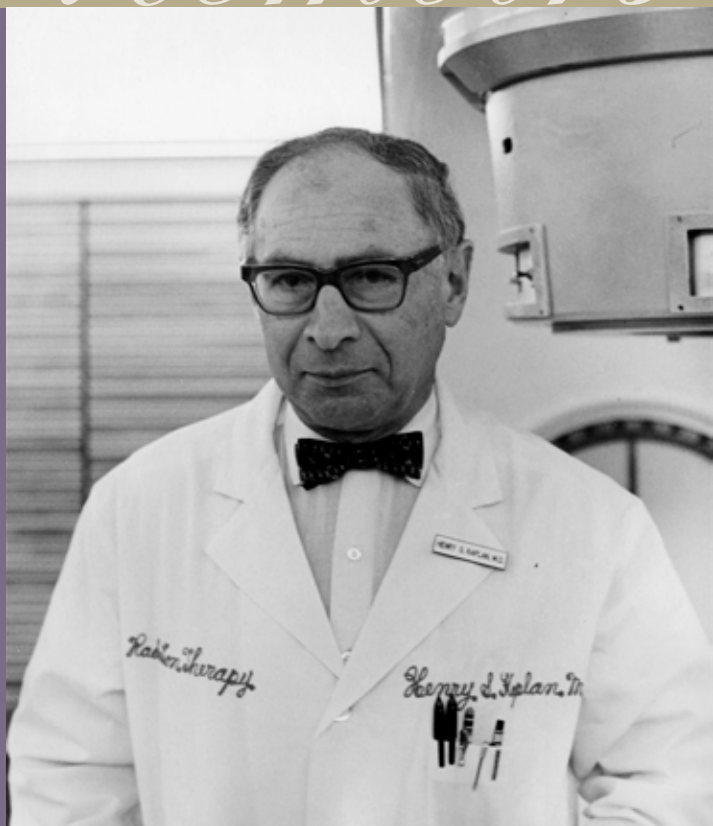
1918–1984

BIOGRAPHICAL

Memoirs

*A Biographical Memoir by
Charlotte D. Jacobs*

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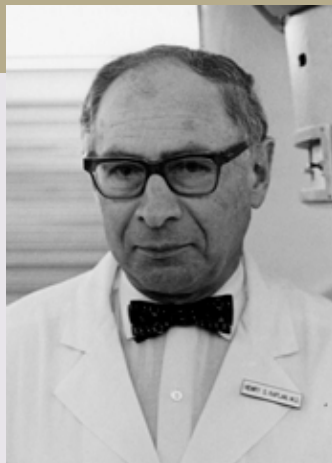
HENRY SEYMOUR KAPLAN

April 24, 1918–February 4, 1984

Elected to the NAS, 1972

Henry Kaplan remains one of the most prominent physician scientists in the history of cancer medicine. A gifted laboratory investigator, he discovered a radiation leukemia virus (RadLV) in mice. His finding—that a latent RNA virus, when activated by radiation exposure, could cause leukemia/lymphoma in mice—established a link between an external cancer-causing agent and a virus. This work was considered a milestone for subsequent studies on leukemogenesis.

With physicist Edward Ginzton, Kaplan invented a medical linear accelerator that revolutionized the treatment of cancer with radiation. When Kaplan began his work on Hodgkin's disease in the early 1950s, it was considered a fatal illness. Today, almost ninety percent of Hodgkin's patients survive, in large part because of his work. He and oncologist Saul A. Rosenberg brought together a multidisciplinary team, initiating the era of modern cancer clinical trials and providing a model for the cure of other cancers. Finally, Henry Kaplan was the consummate clinician and mentor, beloved by his patients and trainees.



Courtesy of Lane Medical Archives, Stanford University Medical Center.

A handwritten signature in black ink, which appears to read "Henry S. Kaplan". The signature is written in a cursive style.

By Charlotte D. Jacobs

Early life

Kaplan's mother, Sarah Brilliant, was born in Kiev during the reign of Tsar Nicholas II. When pogroms targeted the Jewish population, her family emigrated, settling on Chicago's west side. There she met and married dentist Nathan Morris Kaplan. On April 24, 1918, their first son, Henry, was born. He had two giant fingers on his right hand. Horrified, his mother tried to persuade a surgeon to amputate them. "Just make him strong," advised the pediatrician, and that's what she set out to do.¹

When Henry was six, his brother Richard was born, after which four cousins came to live with them. The Kaplans were doing well until 1934, when in the midst of the Great Depression, Nathan was diagnosed with advanced lung cancer. At sixteen, Henry became

his father's nurse while his mother returned to work, opening a pharmacy. Following his father's funeral, Henry announced to his family, "Someday I'm going to cure cancer."²

Initial research experiences

While attending the University of Chicago, Kaplan worked up to seventy hours a week to help maintain the family pharmacy. In 1937, he entered Rush Medical College, where he became intoxicated with basic science. An internship at Michael Reece Hospital followed. At the time, most cancer research was performed by surgeons and radiotherapists. Kaplan chose the latter as his profession, and in 1943 he began radiology training at the University of Minnesota with Leo Rigler.

In Kaplan's first research project, he and Rigler discovered that patients with pernicious anemia had an increased risk of developing gastric adenocarcinoma, which suggested an important role for screening in this disease. Yet, Kaplan was determined to ascertain how healthy cells transformed into malignancies.

Working in Arthur Kirschbaum's laboratory, he learned basic cancer biology research skills. The aim of his first project was to determine whether radiation could induce tumors of lymphoid tissue in mice, which seemed a good system to study carcinogenesis. They treated mice with total body irradiation and found it generated lymphomas and leukemias in certain mouse strains.

In 1945, Kaplan assumed his first academic appointment at Yale University, where he continued to investigate the genesis of leukemia and lymphoma using mice from Leonell C. Strong's famed mouse colony. "I was my own caretaker and technician," Kaplan recalled, "and my first year's entire research budget was approximately \$250."³

He began by irradiating a strain of inbred mice, C57BL blacks, which had a low chance of developing malignancies spontaneously. It was while investigating the influence of age at time of radiation exposure that he made an observation relevant to human disease. Most experts at that time believed that lymphoid cancers arose simultaneously from multiple foci, making them incurable. However, in his irradiated mice, Kaplan noted that lymphomas first appeared in the thymus gland, spread to adjacent lymph nodes, then to other organs, and finally entered the bloodstream. If this was the mode of spread in humans, it had major implications for potentially curative treatment. Exhilarated by science, Kaplan called his laboratory his golf course; his wife, Leah, called it his mistress.⁴

The early years at Stanford University

In 1948, Dean Loren Chandler resolved to renew Stanford's medical school, located in San Francisco, and raise it out of mediocrity. His first recruitment was Henry Kaplan as chairman of radiology. Kaplan accepted the position because he wanted to create his ideal of an academic radiology department, and considering the immense resources on the main campus in Palo Alto, he felt confident he could play a major role in creating a first-rate academic medical center. With his legendary determination, Kaplan helped orchestrate the school's move to Palo Alto. He maintained that a medical school at a great university had a special mission—to innovate, to discover—and he pushed to recruit outstanding researchers. To that end, Kaplan fought hard, whether against other faculty, the dean, or the board of trustees. He remained chairman of the Radiology Department at Stanford University School of Medicine for more than two decades.

Development of a medical linear accelerator

In the 1950s, the cobalt 60 unit was the best available radiotherapy machine. It emitted gamma rays in the 1.2 million volt range, but with limited accuracy. Kaplan referred to the cobalt unit as a “shotgun,” and said he wanted a rifle.⁵ To design such a machine, he had to be able to produce and harness high-energy x-rays and direct them to a target with precision.

Stanford physicists Edward Ginzton and Bill Hansen had recently built a powerful source of microwaves, the klystron, which was the heart of a linear accelerator they constructed for physics research. When Kaplan heard about this atom smasher at a cocktail party, he contacted Ginzton about designing a medical linear accelerator to treat cancer. They planned a six-million-volt accelerator on a moveable base so they could rotate the beam in various directions, allowing them to treat patients from several angles. In 1954, they completed construction of a medical linear accelerator that delivered radiation with such accuracy and potency that it has changed the outcome for cancer patients worldwide.

Research on carcinogenesis

In the midst of organizing his department and developing the linear accelerator, Kaplan began to assemble his laboratory in a renovated Victorian house, with the help of just one assistant. Having discovered that radiation-induced leukemia and lymphoma begin in the thymus gland, he concentrated his efforts specifically on those cells. In his next set of experiments, rather than delivering total body irradiation, he directed the radiation beam to the thymus, because radiation was thought to cause cancers by direct damage to the irradiated tissue. To his surprise, these irradiated mice remained healthy. This presented



Henry Kaplan working on the Stanford linear accelerator, ca. 1953. (Courtesy of Lane Medical Archives, Stanford University Medical Center.)

a paradox: total body radiation induced a cancer in the thymus, but direct radiation to the thymus didn't. Kaplan concluded that the prevailing theory of radiation-induced carcinogenesis was incorrect. These tumors were not caused by direct radiation damage, as always presumed, but rather by some indirect mechanism.

To prove this, he removed the thymus glands from a group of C57 black mice and treated the mice with total body irradiation. Then he transplanted thymus glands from healthy mice that had never been exposed to radiation into the irradiated mice. Lymphomas developed in the transplanted thymus glands even though those glands had not been exposed to radiation. Kaplan concluded that radiation-induced cancers of mouse thymus originated not from cells damaged by direct x-ray exposure, but from some systemic, activated factor that transformed normal lymphocytes into malignant ones.

In 1951, Ludwik Gross maintained that a virus caused leukemia in mice. Although Kaplan initially didn't believe Gross's assertion, he began to follow Gross's work closely, and with time, found the theory more compelling. "Confronted by the paradox that radiation acts by an indirect mechanism," he said, "and stimulated by Gross's discoveries, we were led to consider the possibility that an agent similar to the Gross virus might play a role in the indirect development of thymic lymphomas."⁶ Microbiologist Miriam Lieberman joined Kaplan's lab in 1959, and together they performed what would be considered a landmark experiment in viral oncology.

They began by delivering total body irradiation to C57BL mice, and as anticipated, most of the mice developed lymphoma. The researchers prepared filtrate solutions from

Kaplan's clinical research focused on Hodgkin's disease. In the early fifties, when he entered the field of radiation therapy, only five percent of patients with this malignancy survived. Radiotherapy was the sole effective treatment, but the equipment for this procedure was rudimentary, and treatment planning haphazard.

lymphomatous tissue and inoculated newborn mice with it. If Kaplan was correct, the filtrate should contain viruses that would generate lymphoma in the newborns. After eighteen months of observation, they saw no lymphomas, and Kaplan became discouraged. Then, at two years after inoculation, the first thymic lymphoma appeared in a recipient, and before long, seventeen percent of the mice developed lymphomas.

"The essence of what we discovered," Kaplan said, "is that mouse leukemias, which were ostensibly caused by x-rays and certain chemicals, were in fact due to latent viruses...triggered into activity by exposure to x-rays.... The animals can live a

completely normal life span without ever evincing the fact that they harbor these viruses, if they are not exposed."⁷

Nine years later, in 1968, Kaplan and his colleagues identified an RNA virus in the thymus gland of the mice and then in the filtrates themselves. Furthermore, they could detect these viruses months before the appearance of cancer. Kaplan called this new agent "radiation leukemia virus" (RadLV). Joining the ranks of pioneers in tumor virology, Kaplan, like Gross before him, became obsessed with finding a virus that causes human cancer.

Curing Hodgkin's Disease

Kaplan's clinical research focused on Hodgkin's disease. In the early fifties, when he entered the field of radiation therapy, only five percent of patients with this malignancy survived. Radiotherapy was the sole effective treatment, but the equipment for this procedure was rudimentary, and treatment planning haphazard. Armed with his linear accelerator, Kaplan set out to cure what most considered a fatal cancer. He knew he couldn't do it alone, however; he needed an expert team: a surgeon, a pathologist, a radiologist, and an oncologist. In 1961, medical oncologist Saul Rosenberg came to Stanford. A year later, Stanford commenced randomized clinical trials, setting a model for multidisciplinary trials and opening a new chapter in the history of Hodgkin's disease.

All they knew at the time was that Hodgkin's disease had a predilection for young adults, who usually presented with a mass in the neck or chest. Although their disease could be arrested with irradiation, it frequently recurred. In order to design more effective therapies, the research team needed to determine the stage of the disease at the time of presentation, and they needed to know how far it had spread. So Kaplan and Rosenberg performed a series of tests in newly diagnosed patients to detect all sites of disease—a concept called staging. They began to subject patients to staging laparotomy, in which the surgeon sampled intra-abdominal nodes, biopsied the liver and removed the spleen. What they found was frequent, unsuspected disease in the abdomen, disease that needed to be detected and treated if patients were to be cured.

In the early sixties, most radiotherapists treated Hodgkin's disease with low doses to small fields. Kaplan believed they needed to deliver radical radiotherapy—irradiation to involved lymph nodes and uninvolved adjacent nodes for prophylaxis—using doses as high as 4000 to 5000 rads. To perform treatment in this way, he designed two radiation ports: the mantle, so named because its shape resembled a sleeveless cloak to encompass all major lymphatics of the upper torso while sparing the lung, heart, and spinal cord; and the inverted Y, which covered major lymphatics in the abdomen and both groins. Kaplan advocated doses and radiation ports never before employed. Despite intense criticism, he and Rosenberg persisted and in the first series of randomized trials, they demonstrated improved outcomes in patients who were treated with this approach.

In 1967, oncologist Vince DeVita at the National Cancer Institute reported that with a new four-drug combination called MOPP, he had achieved high response rates in patients with the most advanced stages of Hodgkin's disease. Prior to that, single-agent chemotherapy had been used for palliation. Kaplan postulated that if MOPP was effective in patients with stage IV disease, as DeVita had shown, its potential for earlier stage disease might be even greater, especially if combined with irradiation. The results from the series of Stanford combined-modality treatments proved superb. Their later trials focused on reducing toxicity while maintaining high cure rates. As a result of Kaplan and Rosenberg's collaboration, which spanned two decades, in addition to the efforts of other researchers, the majority of patients with Hodgkin's disease are cured today.

Further cancer biology work

In 1975, Kaplan became director of Stanford's new Cancer Biology Research Laboratory, where he strived to isolate a human lymphoma virus. He postulated that if scientists could determine the causative virus, they could develop a vaccine to prevent cancer.

Although he and co-workers established a number of in vitro human lymphoma cell lines, Kaplan never found a human tumor virus, though the search lasted for the rest of his career. Later in life, he and co-workers worked on developing monoclonal antibodies to treat cancer.

Recognition

Kaplan received numerous honors and awards. In 1969, he was the first physician to receive the Atoms for Peace Prize. He was elected to membership in the American Academy of Arts and Sciences and in 1972 was the first radiologist inducted into the National Academy of Sciences. That same year, he was named the Maureen Lyles D'Ambrogio Professor at Stanford University. He received the David Karnofsky Memorial Award from the American Society for Clinical Oncology, the Robert Roesler de Villiers Award of the Leukemia Society of America, and the first Gold Medal from the American Society of Therapeutic Radiologists.

Kaplan was recognized worldwide for his accomplishments: by the French Legion of Honor in 1965; with the Order of Merit from the Republic of Italy and the Shahbanou Award of the Lila Motley Cancer Research Foundation and the Empress of Iran in 1969. He became an Honorary Fellow of the Royal College of Radiologists, United Kingdom, in 1975; he received the Prix Griffuel from France in 1977; and the Danish Cancer Society awarded him the first Medal of Honor in 1978. In 1979, he was the first recipient of the Charles F. Kettering Prize from the General Motors' Cancer Research Foundation.

A multifaceted man

Among Kaplan's greatest joys were the thousands of patients he treated throughout his career. A superb clinician, he expressed deep compassion for his patients and extended himself to them and their families, even housing a number of them in his home when they came to him for treatment from abroad.

Kaplan also traveled extensively, teaching radiotherapists around the world how to treat Hodgkin's disease. He cared deeply for his trainees. A model physician and teacher, he stimulated them to solve problems through research, thereby fostering their careers. Many of his students and residents became leaders in the cancer field.

Despite his busy schedule, Kaplan also engaged in the politics of science, serving on the National Cancer Advisory Board and numerous other groups to influence cancer care and research nationwide. Perhaps of greatest import was his participation in the

Yarborough Committee, which was responsible for crafting President Nixon's National Cancer Act of 1971. The mastermind behind the effort, Mary Lasker, insisted that the United States needed a "moonshot" for cancer.⁸ She maintained that the cure of cancer would require a specific tactical plan, a major investment in funds, and an independent agency, outside control of the National Institutes of Health (NIH), that would report directly to the President. Although Kaplan agreed they needed more funds, he argued for scientific freedom and railed against what he called the "managed approach to big science."⁹ He thought it ill advised to carve the National Cancer Institute out of the NIH. Kaplan was so forceful at Congressional hearings that he discredited some of the Committee's work. The final legislation substantially increased federal funds for cancer research and made the director of the National Cancer Institute a Presidential appointee, but it did not mandate what specific cancer research scientists could conduct. Kaplan believed in scientific freedom and risked his reputation to preserve it for U.S. scientists.

On an international level, Kaplan helped researchers set up their labs and obtain resources, and he advised several countries how to construct modern facilities to treat patients and conduct research. Kaplan was troubled to see scientists whose potential was hampered by lack of proper instruction and resources, but when he learned of those who had lost their freedom, he became incensed.

Among all the human rights issues with which he became involved, none disturbed him more than the plight of Argentine scientists during the "dirty war," the conflict between Argentine security forces, or the junta, and Argentine citizens who were associated with socialism. In 1978, he led a boycott against the International Cancer Congress, held in Buenos Aires, to draw attention to the thousands of Argentineans who had simply disappeared during the conflict. The junta knew of his role in these activities. Had he been an Argentine scientist, he would likely have been tortured and then executed. Yet, Kaplan risked his life by traveling to Argentina to try to save the scientists who constituted a significant number of those who had disappeared.¹⁰

Family

During his third year of medical school, Kaplan met Leah Lebeson, whom he married in 1942. Leah was the perfect wife for Kaplan. She allowed, and even encouraged, her husband to be single-minded in his quest to cure cancer. While raising their two children—Ann, who became a lawyer, and Paul, who became a film maker and massage therapist—Leah developed her own career, first as a psychiatric social worker, then as Stanford's assistant dean of student affairs. She had an incredible warmth and sense



Henry Kaplan with his wife Leah. (Courtesy of the Kaplan family.)

of humor. And she understood that at her husband's core lay a passion—a passion to cure cancer—that dominated his life and his relationships. He once told Leah that he considered cancer his “Moby Dick.”¹¹

Illness and death

On September 28, 1983, Kaplan was diagnosed with locally advanced lung cancer. He had never smoked, and so he thought he had contracted it from inhaling radioactive gas as he prepared radon paste during his residency. Although treated with the linear accelerator he had built to cure cancer, his tumor spread rapidly and he died on February 4, 1984.

Asked in an interview a few weeks before his death about how he would like to be remembered, Henry Kaplan answered: “...for my accomplishments that stand the test of time such as the work on Hodgkin's disease and malignant lymphomas...as the co-developer of the medical linear accelerator for cancer treatment...and for developing not just the machine but the standards for its use...as somebody who has been basically kind and deeply concerned about his patients, at the same time...as somebody who was tough enough to be willing to fight the battles. I'd also like to be remembered as somebody with a reasonably good sense of humor...and hopefully, as a good husband, a good father, and a loyal friend.”¹²

NOTES

- 1 Charlotte D. Jacobs (2010). *Henry Kaplan and the Story of Hodgkin's Disease*. Stanford, CA: Stanford University Press. p. 31.
- 2 *Ibid.* p. 41.
- 3 Kaplan to Astin (Aug 2, 1972). Henry Seymour Kaplan Papers, Stanford University Archives, Stanford, CA.
- 4 Jacobs (2010) p. 4.
- 5 Spyros Andreopoulos (2008). Reinventing the Stanford Medical School: A Conversation with Henry S. Kaplan. *Sandstone & Tile* 32:13–21.
- 6 Henry Seymour Kaplan (1967). On the natural history of the murine leukemias: presidential address. *Cancer Res.* 27:1326.
- 7 *Modern Medicine*, April 16, 1973.
- 8 Richard A. Rettig (1977). *Cancer Crusade: The Story of the National Cancer Act of 1971*. Princeton, NJ: Princeton University Press.
- 9 Henry Seymour Kaplan (1972). Emotion versus objectivity in the funding of biomedical research. *Ann. New York Acad. Sci.* 196:277.
- 10 Low-Beer, GA: Report to the Royal College of Psychiatrists, Oct 24, 1978, Henry Seymour Kaplan Papers, Stanford University Archives, Stanford CA; *Le Monde*, Feb 22, 1984.
- 11 Jacobs (2010) p. 4.
- 12 Spyros Andreopoulos (1984). "A Conversation with Henry Kaplan," Henry Seymour Kaplan Papers, Stanford University Archives, Stanford, CA.

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