THE THIRTY YEARS' WAR

Have we been fighting cancer the wrong way?

BY JEROME GROOPMAN

To judge from recent headlines, we are on the verge of conquering cancer. The feature story in last week's issue of *Barron's*, entitled "Investing in Health: Curing Cancer," ended by saying that "we are finally winning the war," and predicted that for our children cancer will be just another chronic illness, for which they will simply "pop a few pills every day." The cover of the May 28th issue of *Time* read, "There Is New Ammunition in the War Against Cancer. These Are the Bullets," and Dr. Michael Gordon, an oncologist at the University of Arizona, told *Time* reporters that in 20 years or so he "might just be out of a job." The annual meeting of the American Society of Clinical Oncology, earlier this month, was buoyed by a spirit of optimism, and in the days that followed there was a sharp rise in the share prices of biotechnology and pharmaceutical companies that are developing cancer drugs. Meanwhile, Senator Dianne Feinstein, of California, has constituted a committee under the auspices of the American Cancer Society to consider how the government should respond to the challenges of cancer in the new millennium.

Important advances have been made in oncology in recent years, and the current atmosphere of hope is not without foundation. But it is not without precedent, either: ever since 1971, when President Nixon declared war on cancer, oncologists and cancer patients have been caught in a cycle of euphoria and despair as the prospect of new treatments has given way to their sober realities. The war on cancer turned out to be profoundly misconceived—both in its rhetoric and in its execution.

The most ambitious health initiative ever undertaken by a country on behalf of its citizens began not with scientists, physicians, politicians, or patients but with a middle-aged New Yorker named Mary Lasker. Born in Wisconsin and educated at Radcliffe, Lasker had achieved great success in the fashion industry; her husband, Albert, had made a fortune in advertising. After the Laskers retired, they devoted themselves to Democratic Party politics and health-care issues. Mary Lasker was the quintessential American idealist; she believed that with enough money, influence, energy, and conviction you could accomplish anything. Then, in 1950, Albert Lasker developed intestinal cancer.

For the first half of the twentieth century, cancer was mainly the province of surgeons. Small tumors that had not spread were cut out, along with large amounts of normal tissue, in an attempt to catch any stray malignant cells. Still, microscopic deposits of cancer often remained, and patients were given radiation treatments, intended to destroy the residual cells. A few chemotherapy drugs were used as well, some of them

In 1971, the United States government resolved to find a cure for the disease in a congressional act that was signed into law by Richard

derived from mustard gas, which had been used in the First World War. These treatments were highly toxic but seemed to shrink the cancer, at least temporarily, in patients with diseases such as Hodgkin's lymphoma. But for the vast majority of patients whose cancers had metastasized, or spread beyond the initial site, there was little that could be done.

Lasker had surgery, which did not completely remove the tumor. Intestinal cancer spreads within the abdomen, destroying the liver and often causing great pain. After two years of unsuccessful treatment, Lasker died, and his wife—using her network of political, medical, and business contacts, the advertising savvy that he had embodied, and the considerable resources from his estate—set out to transform the nation's response to the disease that had killed him.

The Laskers had been major contributors to the American Cancer Society, but after her husband's death Mary Lasker came to believe that only the government had the financial and organizational resources to launch a full-fledged crusade against cancer. In order to gain greater credibility in Washington, she cultivated relationships with high-profile academic physicians, most notably Sidney Farber, the scientific director of the Children's Cancer Research Foundation, in Boston. In the late forties, Farber had discovered that chemotherapeutic drugs that blocked folic acid, an essential vitamin, brought about remissions in some children with acute leukemia. His success in fighting this devastating pediatric cancer made him a frequent "citizen witness," invited by Congress to testify on behalf of medical legislation. Farber believed that, if the right drugs were developed, the gains he had seen in children with leukemia could be reproduced and improved upon. Lasker was also impressed by "Cure for Cancer: A National Goal" (1968), a book by a Denver physician named Solomon Garb, who asserted that cancer cures could emerge quickly if scientists stopped searching for new answers and devoted themselves instead to aggressively exploiting existing knowledge.

By the late sixties, however, the governmental largesse that had characterized Lyndon Johnson's Great Society programs had run its course; Nixon was determined to fight inflation, and Congress was under pressure to hold down domestic spending. To overcome this resistance, Mary Lasker organized the first major grass-roots cancer-advocacy group, the Citizens Committee for the Conquest of Cancer. On December 9, 1969, it began a campaign to make eradication of the disease a federal responsibility, running a full-page advertisement in the *Times* that declared, "Mr. Nixon: you can cure cancer."If American determination and ingenuity had put a man on the moon just months before, why shouldn't the nation attempt to conquer cancer by America's two-hundredth birthday? This political gambit quickly gained momentum. By the end of the following summer, both the Senate and the House of Representatives had unanimously passed a resolution to cure cancer by the Bicentennial.

In the ensuing debates over how this was to be accomplished, Farber argued before the House health subcommittee that researchers did not need to fully understand the workings of cancer in order to proceed: "The 325,000 patients with cancer who are going to die this year cannot wait; nor is it necessary, in order to make great progress in the cure of cancer, for us to have the full solution of all the problems of basic research." He pointed out that vaccination, digitalis, and aspirin were unquestionably beneficial, even if doctors didn't know exactly how they functioned: "The history of medicine is replete with examples of cures obtained years, decades, and even centuries before the mechanism of action was understood for these cures." What was needed, he maintained, was a generously funded cancer institute with

n. The war on cancer has been generating cycles of euphoria and disappointment among patients and doctors ever since.

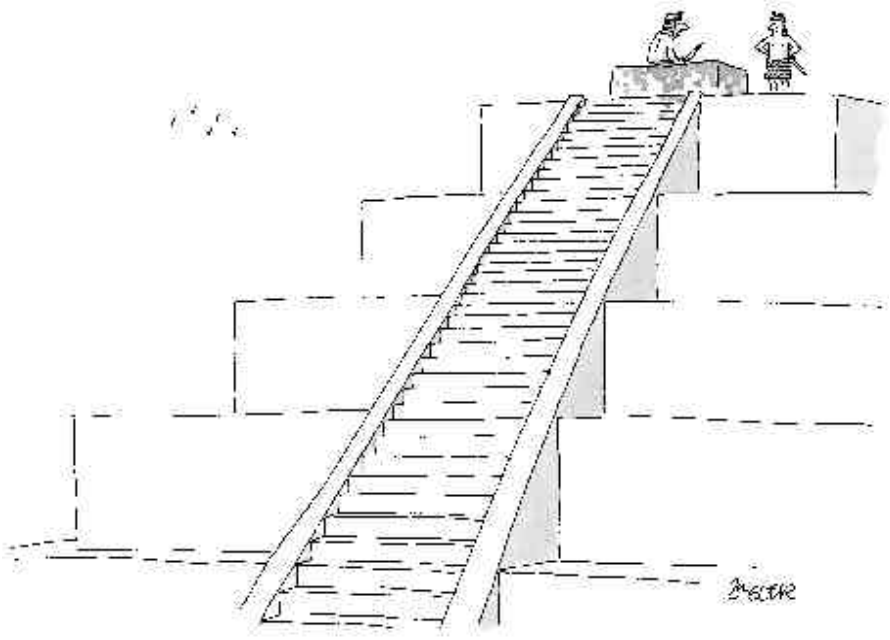
strong leadership and a clearly articulated battle plan.

Richard A. Rettig points out, in his book "Cancer Crusade" (1977), that Farber's view was not universally accepted. Some scientists argued that a cure for cancer could not come about by directive. One such dissenter was a colleague of Farber's at Harvard, Dr. Francis Moore, the surgeon-in-chief at the Peter Bent Brigham Hospital. Moore, a medical-history buff, invoked what might be called the law of unintended consequences in scientific discovery. If there had been a diabetes institute in the late nineteenth century, for example, it would not have funded Langerhans's research on the pancreas, which led to the discovery of insulin, because the link between diabetes and insulin was not recognized at that time. Similarly, a government institute on polio probably wouldn't have supported the work of Dr. John Enders in the late nineteen-forties, when he was attempting to grow the mumps virus and found the method that ultimately proved essential to producing the polio vaccine. Advances had occurred in medical research, Moore argued, because support had gone to creative researchers in universities, "often young people, often unheard-of people." In fact, he could not recall a single example of a scientific breakthrough of clinical importance which had come from the sort of directed funding that was now being proposed.

Farber dismissed such critics, saying that they were not "cancer people," and were therefore ignorant of the possibilities at hand. Congressmen who expressed doubts about the wisdom of rapidly spending vast sums of money in response to what was essentially anecdotal testimony became targets of the Citizens Committee. They received hundreds of thousands of pleading letters, and committee members threatened to work against their reëlection if they didn't reconsider their position.

Lasker also persuaded Congress to convene a panel of experts, with Sidney Farber as the co-chairman, which laid out the battle plan for the war against cancer. The President would henceforth appoint the director of the National Cancer Institute, and the institute's budget would be submitted directly to the White House, bypassing the regular channels of the National Institutes of Health. In December, 1971, Congress passed the National Cancer Act, and Nixon signed it into law less than two weeks afterward. At a ceremony that made front-page headlines in newspapers across the country, Nixon declared, "This legislation—perhaps more than any legislation I have signed as President of the United States—can mean new hope and comfort in the years ahead for millions of people in this country and around the world."

Three decades later, the high expectations of the early seventies seem almost willfully naïve. This year alone, more than a million new diagnoses of major cancers will be made and about five hundred and fifty thousand Americans will die of cancer, an average of fifteen hundred a day. In the course of a lifetime, one of every three American women will develop a potentially fatal malignancy. For men, the odds are one in two. All the same, the triumphalist rhetoric that animated the war on cancer still shapes public opinion: many people believe that cancer is, in essence, a single foe, that a single cure can destroy it, and that the government is both responsible for and capable of spearheading the campaign. The military metaphors have retained their potency—even though they have proved to be inappropriate and misleading.



"What I'd like to know is what the hell happened to all the virgins in this town."

In the early nineteen-seventies, many researchers believed that a cancer was generally caused by a virus that triggered important changes in a cell's metabolism, and that these changes accounted for a tumor's uncontrolled growth. Abnormalities in the genes of the cancer cell were thought to be incidental, rather than fundamental, to the disease.

The virus hypothesis was plausible because there were some hundred viruses that were known to cause cancer in amphibians, birds, and mammals. These were so-called retroviruses—RNA viruses that made their way into normal animal cells, copied their genes into a DNA form, and then subverted the ordinary functions of the cells for their own reproduction. The origin of most human cancers, the experts contended, would prove to be retroviruses as well, and hundreds of millions of dollars were poured into research to prove this assumption.

Sidney Farber's panel didn't just set the government's bureaucratic approach to cancer; it also dictated the National Cancer Institute's scientific agenda in research and clinical testing. The N.C.I. awarded contracts to refine systems for growing cancer cells in bulk, and for producing enzymes that cut and copied DNA and RNA so that the nucleus of the cancer cell could be dissected and the hidden human cancer viruses ex-

posed. Hundreds of thousands of botanical extracts and chemical poisons were systematically screened against different cancer cells to find the next generation of curative drugs. To test these new drugs, the N.C.I. utilized a vast clinical-trials network of "coöperative groups," which were organized with the help of fifteen new cancer centers across the nation. The N.C.I. also designated funding to train young physicians to become oncologists, the specialists who would prescribe the new drugs.

The N.C.I. clinical-trials network employed three phases of testing new drugs. Phase I sought to determine the toxicity of the treatment and the maximum dose that patients could tolerate. Phase II assessed whether the therapy was of any benefit, and what doses of the drug and schedule of treatment seemed to work; it also established objective standards to measure success rates. Phase III studies compared the safety and benefits of the treatment under review with standard therapies. If the results were conclusively favorable, then the therapy would be submitted to the F.D.A. for approval.

Within two years, the war on cancer was well under way, but the miraculous cures failed to appear. Many of the new chemotherapeutic drugs proved to be so toxic that they were quickly abandoned. In the absence of effective single agents, doctors began using combinations of less effective drugs, given at the highest dose a patient could tolerate. At the same time, the clinical-trials network had to justify its existence. Dr. Vincent DeVita, a prominent cancer specialist and a former director of the N.C.I., who is now the head of the Yale Cancer Center, recalls his frustration with the N.C.I. when he was working there in the seventies, before he became the director. His research group developed a treatment regimen for an aggressive form of cancer called large-cell lymphoma, using a combination of chemotherapy drugs. In 1975, about forty-one per cent of the patients with this lymphoma were cured using DeVita's regimen. The N.C.I. proceeded to compare the therapy with four similar treatments. "I screamed my head off, saying, 'You are all crazy! None of these regimens is good enough to merit being tested against another,'" DeVita recalled. " 'You will wrap up all the lymphoma research in this country. It will cost five million dollars, and in the end it will show that the treatment we started with is as good as but no better than any of the others.' "And this, indeed, was the result. The need to justify the bureaucracy meant that scores of clinical trials of relatively ineffective but toxic drugs were conducted with little benefit to the patient or to science.

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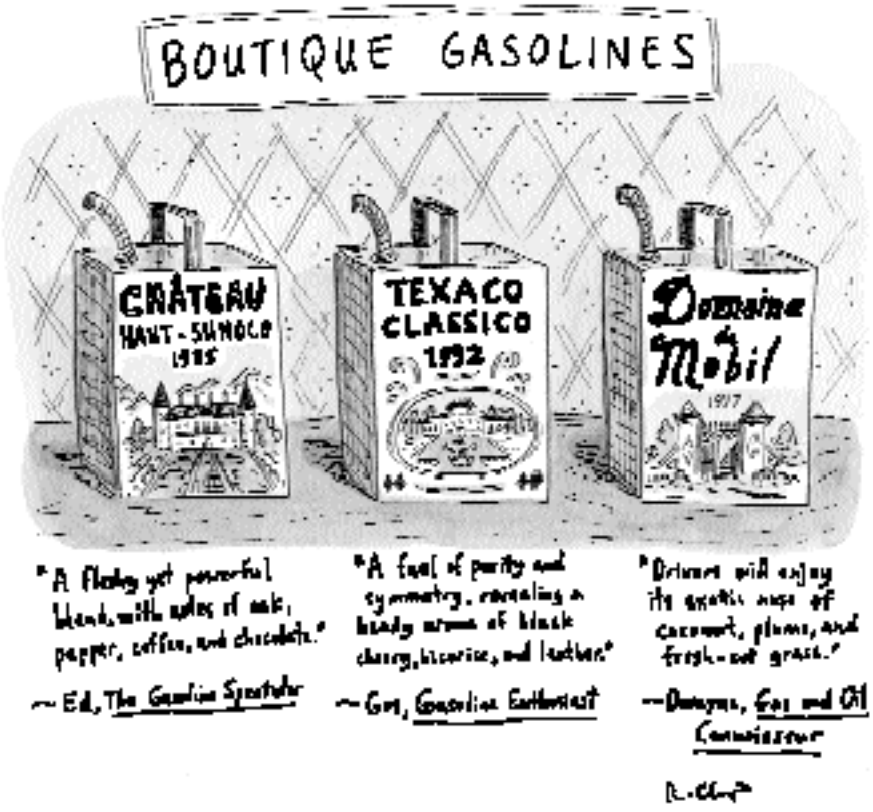
The same year that Nixon signed the National Cancer Act, my grandmother Rose, an energetic sixty-seven-year-old Bronx homemaker, fell ill. She experienced frequent bouts of exhaustion, her lower back ached, and mysterious bruises began to appear on her arms and legs. A blood test showed that her white-blood-cell count was extremely high, and that many of the cells were abnormally large and immature. My grandmother had chronic myelogenous leukemia, or CML, a cancer of the bone-marrow stem cells. Malignant white cells grow uncontrollably, filling the marrow and flooding the bloodstream. The ache in my grandmother's back came from this expanding mass of leukemia pressing within her bones. Her exhaustion was caused by severe anemia, and the depletion of platelets in her blood was preventing it from clotting normally.

The prognosis for leukemia patients was grim, but my family was extremely hopeful; my grandmother's doctors told us that scientists were close to identifying human cancer viruses, and that new treatments would soon be available. Building on the logic of cancer as an infectious disease, researchers thought that, if the body could somehow be made to recognize the cancer cell as aberrant, its immune system would attack the tumor; by injecting the cancer patient with extracts of microbes, they hoped to jump-start that immune response.

After two years of standard chemotherapy, when my grandmother's condition began to deteriorate once more, a specialist recommended moving her to the front lines of immune therapy. She was enrolled in an experimental trial that used an immune booster called MER (methanol-extracted residue), a preparation from tuberculosis-like bacilli. This extract was injected under the skin of her back. Each injection was meant to cause severe inflammation, thereby stimulating her immune system to attack the cancer. I was a medical student at the time, and I remember examining her after the treatments. Her back was studded with raised welts, the size of silver dollars, that ran parallel to her spine. When I touched them, they felt hot and



she winced in pain. Nevertheless, Rose resolutely kept every weekly appointment and received every injection. "I'm going to lick this," she said to my mother after each treatment. "They didn't give me a placebo. I'm lucky. I'm getting the cure."

After nearly a year, it was clear that the immune therapy wasn't working. We were not told at the time, but MER wasn't working for anyone else in the study, either. My grandmother's leukemia soon accelerated, then exploded into "blast crisis," which means that hordes of primitive cells invade vital organs like the lungs, the liver, and the kidneys, and the patient becomes susceptible to infections. In 1976, Grandma Rose contracted a bacterial pneumonia and died.

In many respects, my grandmother's experience in Phase I and Phase II trials was typical; most cancer treatments are unpleasant at best, and there is no way to judge the efficacy of a new approach without testing it on human beings. What was unusual was how little scientific basis there was for these particular experiments, and how much sensationalism surrounded them. Everyone involved in the war on cancer—from Mary Lasker and President Nixon to my grandmother's oncologist—had raised the hopes of Americans suffering from the disease to extraordinary heights. The Bicentennial celebrations came and went, and more people were dying of cancer than ever before.

In 1977, when Dr. Arthur Upton, a radiation expert, was appointed director of the National Cancer Institute, he was immediately attacked for the N.C.I.'s failures. "I spent much of my time disabusing the public of the notion that the war on cancer was like the Manhattan Project or the Apollo space program," he told me recently. "It wasn't merely engineering. We didn't know enough about biology to understand the problem and point to solutions." Clinicians argued that not enough money had been earmarked for trials of different therapies, while scientists doing basic research pointed to millions of dollars that had been spent chasing nonexistent viruses. Upton began to question how the N.C.I.'s budget was being handled. "Bureaucrats were spending vast sums of money at the N.C.I. without rigorous peer review," he said. "Contracts were awarded without any real scrutiny. I was besieged by scientists who felt money was being wasted." Instead of letting the senior staff at the N.C.I. continue to dictate research objectives and then contract outside laboratories to perform much of the work, Upton gave priority to non-government scientists who applied for grants. These applications were assessed by an independent committee of scientific peers. "I took a lot of heat for it," Upton said. "Bureaucrats didn't like their turf being invaded."

During this period, Dr. Harold Varmus and Dr. Michael Bishop, at the University of California, San Francisco, who were using federal funds to study viruses as the cause of cancer, found evidence to suggest the opposite: that the seeds of our destruction are present within our DNA. These seeds are oncogenes, genes that can cause cancer when they mutate. Although the significance of oncogenes was not immediately understood, by the early nineteen-eighties the notion that most cancers were caused by human retroviruses had been largely discarded. The bulk of cancer research had been built on a false premise.

Yet the idea that the immune system could be stimulated to recognize and attack cancer cells—that the power to heal ourselves lies within our own bodies—remained tantalizing, even after the failure of treatments like MER. Some conjectured that the crude immune boosters like the ones my grandmother received had failed only because the triggers were not powerful enough, and that what was needed was a pure and potent stimulus. Interferon, a natural protein that functions as part of the body's immune system, was believed to be such a trigger.

Three major types of interferon had been identified—alpha, beta, and gamma—and laboratory experiments suggested that all of them might be effective in fighting aggressive, chemotherapy-resistant cancers, such as melanoma, metastatic breast cancer, and kidney cancer. Animal tests were encouraging; in mice, interferon caused tumors to melt away without harming normal tissue. Soon oncologists and journalists were speaking of interferon as the long-awaited panacea, and on March 31, 1980, *Time* ran a cover story on the drug. The American Cancer Society spent two million dollars on interferon that had been puri-

fied in Finland from the blood of volunteer donors. Pharmaceutical and biotechnology companies spent hundreds of millions of dollars to genetically engineer alpha, beta, and gamma interferon, then produced the proteins in large quantities. With great fanfare, clinical trials began.

As a cancer researcher in Boston, I participated in Phase II studies of alpha and gamma interferon. As soon as the trials were announced, we were deluged with requests from cancer patients who were desperate to participate; we could admit only a few, and then had to explain to hundreds of others that the rosters were filled.

A woman I will call Nora Dusquette was accepted for treatment in 1983. Nora, a middle-aged schoolteacher, was in the late stages of malignant melanoma. The cancer not only had formed large black deposits in the skin on her arms and back but had spread to her lymph nodes, her lungs, and her liver. We treated her with high doses of interferon by injection three times a week. Nora lived in New Hampshire, and was still teaching full time when she first came to see me, and yet she was more than willing to drive two and a half hours to Boston for her therapy.

Nora experienced intense side effects: fevers, chills, loss of appetite, and extreme fatigue. After her injections, she was rarely able to sleep through the night. She also started losing weight rapidly. Soon she was no longer able to teach or to maintain her household, and she had to rely on family members to take care of her. After four months, it was clear that the treatment wasn't having any impact. The cancer spread to her brain, and a few weeks later she died.

For the vast majority of cancers, it turned out, interferon just didn't work. Alpha interferon did prove successful in the treatment of some rare cancers—especially hairy-cell leukemia—but Nora's experience was typical: like the majority of cancer patients who participate in these kinds of studies, she suffered considerable toxicity with no apparent benefit.

By 1985, hopes had shifted to a protein called interleukin-2, which had been discovered at an N.C.I. laboratory. Interleukin-2 stimulates immune cells called T lymphocytes. Dr. Steven Rosenberg, at the N.C.I., experimented with removing lymphocytes from cancer patients, stimulating them with interleukin-2, and returning them to the patients. In a few instances, there seemed to be significant shrinkage of metastatic melanoma and kidney cancer. Again, the news media were filled with speculations that a cure had been found. The N.C.I. spent millions of dollars supporting interleukin-2 trials, which were administered to cancer patients both at the N.C.I. and in cancer centers across the nation. The new treatment was also extremely toxic. A few patients experienced severe cardiac and pulmonary complications and died.

In 1987, a fifty-seven-year-old friend and colleague I will call Samuel Driscoll received a diagnosis of kidney cancer. He underwent extensive surgery to excise the primary cancer and the metastatic deposits, which were in his abdomen and lungs, but within a year the cancer had returned. Sam participated in a Phase II study using interleukin-2. Lymphocytes were removed from his blood, treated in the laboratory with the immune-stimulating protein, and then reinfused. As with virtually all other patients in these clinical trials, he suffered severe side effects and had to be hospitalized. He had high fevers, a widespread rash, and difficulty breathing; his body became painfully bloated. Sam did enjoy a six-month remission, during which he continued to teach and do research. Then the cancer recurred—this time in his lungs—and he died of pulmonary failure within a month.

Why did doctors welcome therapies with known toxicity and uncertain gain, and why did patients like Sam Driscoll subject themselves to them? Because the conventional therapies were no better. The best way to treat tumors is by detecting them early enough to prevent their growth and spread, but many oncologists don't meet their patients until long after that point. As one doctor said bitterly to me, "What do you say to these people—'Too bad, you flunked prevention'?" Ironically, the nature of the N.C.I. studies meant that in Phase III trials treatments with slight benefits were used on more patients for a longer time; interferon, for example, affords at best a marginal improvement, so it is possible to discern its benefits only in large studies conducted over long periods.

Most of the new cancer drugs were extremely toxic, and the real advances were in finding drugs that would temper their side effects. Platinol, which can cure testicular cancer, caused intense nausea and projectile vomiting that could last for days; in some patients, the retching was so severe that it tore the esophagus. It led researchers to develop potent anti-emetics. Other chemotherapy drugs, like Adriamycin, destroyed so many white blood cells that the patient was susceptible to fatal infections. Proteins like G-CSF were found that could stimulate the bone marrow to produce white cells, thereby greatly reducing the likelihood of such complicating infections. Even some of the toxicity of interleukin-2 was ameliorated. Thus, the horrors of chemotherapy were sometimes made less severe, or, at least, less prolonged. Chemo also became easier to administer, and oncologists could offer some reassurance to their patients that refinements in supportive therapy would reduce the suffering.

By the nineteen-eighties, a huge superstructure had resulted from the government's war on cancer. Some eight billion dollars had been spent. About thirty government-funded comprehensive cancer centers and major regional coöperative treatment groups linked virtually all university hospitals and community-based specialists. The American Society of Clinical Oncology had grown from several hundred members to nearly ten thousand. Cancer treatment had become one of the cash cows of academic and community hospitals, which competed fiercely for patient referrals. Treatment had also become the focus of a wide range of cancer-advocacy groups, whose constituents forcefully lobbied Congress for more funds to address their needs.

There were some success stories; by laboriously cobbling together combinations of chemotherapy agents, researchers had discovered that the majority of patients with Hodgkin's lymphoma and nearly all patients with testicular cancer could be saved. Great strides were also made in treating several pediatric cancers. Unfortunately, all of these types of

tumors are relatively unusual. Hundreds of thousands of cancer patients underwent experimental treatments; in most cases, the pain and discomfort caused by the side effects were unaccompanied by genuine benefit, and in some cases the treatments were fatal.

In 1984, Vincent DeVita, who had become the director of the National Cancer Institute four years earlier, provided Congress with a new goal in the war on cancer: a fifty-per-cent reduction in cancer-related mortality by the year 2000. According to an article by John C. Bailar III and Elaine Smith, which appeared in *The New England Journal of Medicine*, in 1986, this prediction was not justified by clinical data. Bailar, who had worked at the National Cancer Institute as a statistician studying trends in cancer incidence and outcomes, had grown wary of the predictions surrounding the war on cancer. Bailar and Smith's paper, dispassionately analyzing the claims of recent "advances" in treating cancer, demonstrated that there had been a slow and steady *increase* in cancer deaths over several decades. It concluded that "we are losing the war against cancer."

The paper was extremely controversial. Some felt that the authors hadn't given certain treatments adequate time to be properly measured; others felt that their statistics were not meaningful without more specifics. In response, in 1997 Bailar and Heather Gornik published a more sophisticated analysis in the same journal, entitled "Cancer Undefeated." Here the authors examined all American cancer deaths between 1970 and 1994 according to age, sex, and type of disease. They showed that there had been a six-per-cent increase in age-adjusted mortality due to cancer since Congress first acted, at the behest of Mary Lasker. There had been a recent dip, about a quarter of a per cent per year, which they attributed to reduced cigarette smoking and improved screening (thanks to mammograms, colonoscopies, and Pap smears). This said little for the enormous efforts that had been made over the previous decades on the therapeutic front. Bailar believes that, instead of focussing exclusively on fighting this generation of cancers, our work should be directed toward thwarting future generations of tumors through prevention and early detection.

In fact, the principal benefits from the war on cancer have been in other realms. The technologies developed to seek out cancer viruses in the seventies and eighties coalesced in the new field of molecular biology, which opened up the cell and its genetic blueprint to examination for the first time. This revolutionary DNA work also spawned a highly lucrative industry. Using the tools developed through the National Cancer Institute's contracts, biotechnology companies have created lifesaving treatments for heart disease, sepsis, colitis, and countless other serious maladies. Equally dramatic gains were made in AIDS research: the molecular techniques and reagents used to search for human cancer viruses proved essential in identifying H.I.V. and mapping its genes. In addition, the inventory of failed cancer drugs includes agents like AZT, which proved beneficial in treating AIDS. These unintended consequences of the war on cancer make it more difficult to gauge its success or failure.

"The idea of a war sets up a false metric," says Dr. David Golde, who, as the physician-in-chief at Memorial Sloan-Kettering Cancer Center, oversees all the institution's clinical programs. "If a complete victory is not achieved, then it is deemed a failure." Do we examine the impact on patients and their families? Do we ask whether patients' quality of life is improved—do they get more time without cancer, even if the tumor ultimately returns and kills them? Do we measure success and failure in terms of cost and benefit, calculating how much money is spent in treatment and how much economic productivity is gained for the nation? Or do we measure it by knowledge gained, progress in scientific understanding, even if that knowledge is not readily translated into improvements for patients? There is no consensus among cancer specialists on these questions.

In the past decade, cancer research has progressed in a number of different directions. In the area of immune therapy, there have been some promising results from so-called monoclonal antibodies, like Rituxan, which train the immune system to recognize tumor cells. Three years ago, a flurry of excitement greeted some early results in animal

SHOWCASE BY ALEX & LAILA

MOBY-DICK

Carlo Adinolfi trained first as a dancer, and then, because money was an object, as a carpenter. His solo show "One-Man 'Moby-Dick'" will be presented at the New Bedford Whaling Museum, in Massachusetts, on July 19th, to celebrate the hundred-and-fiftieth anniversary of the novel's publication, and later this summer at the Shakespeare & Company studio festival in the Berkshires. In it, Adinolfi plays Ishmael (a surprisingly spry, chatty Ishmael, with something of an English accent, since Adinolfi, who is Italian, grew up in South London); he plays Ahab, pegging the stage in a fury; and, in a remarkable piece of species-shifting, Adinolfi also plays the whale. To become the monstrous, mysterious creature, he turns away from the audience, tucks his head below his shoulders, twists his feet around each other, and rolls and ripples his dorsal muscles. The carpenter Adinolfi—he makes a living building sets—has constructed a series of props, the gradual unveiling of which amounts to an adventure story all its own: a few struts of wood become the prow of a whaling boat; Pip, the boy driven mad by a fall overboard, is a wooden artist's model suspended on a string; a length of silk fabric becomes, variously, the rippling water, the whale's flank, and, when squeezed between Adinolfi's hands, a mound of precious sperm-aceti. Adinolfi transforms a tiny stage into both the sea-locked world of the Pequod's decks and the vast, unfathomable sea itself. In an extraordinary scene based on the chapter "The Grand Armada," he drags a tiny wooden vessel on a wire across the stage, which thereby becomes the ocean's surface, arched with endless sky. Then he picks up the model and hangs it from a hook overhead, and suddenly we are in the other element—the deep, where only the whales are at home.

—*Rebecca Mead*

studies of angiogenesis, conducted by the researcher Judah Folkman. Folkman's research identified compounds that might prevent a tumor from generating its own blood supply, and so choke its growth. Unfortunately, the first clinical studies have not shown significant shrinkage of tumors.

By far the greatest source of excitement in cancer research, however, has been targeted therapies, an approach to treatment that is tailored to specific kinds of cancers. Unlike most experimental treatments of the past three decades, targeted therapies are based on a growing understanding of the molecular machinery of the diseased cell. The oncogene is the cornerstone of the new approach—which is based on the work of Robert Weinberg, a scientist at M.I.T.

In the late seventies, Weinberg began conducting just the sort of research that Farber had insisted was no longer necessary: an exploratory investigation of the oncogene's possible relationship to the origin of human cancer. Within a few years, he had found a conclusive link between the mutations of an oncogene and the development of a bladder tumor. Mutations in all our genes occur every minute, because there is an intrinsic error rate when DNA is copied. If the errors are extreme, the cell will self-destruct, but otherwise the aberrant cell survives. Normally, oncogenes provide the blueprint for proteins that signal when a cell should divide, mature, and die; they are often described as the accelerators of the cell's growth. A mutated oncogene may direct a cell to reproduce wildly, and this means, in turn, that more mutations are likely to occur.

In 1986, Weinberg isolated another type of genes, called tumor suppressors. These act as brakes on growth, but, when they mutate, the brakes can fail. Yet a third genetic control, the so-called telomerase gene, helps determine how long a cell can perpetuate itself. Normal cells can divide only a set number of times, but an alteration in the telomerase gene can make a cell immortal. A cell becomes cancerous when several preconditions are met: mutations in oncogenes, or simply an excess of oncogenes, either of which promotes growth; changes in tumor-suppressor genes, which then fail to restrain growth; and changes in telomerase genes, which sustain the mutating cell. In 1999, Weinberg demonstrated this when he produced a cancer cell from a normal cell in the test tube by introducing oncogenes, tumor-suppressor genes, and telomerase into a healthy cell. It was the first time that human cancer had been artificially created.

As the significance of Weinberg's work became clear, researchers in both the private and the public sectors began searching for ways to target these malfunctioning genes. Chemotherapy and radiation have traditionally been crude tools against cancer, indiscriminately smashing not only the diseased cells but the healthy tissue around them. A sophisticated understanding of the cell's workings greatly increases the likelihood that the mutant genes can be shut down without affecting the healthy cells. In 1993, the Swiss drug company Ciba-Geigy synthesized hundreds of thousands of possible targeted therapies, which it then tested against dozens of oncogene proteins. One of the targeted drugs was STI-571.

"Let's not waste missiles on cities not important enough to have a professional sports franchise."

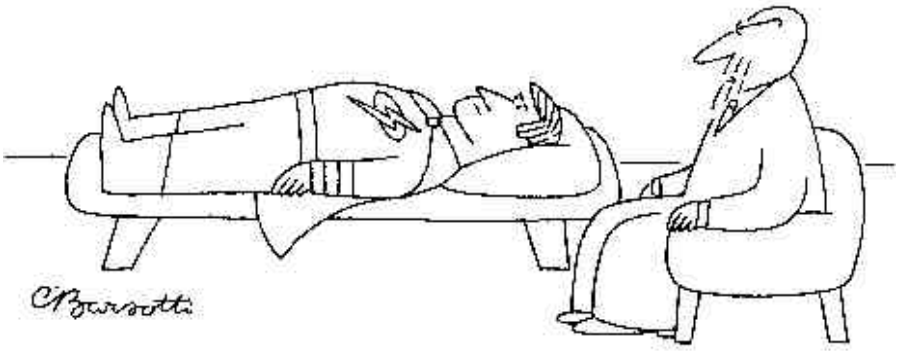
Doug Jenson is a sixty-seven-year-old retired systems engineer who lives in the Pacific Northwest. Four years ago, attending a Promise Keepers rally in Washington, D.C., he was overcome by exhaustion. A month later, after lunch at his church, he noted that his urine was "the color of cranberry juice." This was followed by wheezing and shortness of breath. He went to his local doctor, who gave him a blood test. The doctor called back that evening. "I hate to tell you this over the phone," he said, "but your white count is more than three hundred thousand." Jenson's diagnosis was chronic myelogenous leukemia, the same cancer that killed my grandmother. "They told me I had three to five years at the most," Jenson said. He was a robust man, five feet eleven and two hundred and twenty pounds, but his condition deteriorated rapidly. Initially, he was treated with chemotherapy, and that brought his white count down to about fifty thousand. This was a temporizing measure. Later, he began interferon treatments. Interferon has a modest benefit for CML patients, and significant side effects. Jenson became severely anemic, and then suffered a seizure. "The stuff is killing you," his hematologist said. But there seemed to be no alternative. Then, in September of 1998, Doug Jenson was referred to Dr. Brian Druker, a leukemia expert at Oregon's Health Sciences University, who enrolled him in a Phase I study of an experimental drug, STI-571.

Five years earlier, Druker had received a series of compounds from Ciba-Geigy to test on malignant cells, and he worked with the company to choose what ap-

peared to be the best of the series of candidate drugs. Among them was the compound STI-571, which appeared to be an ideal tool: it deftly dismantles three oncogene proteins,including one called Abl, which is the accelerator of chronic myelogenous leukemia. When it was tested in small animals, however, it was found to cause liver damage in dogs, and the pharmaceutical company, with meagre experience in cancer drugs, was leery about beginning human trials. But Druker pushed hard, because of the striking effects in the test tube against CML. In June of 1998, three institutions—Oregon, U.C.L.A., and M. D. Anderson, in Houston—began a Phase I safety study in patients with CML. To date, they have not reached a maximally tolerated dose, meaning a dose of STI-571 that causes significant toxicity in patients. The alarming dog studies proved not to be relevant for human beings.

Jenson had lost seventy pounds during his illness and prior treatment, and he gained it all back when he started taking STI-571. Within a few weeks, his white count fell to fifteen thousand. Not long after that, his anemia was ameliorated, and his platelets returned to normal. Few white cells that show the mutated Abl oncogene remain. "I go up to the health club every day, sometimes twice a day," he said. "I take spinning classes three times a week." The only side effect has been "a little puffiness around the eyes, which comes and goes." How long the benefits will continue is unknown, but, like the vast majority of the more than five hundred patients with CML who have been treated with STI-571 in the Phase II study, Jenson has enjoyed a profound and sustained remission. "It is a journey I don't wish on anyone," he said. "But, all things considered, I've been very, very fortunate."

Druker is cautious about the drug's dramatic results; negative side effects could still manifest themselves in the future, and the leukemia could also become resistant to the drug, precipitating relapse. Still,STI-571 is the most exciting new cancer drug in years. It turns out that the drug blocks oncogenes that may be critical to other kinds of cancer, such as glioblastoma, a type of brain tumor, and gastrointestinal stromal tumor, a rare sarcoma of the intestine. On May 10th, at a Washington press conference, the Secretary of Health and Human Services, Tommy Thompson, announced the F.D.A.'s approval of STI-571,after only two and a half months of review. It was the fastest agency clearance ever for a cancer drug.



"Surely you can tell me your secret identity."

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DeVita believes that the recent advances in cancer genetics will allow us to make enormous strides in treatment almost immediately. For him, STI-571—now known as Gleevec—is the proof of the principle. "I think we have the targets," he said. "It's not difficult to synthesize chemicals that block those targets. And when they come into clinical trials they work—surprisingly well." In the *Barron's* article, he said, "Within 15-20 years, I think cancer will become just another chronic, survivable disease, much like hypertension or diabetes." He predicts that the difficulties will lie not with the science but with the lack of resources for clinical trials to test all the drugs that will soon be discovered.

But is making Gleevec the poster child of imminent targeted cures premature—a replay of Sidney Farber's response to his success with childhood leukemia? After all, curing cancer entails understanding a hundred-odd diseases, which behave in different ways in different individuals. In the lab, the chemicals that are being screened are interacting only with the proteins of oncogenes or tumor-suppressor genes. In the patient, however, they are interacting with a complex living organism; it is impossible to accurately predict the success of chemicals that look promising in the lab.

I spoke with Dr. Glenn Bubley, a cancer researcher at Boston's Beth Israel Deaconess Medical Center, who, in 1997,conducted a clinical trial of a drug called SU-101. "SU-101 was touted as the Second Coming a few years ago," Bubley told me. It is a small molecule that, like STI-571, blocks PDGF-r, an oncogene that is believed to be important in the proliferation of a number of intractable cancers. When human tumors that had high levels of PDGF-r were implanted in mice, treatment with SU-101 blocked their growth. Safety tests in animals, unlike those involving STI-571,were promising, with no major liver toxicity or other red flags, and researchers anticipated dramatic succcess in the clinical trials.

A patient I will call George Mitsopoulos was a restaurant owner who had prostate cancer. He was still working when he entered the trial, despite the fact that his cancer had spread to his bones. The tumors could no longer be controlled by hormonal therapy, and so he began treatment with great hopes that SU-101 would ameliorate his condition. He quickly discovered,however, that the drug had severe side effects. "I am exhausted," he told Dr. Bubley. "I feel like I can hardly move out of bed." He also had immense difficulty sleeping, because he felt terrible even when he was lying down. Other patients in the trial begged to interrupt the therapy because of the exhaustion it caused, but Mitsopoulos was determined to persevere. The course of treatment had no lasting impact, and he died shortly afterward.

Mitsopoulos's experience with SU-101

"And do you, Stephanie, promise to love, honor, and 'obey'?"

• •

proved to be typical. What went wrong? Many cancer cells may have redundant machinery, with several different oncogenes driving growth; if you block one, the others may take up the slack. The pharmaceutical company that had supported the research was not enthusiastic about publishing negative data, Bubley said—even high-profile journals prefer articles with positive results—but he believes that it is equally important to publish accounts of the failures, in order to inject a note of realism into the scientific debate. (An article about the failure of SU-101 in treating prostate cancer was published last month in *Clinical Cancer Research.*)

Other targeted treatments, like Herceptin, an antibody developed by Genentech, have performed better—but not nearly as well as some clinicians initially expected them to. Herceptin targets Her-2, a protein produced by an oncogene that is found in between twenty and thirty per cent of breast-cancer cases. The early news was exciting, and magazines and morning talk shows reported that Herceptin would make chemotherapy treatment for breast cancer a thing of the past. When Herceptin is used in conjunction with chemotherapy, it nearly doubles the likelihood of significant shrinkage of breast cancers with Her-2. But as a solo treatment for breast cancer its impact has been modest. Last year, Genentech alerted physicians to a potentially lethal respiratory problem among women who had breast cancer that had spread to their lungs or who had prior lung disease. It can also cause significant heart damage in some women—particularly those receiving Adriamycin, a mainstay chemotherapy drug in the treatment of the disease. This is because in this form of breast cancer, as in some other cancers, the problem lies not with a mutated oncogene but with an excess of normal oncogenes, and targeting them can damage healthy heart tissue as well. *The New England Journal of Medicine* recently described the Herceptin study as "a landmark trial," even though it extended life for an average of only five months, and only in the subset of patients who qualified for the treatment. The description is less an example of hyperbole than a sobering reminder of the fact that no prior therapies had been shown to significantly extend the lives of women with metastatic breast cancer.

These limitations reveal how complex the biology of cancer is, and how little can be predicted about the efficacy of any particular treatment. The statistician John Bailar, for one, remains skeptical of the new therapies. "In the nineteen-fifties, there was huge excitement about laboratory programs to screen for chemotherapy drugs," he says. "We found a few drugs, but not many. Then, in the nineteen-seventies, there were cancer viruses. In the eighties, it was immunotherapy, with biologics like interferon and interleukin-2 as the model magic bullets. Now it's cancer genetics. The rhetoric today sounds just the way it did forty years ago. I have no doubt that there has been a huge increase in knowledge about cancer. The problem is to translate it into public benefits we can measure. I want to see an impact on population mortality rates. If the treatments are really that good, then we'll see it."

After decades of listening to unrealistic predictions, cancer-patient advocates have a jaundiced view of researchers who inflate preliminary anecdotes of success. Fran Visco, the president of the National Breast Cancer Coalition, told me recently that she was dismayed, at a meeting of cancer clinicians, at the way researchers interacted with members of the press. "These clinical scientists receive media training and are scripted by their hospitals," she said. "There are so many agendas here: fame, patient referrals, fund-raising, pharmaceutical grants, academic advancement." Ellen Stovall, the president of the National Coalition for Cancer Survivorship, agreed: "The headlines are dreadful." She referred to the sensationalism surrounding the disease as "the pornography of cancer," adding, "I am excited by the new science, but show me hard data. We need to raise the skepticism barometer."

Many former members of the cancer establishment express similar misgivings. Samuel Broder, who succeeded DeVita in 1988 as the director of the National Cancer Institute, and who is currently the chief medical officer at Celera Genomics, believes that we require new breakthroughs in the lab—particularly in understanding the process of how cancer spreads—before we can be confident of great gains in treatment.

"I call it the iron-lung syndrome,"

he told me. "If you had demanded that the N.I.H. solve the problem of polio not through independent, investigator-driven discovery research but by means of a centrally directed program, the odds are very strong that you would get the very best iron lungs in the world—portable iron lungs, transistorized iron lungs—but you wouldn't get the vaccine that eradicated polio." He thinks that, given the performance of the targeted therapies available so far, it would be premature to invest more in the federal bureaucracy that oversees clinical trials.

Broder argues that the creation of new therapies is no longer the sole or even the primary provenance of the government. "Initiative and creativity have moved to the private sector," he said. "There is just no way of getting around it, and anyone who tells you otherwise is on a different planet. What was done in the early seventies was necessary, even in retrospect, but that doesn't mean we should do it that way now." Furthermore, pharmaceutical companies prefer to run their own clinical trials: both Gleevec and Herceptin were submitted to the F.D.A. for approval without having entered N.C.I.-sponsored studies. This frees more money for the sort of basic research supported by the National Institutes of Health—the grant system and research laboratories that Broder refers to as the jewels in the crown of the N.I.H. Any scientist or clinician in the United States can propose a new idea and seek support for testing it. "When the N.I.H. sticks to that," Broder said, "it does an astonishing job, and it is the envy of the world."

Harold Varmus is a former director of the National Institutes of Health, and, like Broder, his experience as the head of a large government institute has made him wary of bureaucratic efforts to direct scientific research. Now, as the president of Memorial Sloan-Kettering, he finds himself in a curious position. "My view here is not very popular—especially among cancer researchers and cancer-focussed senators—but I believe cancer doesn't deserve unique distinction for funding," he said recently. Giving one advocacy group special treatment simply doesn't help the balance of research. Varmus also believes that the greatest advances in new knowledge will come not from cancer genetics alone but from a variety of disciplines working together to understand the complex mechanisms of the cancer cell. After all, genes are merely the blueprints for proteins, and it is the proteins that do the cell's work. An ability to decipher protein shapes—how they change in health and disease—will be important in combatting cancer, and this will require advances in chemistry, in computer science, and in physics.

In recent years, the mission to reëducate Congress and the public about the realities of cancer and to reverse the unrealistic attitudes and expectations that we have inherited from Nixon's war has been taken up by an unlikely advocate—the current head of the National Cancer Institute, Dr. Richard Klausner. "I'm pretty well plugged in to what's going on in research," he remarked. "I hear on the news 'Major breakthrough in cancer!' And I think, Gee, I haven't heard anything major recently. Then I listen to the broadcast and realize that I've never heard of this breakthrough. And then I never hear of it again." Klausner himself has been under considerable pressure to predict the eradication of cancer, because powerful members of Congress have promised that such a prediction could mean millions of additional government dollars for the N.C.I. But he refuses—not only because to do so is impossible but because it would propagate the scientific fallacy that cancer is a single disease.

The most productive way to move forward in cancer research, Klausner believes, is to call off the war. He prefers to think of cancer as an intricate puzzle—one that we currently lack both the knowledge and the tools to solve. Clues could come from any field, and the reforms that he has undertaken at the N.C.I. reflect the need for such disciplinary openness. He has tackled the vast clinical-trials bureaucracy of the cooperative groups so that they no longer function as a closed shop controlled by inbred committees but are, instead, responsive to any researcher with good ideas. He also recognizes that the N.C.I. should complement the drug companies' efforts rather than duplicate them; to this end, the N.C.I. provides assistance to university-based laboratories that are pursuing molecular targets and candidate drugs but lack sufficient resources to develop and market them. So far, more than fifty compounds and molecular targets have been developed in this manner, and two have entered the first phase of clinical testing.

Klausner refers to these reforms as "an experiment, to see if science can take over the National Cancer Institute, instead of politics and hype." He continued, "Human beings seem to have this endless ability to think they are at the end of history. The only people who now are saying we know enough are people who don't know enough."

Francis Moore's congressional testimony about science's law of unintended consequences has been amply proved over the past thirty years. The failures of the government's war on cancer have been matched by the unforeseen successes it led to in fighting other diseases; indeed, its greatest successes came from shattering its central premise—the belief in cancer viruses. As Moore predicted, the most promising results stemmed from basic biological inquiry. And yet both Congress and the public continue to view open-ended scientific investigations as nebulous, self-indulgent, and wasteful of taxpayers' money, and are reluctant to fund them. For this reason, oncologists talk in terms of imminent cures through directed research—both in their proposals for new projects and in their assessments of ongoing work. The media attention that results further misleads the public.

If Americans are unwilling to reject the national mythology of cancer, it may be because they fear that the only alternative is despair. That fear can be tempered by the rapid pace and diversity of new discoveries in science and technology that are influencing every dimension of cancer research. Of course, it is impossible to say which type of currently intractable cancer will be cured first. In the next ten years, the survival rate of people with a certain type of melanoma or lung tumor or lymphoma or breast cancer may not change. But it also might improve by fifty per cent, or ninety per cent. Because of the uncertainty inherent in scientific discovery, there is simply no way of knowing. Paradoxically, for cancer patients and their families this inability to predict the future becomes their sustaining hope. ♦