

Newsweek

We Fought Cancer...And Cancer Won.

After billions spent on research and decades of hit-or-miss treatments, it's time to rethink the war on cancer.

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NEWSWEEK

Updated: 1:55 PM ET Sep 6, 2008

There is a blueprint for writing about cancer, one that calls for an uplifting account of, say, a woman whose breast tumor was detected early by one of the mammograms she faithfully had and who remains alive and cancer-free decades later, or the story of a man whose cancer was eradicated by one of the new rock-star therapies that precisely target a molecule that spurs the growth of malignant cells. It invokes Lance Armstrong, who was diagnosed with testicular cancer in 1996 and, after surgery and chemotherapy beat it back, went on to seven straight victories in the Tour de France. It describes how scientists wrestled childhood leukemia into near submission, turning it from a disease that killed 75 percent of the children it struck in the 1970s to one that 73 percent survive today.

But we are going to tell you instead about Robert Mayberry. In 2002 a routine physical found a lesion on his lung, which turned out to be cancer. Surgeons removed the malignancy, which had not spread, and told Mayberry he was cured. "That's how it works with lung cancer," says oncologist Edward Kim of the University of Texas M. D. Anderson Cancer Center in Houston, who treated Mayberry. "We take it out and say, 'You're all set, enjoy the rest of your life,' because really, what else can we do until it comes back?" Two years later it did. The cancerous cells in Mayberry's lung had metastasized to his brain—either after the surgery, since such operations rarely excise every single microscopic cancer cell, or long before, since in some cancers rogue cells break away from the primary tumor as soon as it forms and make their insidious way to distant organs. It's impossible to know. Radiation therapy shrank but did not eliminate the brain tumors. "With that level of metastasis," says Kim, "it's not about cure. It's about just controlling the disease." When new tumors showed up in Mayberry's bones, Kim prescribed Tarceva, one of the new targeted therapies that block a molecule called epidermal growth factor receptor (EGFR) that acts like the antenna from hell: it grabs growth-promoting signals out of the goop surrounding a cancer cell and uses them to stimulate proliferation. Within six months—it was now the autumn of 2005—the tumors receded, and Mayberry, who had been unable to walk when the cancer infiltrated his brainstem and bones, was playing golf again. "I have no idea why Tarceva worked on him," says Kim. "We've given the same drug to patients in the same boat, and had no luck." But the luck ran out. The cancer came back, spreading to Mayberry's bones and liver. He lost his battle last summer.

We tell you about Mayberry because his case sheds light on why cancer is on track to kill 565,650 people in the United States this year—more than 1,500 a day, equivalent to three jumbo jets crashing and killing everyone aboard 365 days a year. First, it shows the disconnect between the bench and the bedside, between what science has discovered about cancer and how doctors treat it. Biologists have known for at least two decades that it is the rare cancer that can be completely cured through surgery. Nevertheless, countless proud surgeons keep assuring countless anxious patients that they "got it all." In Mayberry's case, says Kim, "my gut feeling is that [cells from the original lung tumor] were smoldering in other places the whole time, at levels so low not even a whole-body scan would have revealed them." Yet after surgery and, for some cancers, radiation or chemotherapy, patients are still sent back into the world with no regimen to keep those smoldering cells from igniting into a full-blown metastatic cancer or recurrence of the original cancer. Mayberry's story also shows the limits of "targeted" cancer drugs such as Tarceva, products of the golden age of cancer genetics and molecular biology. As scientists have learned in just the few years since the drugs' introduction, cancer cells are like brilliant

military tacticians: when their original route to proliferation and invasion is blocked, they switch to an alternate, marching cruelly through the body without resistance.

We also tell you about Mayberry because of something Boston oncologist (and cancer survivor) Therese Mulvey told us. She has seen real progress in her 19 years in practice, but the upbeat focus on cancer survivors, cancer breakthroughs and miracle drugs bothers her. "The metaphor of fighting cancer implies the possibility of winning," she said after seeing the last of that day's patients one afternoon. "But some people are just not going to be cured. We've made tremendous strides against some cancers, but on others we're stuck, and even our successes buy some people only a little more time before they die of cancer anyway." She pauses, musing on how the uplifting stories and statistics—death rates from female breast cancer have fallen steadily since 1990; fecal occult blood testing and colonoscopy have helped avert some 80,000 deaths from colorectal cancer since 1990—can send the wrong message. "With cancer," says Mulvey, "sometimes death is not optional."

Yet it was supposed to be. In 1971 President Richard Nixon declared war on cancer (though he never used that phrase) in his State of the Union speech, and signed the National Cancer Act to make the "conquest of cancer a national crusade." It was a bold goal, and without it we would have made even less progress. But the scientists and physicians whom Nixon sent into battle have come up short. Rather than being cured, cancer is poised to surpass cardiovascular disease and become America's leading killer. With a new administration taking office in January, and with the new group Stand Up to Cancer raising \$100 million (and counting) through its telethon on ABC, CBS and NBC on Sept. 5, there is no better time to rethink the nation's war on cancer.

In 2008, cancer will take the lives of about 230,000 more Americans—69 percent more—than it did in 1971. Of course, since the population is older and 50 percent larger, that raw number is misleading. A fairer way to examine progress is to look at age-adjusted rates. Those statistics are hardly more encouraging. In 1975, the first year for which the National Cancer Institute has solid age-adjusted data, 199 of every 100,000 Americans died of cancer. That rate, mercifully, topped out at 215 in 1991. In 2005 the mortality rate fell to 184 per 100,000, seemingly a real improvement over 1975. But history provides some perspective. Between 1950 and 1967, age-adjusted death rates from cancer in women also fell, from 120 to 109 per 100,000, found an analysis by the American Cancer Society just after Nixon's speech. In percentage terms, the nation made more progress in keeping women, at least, from dying of cancer in those 17 years, when cancer research was little more than a cottage industry propelled by hunches and trial-and-error treatment, as it did in the 30 years starting in 1975, an era of phenomenal advances in molecular biology and genetics. Four decades into the war on cancer, conquest is not on the horizon. As a somber statement on the NCI Web site says, "the biology of the more than 100 types of cancers has proven far more complex than imagined at that time." Oncologists resort to a gallows-humor explanation: "One tumor," says Otis Brawley of the ACS, "is smarter than 100 brilliant cancer scientists."

The meager progress has not been for lack of trying. Since 1971, the federal government, private foundations and companies have spent roughly \$200 billion on the quest for cures. That money has bought us an estimated 1.5 million scientific papers, containing an extraordinary amount of knowledge about the basic biology of cancer. It has also brought real progress on a number of fronts, not least the invention of drugs for nausea, bowel problems and other side effects of the disease or treatment. "These have reduced suffering and changed people's ability to live with cancer," says Mulvey. In fact, just a few months after Nixon's call to arms, Bernard Fisher of the University of Pittsburgh began studies that would show that a woman with breast cancer has just as good a chance of survival if she receives a mastectomy rather than have her breast, chest-wall muscles and underarm tissue cut out, the standard at the time. The new approach spared millions of women pain and disfigurement. In 1985, treatment improved again when Fisher showed that lumpectomy followed by radiation to kill lingering cells was just as effective for many women as mastectomy. It wasn't a cure, but it mattered. "One can wait for the home run," says Fisher, now 90, "but sometimes you get runs by hitting singles and doubles. We haven't hit a home run yet; we can't completely prevent or completely cure breast cancer."

Nixon didn't issue his call to arms in order to reduce disfigurement, however. The goal was "to find a cure for cancer." And on that score, there are some bright spots. From 1975 to 2005, death rates from breast cancer fell from 31 to 24 per 100,000 people, due to earlier detection as well as more-effective treatment. Mortality from colorectal cancer fell from 28 to 17 per 100,000 people, due to better chemotherapy and, even more, to screening: when colonoscopy finds precancerous polyps, they can be snipped out before they become malignant.

But progress has been wildly uneven. The death rate from lung cancer rose from 43 to 53 per 100,000 people from 1975 to 2005. The death rate from melanoma rose nearly 30 percent. Liver

and bile-duct cancer? The death rate has almost doubled, from 2.8 to 5.3 per 100,000. Pancreatic cancer? Up from 10.7 to 10.8. Perhaps the most sobering statistic has nothing to do with cancer, but with the nation's leading killer, cardiovascular disease. Thanks to a decline in smoking, better ways to control hypertension and cholesterol and better acute care, its age-adjusted mortality has fallen 70 percent in the same period when the overall mortality rate from cancer has fallen 7.5 percent. No wonder cancer "is commonly viewed as, at best, minimally controlled by modern medicine, especially when compared with other major diseases," wrote Harold Varmus, former director of NCI and now president of Memorial Sloan-Kettering Cancer Center in New York, in 2006.

About all scientists knew about cancer 50 years ago was that cancer cells make copies of their DNA and then of themselves more rapidly than most normal cells do. In the 1940s, Sidney Farber, a Boston oncologist, intuited that since cells need a biochemical called folate to synthesize new DNA, an anti-folate might impede this synthesis. After a friend at a chemical company synthesized an anti-folate—it was named methotrexate—Farber gave it to cancer patients, sending some into short-term remission, he reported in 1948. (Two years earlier, scientists had serendipitously discovered that mustard gas, a chemical weapon, could reduce tumors in patients with non-Hodgkin's lymphoma, but no one had any idea how it worked.) Thus was born the era of chemotherapy, one that continues today. It is still based on the simple notion that disrupting DNA replication and cell division will halt cancer. Soon there would be dozens of chemo drugs that target one or more of the steps leading to cell proliferation. Almost all of those approved in the 1970s, 1980s and 1990s were the intellectual descendants of Farber's strategy of stopping cancer cells from making copies of their DNA, and then themselves, by throwing a biochemical wrench into any of the steps involved in those processes. And none of it had anything to do with understanding why cancer cells were demons of proliferation. "The clinical-research community was expending enormous effort mixing and matching chemotherapy drugs," recalls Dennis Slamon, who began a fellowship in oncology at UCLA in 1979 and is now director of clinical/translational research at the Jonsson Cancer Center there. "There was nothing coming out of the basic science that could help" patients.

In the high-powered labs funded by the war on cancer, molecular biologists thought they could change that. By discovering how genetic and other changes let cancer cells multiply like frisky rabbits, they reasoned, they could find ways to stop the revved-up replication at its source. That promised to be more effective, and easier on healthy cells than chemotherapy drugs, which also kill normal dividing cells, notably in the gut, bone marrow, mouth and hair follicles. In the 1970s, cancer scientists discovered cancer viruses that alter DNA in animals, and for a while the idea that viruses cause cancer in people, too, was all the rage. (The human papilloma virus causes cervical cancer, but other human cancers have nothing to do with viruses, it would turn out.) In the 1970s and 1980s they discovered human genes that, when mutated, trigger or promote cancer, as well as tumor suppressor genes that, when healthy, do as their name implies but when damaged release the brakes on pathways leading to cancer.

It made for a lot of elegant science and important research papers. But it "all seemed to have little or no impact on the methods used by clinicians to diagnose and treat cancers," wrote Varmus. Basic-science studies of the mechanisms leading to cancer and efforts to control cancer, he observed, "often seemed to inhabit separate worlds." Indeed, it is possible (and common) for cancer researchers to achieve extraordinary acclaim and success, measured by grants, awards, professorships and papers in leading journals, without ever helping a single patient gain a single extra day of life. There is no pressure within science to make that happen. It is no coincidence that the ratio of useful therapy per basic discovery is abysmal. For other diseases, about 20 percent of new compounds arising from basic biological discoveries are eventually approved as new drugs by the FDA. For cancer, only 8 percent are.

A widely discussed 2004 article in *Fortune* magazine ("Why We're Losing the War on Cancer") laid the blame for this at the little pawed feet of lab mice and rats, and indeed there is a lot to criticize about animal studies. The basic approach, beginning in the 1970s, was to grow human cancer cells in a lab dish, transplant them into a mouse whose immune system had been tweaked to not reject them, throw experimental drugs at them and see what happened. Unfortunately, few of the successes in mice are relevant to people. "Animals don't reflect the reality of cancer in humans," says Fran Visco, who was diagnosed with breast cancer in 1987 and four years later founded the National Breast Cancer Coalition, an advocacy group. "We cure cancer in animals all the time, but not in people." Even scientists who have used animal models to make signal contributions to cancer treatment agree. "Far more than anything else," says Robert Weinberg of MIT, the lack of good animal models "has become the rate-limiting step in cancer research."

For this story, NEWSWEEK combed through three decades of high-profile successes in mice for clues to why the mice lived and the people died. Two examples make the point. Scientists were

tremendously excited when Weinberg and colleagues discovered the first cancer-causing gene (called ras) in humans, in 1982. It seemed obvious that preventing ras from functioning should roll back cancer. In this decade, scientists therefore began testing drugs, called FTIs, that do exactly that. When FTIs were tested on human cancers that had been implanted into mice, they beat back the cancer. But in people, the drugs failed. One reason, scientists suspect, is that the transplanted cancers came from tumors that had been growing in lab dishes for years, long enough to accumulate countless malignant genes in addition to ras. Disabling ras but leaving those other mutations free to stoke proliferation was like using a sniper to pick off one soldier in an invading platoon: the rest of the platoon marches on. That general principle—not even the malignancy in a single cancer has one cause—would haunt cancer research and treatment for years. A compound called TNF, for tumor necrosis factor, raised hopes in the 1980s that it would live up to its name. When it was injected into mice carrying human tumors, it seemed to melt them away. But in clinical trials, it had little effect on the cancer. "Animal models have not been very predictive of how well drugs would do in people," says oncologist Paul Bunn, who leads the International Society for the Study of Lung Cancer. "We put a human tumor under the mouse's skin, and that microenvironment doesn't reflect a person's—the blood vessels, inflammatory cells or cells of the immune system," all of which affect prognosis and survival.

If mouse models have a single Achilles' heel, it is that the human tumors that scientists transplant into them, and then attack with their weapon du jour, almost never metastasize. Even in the 1970s there was clear evidence—in people—of the deadly role played by cells that break off from the original tumor: women given chemo to mop up any invisible malignant cells left behind after breast surgery survived longer without the cancer's showing up in their bones or other organs, and longer, period, than women who did not receive such "adjuvant" therapy, scientists reported in 1975. "Every study of adjuvant therapy shows it works because it kills metastatic cells even when it appears the tumor is only in the breast or in the first level of lymph nodes," says the ACS's Brawley. By the mid-1990s studies had shown similar results for colon cancer: even when surgeons said they'd "got it all," patients who received chemo lived longer and their cancer did not return for more years.

Yet for years, despite the clear threat posed by metastatic cells, which we now know are responsible for 90 percent of all cancer deaths, the war on cancer ignored them. Scientists continued to rely on animal models where metastasis didn't even occur. Throughout the 1980s and 1990s, says Visco, "researchers drilled down deeper and deeper into the disease," looking for ever-more-detailed molecular mechanisms behind the initiation of cancer, "instead of looking up and asking really big questions, like why cancer metastasizes, which might help patients sooner."

There was another way. At the same time that molecular biologists were taking the glamorous, "look for the cool molecular pathway," *cojones*-fueled approach to seeking a cure, pediatric oncologists took a different path. Pediatric cancer had long been a death sentence: in Farber's day, children with leukemia rarely survived more than three months. (President Bush's sister Robin died of the disease in 1953; she was 3.) Fast-forward to 2008: 80 percent of children with cancer survive well into adulthood.

To achieve that success, pediatric oncologists collaborated to such a degree that at times 80 percent of the children with a particular cancer were enrolled in a clinical trial testing a new therapy. In adults, it has long been less than 1 percent. The researchers focused hardly at all on discovering new molecular pathways and new drugs. Instead, they threw everything into the existing medicine chest at the problem, tinkering with drug doses and combinations and sequencing and timing. "We were learning how to better use the drugs we had," says pediatric oncologist Lisa Diller of Dana-Farber Cancer Institute and Children's Hospital Boston. By 1994, combinations of four drugs kept 75 percent of childhood leukemia patients—and 95 percent of those enrolled in a study—cancer-free. Childhood brain cancer has been harder to tame, but while 10 percent of kids survived it in the 1970s, today 45 percent do—a greater improvement than in most adult cancers. (To be sure, some scientists who work on adult cancers are sick of hearing about the noble cooperation of their pediatric colleagues. Childhood cancers, especially leukemias, are simpler cancers, they say, often characterized by a single mutation, and that's why the cure rate has soared. Neutral observers say it's a little of both: pediatric-cancer scientists really did approach the problem in a novel, practical way, but their enemy is less wily than most adult cancers.)

Biologists who never met a signaling pathway they didn't love tend to dismiss the success in pediatric oncology. It involved no discoveries of elegant cell biology, just plodding work. Ironically, however, it is these "singles," not the grand slams of molecular biology, that have made the greatest difference in whether people develop cancer and die of it. Fewer smokers (54 percent of men smoked in 1971; 21 percent do today), more women having mammograms and fewer taking hormone-replacement therapy (the incidence of breast cancer fell an unheard-of 7

percent from 2002 to 2003, after a 2002 study found that HRT can stimulate the growth of tiny breast tumors) have had at least as great an impact on cancer as the achievements of basic-science labs that received the bulk of the funding in the war on cancer. Similarly, the widespread use of Pap smears to detect precancerous changes in cells of the cervix is almost entirely responsible for the drop in both incidence of and deaths from cervical cancer. Incidence has fallen some 65 percent since 1975, and mortality at least 60 percent. Little wonder, then, that by the 1980s critics were asking why the war on cancer was spending the vast majority of taxpayers' money on elegant biology that cured millions of mice rather than on the search for more practical advances like these.

By "critics," we don't mean disgruntled laypeople. At UCLA, Denny Slamon had been inspired by Robert Weinberg's discovery of the first human oncogene, *ras*, in 1982. Although drugs to squelch the gene directly did not pan out, the discovery did lead to the first real success of the reductionist, "let's get in there and study the genetics and molecules of cancer" approach. Slamon was at first following the crowd, examining animal cancers for signs of DNA changes. But in 1982 he had an idea: look for unusual genes in tissue samples taken from human tumors. He applied to NCI for funding and, he recalls, "they basically sent it back with a laugh track. They said it was just a fishing expedition, that it wasn't hypothesis-driven. We tried to explain the logic—that if cancer reflects a problem of genetic control, then finding mutated genes should be important—but still didn't get funded." The same year that NCI laughed at Slamon's idea, MIT's Weinberg and colleagues discovered another gene involved in cancer. Called HER2, it makes a molecule that sits on the outside of cells and acts like an antenna, picking up growth signals that are then carried to the cell nucleus, where they deliver a simple if insidious message: go forth and multiply, really really fast. That made Slamon wonder whether HER2 might play a role in major human cancers.

In 1984, backed by private funding, Slamon found that 27 percent of breast cancers contain extra copies of HER2. Over the next decade he and other scientists showed that HER2 caused the cancer, rather than being an innocent bystander (or "marker," as scientists say). They also found an antibody that attaches to HER2 like a squirrel's nest on a TV antenna, preventing it from picking up signals. In 1998 the FDA approved that antibody, called Herceptin, for use in breast cancers fueled by HER2. It was stunning proof of the principle that drugs could be precisely crafted to cripple molecules that lie upstream of cell replication, stoking the growth of cancer cells and only cancer cells, not healthy ones, and has cured thousands of women. After the 1984 discovery, NCI was happy to fund Slamon. "It was only because we had already shown that the research would work," he says wistfully. "It is, shall we say, a conservative way to spend your money."

Slamon was not the only scientist who noticed NCI's preference for elegant molecular studies over research that offered the possibility of new treatments. (We should note that funding decisions are made not by NCI bureaucrats but by panels of scientists from, mostly, universities and medical institutions.) In the mid-1990s Brain Druker of the Oregon Health and Science University Cancer Institute wanted to study a molecule involved in chronic myelogenous leukemia. Targeting that molecule, he thought, might cure CML. "People rolled their eyes and asked, 'What's new and different about this?'" By "new and different," they meant scientifically novel, elegant, offering new insight into a basic cellular process. He didn't even apply for an NCI grant. "I knew I'd just be wasting my time," he says. "NCI would have looked at what I wanted to do and said it was too high-risk. Instead I took the tried-and-true approach of getting funded for basic research, seeing how cell growth is regulated" by molecules that are grabbed by receptors on a leukemia cell and that send proliferation orders to the cell nucleus. This work led to a useful clinical test, but the work NCI did not fund (a private foundation did) eventually led to Gleevec, the blockbuster CML drug.

Indeed, there is no more common refrain among critics of how the war on cancer has been waged: that innovative ideas, ideas that might be grand slams but carry the risk of striking out, are rejected by NCI in favor of projects that promise singles. "We ask the scientists all the time why aren't we further along," says Visco. "Part of the answer is that the infrastructure of cancer is to keep things moving along as they have been and to reward people doing safe research. Exciting new ideas haven't fared well." As coincidence would have it, in the very year that Nixon launched the war on cancer, an unknown biologist named Judah Folkman published a paper proposing that metastatic cells survive, and become deadly, only if they grow blood vessels to keep themselves supplied with nutrients. That process is called angiogenesis, and it had nothing to do with the genes and proteins that the soldiers in the war on cancer were fixated on. Throughout the 1970s "the reaction was mainly hostility and ridicule," Folkman (who died earlier this year) recalled to NEWSWEEK in 1998. "People would ask me [at scientific meetings], 'You really don't believe that, do you?'" NCI turned down his request for funds to continue his work, calling his ideas about the importance of angiogenesis in metastasis "just your imagination,"

Folkman said. He persisted, of course, laying the groundwork for what would become anti-angiogenesis drugs. Avastin was approved for colorectal cancer in 2004.

If the 1990s were the era of identifying cellular processes and molecules unique to cancer cells—not the blunderbuss approach of wrecking DNA and stopping replication, which brings friendly fire down on healthy cells—the focus of the 2000s is to personalize treatment. The reason is that, just as cancer cells develop resistance to standard chemo drugs, so they are finding ways to elude the new targeted drugs such as Avastin, Gleevec and Herceptin. In the studies that led the FDA to approve Avastin, for instance, the drug prolonged life in patients with advanced colorectal cancer by a median of four months. In later studies, it increased survival in advanced lung-cancer patients by a couple of months, says Roy Herbst, a lung oncologist at M. D. Anderson. Why so little? "Angiogenesis is a redundant process," Herbst explains. "Most cells use the VEGF pathway [that Avastin blocks], but there are at least 12 other pathways, and Avastin doesn't block any of them." With VEGF out of commission, malignant cells turn to these alternatives. Or consider Tarceva, given to lung-cancer patients, which turns off a molecule called EGFR that fuels the proliferation of some lung and other cancer cells. "It shrinks the tumor 60 to 80 percent of the time, and the effect lasts about a year," says David Johnson, a thoracic oncologist at Vanderbilt (University) Ingram Cancer Center. But if even a tiny fraction of malignant cells in the tumor or at metastatic sites use a proliferation pathway other than EGFR, they laugh off Tarceva and proliferate unchecked; most patients are dead within three years. Of the first patients with a rare gastric cancer whom George Demetri of Dana-Farber treated with Gleevec in 2000, 85 percent became resistant to it after five years. (Before Gleevec, though, patients with this cancer died within six weeks.) The malignant cells, it turns out, change the shape of the molecule that Gleevec blocks. It's as if a teenager, knowing Mom has a key to his room and wanting his privacy, changed the lock before she arrived.

In response to the limits of targeted therapies, scientists are pursuing the next big idea: that there is no such thing as cancer. There are only cancers, plural, each one characterized by a different set of mutations, a different arsenal it uses to fight off drugs and proliferate. "By the time there are 10 cancer cells, you probably have eight different cancers," says Demetri. "There are different pathways in each of the cells." And that's why cancer patients keep dying. One woman found a lump in her breast in 2002, nine months after a mammogram had shown nothing amiss. She had the breast tumor removed, says oncologist Julie Gralow, who treated her at the Fred Hutchinson Cancer Center, and chemotherapy to kill any remaining malignant cells. The woman did well for three years, but in 2005 an exam found cancer in her bones. She underwent half a dozen different chemotherapies over the next three years, until last March the cancer was detected in her brain. She received radiation—because chemo drugs generally do not cross the blood-brain barrier, radiation rather than chemo is the treatment of choice for brain cancer—but by July tumors had riddled her body. She died that month.

To beat down cancer mortality, oncologists need to target all the many cancers that make up a cancer—the dozens of different pathways that cells use to proliferate and spread. That is the leading edge of research today, determining how *this* patient's tumor cells work and hitting those pathways with multiple drugs, simultaneously or sequentially, each chosen because it targets one of those growth, replication and angiogenesis pathways. "The hope is to match tumor type to drug," says Roy Herbst. "We need to make the next leap, getting the right drug to the right patient."

Both presidential candidates have vowed to support cancer research, which makes this a propitious time to consider the missed opportunities of the first 37 years of the war on cancer. Surely the greatest is prevention. Nixon never used the word; he exhorted scientists only to find a cure. Partly as a result, the huge majority of funding for cancer has gone into the search for ways to eradicate malignant cells rather than to keep normal cells from becoming malignant in the first place. "The funding people are interested in the magic-bullet research because that's what brings the dollars in," says oncologist Anthony Back, of the Hutch. "It's not as sexy to look at whether broccoli sprouts prevent colon cancer. A reviewer looks at that and asks, 'How would you ever get that to work?' " And besides, broccoli can't be patented, so without the potential payoff of a billion-dollar drug there is less incentive to discover how cancer can be prevented.

Another missed opportunity involves the environment around a tumor cell. "We used to focus on cancer cells with the idea that they were master of their own destiny," says MIT's Weinberg. "By studying genes inside the cell we thought we could understand what was going on. But now [we know] that many tumors are governed by the signals they receive from outside"—from inflammatory cells, cells of the immune system and others. "It's the interaction of signals inside and outside the tumor that creates aggressiveness and metastasis."

Which leads to the third big missed opportunity, the use of natural compounds and nondrug interventions such as stress reduction to keep the microenvironment inhospitable to cancer.

(Cancer cells have receptors that grab stress hormones out of the bloodstream and use them to increase angiogenesis.) "Funding has gone to easier areas to research, like whether a drug can prevent cancer recurrence," says Lorenzo Cohen, who runs the integrative care center at M. D. Anderson. That's simpler to study, he points out, than whether a complicated mix of diet, exercise and stress reduction techniques can keep the micro-environment hostile to cancer. And while we're on the subject of how to reduce mortality from cancer, consider these numbers: 7 percent of black women with breast cancer get no treatment, 35 percent do not receive radiation after mastectomy (the standard of care), and 26 percent of white women do not. As long as scientists are discovering how to thwart cancer, it might make sense to get the advances into the real world.

Breakthroughs continue to pour out of labs, of course. Cutting-edge techniques are allowing scientists to identify promising experimental drugs more quickly than ever before. And just last week separate groups of scientists announced that they had identified dozens of genes involved in glioblastoma, the most common brain cancer, as well as pancreatic cancer. That raises the possibility that the mutations cause the cancer, and that if the pathways they control can be blocked the cancer can be beaten back. Stop us if you've heard that before. Hope springs eternal that such findings will not join the long list of those that are interesting but irrelevant to patients.

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