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Drugs Against Cancer: Stories of Discovery and the Quest for a Cure

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INTRODUCTION

I should perhaps begin by relating how it happened that I was to devote nearly 60 years of my life to anti-cancer drug research at the National Cancer Institute (NCI) in Bethesda, Maryland. In his recent book, "The Death of Cancer, 2015" (DeVita Jr., 2015), Vincent DeVita writes of his early life, which in some ways parallels my own. We both grew up in New York in the 1940's, although he is a few years younger, and we did not know each other. We attended different medical schools, and independently joined the United States Public Health Service as an alternative to becoming inducted as young doctors in the armed forces of the United States. We both became Clinical Associates (physicians in training) at the National Cancer Institute, which, for both of us was a second choice. DeVita's first choice would have been the Heart Institute, while I had at first aimed for a research position in a neurophysiology group. He relates his early formative experience at the age of 6 when a beloved aunt died of disseminated cancer. Mine would have been our family's narrow escape from Nazi Vienna in August 1938, when I was nearly 8 years old.

DeVita then spent his career developing cancer cures in clinical research, whereas my bent was for laboratory research to try to find out how anti-cancer drugs work. Upon arriving at NCI in 1957, I was assigned to a Clinical Pharmacology unit and thought it a promising direction to take in view of my interest in chemistry, in which I had majored at Harvard College (chemistry and physics combined major). My first assignment however was to help care for children on the acute leukemia service, after which I was assigned to the adult cancer ward. That occupied much of my first year at NCI.

In his book, DeVita tells of a pretty 10 year old girl with acute leukemia to whose room he was called one night, while he was an intern at the University of Michigan in 1962 (DeVita Jr., 2015). She was in the last stage of her disease and he was called

upon to restart an I.V. that had stopped working. Her overused veins were difficult to access, but he was lucky and slipped the needle into a vein on the first try. She smiled, because it was long since a needle had not hurt ... and she gave him a 50-cent coin in appreciation. He says that it was this image that he took with him when he came to work in the childhood leukemia ward at NCI.

When I was a third-year medical student I saw a very intelligent young man of about 20 who was in the last stage (blast crisis) of acute leukemia, and for whom nothing more could be done. I saw him vomiting blood continuously . . . but he kept apologizing to the nurses for making such a mess! That poignant image was with me when I arrived to work in the same childhood leukemia ward, 2 East, in 1957, a few years earlier than DeVita.

The childhood leukemia ward in 1957 had some of the same feel to it that DeVita describes when he was a Clinical Associate there about 5 years later. Though depressing to those who knew the score, the nurses managed to keep everyone who was not in immediate pain cheerful. Although some of the children would go into brief remission, all them soon died. Nevertheless, we all suppressed the dreadful facts as we watched cheerful television cartoons with the children on often sunny weekend mornings. The designers of the Clinical Center were wise to place the wards on the South side of the building.

In order to avoid being drafted, I did not go on to residency training and came directly to NCI right after internship. Therefore, I was really under-qualified for my role to help care for very sick children. But, fortunately, I had excellent guidance and supervision from Emil J Freireich ("Jay"), who was chief of the unit.

In our regular meetings with Emil Frei ("Tom"), who headed the entire NCI clinical program, we reviewed the drug treatments and clinical problems and continued our discussions at breakfast in the cafeteria. Tom always carried a stack of big yellow punched cards (the best data management system at the time) in the pocket of his long white coat. I asked many questions, and was impressed by his scholarly answers, which he usually backed up with specific data references.

J Freireich was full of wild ideas that he expressed with great confidence, in contrast to Tom Frei's scholarly precision. But both were intent on getting an effective drug treatment for leukemia. Their different ways of thinking complemented each other, and their collaboration was extraordinarily productive. Any idea of a cure however was far away in the fog. The personalities and extraordinary successes of the Freireich-Frei duo is well described in John Laszlo's book "The Cure of Childhood Leukemia" (Laszlo, 1995). Freireich's delight with any new idea that might come to mind and Frei's scholarly demeaner, are well shown in old photos I found on the internet (Figure 0.4). Frei's scholarly demeaner, by the way, hid a brilliant sense of humor and a talent for vaudeville accentuated by his height and long legs.

In 1957, we were giving only one drug at a time, methotrexate or 6-mercaptopurine. Since two or more antibiotics given together were known to help patients with tuberculosis, I naively suggested in our meetings with Tom Frei that we try giving both drugs together. That idea was promptly shot down, because we didn't yet know enough about the actions of each of those drugs by itself.

DeVita describes the triumphirate: Freireich, Frei and Rall, and their single-minded efforts to cure cancer, particularly leukemia. He well described Freireich and Frei, and how their eccentric personalities helped to eventually get a cure. My wife, Elaine, and I attended many parties at the Rall's and Frei's and were entertained by Tom's Vaudeville talents, although we missed the wild party described by DeVita (DeVita Jr., 2015).

After my stint in the childhood leukemia and adult cancer wards, I joined David Rall (Figure 0.5) in his studies of how drugs could be made to pass the blood-brain barrier. Like DeVita, I had been recruited by Rall for the Clinical Associate position. The blood-brain barrier was one of the road blocks to effective treatment, because it kept the drugs out of the brain where residual leukemia cells were often lurking.

In those early days, I did not have much hope for the trial-and-error clinical drug testing, and felt it was better to take the basic science tack. Therefore, I stuck to the lab and (unfortunately) stopped attending ward rounds.

The first 4-drug combination, VAMP, seemed bizarre . . . but it produced a few cures (DeVita Jr., 2015). I couldn't have been more surprised! It had seemed to me that the drug combination was designed empirically without sufficient basic knowledge. I was mistaken, however, because the combination design was based on careful dosage and toxicity considerations, as well as some general notions of drug mechanisms. The combination worked, even though our knowledge of how it worked was incomplete.

My first research in the Clinical Pharmacology Service of the Medicine Branch (1957-1959) followed up on a clever (albeit unsuccessful) attempt to discover a new anti-cancer vitamin analog. One of the senior scientists in our group, Montague ("Monty") Lane, was engaged in a project that caught my attention. Since methotrexate, an analog of folic acid, was successful as an anti-cancer drug, Monty decided to test an analog of another vitamin, riboflavin. In animal tests, Monty had assured himself that his riboflavin analog was not toxic. He then tried the riboflavin analog on one of his patients whose cancer was very advanced and terminal, and for whom no further therapy was known. (In 1956, constraints on clinical testing were not yet formalized.) When the patient soon died of her disease, Monty wanted to look for the strong fluorescence of riboflavin to see whether it had gotten into her tumors. He indeed saw bright fluorescence in the cancer tissues. But he found that the fluorescence in the tumor was not due to his riboflavin analog. Checking the clinical record, he found that the patient had been given tetracycline to treat an

infection. He found that the bright fluoresce indeed was due to tetracycline that was concentrated in the tumor tissue.

That piqued my interest, and my first research projects at NIH focused on tetracycline as an agent that selectively bound to tumor tissue. It later turned out, however, that tetracycline was binding only in the necrotic (i.e., dead) parts of the cancer tissue. So, that idea led to a dead end as far as therapy was concerned.

Dave Rall, however, was interested in my work for another reason: it seemed a good way to investigate how a drug passed through the blood-brain barrier. I had found that, when tetracycline binds calcium, it can be induced to migrate into a lipid solvent (analogous to the lipid layer that constitutes the blood-brain barrier), where its fluorescence in the lipid phase was greatly enhanced, which made it easy to detect and measure by means of an assay I had developed (Kohn, 1961a). (That first paper of mine, by the way, was published in *Analytical Chemistry*, which was ironic, because I had managed to avoid courses on that seemingly uninteresting area of chemistry at college.)

In order to induce the tetracycline-calcium complex to become highly lipid-soluble, however, a third component was necessary – the most *effective* turned out to be a barbiturate. In order to test various barbiturates, I was able to order them from chemical companies, because access to many drugs that were to become widespread addiction problems was not yet restricted. Years later, I discovered in the back of a high shelf a dusty old brown bottle that contained nearly half a pound of pentobarbital that I had recrystallized and later forgotten, and I had to explain why I had in my possession a large quantity of a restricted drug without proper approval and documentation.

Anyway, I applied those findings to devise a new sensitive assay for tetracycline, which we used to investigate the permeation of tetracycline from the blood into the brain. I also found that calcium mediates the binding tetracycline to DNA (Kohn, 1961b). Those were my first studies at NIH, before I moved to work in Paul Doty's laboratory at Harvard for two years.

When DeVita (Figure 0.6) was Director of the Division of Cancer Treatment at NCI, I was Chief of the Laboratory of Molecular Pharmacology that I had founded in the Division. In our discussions and conferences, we sometimes disagreed, but he listened carefully to alternative views and was always cordial. He had the difficult task of encouraging creative research while keeping on track to curing cancer. It is a difficult task, where one can never be sure that his/her decision is the best one. His viewpoint was well expressed at a Division meeting when a major new effort was being debated; when I brought up why I thought that the planned project was unlikely to succeed, his response was a quote he attributed to Winston Churchill to the effect that "the demand for perfection spells paralysis."

Going back, my interest in science began around age 12 with a passion for astronomy, which led to my becoming active in the Junior Astronomy Club at the American Museum of Natural History in New York, among other teenagers who were passionate about mathematics and science; several of whom were to become well known in those fields. Four of us came to Washington, DC as winners in the Westinghouse Science Talent Search of 1947, where we met other like-minded young people; several of us then attended Harvard College and continued our friendship there. I wanted to become a physicist, but soon found that several of my friends had much more math talent than I did. Therefore, I thought to settle for physical chemistry. But I came to feel that the future was in biology, in which I also had an intense interest (my Science Talent Search project was on how ants recognize members of their nest mates). I guess I was driven by a desire to know how the physical and biological world worked as revealed by the sciences. Finally, I settled on the new field of biophysics, but was advised that in order to get into that field I should first go to medical school, because that was where the best research was being done. I became enthusiastic about that idea, because I wanted to find out how the human body and medical treatments work. And so it happened that my father's urging for me to go to medical school came to fruition after all, whereas I had always denied any intention of doing that because I had thought it a diversion from pure science.

I attended Columbia's medical school, the College of Physicians and Surgeons (P&S) in New York. I had been set to attend Harvard Medical School, but could not give up a New York State Medical Scholarship. However, P&S turned out to become a key to my future research, as I will go on to explain.

My professional life and experiences at P&S were in several ways entangled with some of the stories I tell in this book. This entanglement began in 1953 in Alfred Gilman's pharmacology lectures during my first year as a medical student at P&S. Gilman's lectures, although masterly in clarity and scope, were a challenge in note taking. His crystal-clear delivery was rapid and unrelenting, and there were no practical recording devices, no internet, and the only informative pharmacology textbook, the first edition of Goodman and Gilman's classic, "The Pharmacological Basis of Therapeutics" (1941), was hopelessly out of date.

As already mentioned, I had entered medical school after majoring in chemistry and physics, with the idea of preparing for research in some area of biophysics. For me, Gilman's key lecture turned out to be his description of the chemistry of nitrogen mustard, which he had a major role in elucidating during World War II (Gilman and Philips, 1946) (see Chapter 1). My ears perked up even more than usual in his always insightful lectures when he described how the nitrogen mustard molecule had to have *two* reactive sites in order to be effective as an anti-cancer drug. Moreover, the chemistry Gilman had helped to unravel showed that the two sites could each bind tightly (covalently) to something. Evidently nitrogen mustard worked by forming tight cross-links in or between some important biomolecules;

but what were they? That question intrigued me but remained latent in my mind until aroused unexpectedly 7 years later.

I may have already associated the number *two* from Gilman's lecture with the number of strands in Watson and Crick's 1953 model of DNA. Those two stands have to separate in order to form new copies of the genetic material before the cell divides. If some tight crosslink held them together, the DNA could not be duplicated, and the cell could not divide normally. I'm not sure whether that notion was already hazily in my mind at the time, but it became loud and clear when I started working in Paul Doty's laboratory at Harvard as a post-doc in 1959 (see Chapter 1).

While at medical school, there was another connection with nitrogen mustard. My closest classmate friend, with whom I did my first research projects, was Edgar Haber (1932-1997), who was to have an illustrious clinical and research career in cardiology. Ed was a relative of Fritz Haber, the inventor of mustard gas. Chapter 1 relates the story of how that World War I poison gas was a prelude to the development of nitrogen mustard as the first anti-cancer drug. I will also touch upon the ethical issues of Fritz Haber's poison gas research (see Chapter 1). I will also note that Fritz Haber's development of the process to produce ammonia from atmospheric nitrogen, so as to provide a desperately needed new source for agricultural fertilizer saved more lives from starvation than were lost during both World Wars combined. Benefit-harm dualities, however, are often complicated: the Haber-Bosch process for converting atmospheric nitrogen to ammonia and hence nitrates, also fueled Germany's production of explosives for weaponry and may have prolonged the war.

In the meantime, I had graduated from medical school, interned at Mount Sinai Hospital in New York, joined the U.S, Public Health Service as a medical officer, and gotten a job as a Clinical Associate at the National Cancer Institute in Bethesda, Maryland. Also in the meantime, I had married Elaine Kay Mogels (1931-2013) and we soon had two children, Philip and Julia. During our first year in Bethesda, Elaine and I both had jobs in the new NIH Clinical Center. Living and working in Bethesda in 1957 was wonderful, especially for us New York city dwellers. It was a very pleasant rustic rural setting in which the NIH was mostly manicured lawns, trees, shrubs and flowers. The new Clinical Center stood out as a huge all-brick monument (Figure 0.1).

But my entanglement with the events to be related also had a clinical and biological side, which has to do with how it happened that I came to do research at the then little-known National Institutes of Health (NIH). During my 3rd medical school year (1955), I had a 3-month elective at Goldwater Memorial Hospital on Welfare Island (now known as Roosevelt Island) in New York's East River (Figure 0.2). It was a chronic disease hospital where Columbia had two clinical research units; I was assigned to a unit of all-male patients that was studying hypertension; the other was an all-female unit focused on rheumatoid arthritis. During my time at Goldwater, we had a guest lecturer from the NIH, Sidney Udenfriend (1918-1999), who had worked

on the anti-malarial drug discovery program at Goldwater during the World War II. He was one of the many researchers from Goldwater who were recruited to staff the expanding NIH. Indeed, I heard the NIH referred to as "the Goldwater on the Potomac"! For me, however, it spelled an opportunity for a research career. Moreover, Udenfriend's lecture determined my initial research direction at NIH. He described his use of the new spectrophotoflourometer he had developed together with Robert Bowman and that was manufactured by AMINCO (Udenfriend, 1995) (Figure 0.3). It became the major research instrument in my tetracycline studies (Kohn, 1961b). It was a strange feeling recently to see that instrument in the museum exhibits in the Clinical Center. It was also a strange feeling to see the analytical ultracentrifuge, which was the major research instrument in my DNA crosslinking studies (Kohn et al., 1966), also consigned to "ancient history" museum displays (see Chapter 1). In both cases, I witnessed the finite lifespan of a new research technology.

The present work summarizes some of the main stories behind the discoveries, successes and failures in the early efforts to develop drug treatments for cancer. Tremendous advances have been made in recent decades and the outlook for the future is bright. However, the early history that contributed to those recent advances is not so well known. I focus on past discoveries with the view that the era of cytotoxic cancer chemotherapy may gradually wane as molecularly targeted therapies come to the fore. It may be appropriate therefore for some of us who have experienced that early period, to assemble the highlights of how those discoveries were made and to what they have been and are currently leading .

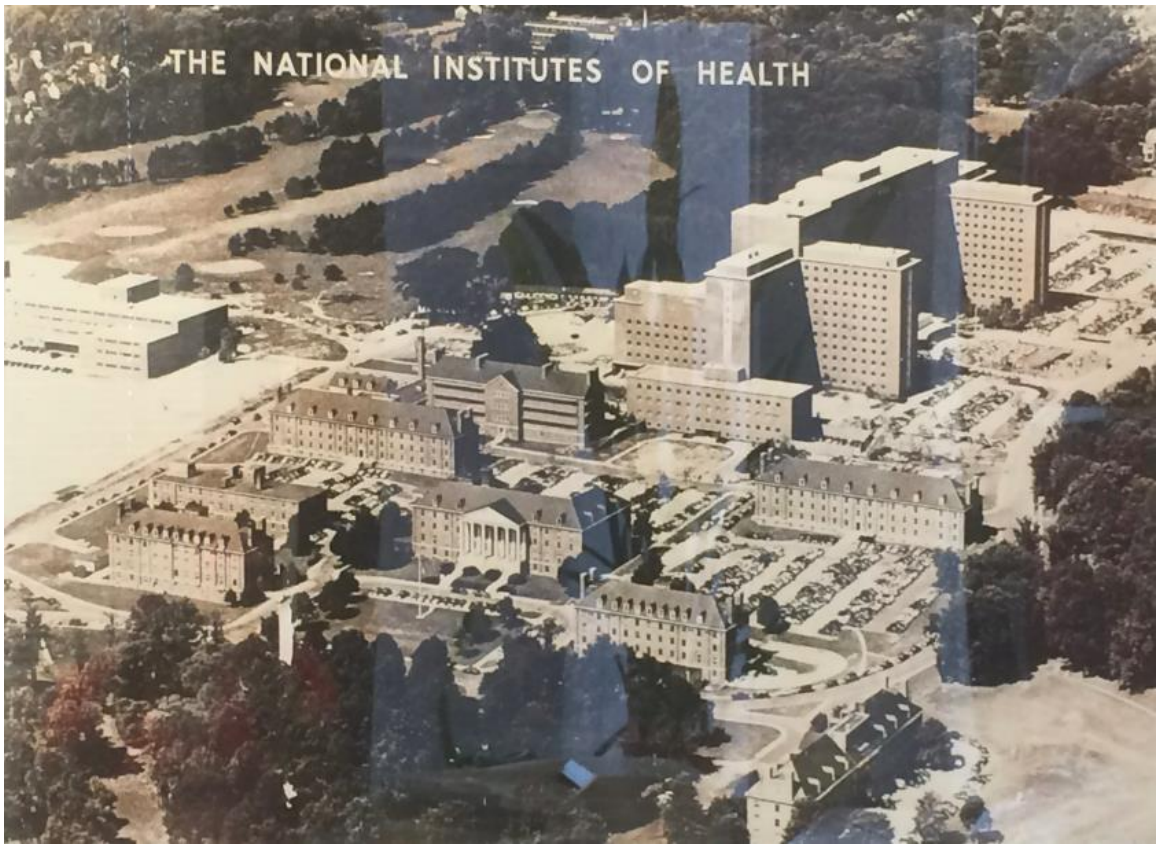


Figure 0.1. The National Institutes of Health (NIH) in 1955, shortly after completion of the Clinical Center (NIH Building 10, upper right), about 2 years before I started working there as a Clinical Associate in the National Cancer Institute. It was by far the largest building on campus (it was said to be one of the largest all-brick buildings in the world) and was to become even much larger with modern additions to right side (the North side) of the building. From the beginning, the Clinical Center included a hospital and research laboratories for several of the NIH Institutes. The meadow in the upper left was later replaced by new buildings. The building with pillars, near the center of the picture, is Building 1, which was the administrative center of NIH. All of the buildings in the foreground that are similar in architecture still existed in 2016, albeit with remodeling of their interiors. The rectangular building at the left edge of the picture, building 13, was the first major addition after the Clinical Center; it included mechanical shops for construction of new apparatus and an area for surplus equipment. The building visible through the trees at the top is the old Suburban Hospital across Old Georgetown Road from NIH.

Figure 0.2. Goldwater Memorial Hospital in 1938, as seen from the Queensborough Bridge. This vast chronic disease hospital was located on Welfare Island (later called Roosevelt Island), a two-mile sliver of land in the East River nestled between the Upper East Side and Astoria. In addition to caring for a large number of chronic disease patients, Goldwater included clinical research departments associated with the Columbia, Cornell, and NYU medical schools. The hospital, opened in 1939, was an immense facility designed to be a new model of medical care for patients with chronic illnesses. The hospital closed in December 2013, but before its destruction, a detailed photographic record was made (http://urbanomnibus.net/2014/04/autopsy-of-a-hospital-a-photographic-record-of-coler-goldwater-on-roosevelt-island/).

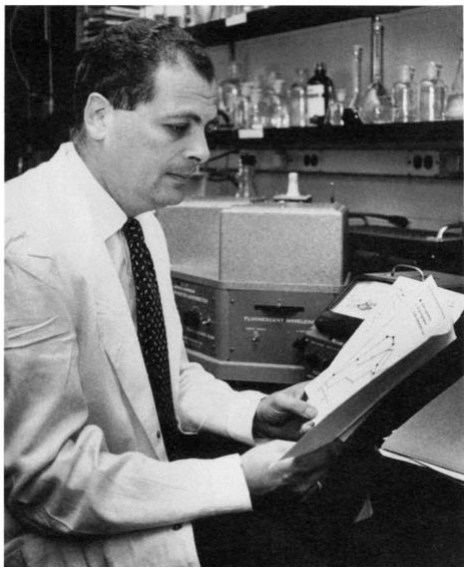
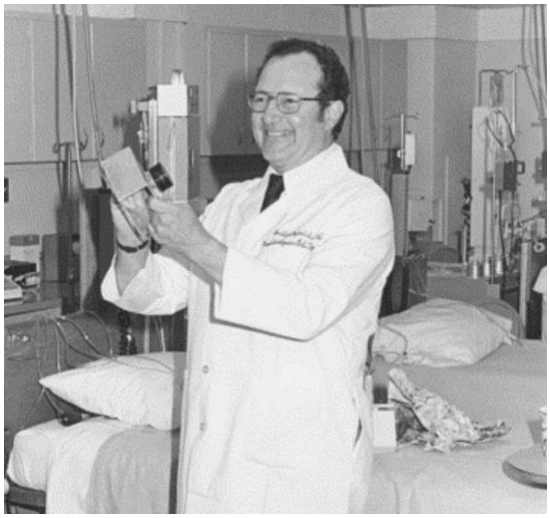


Figure 0.3. Sidney Udenfriend (1918-2000) in the late 1950's. Resting on the tabletop in the background is an AMINCO-Bowman spectrophotofluorometer that he helped to develop, and that I used in my first studies at NIH, (Udenfriend, 1995).



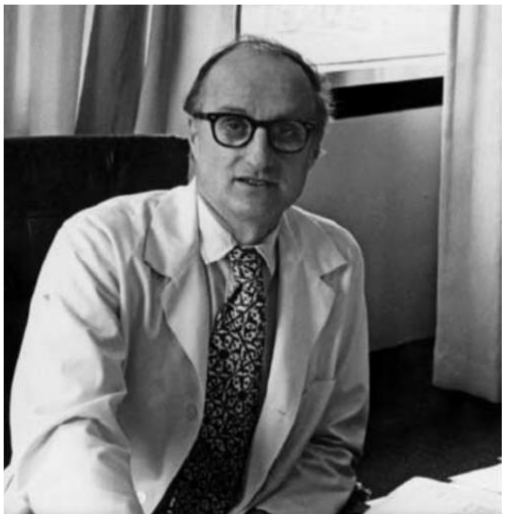


Figure 0.4. Emil J Freireich (1927-2021) (left) and Emil "Tom" Frei III (1924-2013) (right) as I remember them in 1958.

Figure 0.5. David P. Rall (1926-1999).

Figure 0.6. Vincent DeVita in 1999 with the NIH Clinical Center in the background.

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