

# History of chemotherapy and cancer treatment research



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## An Early Victory

A few doors from Freireich's office at the NCI, Min Chiu Li and Roy Hertz had been studying choriocarcinoma, a cancer of the placenta, which often metastasizes rapidly into the lung and the brain. Choriocarcinoma cells secrete a hormone called choriogonadotropin. The level of that hormone, also called the hcg level, was used by Li to track the course of the cancer as it responded to the therapy.

In 1956, a young woman called Ethel Longoria suffered from choriocarcinoma that had metastasized to her lungs. Her tumors had begun to bleed into the linings of her lungs. Li and Hertz stabilized her and then treated her with methotrexate. After the first dose, when the doctors left for the night, they didn't expect that they'd find her in rounds the next morning. But she was alive. After four rounds of therapies, her tumor disappeared; the chest X-ray improved; and the hcg level rapidly plummeted toward zero. The tumors had actually vanished with chemotherapy.

The trouble was the hcg level had not gone all the way to zero. Although the tumor seemed to have vanished, Li continued to treat her with chemotherapy based on her elevated hCG levels. The NCI administration disapproved, feeling that Li was experimenting on his patients, and fired him in July 1957.

However, Li was ultimately proven to be right. Those patients whose chemotherapy were stopped once the visible tumors disappeared inevitably relapsed, while those who continued the treatment until their hcg levels had gone to zero were cured. Li had stumbled on a fundamental principle of

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oncology: “ Cancer needed to be systemically treated long after every visible sign of it had vanished.”

### Mice and Men

Adding vincristine to the arsenal of chemotherapy drugs had put the researchers at the NCI in a bind. It would take forever for the consortium to finish its trials because of the large number of permutations and combinations of drugs needed to be tested.

Howard Skipper, a scientist from Alabama, provided Frei and Freireich a way out of the impasse. Skipper, who called himself a “ mouse doctor,” was an outsider to the NCI. He had tested chemotherapy drugs in mice with leukemia, lymphomas and solid tumors as models for human cancers and came up with two pivotal findings:

1. Chemotherapy kills a fixed percentage of cancer cells per treatment. The patients would need to be treated multiple times to get the compounded iterative effect; and
2. Chemotherapy drugs are more effective when given in combination to optimize cancer killing capacity while minimizing drug resistance and side effects.

Freireich and Frei were now ready to tackle a four-drug regimen known as VAMP, with each letter standing for one drug.

### VAMP

When Frei and Freireich presented their preliminary plan for VAMP to the Acute Leukemia Group B (ALGB) at a national meeting on blood cancers, the audience hesitated. The group refused to sponsor VAMP until the many other trials had been completed. But Frei came up with a compromise: VAMP would be studied at the NCI, outside the purview of the ALGB.

The VAMP trial was launched in 1961. At the end of three intensively painful weeks, the leukemia cells went into remission. The remissions persisted for weeks, exceeding everyone's expectation at the NCI. A few weeks later, the NCI sent another small cohort of patients to try VAMP. Once again, after the initial catastrophic dip, the leukemia vanished. The remissions were reliable and durable.

In the fall of 1963, some children in remission came back to the clinic with minor neurological complaints such as headaches, numbness, and seizures. To investigate the possibility of cancer cells invading the brain, Frei and Freireich examined the children's spinal fluid, and confirmed that leukemia cells were colonizing the brain. The neurological complaints were early signs of a more serious devastation. Eventually all the children came back with neurological complaints and went into coma.

It was a consequence of the body's own defense system. The blood-brain barrier had kept VAMP out of the central nervous system, allowing the leukemia cells to colonize the one place that is unreachable by chemotherapy.

But not all children had relapsed and died. About 5 percent of the treated children never relapsed with leukemia in the central nervous system. They remained in remission not just for weeks or months, but for years.

### An Anatomist's Tumor

In 1832, an English anatomist named Thomas Hodgkin (1798-1866) found a strange systemic disease among a series of cadavers. The disease was characterized by "a peculiar enlargement of lymph glands." He wrote up the case of seven such cadavers and presented it to the Medical and Chirurgical Society. It was received with little enthusiasm. Soon after publishing his paper, Hodgkin drift away from medicine, and his anatomical studies slowly came to a halt.

Hodgkin's disease is a cancer of the lymph glands. The tumor moves from one contiguous node to another. It is a local disease on the verge of transforming into a systemic one. In 1898, an Austrian pathologist named Carl Sternberg discovered the cancerous lymph cells when looking through a microscope at a patient's glands.

Henry Kaplan, a professor of radiology at Stanford wanted to use radiation to treat human cancers. He knew radiation could treat solid tumors could be treated with radiation, but the outer shell of the cancer needed to be penetrated deep enough to kill cancer cells. A linear accelerator (linac) with its sharp, dense beam would be ideal for that purpose. In 1953, he persuaded Stanford to tailor-make a linac for the hospital. With the linac in operation, Kaplan contemplated on his cancer target. Since Linac could only focus on local sites, his natural target was Hodgkin's disease, a predictable

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local tumor. Kaplan wanted to prove that he could improve relapse-free survival by using a technique called extended field radiation (EFR). Under EFR, the X-rays are delivered to an entire area of lymph nodes rather than to a single swollen node.

In 1962, Kaplan conducted a trial. The result showed that EFR had significantly reduced the relapse rate of Hodgkin's disease. In 1964, he did another trial with a larger field of radiation on a limited cohort of patients with tumors in just a few contiguous lymph nodes. The result showed even greater relapse-free intervals, stretching out into years.

Wasn't the logic of extended field radiation similar to radical surgery -carving out larger and larger areas for treatment? Why did Kaplan succeed where others had failed?

Kaplan was successful because he restricted radiotherapy to patients with early stage local cancers. Those are the natural disease for radiotherapy. Advanced-stage cancers are inherently different and would require other forms of treatment.

### An Army on the March

In 1963 at the NCI Clinical Center in Bethesda, a group of researchers, including Zubrod, George Canellos, Frei, Freireich, and Vincent DeVita were making a list of cytotoxic drugs on one side of a blackboard. On the other side was a list of new cancers they want to target - breast, ovarian, lymphomas, lung cancers. Connecting between the two lists were lines matching combinations of drugs to cancers. One question that came to their

mind was whether chemotherapy could ever cure patients with any advanced cancers. The only way to answer that generic question was to direct the growing army of drugs against other cancers. They knew leukemia responded to combination chemotherapy. If another kind of cancer also responded to that strategy, then combination chemotherapy might cure all cancers.

To test the principle, they focused on Hodgkin's disease—a cancer that was both solid and liquid, a stepping-stone between leukemia and, say, breast cancer or lung cancer. Kaplan had proved that radiation therapy can cure local forms of Hodgkin's disease. If they could prove that combination chemotherapy can cure metastatic Hodgkin's disease, then the equation would be fully solved.

In 1964, DeVita led the test of combination chemotherapy for metastatic Hodgkin's disease. He combined four drugs—nitrogen mustard, oncovin, prednisone, and procarbazine into a highly toxic cocktail called MOPP. The nausea that accompanied the therapy was devastating. The toxic cocktail had weakened the immune system allowing pneumocystis carinii (PCP), a rare form of pneumonia, to sprout up. The therapy had caused permanent sterility in men and some women.

The result of the study was remarkable. At the end of six months, 35 of the 43 patients had a complete remission.

The most disturbing side effect would emerge a decade later. Several patients, cured of Hodgkin's disease, would relapse with a second cancer, typically a drug-resistant leukemia caused by the prior MOPP therapy.  
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In May 1968, Frei and Freireich's VAMP combination chemo had cured most of the children with leukemia in their bone marrow, but not the leukemia that had spread to their brain. A 36-year-old oncologist name Donald Pinkel thought that VAMP had not been intensive enough. Pinkel, a protégé of Farber's, had been recruited from Boston to start the leukemia program at St. Jude's Hospital in Memphis. He determined to push the logic of combination chemotherapy to its limit with four crucial innovations:

0. To use combinations of combinations of drugs mixed and matched together for maximum effect;
1. To instill chemotherapy directly into the nervous system via the spinal cord;
2. To kill residual cells in the brain by high-dose radiation; and
3. To continue chemotherapy for month after month, even after the cancer seemed to have disappeared.

The treatment protocol started with the standard chemotherapy drugs given in rapid-fire succession. The spinal canal was injected with methotrexate at defined intervals. The brain was irradiated with high doses of X-rays. The treatment lasted up to 30 months. It was an " all-out combat."

In July 1968, the St. Jude's team published its results: Twenty-seven out of the thirty-one treated had a complete remission. Ten had never relapsed. The median time to relapse had increased to five years.



By 1979, 278 patients had completed their chemotherapy. About 20 percent had relapsed, 80 percent was still in complete remission, disease free, after chemotherapy.

### The Cart and the House

By the fall of 1968, the successes of the trials in Bethesda and in Memphis shifted the landscape of cancer therapy. The success of chemotherapy for both leukemia and Hodgkin's disease made it seem like a unifying solution for cancer. In Boston, Farber celebrated the news by throwing a public party. He recast the occasion as the symbolic twenty-first birthday of Jimmy. Conspicuously missing from the guest list was the original Jimmy himself- Einar Gustafson. The real Jimmy had returned to a private life in Maine, where he now lived with his wife and three kids.

As clinical oncologists were offering their unifying solution for cancer, cancer scientists were offering its unifying cause: viruses. The grandfather of this theory was Peyton Rous, a chicken virologist at the Rockefeller Institute in New York.

In 1911, Rous discovered that a malignant tumor growing on a chicken could be transferred to another chicken by exposing the healthy bird to a filtrate derived from the tumor cells. He concluded that the cancer was transmitted by a virus. This virus is now known as the Rous sarcoma virus, or RSV.

This discovery had set off a frantic search for more cancer viruses. In 1958, an Irish surgeon named Denis Burkitt discovered an aggressive form of lymphoma among children in Africa. Analyzing the cancer cells from these

children, two British virologists discovered a human virus inside them. The new virus was named Epstein-Barr virus or EBV.

Because viral diseases were potentially preventable, the NCI inaugurated a Special Virus Cancer Program in the early 1960s to systematically hunt for human cancer viruses.

The cancer virus theory needed a deeper explanation: how might viruses cause a cell to become malignant? The success of cytotoxic chemotherapy raised a fundamental question: how would the therapy, the cure, connect with the cause of the cancer? As Kenneth Endicott, the NCI director, acknowledged in 1963: “ The program directed by the National Cancer Institute has been derided as one that puts the cart before the horse by searching for a cure before knowing the cause.”

But for Mary Lasker, this cart would have to drag the horse.