# A History of Cancer Chemotherapy

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## Abstract

**The use of chemotherapy to treat cancer began at the start of the 20th century with attempts to narrow the universe of chemicals that might affect the disease by developing methods to screen chemicals using transplantable tumors in rodents. It was, however, four World War II–related programs, and the effects of drugs that evolved from them, that provided the impetus to establish in 1955 the national drug development effort known as the Cancer Chemotherapy National Service Center. The ability of combination chemotherapy to cure acute childhood leukemia and advanced Hodgkin's disease in the 1960s and early 1970s overcame the prevailing pessimism about the ability of drugs to cure advanced cancers, facilitated the study of adjuvant chemotherapy, and helped foster the national cancer program. Today, chemotherapy has changed as important molecular abnormalities are being used to screen for potential new drugs as well as for targeted treatments.** [Cancer Res 2008;68(21):8643–53]

## Introduction

In the early 1900s, the famous German chemist Paul Ehrlich set about developing drugs to treat infectious diseases. He was the one who coined the term "chemotherapy" and defined it as the use of chemicals to treat disease. He was also the first person to document the effectiveness of animal models to screen a series of chemicals for their potential activity against diseases, an accomplishment that had major ramifications for cancer drug development. In 1908, his use of the rabbit model for syphilis led to the development of arsenicals to treat this disease. Ehrlich was also interested in drugs to treat cancer, including aniline dyes and the first primitive alkylating agents, but apparently was not optimistic about the chance for success. The laboratory where this work was done had a sign over the door that read, "Give up all hope oh ye who enter."

Surgery and radiotherapy dominated the field of cancer therapy into the 1960s until it became clear that cure rates after ever more radical local treatments had plateaued at about 33% due to the presence of heretofore-unappreciated micrometastases and new data showed that combination chemotherapy could cure patients with various advanced cancers. The latter observation opened up the opportunity to apply drugs in conjunction with surgery and/or radiation treatments to deal with the issue of micrometastases, initially in breast cancer patients, and the field of adjuvant chemotherapy was born. Combined modality treatment, the tailoring of each of the three modalities so their antitumor effect could be maximized with minimal toxicity to normal tissues, then became standard clinical practice (1–4).

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## The Early Period of Cancer Drug Development

A selected history and timeline of events related to the development of cancer chemotherapy is shown in Fig. 1. The first four decades of the 20th century were primarily devoted to model development. The major limitations of drug discovery were twofold: first, the development of models that could effectively be used to reduce the vast repertoire of chemicals to those few that might have activity against cancer in humans, and second, the access to clinical facilities to test such agents.

A major breakthrough in model development occurred in the early 1910s when George Clowes of Roswell Park Memorial Institute (RPMI) in Buffalo, New York, Roswell Park Memorial Institute developed the first transplantable tumor systems in rodents. This advance allowed the standardization of model systems and the testing of larger numbers of chemicals. Significant efforts were subsequently focused on identifying the ideal model system for cancer drug testing, which then became a major thrust of research for the next several decades (5–11). The early model systems that were developed included Sarcoma 37 (S37), Sarcoma 180 (S180), Walker 256, and Ehrlich's ascites tumor, all carcinogen-induced tumors in mice.

It was Murray Shear, at the Office of Cancer Investigations of the USPHS, a program that was later combined in 1937 with the NIH Laboratory of Pharmacology to become the National Cancer Institute (NCI), who in 1935 set up the most organized program that would became a model for cancer drug screening (7). Shear's program was the first to test a broad array of compounds, including natural products, and had both interinstitutional and international collaborations. He ultimately screened over 3,000 compounds using the murine S37 as his model system. However, because only two drugs ever made it to clinical trials and were eventually dropped because of unacceptable toxicity, the program was dissolved in 1953 just as discussions began about establishing an organized national effort in drug screening. This failure was in part due to the antipathy toward the testing of drugs to treat cancer but also to a lack of information and experience on how to test potentially toxic chemicals in humans.

The most excitement in this era was generated by the introduction of hormonal therapy when, in 1939, Charles Huggins, based on an early observation on the effect of estrogens on breast cancer made by Beatson in 1896 (12), treated men with prostate cancer with hormones and was able to show responses by decreases in acid phosphatase levels (13). Although this exciting piece of work was an important addition to the systemic treatment of cancer and earned Huggins a Nobel Prize, it was not considered to be related to the issue of whether chemicals could ever control cancer.

## World War II and the Immediate Post-War Period

Although gases were not used on the battlefield in World War II (WWII), a great deal of research was done on vesicant war gases (5, 8). The experience in WWI and the effects of an accidental spill of sulfur mustards on troops from a bombed ship in Bari Harbor, Italy, in WWII (14, 15) led to the observation that both bone marrow and lymph nodes were markedly depleted in those men exposed to the mustard gas. Consequently, Milton Winternitz at

Yale, who had worked on sulfur mustards in WWI, obtained a contract to study the chemistry of the mustard compounds from the U.S. Office of Scientific Research and Development and asked two prominent Yale pharmacologists, Alfred Gilman and Louis Goodman, to examine the potential therapeutic effects of these chemicals. Goodman and Gilman carried out experiments in mice bearing a transplanted lymphoid tumor with one compound, nitrogen mustard. When they observed marked regressions, they convinced their colleague Gustaf Lindskog, a thoracic surgeon, to administer nitrogen mustard to a patient with non–Hodgkin's lymphoma and severe airway obstruction. Marked regression was observed in this and other lymphoma patients. The initial study was done in 1943 but because of the secrecy associated with the war gas program, the results were not published until 1946 (16–18). The 1943 results set off a burst of support for the synthesis and testing of several related alkylating compounds, including oral derivatives such as chlorambucil and ultimately cyclophosphamide.

The use of nitrogen mustard for lymphomas spread rapidly throughout the United States after the publication of the Lindskog article in 1946. If one reads the literature of the time, there was a real sense of excitement that perhaps drugs could cure patients with cancer (19). Unfortunately, remissions turned out to be brief and incomplete, and this realization then created an air of pessimism that pervaded the subsequent literature of the 1950s. A cadre of academic physicians, led by the famous hematologist William Dameshek, who having seen apparent success turn to failure could never again be persuaded that cancer was curable by drugs (20), became harsh critics of a national drug development program and the effort to prove that drugs could cure advanced cancers.

Nutritional research before and during WWII had identified a factor present in green leafy vegetables that was important for bone marrow function. This factor turned out to be folic acid, which was first synthesized in 1937. It was later shown that folate deficiency could produce a bone marrow picture reminiscent of the effects of nitrogen mustard. Farber, Heinle, and Welch tested folic acid in leukemia and they came to the conclusion that it actually accelerated leukemia cell growth (21). Although this observation was later proved to be spurious, Farber collaborated with Harriet Kilte of Lederle Laboratories to develop a series of folic acid analogues, which were in fact folate antagonists, and these compounds included aminopterin and amethopterin, now better known as methotrexate. Farber subsequently tested these antifolate compounds in children with leukemia and, in 1948, showed unquestionable remissions (22).

Another WWII-related program was the large-scale screening of fermentation products by the pharmaceutical industry to isolate and produce antibiotics to treat wound infections, based on the observations on penicillin. Antitumor effects were examined for some agents as well. Penicillin was even initially thought to have antitumor properties that were never confirmed. The antibiotic, actinomycin D, came from this program. It had significant antitumor properties and enjoyed considerable use in pediatric tumors in the 1950s and 1960s (23). This drug established the initial interest in the search for more active antitumor antibiotics, and this effort yielded a series of active antitumor antibiotics in common use today.

Finally, a fourth WWII government effort conducted by the Committee on Medical Research of the Office of Scientific Research and Development, the antimalarial program, served as an organizational model and a source of talent. The success in the search for synthesis and production of effective antimalarial compounds in WWII showed that a nationally organized, well-supported effort, tightly focused on a disease, could yield positive results. Several of the individuals who later organized the national effort of the NCI had experience with this program in WWII and believed the same kind of effort would yield positive results developing drugs against cancer (14).

The early activity of nitrogen mustard and methotrexate also provided a great stimulus for the synthesis of other drugs in addition to alkylating agents and antifols. In 1948, the same year that Farber showed the antifolate activity of methotrexate in childhood leukemia, Hitchings and Elion isolated a substance that inhibited adenine metabolism. By 1951, they had developed two drugs that would later play an important role in the treatment of acute leukemia: 6-thioquanine and 6-mercaptopurine (24, 25).

**Figure 1.** Key advances in the history of cancer chemotherapy

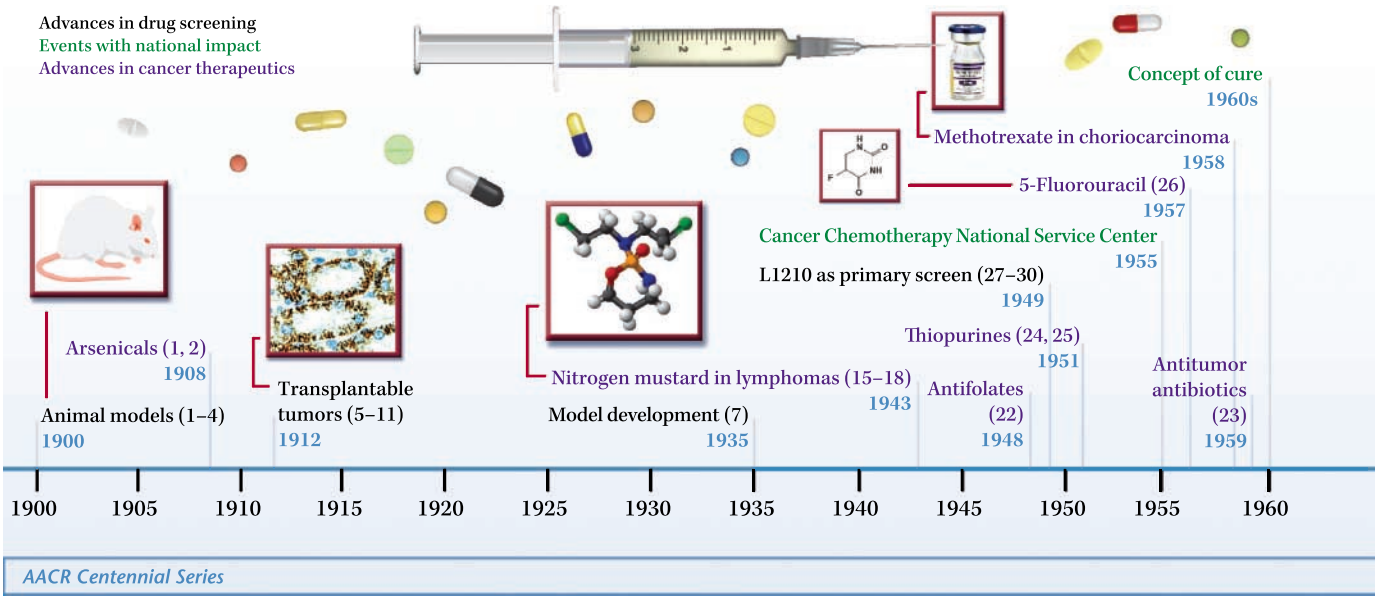

**Figure 2.** Dr. Min Chiu Li. A pioneer chemotherapist who developed new curative chemotherapy for metastatic choriocarcinoma and testicular cancer (circa 1968).

These thiopurines and other related drugs have been widely used not only for acute leukemias but also for other diseases, such as gout and herpes viral infections, and as immunosuppressive agents in the organ transplant setting. As a result of this seminal work, these investigators received the Nobel Prize in Medicine in 1988.

It was not until the middle 1950s that Charles Heidelberger and colleagues at the University of Wisconsin developed a drug that was aimed at nonhematologic cancers (26). They identified a unique biochemical feature of rat hepatoma metabolism in that there was greater uptake and use of uracil relative to normal tissue. Based on this observation, Heidelberger "targeted" this biochemical pathway by attaching a fluorine atom to the 5-position of the uracil pyrimidine base, which resulted in the synthesis of the fluoropyrimidine 5-fluorouracil (5-FU). This agent was found to have broad-spectrum activity against a range of solid tumors and, to this day, remains the cornerstone for the treatment of colorectal cancer. In retrospect, this agent represents the very first example of targeted therapy, which has now become the focus of great attention in current cancer drug development, although the target in this case was a biochemical pathway and not a molecular target. These clinical observations increased the interest in chemotherapy and spurred the emergence of the R.B. Jackson Laboratories as a major source of inbred mice and transplantable tumors, which fostered the establishment of several independent screening programs around the world.

The largest post-war program of drug development before the NCI became involved was at the Sloan-Kettering Institute (SKI) in New York. Under the leadership of Cornelius "Dusty" Rhoads, nearly the entire program and staff of the Chemical Warfare Service, including the pioneer clinical investigator David Karnofsky, were assembled into the SKI drug development program. The SKI investigators used the murine S180 model as their primary screen because it was moderately sensitive to known compounds and was easily transplanted with nearly 100% success, whereas in Japan, Yoshida used an ascites sarcoma model. Additional substantial programs were established at the Chester Beatty Research Institute in London under Alexander Haddow, the Children's Cancer Research Foundation in Boston under Sydney Farber, and the Southern Research Institute in Birmingham, Alabama, under Howard Skipper. At that time, the only institutions that had facilities devoted to clinical drug testing in cancer patients were the Delafield Hospital at Columbia University, Sloan Kettering, the Children's Cancer Research Foundation, and the Chester Beatty (8). Rhoads also attracted the interest of the pharmaceutical companies by offering to screen and evaluate the pharmacology of submitted compounds under special conditions of confidentiality. This practice was later adopted into the program of the NCI by Endicott as the very important "Commercial Discreet Agreements," without which the industry would not have been willing to cooperate.

As larger numbers of tumor systems became available, the central question for drug screeners at that time was which

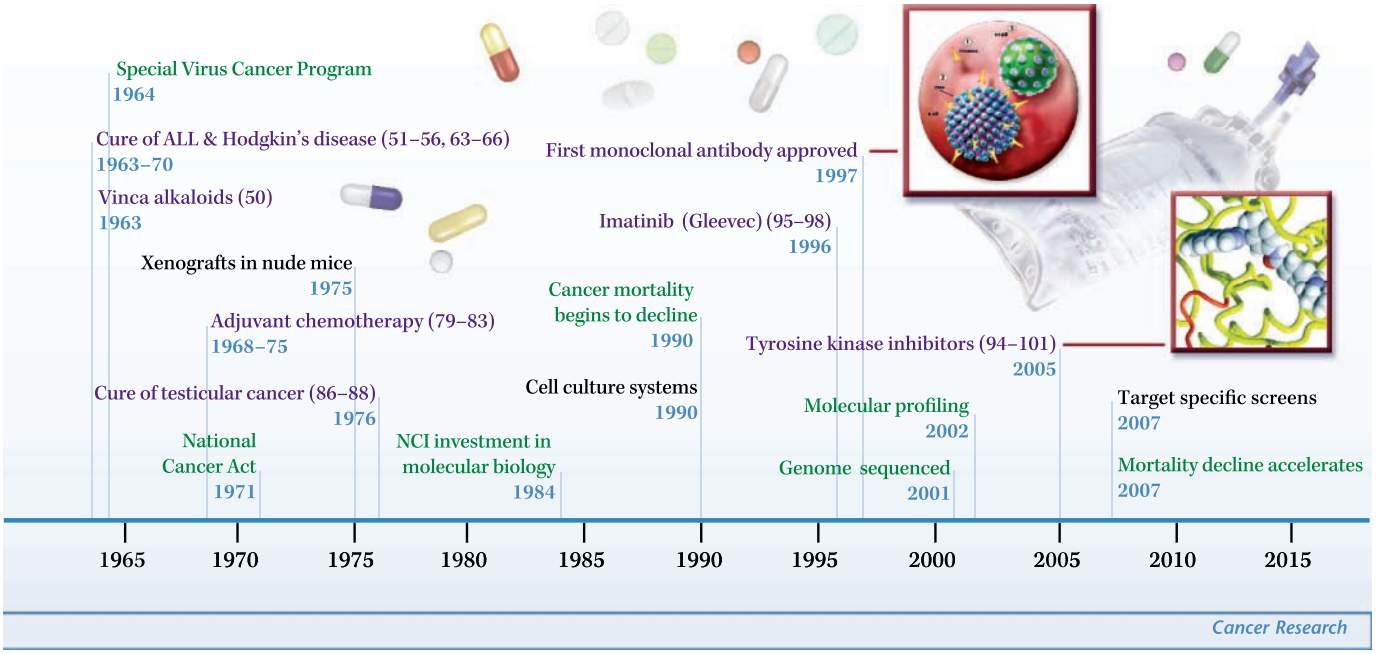


**Figure 1** *Continued.*

**Figure 3.** Dr. James Holland directed cooperative group studies in childhood leukemia (circa 1970).

transplantable tumor was the best at predicting human activity. Among those available for use was a murine leukemia induced by a carcinogen, Leukemia 1210 (L1210), described by Lloyd Law at the NCI (27). This model system was adopted, and its kinetics were carefully studied by Skipper and colleagues at Southern Research Institute (28, 29) and later by DeVita and colleagues (30). The L1210 model emerged as the most versatile animal tumor screening system and was adopted by the NCI as its primary screen. The research that went into the selection of the best screening system is reviewed in an article by Goldin and colleagues (5).

## The 1950s

The 1950s were a period of undue pessimism due to the disappointment over the failed promise of nitrogen mustard to produce durable remissions. This negative view was somewhat offset by the discovery of corticosteroids, which were to be used in cancer patients but were also quickly found to produce only brief responses when used alone (31, 32). Although 5-FU was introduced into the clinic in 1958, there were few data of substance about the usefulness of this drug until many years later.

However, the ferment created by the response of acute leukemia in children to methotrexate, and the availability of new screening systems, led to the development of the Cancer Chemotherapy National Service Center (CCNSC) in 1955. Although the story of how this program was developed is half science and half politics, without question it changed the face of cancer drug development in the world and changed the NCI and NIH irrevocably. This fascinating history is reviewed in detail in the excellent articles by Zubrod and colleagues (8) and Goldin and colleagues (5). Given the interest in the childhood leukemia data, the National Advisory Cancer Council, the predecessor to today's National Cancer Advisory Board, convened a panel in 1952 to discuss the subject of a national program of cancer drug development and concluded that the state of knowledge was inadequate to permit the design of a "crash" program. The view that it was premature to develop such a program was bolstered by another review in 1954 by a committee of the American Cancer Society, chaired by Alfred Gellhorn, a prominent academician involved in cancer treatment and Director of Columbia's Frances Delafield Cancer Center (33).

During this time and behind the scenes, the activist and philanthropist Mary Lasker, in touch with Sydney Farber and impressed with the data in childhood leukemia and the antimalarial program, had been trying to interest the U.S. Congress in providing funds for such a program. In 1954, the Senate Appropriations Committee encouraged the NCI to develop a program and provided $1 million for cancer drug development. There began a tug of war over the proper way to use these funds between members of the academic community who preferred that funds be supplied for investigator-initiated research and those interested in cancer drug screening who preferred a centralized national program. Ultimately frustrated by the slow progress, the Senate Appropriations Committee, at Mary Lasker's urging, provided $5 million to NCI with a mandate for the establishment of the CCNSC (8). Ken Endicott became its first director and was to later become the fifth director of NCI. The entire program was set up between May and October of 1955, a tribute to Endicott's organizational skills, and provisions were made for commercial discreet agreements with the industry, access to clinical testing facilities, and the establishment of contracts with organizations to procure mice and testing sites. In addition, resources were made available for pharmacology and toxicology testing and drug production and formulation and ultimately an organized decision making process called the "Linear Array with a Decision Network" whereby drugs coursing through the system had to meet specific criteria before passing to the next step toward the clinic (34–36).

As part of the initial development program, the CCNSC set up a Cancer Chemotherapy National Committee made up of NCI staff with representation from several national organizations as well, including the American Cancer Society. This committee then established a series of panels to further address each of the major issues facing those involved in cancer drug development. This effort was the most extensive review of requirements of drug development ever conducted. One of the panels of the Cancer Chemotherapy National Committee was the clinical panel directed by Gordon Zubrod. Out of this effort came the current cooperative group program starting with the "Eastern Solid Tumor Group" (now the Eastern Cooperative Oncology Group). Subcommittees of this panel also addressed the issues of the development of hormone therapy, statistical analysis, protocol development, and the design and conduct of clinical trials, many of which are still in use today but were not in existence in older screening programs like Shear's at NCI. This ensured a wider collaborative effort and provided standardized techniques and a stable source of funds, heretofore unavailable, for the testing of new approaches to cancer treatment (37, 38).

The CCNSC programs were supported by contracts, not grants. This was the first time contracts had been used at the NCI or NIH for any type of program, and it created considerable consternation, which was to dog this and a later NCI program, the Special Virus Cancer Program (SVCP), for several decades. The use of contracts became synonymous with "targeted research," and was often considered anathema in the academic world. Regardless of the quality of the work, it was often discounted if it had been supported by contracts.

In 1966, the CCNSC was incorporated into the NCI structure as part of the Chemotherapy Program directed by Zubrod. Now named the Developmental Therapeutics Program, it was more tightly linked to both the extramural clinical trials program and the NCI intramural program. This was done over the loud protests of the Deputy Director for Science at NIH, Robert Berliner, who feared the contamination of the NIH with a contract-supported research effort. By 1974, the CCNSC and its successors had grown into an annual budget of $68 million and was producing almost 3 million mice

bearing transplantable tumors and screening over 40,000 compounds a year until parts of its effort began to be supplanted by the pharmaceutical industry as they began to see an emerging market for cancer drugs that worked.

Still, skepticism surrounded the clinical usefulness of chemotherapy for cancer in the 1950s. A great deal of resources were being invested in a controversial effort to develop drugs, yet there was no evidence that drugs could cure or, for that matter, even help cancer patients in any stage despite some impressive antitumor responses. The very rare tumor of the placenta, choriocarcinoma, was the first to be cured. The preliminary results of a unique treatment program were reported in 1958 (39). The principal architect of the treatment, using methotrexate in an unusual way for the time, was Min Chiu Li (Fig. 2). The problem was no one was prepared to believe the results were significant because the primary site of the tumor was a parental hybrid tissue, subject, it was thought, to immunologic control. As a sign of the times, after the first two patients went into remission, they were presented at NCI Grand Rounds at the Clinical Center. The subject of the rounds was "the spontaneous regression of cancer" with the speaker being none other than Gordon Zubrod. Li was also told that if he persisted in using his radical treatment, he would have to forfeit his position at the newly opened clinical center. He persisted and was asked to leave (40, 41). Later, when the Lasker Prize was given in 1972 to investigators who had participated in the studies of the cure of gestational choriocarcinoma, Li shared his part of the prize with the person who discharged him. He later was to develop the first effective combination chemotherapy programs for metastatic testicular cancer (42).

Clinically, the 1950s ended on the same sour note on which they began, but eventually the creation of the CCNSC established one of the most successful government programs ever. Although it was often criticized (43–46), it gave birth to the multibillion-dollar cancer pharmaceutical industry. When he was Director of the NCI, Vince DeVita was often asked how many drugs came out of the program. The answer is, up until 1990, all of them because the CCNSC provided a unique central resource, unavailable in medical centers or in industry,

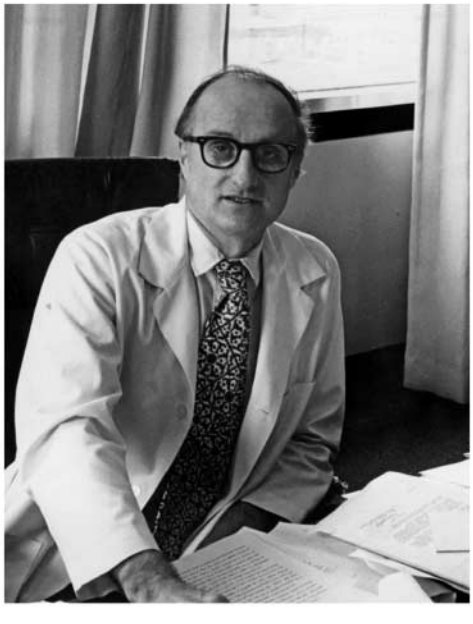

**Figure 4.** Dr. Emil Frei (circa 1965).

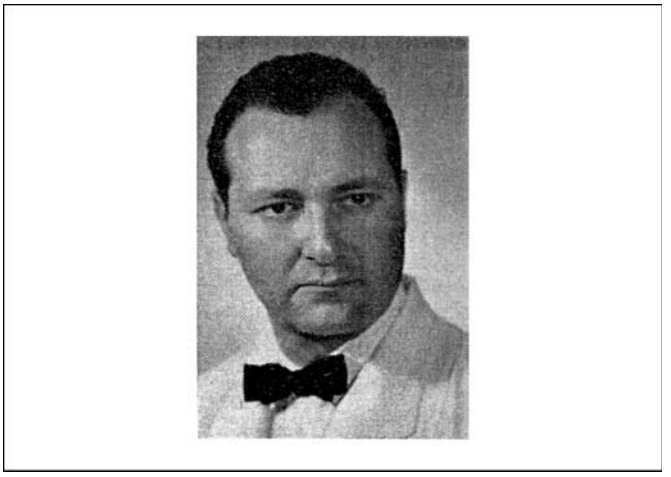

**Figure 5.** Dr. Emil J. Freireich during his days at NCI (circa 1964).

to test, develop, and produce drugs whatever the source. Drugs that were not identified in the primary screen itself often were evaluated in the ancillary tumor systems, and the necessary toxicology and pharmacology for regulatory approval for many drugs was done under the auspices of the CCNSC. Clinical studies were then often done under contract with the NCI or in one of the national cooperative groups. None of this would have been possible in the academic medical centers as even today the kinds of resources are not available at the majority of university cancer programs nor were these studies considered to be worthy of investigator-initiated research.

## The 1960s—The Concept of Cure

In the 1960s, medical oncology did not exist as a clinical specialty. Those who were given the task of administering chemotherapy at most medical centers were regarded as underachievers at best. The main issue of the day was whether cancer drugs caused more harm than good, and talk of curing cancer with drugs was not considered compatible with sanity. The prevailing attitude toward the use of chemotherapy can only be described as hostile. A few vignettes will illustrate this point rather graphically.

At the medical institution where Vince DeVita began his career, the "chemotherapist" was an endocrinologist, Louis K. Alpert, who had published one of the early reports on the use of nitrogen mustard in lymphomas and administered chemotherapy as a sideline. Because of his stern and pointed visage, and because he appeared when chemotherapy was to be administered, he was referred to by the house staff and the faculty as "Louis the Hawk and his poisons," a designation he took gracefully. Unfortunately, poison was the term in general use for anticancer drugs.

The Francis Delafield Hospital, although connected with Columbia University College of Physicians and Surgeons, was ultimately denied access to residents and interns from Columbia because two successive chairmen of medicine, Robert Loeb and Stanley Bradley, did not want their house staff exposed to cancer patients receiving these cancer poisons, although their mentor would have been the distinguished Alfred Gellhorn. As Alfred Gellhorn recently recounted to the authors,[1] the otherwise great clinician Loeb, a giant in the field at the time, had a blind spot when it came to caring for cancer patients and testing

[1] Interview with Dr. Alfred Gellhorn (November 26, 2007).

chemotherapy. He was fond of saying to Gellhorn, rather openly, "Alfred, you belong to the lunatic fringe." The Delafield Hospital program, the first example of a university-based cancer center, with many illustrious graduates, including Bernard Weinstein, Elliot Osserman, John Ultmann, Jim Holland, Paul Marks, Franco Muggia, Helen Ranney, and Jack Davidson, was closed in 1971. The leaders at Delafield provided the nidus to create a new cancer center at Columbia in 1974, after the cancer act in 1971 provided a mandate to create new university-based cancer centers.

At Yale, the first institution to test chemotherapy in humans in the modern era, the chemotherapist Paul Calabresi, a distinguished professor and founding father in the field, was forced to leave because he was involved in too much early testing of new anticancer drugs, an exercise as unpopular with the faculty and house staff at Yale as it was at Columbia.

At the Clinical Center of the NCI, where so many of the early breakthroughs with chemotherapy occurred, the well-known hematologist George Brecher, who read all the bone marrow slides of the leukemic patients, routinely referred to the Leukemia Service as the "butcher shop" at rounds.

And these are only the stories that can be told. It took plain old courage to be a chemotherapist in the 1960s and certainly the courage of the conviction that cancer would eventually succumb to drugs. Clearly, proof was necessary, and that proof would come in the form of the cure of patients with childhood acute leukemia and in adults with advanced Hodgkin's disease.

By 1960, the L1210 leukemia system had been established as both the primary screen and the model for treating acute leukemia. Work on L1210, childhood acute leukemia, and Hodgkin's disease was going on in parallel. At the turn of the decade, complete remissions were occurring in about 25% of children with leukemia, but with single agents, they were brief, measured in months. Several institutions were cooperating in protocols with a design that hinted at cure, not palliation, as an end point. Such studies were in progress at RPMI in Buffalo under Jim Holland (Fig. 3), St. Jude's in Memphis under Don Pinkel, Boston Children's Cancer Center under Sydney Farber, Memorial Sloan-Kettering Hospital under Joe Burchenal, and the Clinical Center program at the NCI under Emil (Tom) Frei (Fig. 4) and Emil (Jay) Freireich (Fig. 5) (46–49). Gordon Zubrod, then director of the National Chemotherapy Program, the organizer of this effort, played a major role in linking the work of Howard Skipper (Fig. 6) on L1210 at Southern Research Institute with the clinical programs at the Clinical Center of the NCI and elsewhere.

A major breakthrough occurred for both leukemia and Hodgkin's disease with the discovery of the activity of the plant alkaloids from *Vinca rosea* at the Eli Lilly Company (50) and discovery of the activity of ibenzmethyzin in Hodgkin's disease (soon to be renamed procarbazine) by Brunner and Young (51) and DeVita and colleagues (52).

Furth and Kahn (53) had shown that a single implanted leukemic cell was sufficient to cause the death of an animal. At Southern Research, Skipper had suggested that to cure L1210, it was necessary to eradicate the last leukemia cell because back extrapolations of survival after treatment suggested that one surviving cell was sufficient to kill a mouse. He offered the "Cell Kill" hypothesis, which stated that a given dose of drug killed a constant fraction of tumor cells not a constant number, and therefore success would depend on the number of cells present at the beginning of each treatment (54). This observation changed the existing approach to dosing in the clinic in favor of more aggressive use of chemotherapy. In L1210, the schedule of administration of drugs was also proving to be important. Finally, combinations of drugs, an anathema in medicine at the time, were superior to single agents. Whereas Skipper tested

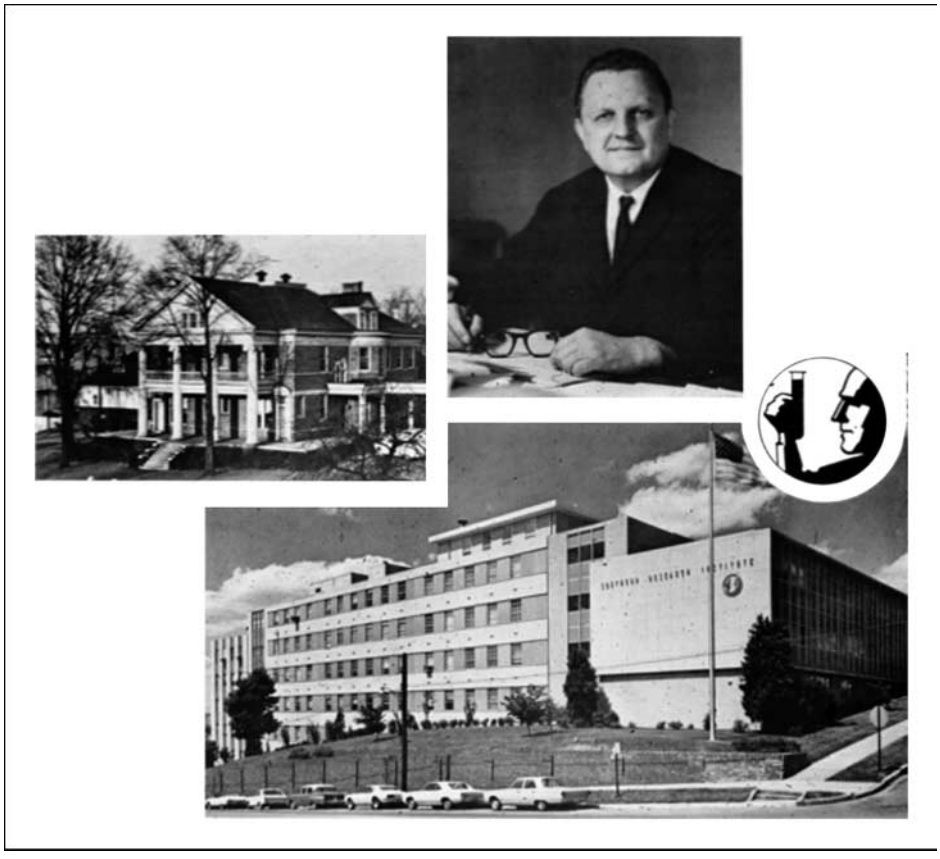

**Figure 6.** Dr. Howard Skipper, a mathematical biologist. He was the premier mouse expert at the Southern Research Institute in Birmingham, Alabama.

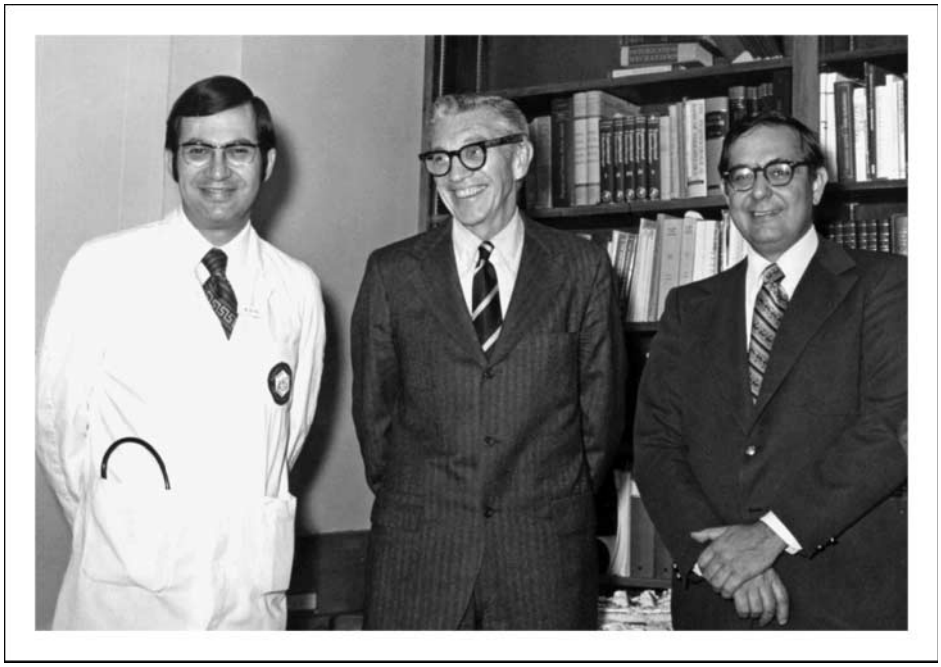

**Figure 7.** Drs. Vincent T. DeVita, C. Gordon Zubrod, and Paul P. Carbone in 1972 at the time of the Lasker Award.

these approaches in mice bearing L1210, Frei, Freireich, and others were doing the same in children with leukemia, taking advantage of the newly discovered *Vinca* alkaloid, vincristine, to design the program known as "VAMP" (vincristine, amethopterin, 6-mercaptopurine, and prednisone). This was the first of a series of cyclically administered treatment programs that increased the remission rate and duration in a stepwise fashion to 60% by the end of the decade, with half of the remissions lasting well beyond the norm, measured in years and compatible with cure (55, 56).

Astute cancer clinicians were also making treatment easier by surmounting deficiencies caused by the disease and the toxicity of chemotherapy using platelet transfusions to prevent bleeding (57) and the aggressive use of combinations of new and old antibiotics to identify and treat common and unusual infections to support patients through the rigors of combination chemotherapy (58, 59). The results of the important VAMP study were only published in abstract form at AACR meetings (55, 56), but because of the large cooperative effort in childhood leukemia, led by Jim Holland, the precept of curability was quickly tested in large numbers of children with leukemia, with promising indications of feasibility (60).

Skipper reported the cure of L1210 in the mouse in 1964 (54), the first curative treatment of a mouse leukemia with drugs, and by 1970, most investigators felt that some fraction of childhood leukemia was curable (60). Today, the majority of children with acute lymphocytic leukemia are cured by the aggressive use of combination chemotherapy programs (61, 62). In the early 1960s, advanced Hodgkin's disease was also uniformly fatal and treated with single alkylating agents. Although remissions were attainable in up to 25% of patients, as in acute childhood leukemia, they were brief and usually incomplete. DeVita, Moxley, and Frei took advantage of the availability of the *Vinca* alkaloids, and the NCI data on procarbazine in Hodgkin's disease, to develop first the MOMP program (63, 64), which combined nitrogen mustard with vincristine, methotrexate, and prednisone, and then the MOPP program (65, 66), which omitted methotrexate and took advantage of the availability of procarbazine to test the precepts of combination chemotherapy in advanced, previously untreated Hodgkin's disease. Because these were adults and their tumor was not derived from their bone marrow, additional studies were done on the comparative kinetics of cell production in the marrow in mouse and man to adjust the novel treatment schedules around the time to recovery of the bone marrow after exposure to cytotoxic chemotherapy (30, 67–72). The MOMP and MOPP protocols were met with fierce resistance both in and out of the NIH Clinical Center as they were regarded as too big a departure from the norm. Only the intersession of Tom Frei, who overruled the critics in the intramural program, permitted the studies to proceed.

The results were startling. The complete remission rate went from near zero to 80%, and unlike the stepwise increase in remission duration noted over the decade in childhood acute leukemia, about 60% of patients with advanced Hodgkin's disease who attained a complete remission in the original MOPP study never relapsed with follow-up now into its 40th year.[2] The results of MOMP and MOPP were first presented at meetings of the AACR in 1965 and 1967, respectively (63, 65), and the MOPP study was published in *Annals of Internal Medicine* in 1970 (66). As a measure of the hunger for treatments that worked, the *Annals* article remains to this day the most cited article in the history of the journal. By 1970, advanced Hodgkin's disease was also regarded as curable with drugs and provided the first example of an advanced cancer of a major organ system in adults cured by chemotherapy. Today, Hodgkin's disease is curable in 90% of cases, and chemotherapy is integrated with radiotherapy for early-stage disease as well.

Patients with what was then called diffuse histiocytic lymphoma (now diffuse large B-cell lymphoma) were treated with the same programs as well. In 1975, the NCI investigators reported the cure of advanced diffuse large B-cell lymphoma with the regimen referred to as C-MOPP, which substituted cyclophosphamide for nitrogen mustard (73).

As in leukemia, the results of the MOPP program were quickly confirmed. In the United States, by 1984, national mortality from childhood leukemia and Hodgkin's disease had both fallen by 65% as the new therapies were quickly adopted. By the end of the 1960s, the

[2] V.T. DeVita, unpublished observations.

missing link of the chemotherapy program had been forged, and it was now clear that anticancer drugs could cure cancer (74).

In 1972, the Albert and Mary Lasker Prize in Medical Research was awarded to the group of investigators responsible for showing proof of principle for the cure of cancer with drugs. The Lasker Prize for Public Service was given that year to C. Gordon Zubrod for his pivotal role in organizing the various programs that made these studies possible (Fig. 7). In 1973, the field of medical oncology was officially established as a subspecialty of internal medicine with chemotherapy the tools of its trade.

## The 1970s: The Age of Adjuvant Chemotherapy

The concept of cure had a remarkably permissive effect on the use of chemotherapy in earlier stages of cancers. For example, about 90% of patients with breast cancer present with locoregional disease. Yet, the majority will develop recurrences if only the best locoregional treatment is used. Similar circumstances existed for other solid tumors, such as colorectal cancers. But a significant fraction of patients with locoregional disease will also stay free of tumor after regional treatment alone. If chemotherapy were to be used as an adjunct to local treatments, many other patients would be unnecessarily exposed to the potential side effects of drugs, hence the dilemma. To use chemotherapy as an adjunct to surgery or radiotherapy, one needed evidence that the relapse rate was likely to be high in the treated population, the program to be used was effective in patients with the same tumor type in its advanced stages, and some confidence that chemotherapy might have the capacity to cure patients with micrometastases while not being excessively toxic. The demonstration that combination chemotherapy could cure some types of advanced cancer gave hope that the same results could be achieved under ideal circumstances for more common solid tumors. Moreover, Skipper's cell kill hypothesis, and the invariable inverse relation between cell number and curability, suggested that drugs effective against advanced disease might work better in the adjuvant situation with only micrometastases to deal with (75–77).

Investigators began to use combination chemotherapy in advanced breast cancer in the late 1960s with some encouraging results (78). However, the study of these programs in the adjuvant situation had not been possible. Two programs were designed and field tested at the Clinical Center of the NCI, L-phenylalanine mustard (L-PAM) used alone and the CMF program, a combination of cyclophosphamide, methotrexate, and 5-flurouracil, specifically designed for use as adjuvant chemotherapy (79, 80). Both programs were active in patients with metastatic cancer but the results with CMF, structured along the lines of the MOPP program as a cyclical chemotherapy regimen, and tolerable as an outpatient treatment, were, for the time, impressive. The overall response rate was over 50%, and about 20% of patients actually attained complete remissions.

The main problem was where to test these treatment regimens as adjuvants to surgery. Despite the excitement over the new chemotherapy data, most surgeons in the United States were still reluctant to participate in clinical trials testing its use postoperatively. The courageous Bernard Fisher was the first choice (Fig. 8). He and his group, the National Surgical Adjuvant Breast Project (NSABP), had done an early adjuvant study, sponsored by the CCNSC, testing the use of the alkylating agent thiotepa postoperatively to kill cancer cells dislodged at surgery (81). They were also in the process of challenging the status quo, questioning the need for radical mastectomy and postoperative radiotherapy, and were in position to test chemotherapy. The late Paul Carbone of NCI contacted Bernard Fisher, and he agreed to test L-PAM in a randomized controlled trial. But still no person or institution in the United States was prepared to test combination chemotherapy as an adjunct to surgery in breast cancer. Paul Carbone then contacted Gianni Bonadonna of the Istituto Nazionale Tumori, in Milan, Italy, about doing the study. Under its director, the surgical pioneer Umberto Veronesi, the Istituto was treating a large number of breast cancer patients and, like Fisher, was exploring the use of lesser operations than the radical mastectomy. Bonadonna came to the NIH Clinical Center to review the results of the CMF protocol, which had not yet been published and agreed along with Veronesi to conduct a randomized controlled trial of a slightly dose-reduced version of CMF versus no therapy. The U.S. NCI Chemotherapy program, under Zubrod, paid for the study through a contract with the Istituto Tumori. This contract also provided for costs of a permanent statistical center and was the beginning of long time collaboration between the two National Cancer Centers.

Within 5 years, both studies were complete and the L-PAM study was reported to much fanfare when published in the New England Journal of Medicine in 1975, simultaneous with the announcement that the wives of the President, Betty Ford, and the Vice President, Happy Rockefeller, were diagnosed with breast cancer (82). The Bonadonna CMF study was published a year later (83). Both studies were positive, and the results set off a cascade of adjuvant studies in breast cancer (84, 85) and other tumor types, including colorectal cancer, with exciting results that have contributed to the significant decline in national mortality for breast and colorectal cancer, which we now are witnessing in 2008. In 1985, Bernard Fisher was awarded the Albert and Mary Lasker Prize for this work on breast cancer, particularly for opening up the field of adjuvant chemotherapy.

In mid-1974, following the work on acute leukemia, lymphomas and breast cancer, Lawrence Einhorn and his group, building on the initial work of M.C. Li at Memorial Hospital (42), began a series of studies that resulted in the cure rate of metastatic testicular cancer going from about 10% to 60% by 1978 through the use of a combination of cis-platinum, vinblastine, and bleomycin. Thus, another solid tumor in adults fell to the use of combination chemotherapy. Today, chemotherapy is used for all stages of this tumor and testicular cancer is curable in most patients (86–88).

**Figure 8.** Dr. Bernard Fisher at magnetic board used to follow all patients in first NSABP Breast Adjuvant Study (1970).

**Table 1.** Primary chemotherapy: neoplasms for which there is an expanding role for primary chemotherapy of advanced disease

| |
|---|
| Bladder cancer |
| Breast cancer |
| Cervical cancer |
| Colorectal cancer |
| Esophageal cancer |
| Gastric cancer |
| Head and neck cancer |
| Nasopharyngeal cancer |
| Non–small cell lung cancer |
| Ovarian cancer |
| Pancreatic cancer |
| Prostate cancer |

## Passage of the Cancer Act of 1971 and Beyond

One unanticipated benefit of the report of the curability of choriocarcinoma, lymphomas, and acute leukemias with combination chemotherapy was the passage of the National Cancer Act in 1971. One of the patients with non–Hodgkin's lymphoma initially treated with the C-MOPP program at the NCI Clinical Center in 1969 was a lobbyist for the American Cancer Society who had been hired at the request of Mary Lasker to be her eyes and ears on Capital Hill. His complete response to combination chemotherapy caught Mary Lasker's attention, and she became convinced that the data on the lymphomas and leukemias were the missing link in treatment needed to eradicate cancer (73, 89). What followed was an extraordinary series of events that culminated in the passage of the National Cancer Act of 1971 that launched the nation's ever-controversial "war on cancer" (90). Those events are a story in itself too long to recount in this review, but it had a profound effect on the expansion and development of chemotherapy for the next 4 decades.

Although 85% of the new monies provided for "the war on cancer" went into investigator-initiated research projects, the clinical testing of new drugs and new chemotherapy programs were also markedly expanded. The monies devoted to cooperative groups alone went from $9 million in 1972 to $119 million in 1980. Groups like the NSABP were able to provide funds for follow-up of studies that heretofore had been forced to lie fallow, and many large-scale studies were done testing novel ways to approach adjuvant chemotherapy and combined modality therapy that have contributed to the national decline in mortality from cancer.

With funds available to expand, the Developmental Therapeutics Program screened more drugs and then developed a new series of screening systems. In 1975, the mouse L1210 model was abandoned as the primary screen in favor of a panel of tumors, human xenografts in nude mice matched to transplanted animal tumors of the same tissue. The goals were to test, *in vivo*, the comparative efficacy of human xenografts and murine transplanted tumors at predicting anticancer activity in humans. The taxanes had their antitumor effects identified in this panel. Because of the complexity and expense of this new screening panel, the number of drugs screened was diminished from its high of 40,000 per year to 10,000, but despite the reduction, the change resulted in the same number of positive leads. In the 1990s, the screening system was again changed to a panel of 60 human cancer cell lines grown in culture as cell culture systems became more sophisticated, and adjustments could be made for drugs metabolized to their active form *in vivo*.

It is still too early to know the full effect of all these changes in the screening program because the lag time between discovery of activity and ultimate proof of usefulness is quite long, sometimes measured in decades. However, something else has happened to change the landscape of drug development. As information about the molecular aberrations that occur in cancer cells has become available, random screening is being replaced by screening against specific critical molecular targets. As the market for cancer drugs has grown, so has the willingness of the industry to invest in new drugs, and discovery and development are now largely in the hands of a segment of the pharmaceutical industry that did not exist before the advent of the CCNSC. As a consequence, many new drugs and new classes of anticancer drugs have been introduced since the 1980s, too many to discuss here, and are now available to clinicians.

The advent of monoclonal antibodies has enhanced the effects of chemotherapy. Hybridomas were described in 1975, and monoclonal antibodies were proven clinically useful starting in the mid-1990s. Although they are not chemotherapy per se, they seem to work best when they are used in conjunction with chemotherapy, as is the case for trastuzumab in breast cancer, cetuximab and bevacizumab in colorectal cancer, and rituximab in non–Hodgkin's lymphoma, and each are an integral part of chemotherapy regimens for these common tumors.

Chemotherapy has, in fact, transitioned to the age of "targeted therapy." The story of how we got to the point of identifying many molecular targets takes us back again to the 1960s to a seemingly unrelated program—the Special Virus Cancer Program (SVCP). It was established in 1964 with another $5 million from the Senate Appropriations Committee, again at the urging of the ubiquitous and visionary Mary Lasker. It was also supported by research contracts and was conceived as a crash program to find viruses reported to be associated with cancer. When it failed to identify actual viruses, it morphed into a Program of Molecular Biology to study genes that were coopted by tumor viruses. The SVCP was often criticized because of the use of research contracts, but work in this program identified oncogenes, suppressor oncogenes, and signaling pathways essential for developmental biology itself (91–94). This work eventually led to the identification of most of the new drug targets that are currently the focus of cancer drug development. The technology developed in this program also facilitated the sequencing of the genome.

**Table 2.** Adjuvant chemotherapy: neoplasms for which adjuvant therapy is indicated after surgery with survival prolongation

| |
|---|
| Anaplastic astrocytoma |
| Breast cancer |
| Colorectal cancer |
| Cervical cancer |
| Gastric cancer |
| Head and neck cancers |
| Pancreas cancer |
| Melanoma |
| Non–small cell lung cancer |
| Osteogenic sarcoma |
| Ovarian cancer |

The first and best example of targeted therapy is the development of the Bcr-Abl tyrosine kinase inhibitor imatinib for the treatment of chronic myelocytic leukemia (95–98). The translocation known as the Philadelphia chromosome was first identified by Nowel and Hungerford in 1961 (99), but it has only recently been possible to design a drug that fits into the ATP-binding site of the Bcr-Abl protein created by the translocation and inhibits the function of this aberrant kinase. The management and outcome of chronic myelogenous leukemia (CML) has been drastically altered as a result. CML may be unique in that a single molecular abnormality drives the disease, whereas in most cancers there are multiple abnormalities that must be targeted. Nonetheless, the results provide proof of principle, much as the early cures of leukemia and Hodgkin's disease did, for the therapeutic power of the knowledge of molecular targets.

Data from the genome sequence also suggested that many of the abnormalities associated with cancer are due to the abnormal function of protein kinases, and a major thrust of the current drug development era has been to develop a series of kinase inhibitors (94). Several of these small molecules have now been approved by the U.S. Food and Drug Administration for the treatment of renal cell cancer, hepatocellular cancer, and gastrointestinal stromal tumor, cancers heretofore resistant to standard chemotherapy (95–101). Clearly, these agents hold significant promise to treat a broad range of solid tumors and hematologic malignancies. The recent history of the development of molecular targeted therapies will be covered in more detail in a subsequent review in this Centennial Series.

Cancer chemotherapy is curative in subsets of patients who present with advanced disease, including Hodgkin's and non–Hodgkin's lymphoma, acute lymphoblastic and acute myelogenous leukemia, germ cell cancer, small cell lung cancer, ovarian cancer, and choriocarcinoma. In pediatric patients, the curable cancers include acute leukemias, Burkitt's lymphoma, Wilm's tumor, and embryonal rhabdomyosarcoma. There is now an expanding role of chemotherapy to treat a wide range of solid tumors as seen in Table 1. Although treatment is not often curative for these cancers, there has been a significant improvement in progression-free survival. Moreover, several of the most active chemotherapy regimens, some of which are combined with the novel targeted therapies, are being used in the neoadjuvant setting to reduce the size of the primary tumor to allow for improved surgical outcome as well as preserve vital organs. Over the past 10 years, neoadjuvant chemotherapy has been widely used for anal, bladder, breast, gastroesophageal, rectal head and neck cancers, and osteogenic and soft tissue sarcomas.

The active chemotherapy regimens for metastatic and locally advanced disease have now been extended for an increasing number of more common solid tumors following surgical resection with curative effect. The list of cancers for which adjuvant chemotherapy has been established to reduce the incidence of both local and systemic recurrence and to improve overall survival is presented in Table 2. With the ever-increasing and rapid development of active cytotoxic and biological agents, the expectation is that the list of cancers effectively treated and cured using combined modalities will continue to expand.

Finally, in 1990, the national incidence and mortality of cancer began to decline. Mortality has continued to decline each year since 1990, and in 2005, overall deaths from cancer have declined despite the larger and older U.S. population. In 2007, the rate of decline actually doubled. Whereas half of this decline is due to prevention and early diagnosis, the other half is largely due to advances in cancer treatment, much of it due to the inclusion of chemotherapy in most treatment programs.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## References


1. Brested JH. The Edwin Smith surgical papyrus. Translated for The New York Historical Society. Chicago (IL): University of Chicago Press; 1930.
2. Papac RJ. Origins ofsf cancer therapy. Yale J Biol Med 2001;74:391–8.
3. DeVita VT. The evolution of therapeutic research in cancer. N Engl J Med 1978;298:907–10.
4. Osler W. The principles and practice of medicine. New York: D. Appleton and Company; 1893. p. 708.
5. Goldin A, Schepartz SA, Venditti JM, DeVita VT. Historical development and current strategy of the National Cancer Institute Drug Development Program. In: Busch H, DeVita VT, editors. Methods in cancer research, V16 (A). New York: Academic Press; 1979. p. 165–245.
6. Hirschberg E. Patterns of response of animal tumors to anticancer agents. Cancer Res 1963;23:521–980.
7. Shear MJ, Hartwell JL, Peters VB, et al. Some aspects of a joint institutional research program on chemotherapy of cancer: current laboratory and clinical experiments with bacterial polysaccharide and with synthetic organic compounds. In: Moulton FR, editor. Approaches to tumor chemotherapy. Washington (DC): American Association for the Advancement of Science; 1947. p. 236–84.
8. Zubrod CG, Schepartz S, Leiter J, Endicott JM, Carrese LM, Baker CG. The chemotherapy program of the National Cancer Institute: History, analysis, and plans. Cancer Chemother. Rep 1966;50:349–540.
9. Zubrod CG, Schepartz SA, Carter SK. Historical background for the National Cancer Institute's drug development thrust. Natl Cancer Inst Monogr 1977;45:7–11.
10. Boyland E. Experiments on the chemotherapy of cancer. I. The effects of certain antibacterial substances and related compounds. Biochem J 1938;32:1207–13.
11. Yoshida T. The Yoshida sarcoma, an ascites tumor. Gann 1949;40:1–20.
12. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet 1896;2:104–7;162–165.
13. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effects of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.
14. Marshall EKJR. Historical perspectives in chemotherapy. In: Golding A, Hawking IF, editors. Advances in chemotherapy, vol. 1. New York: Academic Press; 1964. p. 1–8.
15. Krumbhaar EB, Krumbhaar HD. The blood and bone marrow in yellow gas (mustard gas) poisoning. Changes produced in bone marrow in fatal cases. J Med Res 1919;40:497–508.
16. Gilman A. Symposium on advances in pharmacology resulting from war research: therapeutic applications of chemical warfare agents. Fed Proc 1946;5:285–292.
17. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen mustard therapy: use of methyl-bis (β-chloroethyl) amine hydrochloride and tris (β-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia, and certain allied and miscellaneous disorders. JAMA 1946;132:126–32.
18. Gilman A, Philips FS. The biological actions and therapeutic applications of the β-chloroethylamines and sulfides. Science 1946;103:409–15.
19. Karnofsky DA, Burchenal JH, Ormsler RA, Corman I, Rhoads CP. Experimental observations on the use of nitrogen mustard in the treatment of neoplastic diseases. In: Moulton FR, editor. Approaches to tumor chemotherapy. Washington (DC): American Association for the Advancement of Science; 1947. p. 298–305.
20. Gilman A. The initial clinical trial of nitrogen mustard. Am J Surg 1963;105:574–8.
21. Farber S. Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. Blood 1949;4:160–7.
22. Farber S, Diamond LK, Mercer RD, et al. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N Engl J Med 1948;238:787–93.
23. Pinkel D. Actinomycin D in childhood cancer; a preliminary report. Pediatrics 1959;23:342–7.
24. Hitchings GH, Elion GB. The chemistry and biochemistry of purine analogs. Ann NY Acad Sci 1954;60:195–9.
25. Elion GB, Singer S, Hitchings GH. Antagonists of nucleic acid derivatives. VIII. Synergism in combinations of biochemically related antimetabolites. J Biol Chem 1954;208:477–88.
26. Heidelberger C, Chaudhuari NK, Danenberg P, et al.

Fluorinated pyrimidines. A new class of tumor inhibitory compounds. Nature 1957;179:663–6.
27. Law LW, Dunn TB, Boyle PJ, Miller JH. Observations on the effect of a folic-acid antagonist on transplantable lymphoid leukemias in mice. J Natl Cancer Inst 1949;10:179–92.
28. Skipper HE, Schabel FM, Jr., Mellet LB, et al. Implications of biochemical, cytokinetic, pharmacologic and toxicologic relationships in the design of optimal therapeutic schedules. Cancer Chemother Rep 1950;54:431–50.
29. Skipper HE. Reasons for success and failure in treatment of murine leukemias with the drugs now employed in treating human leukemias. Cancer Chemother 1978;1:1–166. Ann Arbor (MI): University Microfilms International.
30. Yankee RA, DeVita VT, Perry S. The cell cycle of leukemia L1210 cells *in vivo*. Cancer Res 1967;27:2381–5.
31. Farber S, Schwachman H, Toch R, Downing V, Kennedy BH, Hyde J. The effect of ACTH in acute leukemia in childhood. In: Mote JR, editor. Proceedings of the First Clinical ACTH Conference. New York: McGraw-Hill-Blakiston; 1950. p. 328–30.
32. Pearson OH, Eliel LP, Rawson RW, Dobriner K, Rhoads CP. ACTH- and cortisone-induced regression of lymphoid tumors in man: a preliminary report. Cancer 1949;2:943–5.
33. Gellhorn A, Hirschberg E, editors. Investigation of diverse systems of cancer chemotherapy screening. Cancer Res Supp 1955;3:125.
34. Endicott KM. Progress report. Bethesda (MD): Cancer Chemotherapy National Service Center; 1957. p. 10.
35. Endicott KM. The chemotherapy program. J Nat Cancer Inst 1959;19:275–93.
36. Cancer Chemotherapy National Service Center specifications for screening chemical agents and natural products against animal tumors. Cancer Chemother Rep 1959;1:42–64.
37. Armitage P, Schneiderman MA. Statistical problems in a mass screening program. Ann NY Acad Sci 1958;76:896–908.
38. DeVita VT, Oliverio VT, Muggia FM, et al. The drug development and clinical trials programs of the Division of Cancer Treatment, National Cancer Institute. Cancer Clin Trials 1979;2:195–216.
39. Li MC, Hertz R, Bergenstal DM. Therapy of choriocarcinoma and related trophoblastic tumors with folic acid and purine antagonists. N Engl J Med 1958;259:66–74.
40. DeVita VT. Therapeutic research in the National Cancer Institute. In: Stetten D, Carrigan WT, editors. NIH: an account of research in its laboratories and clinics. New York: Academic Press; 1984. p. 500–526.
41. Hertz R, Lewis J, Lipsett MB. Five years experience with chemotherapy of metastatic trophoblastic disease in women. Am J Obstet Gynecology 1963;86:808–14.
42. Li MC, Whitmore WF, Goldbey RB, Grabstald H. Effects of combined drug therapy on metastatic cancer of the testis. JAMA 1969;174:1291.
43. Biomedical science and its administration. A study of the National Institutes of Health. Report of Wooldridge Committee to the President. Washington (DC): U.S. Government Printing Office; 1955. p. 213.
44. DeVita VT. Contrasting viewpoints on cancer drug development: the Wooldridge and Richardson reports. Cancer Treat Rep 1984;68:339–40.
45. Sessoms SM. Review of the Cancer Chemotherapy National Service Center programs; development and organization. Cancer Chemother Rep 1960;7:25–8.
46. Burchenal JH. Treatment of leukemias. Seminars in Hematology 1966;31:122.
47. Zuelzer WW. Implications of long term survival in acute stem cell leukemia of childhood treated with composite cyclic therapy. Blood 1964;24:477.
48. Frei E III, Karon M, Levin RH, et al. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. Blood 1965;26:642–56.
49. Frei E III, Freireich EJ, Gehan E et al. Studies of sequential and combination antimetabolite therapy in acute leukemia: 6-mercaptopurine and methotrexate: from the acute leukemia group. Blood 1961;18:431–54.
50. Johnson TS, Armstrong JG, Gorman M, Burnett JP, Jr. The vinca alkaloids: a new class of oncolytic agents. Cancer Res 1963;23:1390–427.
51. Brunner KW, Young CS. A methyl hydrazine derivative in Hodgkin's disease and other malignant lymphomas. Ann Int Med 1967;66:144.
52. DeVita VT, Serpick A, Carbone PP. Preliminary clinical studies with ibenzmethyzin. Clin Pharmacol Ther 1966;7:542–6.
53. Furth J, Kahn MC. The transmission of leukemia of mice with a single cell. Am J Cancer 1937;31:276–82.
54. Skipper HE, Schabel FR, Jr., Wilcox WS. Experimental evaluation of potential anticancer agents. XII. On the criteria and kinetics associated with "curability" of experimental leukemia. Cancer Chemother Rep 1964;35:1–111.
55. Freireich EJ, Karon M, Frei E III. Quadruple combination therapy (VAMP) for acute lymphocytic leukemia of childhood. Proc Am Assoc Cancer Res 1964;5:20.
56. Frei E III. Potential for eliminating leukemic cells in childhood acute leukemia. Proc Am Assoc Cancer Res 1963;5:20 (abstract).
57. Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med 1962;266:905–9.
58. Hersh EM, Bodey GP, Nies BA, Freireich EJ. Causes of death in acute leukemia: a ten-year study of 414 patients from 1954-1963. JAMA 1965;193:105–9.
59. DeVita VT, Emmer M, Levine A, Jacobs B, Berard C. *Pneumocystis carinii* pneumonia: successful diagnosis and treatment of two patients with associated malignant processes. N Engl J Med 1969;280:287–91.
60. Holland JF. Hopes for tomorrow versus realities of today: therapy and prognosis in acute lymphocytic leukemia of childhood. Pediatrics 1970;45:191–3.
61. George P, Hernandez K, Hustu O, Borella L, Holton C, Pinkel D. A study of total therapy of acute lymphocytic leukemia in children. J Pediatr 1968;72:399–408.
62. Pinkel D, Hernandez K, Borella L, et al. Drug dose and remission duration in childhood lymphocytic leukemia. Cancer 1971;27:247–56.
63. DeVita VT, Moxley JH, Brace K, Frei E III. Intensive combination chemotherapy and X-irradiation in the treatment of Hodgkin's disease. Proc Am Assoc Cancer Res 1965;6:15.
64. Moxley JH III, DeVita VT, Brace K, Frei E III. Intensive combination chemotherapy and X-irradiation in Hodgkin's disease. Cancer Res 1967;27:1258–63.
65. DeVita VT, Serpick A. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Proc Am Assoc Cancer Res 1967;8:13.
66. DeVita VT, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970;73:881–95.
67. DeVita VT. Cell kinetics and the chemotherapy of cancer. Cancer Chemother Rep 1971;2:23–33.
68. DeVita VT, Denham C, Perry S. Relationship of normal CDF1 mouse leukocyte kinetics to growth characteristics of leukemia L1210. Cancer Res 1969;29:1067–71.
69. Skipper HD, Perry S. Kinetics of normal and leukemic leukocyte populations and relevance to chemotherapy. Cancer Res 1970;30:1883.
70. DeVita VT, Schein PS. The use of drugs in combination for the treatment of cancer: rationale and results. N Engl J Med 1973;288:998–1006.
71. DeVita VT, Young RC, Canellos GP. Combination versus single agent chemotherapy; a review of the basis for selection of drug treatment of cancer. Cancer 1975;35:98–110.
72. Young RC, DeVita VT. The effect of chemotherapy on the growth characteristics and cellular kinetics of leukemia L1210. Cancer Res 1970;30:1789–94.
73. DeVita VT, Canellos GP, Chabner B, Schein P, Young RC, Hubbard SM. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Results with combination chemotherapy. Lancet 1975;1:248–54.
74. DeVita VT, Canellos GP, Moxley HH III. A decade of combination chemotherapy for advanced Hodgkin's disease. Cancer 1972;30:1495–504.
75. Schabel FM. Concepts for systemic treatment of micrometastases. Cancer 1975;35:15.
76. Salmon SE. Kinetic rationale for adjuvant chemotherapy for cancer. In: Salmon SE, Jones SE, editors. Adjuvant therapy of cancer. Amsterdam: Elsevier/North Holland Biomedical Press; 1977.
77. Young RC, DeVita VT. Cell cycle characteristics of human solid tumors *in vivo*. Cell Tissue Kinet 1970;3:285–90.
78. Greenspan EM, Fieber M, Lesnick G, Edelman S. Response of advanced breast cancer to the combination of the anti-metabolite methotrexate and the alkylating agent thiotepa. J Mt Sinai Hosp 1963;30:246–67.
79. Canellos GP, DeVita VT, Gold GL, Chabner BA, Schein PS, Young RC. Cyclical combination chemotherapy in the treatment of advanced breast carcinoma. Proc Am Assoc Cancer Res 1974;15:148.
80. Canellos GP, DeVita VT, Gold GL, Chabner BA, Schein PS, Young RC. Cyclical combination chemotherapy in the treatment of advanced breast carcinoma. Brit Med J 1974;1:218–20.
81. Fisher B, Ravdin RG, Ausman RK, Slack NH, Moore GE, Noer RJ. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. Ann Surg 1968;168:337–56.
82. Fisher B, Carbone P, Economou SG, et al. L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. N Engl J Med 1975;292:110–22.
83. Bonadonna G, Brusamolino E, Valegussa P, et al. Combination chemotherapy as an adjunct treatment in operable breast cancer. N Engl J Med 1976;294:405–10.
84. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. In: Peto R, editor. Worldwide evidence 1985-1990, vol. 1. Oxford: Oxford University Press; 1990.
85. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405–10.
86. Einhorn LH, Donohue JP. Combination chemotherapy in disseminated testicular cancer: the Indiana University experience. Semin Oncol 1979;6:87–93.
87. Einhorn LH, Donohue J. *Cis*-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Int Med 1977;87:293–8.
88. Einhorn LH. Testicular cancer as a model for a curable neoplasm: The Richard and Linda Rosenthal Foundation award lecture. Cancer Res 1981;41:3275–80.
89. DeVita VT. Le plan Nixon contre le cancer portée et limites. In: Bez G, Jasmin C, editors. Cancer, sida et société: pour une approche globale de la santé. Paris: ESF; 1993.
90. DeVita VT. A perspective on the war on cancer. Cancer J 2002;8:352–6.
91. Fischinger P, DeVita VT. Perceptions and opportunities in oncogene research. Cancer Res 1984;44:4693–6.
92. DeVita VT. The governance of science at the National Cancer Institute: a perspective of misperceptions. Cancer Res 1983;43:3969–73.
93. DeVita VT. The governance of science at the National Cancer Institute: management of resources in an era of scarcity. Cancer Research 1983;43:6106–8.
94. DeVita VT. On special initiatives, critics and the National Cancer Program. Cancer Treat Rep 1984;68:1–4.
95. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561–6.
96. Manning G, Whyte DB, Martinez R, et al. The protein kinase complement of the human genome. Science 2002;298:1912–34.
97. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172–87.
98. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038–42.
99. Nowel PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. Science 1960;132:1497–501.
100. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006;5:835–44.
101. Herbst RS. Therapeutic options to target angiogenesis in human malignancies. Expert Opin Emerg Drugs 2006;11:635–50.