FORTUNE

WHY WE'RE LOSING THE WAR ON CANCER [AND HOW TO WIN IT]

BY CLIFTON LEAF

Avastin, Erbitux, Gleevec . . . The new wonder drugs might make you think we're finally beating this dreaded scourge. We're not. Here's how to turn the fight around.

It's strange to think that I can still remember the smell after all this time. The year was 1978, not long after my 15th birthday, and I'd sneaked into my brother's bedroom. There, on a wall of shelves that stretched to the ceiling, were the heaviest books we had in our house—24 volumes of the *Encyclopedia Britannica*. The maroon spines were coated in a film of dust, I remember. The pages smelled as if a musty old pillow had been covered in mint.

I carefully pulled out the volume marked HALICARNASSUS TO IMMINGHAM and turned to the entry for Hodgkin's disease. It took forever to read the half-dozen paragraphs, the weighty book spread open on my lap like a Bible. There was talk of a mysterious "lymphatic system," of "granulomas" and "gamma rays," as though this disease—the one the doctor had just told me I had—was something out of science fiction. But the last line I understood all too well: Seventy-five percent of the people who got it would die within five years.

As it turns out, I did not die from Hodgkin's, though the cancer had already spread from my neck to my lungs and spleen. I lost my spleen to surgery and most of my hair to chemotherapy and radiation. But I was lucky enough to get into a clinical trial at the National Cancer Institute that was testing a new combination therapy—four toxic chemicals, together called MOPP, plus those invisible gamma rays, which flowed from an enormous cobalt 60 machine three stories below ground. The nurses who stuck needles in my arm were so kind I fell in love with them. The brilliant doctor who tattooed the borders of an imaginary box on my chest, then zapped me with radiation for four weeks, had warm pudgy hands and a comic look of inspiration, as though he'd thought of something funny just before entering the exam room. The American taxpayer even footed the bill.

Most of all, of course, I was lucky to survive. So it makes the question I am about to ask sound particularly ungrateful: Why have we made so little progress in the War on Cancer?

The question may come as a shock to anyone who has witnessed a loved one survive the dread disease—or marveled at Lance Armstrong powering to his fifth Tour de France victory after beating back testicular cancer, or received a fundraising letter saying that a cure is within our grasp. Most recently, with media reports celebrating such revolutionary cancer medicines as Gleevec, Herceptin, Iressa, Erbitux, and the just-approved Avastin, the cure has seemed closer than ever.

But it's not. Hope and optimism, so essential to this fight, have masked some very real systemic problems that have made this complex, elusive, relentless foe even harder to defeat. The result is that while there have been substantial achievements since the crusade began with the National Cancer Act in 1971, we are far from winning the war. So far away, in fact, that it looks like losing.

Optimism is essential, but the percentage of Americans dying from cancer is still what it was in 1970 … and in 1950.

Just count the bodies on the battlefield. In 2004, cancer will claim some 563,700 of your family, friends, co-workers, and countrymen. More Americans will die of cancer in the next 14 months than have perished in every war the nation has ever fought … *combined.* Even as research and treatment efforts have intensified over the past three decades and funding has soared dramatically, the annual death toll has risen 73%—over one and a half times as fast as the growth of the U.S. population.

Within the next decade, cancer is likely to replace heart disease as the leading cause of U.S. deaths, according to forecasts by the NCI and the Centers for Disease Control and Prevention. It is already the biggest killer of those under 75. Among those ages 45 to 64, cancer is responsible for more deaths than the next three causes (heart disease, accidents, and stroke) put together. It is also the leading disease killer of children, thirtysomethings—and everyone in between.

Researchers point out that people live a lot longer than they used to, and since cancer becomes more prevalent with age, it's unfair to look just at the raw numbers when assessing progress. So when they calculate the mortality rate, they adjust it to compare cancer fatalities by age group over time. But even using this analysis (in which the proportion of elderly is dialed back to what it was during the Nixon administration), the percentage of Americans dying from cancer is about the same as in 1970 … and in *1950*. The figures are all the more jarring when compared with those for heart disease and stroke—other ailments that strike mostly older Americans. Age-adjusted death rates for those diseases have been slashed by an extraordinary 59% and 69%, respectively, during the same half-century.

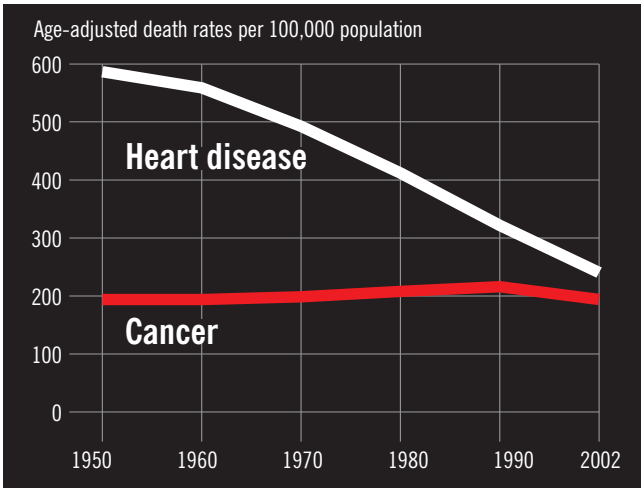
Researchers also say more people are surviving longer with cancer than ever. Yet here, too, the complete picture is more disappointing. Survival gains for the more common forms of cancer are measured in additional *months* of life, not years. The few dramatic increases in cure rates and patient longevity have come in a handful of less common malignancies—including Hodgkin's, some leukemias, carcinomas of the thyroid and testes, and most childhood cancers. (It's worth noting that many of these successes came in the early days of the War on Cancer.) Thirty-three years ago, fully half of cancer patients survived five years or more after diagnosis. The figure has crept up to about 63% today.

Yet very little of this modest gain is the result of exciting new compounds discovered by the NCI labs or the big cancer research centers—where nearly all the public's money goes. Instead, simple behavioral changes such as quitting smoking have helped lower the incidence of deadly lung cancer. More important, with the help of breast self-exams and mammography, PSA tests for prostate cancer, and other testing, we're catching more tumors earlier. Ruth Etzioni, a biostatistician at Seattle's Fred Hutchinson Cancer Research Center, points out that when you break down the Big Four cancers (lung, colon and rectal, breast, and prostate) by stage—that is, how far the malignant cells have spread—long-term survival for advanced cancer has barely budged since the 1970s (see charts opposite).

And the new cases keep coming. Even with a dip in the mid-1990s,

PUBLIC ENEMY NO. 1

Doctors have dramatically reduced deaths from heart disease. But cancer is as lethal as ever and may soon overtake it as the biggest killer of Americans.



FORTUNE CHART / SOURCE: CDC

the incidence rate has skyrocketed since the War on Cancer began. This year an additional 1.4 million Americans will have that most frightening of conversations with their doctor. One in two men and one in three women will get the disease during their lifetime. As a veteran Dana-Farber researcher sums up, "It is as if one World Trade Center tower were collapsing on our society every single day."

So why aren't we winning *this* decades-old war on terror—and what can we do now to turn it around?

That was the question I asked dozens of researchers, physicians, and epidemiologists at leading cancer hospitals around the country; pharmacologists, biologists, and geneticists at drug companies and research centers; officials at the FDA, NCI, and NIH; fundraisers, activists, and patients. During three months of interviews in Houston, Boston, New York, San Francisco, Washington, D.C., and other cancer hubs, I met many of the smartest and most deeply committed people I've ever known. The great majority, it should be said, were optimistic about the progress we're making, believing that the grim statistics belie the wealth of knowledge we've gained—knowledge, they say, that will someday lead to viable treatments for the 100-plus diseases we group as cancer. Most felt, despite their often profound misgivings about the way research is done, that we're on the right path.

Yet virtually all these experts offered testimony that, when taken together, describes a dysfunctional "cancer culture"—a groupthink that pushes tens of thousands of physicians and scientists toward the goal of finding the tiniest improvements in treatment rather than genuine breakthroughs; that fosters isolated (and redundant) problem solving instead of cooperation; and rewards academic achievement and publication over all else.

At each step along the way from basic science to patient bedside, investigators rely on models that are consistently lousy at predicting success—to the point where hundreds of cancer drugs are thrust into the pipeline, and many are approved by the FDA, even though their proven "activity" has little to do with curing cancer.

"It's like a Greek tragedy," observes Andy Grove, the chairman of Intel and a prostate-cancer survivor, who for years has tried to shake this cultural mindset as a member of several cancer advisory groups. "Everybody plays his individual part to perfection, everybody does what's right by his own life, and the total just doesn't work."

Tragedy, unfortunately, is the perfect word for it. Heroic figures battling forces greater than themselves. Needless death and destruction. But unlike Greek tragedy, where the Fates predetermine the outcome, the nation's cancer crusade didn't have to play out this way. And it doesn't have to stay this way.

"A VERY TOUGH SET OF PROBLEMS"

NUCLEAR FISSION WAS A MERE eight months old when the Panzers rolled into Poland in September 1939, beginning the Second World War. Niels Bohr had announced the discovery at a conference on theoretical physics at George Washington University. Three years later the crash program to build an atomic device from a uranium isotope began in earnest. And within three years of that—Aug. 6, 1945—a bomb named Little Boy exploded over Hiroshima.

NASA came into existence on Oct. 1, 1958. Eleven years later, two men were dancing on the moon. Sequencing the entire human genome took just 18 years from the time the idea was born at a small gathering of scientists in Santa Cruz, Calif. Go back as far as Watson and Crick, to the discovery of the structure of DNA, and the feat was still achieved in a mere half-century.

Cancer researchers hate such comparisons. Good science, say many, can't be managed. (Well, sure, maybe easy stuff like nuclear physics, rocket science, and genetics—but not cancer.)

And to be sure, cancer *is* a challenge like no other. The reason is that this killer has a truly uncanny ability to change its identity. "The hallmark of a cancer cell is its genetic instability," says Isaiah "Josh" Fidler, professor and chair of the department of cancer biology at Houston's M.D. Anderson Cancer Center. The cell's DNA is not fixed the way a normal cell's is. A normal cell passes on pristine copies of its three-billion-letter code to every next-generation cell. But when a cancer cell divides, it may pass along to its daughters an altered copy of its DNA instructions—and even the slightest change can have giant effects on cell behavior. The consequence, says Fidler, is that while cancer is thought to begin with a single cell that has mutated, the tumors eventually formed are made up of countless cellular cousins, with a variety of quirky traits, living side by side. "That heterogeneity of tumors is the major, major obstacle to easy therapy," he says.

Harold Varmus, president of Memorial Sloan-Kettering Cancer Center in New York City, agrees. "I just think this is a very tough set of problems," says Varmus, who has seen those problems from more angles than just about anybody. He shared a Nobel Prize for discovering the first oncogene (a normal gene that when mutated can cause cancer) in 1976. That crucial finding, five years into the War on Cancer, helped establish that cancers are caused by mutated genes. Later Varmus served as NIH director under Bill Clinton, presiding over a period of huge funding increases. "Time always looks shorter in retrospect," he says. "I think, hey, in 30 years mankind went from being almost completely ignorant about how cancer arises to being pretty damn knowledgeable."

Yet all that knowledge has come at a price. And there's a strong argument to be made that maybe that price has been too high.

President Nixon devoted exactly 100 words of his 1971 State of the Union speech to proposing "an intensive campaign to find a cure for cancer." The word "war" was never mentioned in the text, yet one would flare up in the months that followed—a lobbying war over how much centralized control the proposed national cancer authority would exert. Between the speech and the signing of the National Cancer Act that December, there was a "battle line between 'creative research' and 'structured research,' " as a news report headlined it. A massive alliance of virtually all the medical societies, the medical schools, the then–Big Three cancer hospitals (Memorial Sloan-Kettering, M.D. Anderson, and Roswell Park in Buffalo) said yes to federal money but wanted very little direction and only loose coordination from Uncle Sam.

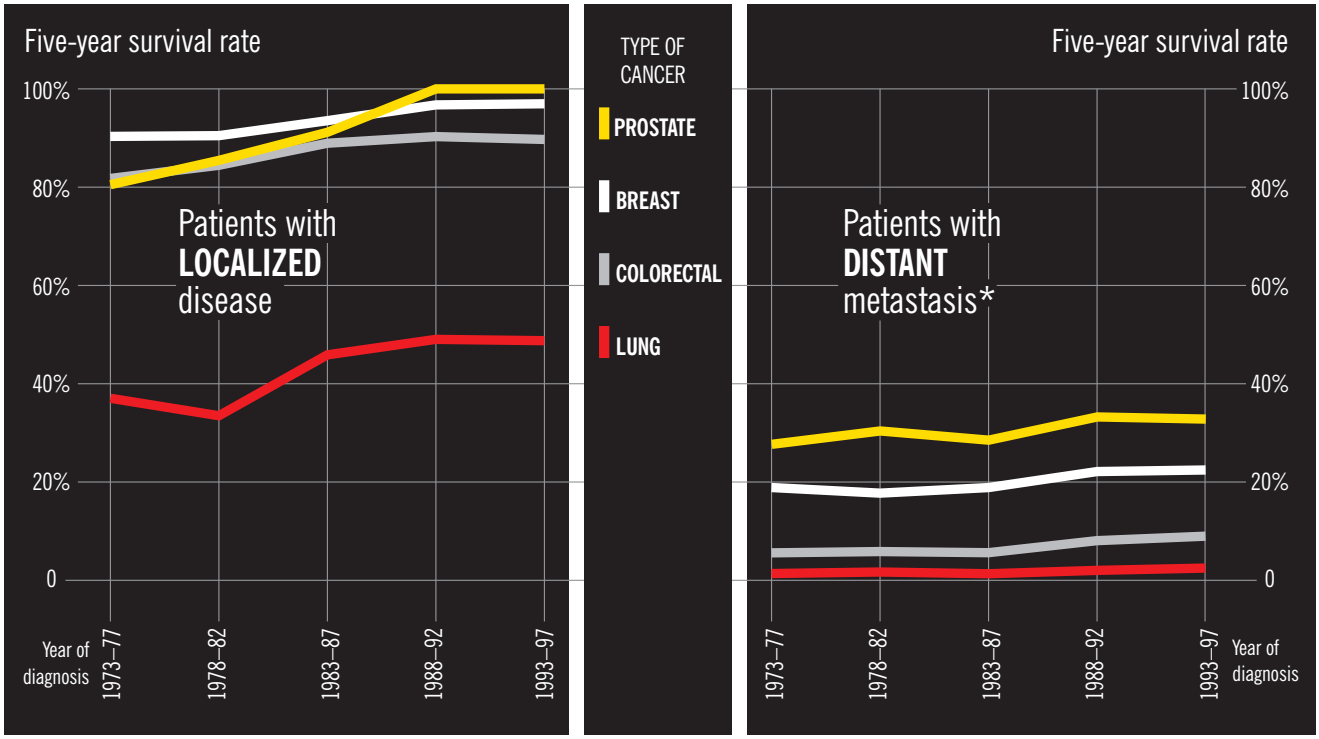
On the other side was Sidney Farber, the Boston physician known as the godfather of cancer research. He wanted public backing for a massive, coordinated assault. "We cannot wait for full understanding; the 325,000 patients with cancer who are going to die this year cannot wait; nor is it necessary, in order to make great progress in the cure of cancer, for us to have the full solution of all the problems of basic research," Farber testified in congressional hearings that fall. "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—from vaccination, to digitalis, to aspirin."

Farber lost.

Today the cancer effort is utterly fragmented—so much so that it's nearly impossible to track down where the money to pay for

CANCER'S BIG FOUR KILLERS

In 1971, when the war on cancer began, 50% of people diagnosed with the disease went on to live at least five years. Today, 33 years and some $200 billion later, the five-year survival rate is 63%, a modest 13-point gain. But a look behind the numbers for the four biggest killers—lung, colon and rectal, breast, and prostate cancer—reveals that progress isn't being made where you might think it is. With the help of early detection and treatment, more patients are living longer. Once a cancer has spread, however, chances of survival are scarcely better now than they were three decades ago.



FORTUNE CHARTS / SOURCE: SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS (SEER)

*Cancer that has spread beyond the primary site region.

all this research is coming from. But let's try anyway.

We begin with the NCI budget. Set by Congress, this year's outlay for fighting cancer is $4.74 billion. Critics have complained that is a mere 3.3% over last year's budget, but Uncle Sam gives prodigiously in other ways too—a fact few seem to realize. The NIH, technically the NCI's parent, will provide an additional $909 million this year for cancer research through the National Institute of Environmental Health Sciences and other little-noticed grant mechanisms. The Department of Veterans Affairs will likely spend just over the $457 million it spent in 2003 for research and prevention programs. The CDC will chip in around $314 million for outreach and education. Even the Pentagon pays for cancer research—offering $249 million this year for nearly 500 peer-reviewed grants to study breast, prostate, and ovarian cancer.

Now throw state treasuries into the mix—governors signed 89 cancer-related appropriations from 1997 to 2003—plus the fundraising muscle of cancer charities, cancer centers, and research hospitals, which together will raise some $2 billion this year from generous donors, based on recent tax forms. And finally, that huge spender Big Pharma. The Tufts Center for the Study of Drug Development estimates that drug companies will devote about $7.4 billion, or roughly a quarter of their annual R&D spending, to products for cancer and metabolic and endocrine diseases.

When you add it all up, Americans have spent, through taxes, donations, and private R&D, close to $200 billion, in inflation-adjusted dollars, since 1971. What has that national investment netted so far?

Without question, the money has bought us an enormous amount of knowledge, just as Varmus says. Researchers have mapped the human cell's intricate inner circuitry in extraordinary detail, identifying dozens of molecular chains of communication, or "signaling pathways," among various proteins, phosphates, and lipids made by the body. In short, scientists now know (or think they know) nearly all the biochemical steps that a healthy cell uses to multiply, to shut down its growth, and to sense internal damage and die at the right time—as well as many of the genes that encode for these processes. What's more, by extension, they know how these same gene-induced mechanisms go haywire in a cancer cell.

According to PubMed, the NCI's online database, the cancer research community has published 1.56 million papers—that's right: 1.56 million!—largely on this circuitry and its related genes in hundreds of journals over the years. Many of the findings are shared at the 100-plus international congresses, symposiums, and conventions held each year.

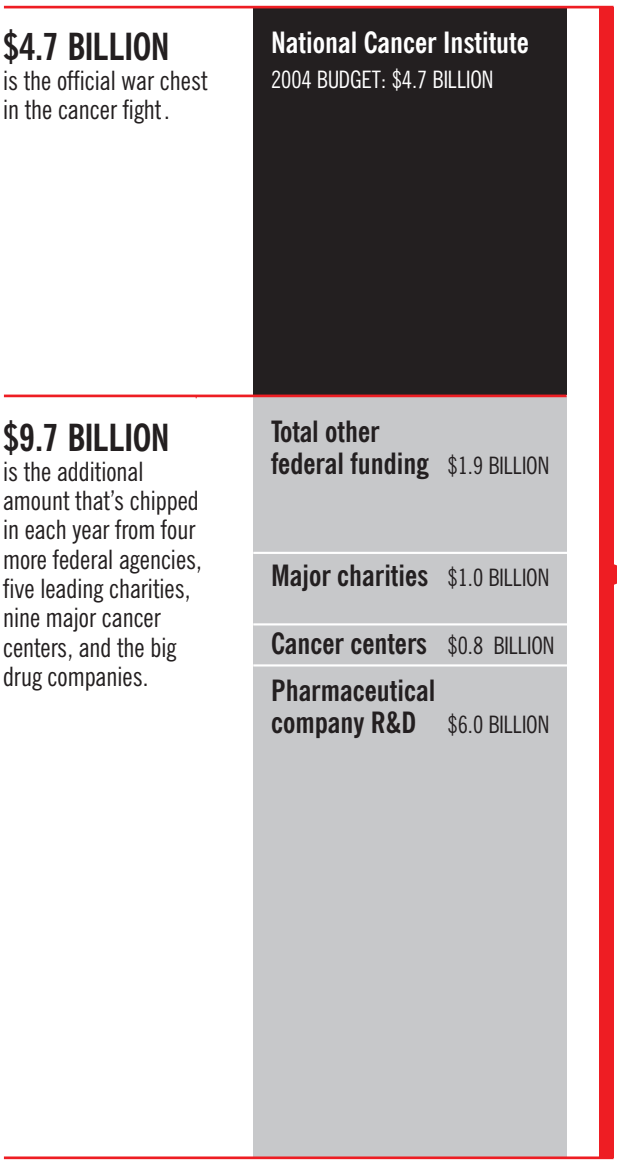
Yet somehow, along the way, something important has gotten lost. The search for knowledge has become an end unto itself rather than the means to an end. And the research has become increasingly narrow, so much so that physician-scientists who want to think systemically about cancer or the organism as a whole—or who might have completely new approaches—often can't get funding.

Take, for instance, the NCI's chief funding mechanism, something called an RO1 grant. The grants are generous, averaging $338,000

apiece in 2003. And they are one of the easiest sweepstakes to win: One in three applications is accepted. But the money goes almost entirely to researchers who focus on very specific genetic or molecular mechanisms within the cancer cell or other tissue. The narrower the research niche, it sometimes seems, the greater the rewards the researcher is likely to attain. "The incentives are not aligned with the goals," says Leonard Zwelling, vice president for research administration at M.D. Anderson, voicing the feeling of many. "If the goal is to cure cancer, you don't incentivize people to have little publications."

FUNDING APLENTY

The National Cancer Institute isn't the half of it. Major bucks for cancer R&D come from many sources—some you'd never expect (like the Pentagon).



FORTUNE CHART / SOURCES: Totals derive from data for the most recent year available. Other federal funding includes cancer spending by NIH (except NCI) and the VA (excluding treatment), CDC, and Pentagon. Data on charities and cancer centers are from federal tax forms; state figures are not included. Pharma total is from Tufts Center for the Study of Drug Development and *Fortune* estimates.

Jean-Pierre Issa, a colleague of Zwelling's who studies leukemias, is equally frustrated by the community's mindset. Still, he admits, the system's lure is powerful. "You get a paper where you change one gene ever so slightly and you have a drastic effect of cancer in the mouse, and that paper gets published in *Science* or *Nature*, and in your best journals. That makes your reputation. Then you start getting grants based on that," he says. "Open any major journal and 80% of it is mice or drosophila [fruit flies] or nematodes [worms]. When do you get human studies in there?"

Indeed, the cancer community has published an extraordinary 150,855 experimental studies on mice, according to a search of the PubMed database. Guess how many of them have led to treatments for cancer? Very, very few. In fact, if you want to understand where the War on Cancer has gone wrong, the mouse is a pretty good place to start.

THE MODELS OF CANCER STINK

OUTSIDE ERIC LANDER'S OFFICE is a narrow, six-foot-high poster. It is an org chart of sorts, a taxonomy, with black lines connecting animal species. The poster's lessons feel almost biblical—it shows, for example, that the zebrafish has much in common with the chicken; that hedgehog and shrew are practically kissing cousins; and that while a human might look more like a macaque than a platypus or a mouse, it ain't that big of a leap, really.

The connection, of course, is DNA. Our genomes share much of the same wondrous code of life. And therein lie both the temptation and the frustration inherent in cancer research today. Certain mutated genes cause cells to proliferate uncontrollably, to spread to new tissues where they don't belong, and to refuse to end their lives when they should. That's cancer. So research, as we've said, now revolves around finding first, the molecular mechanisms to which these mutated genes give rise, and second, drugs that can stop them.

The strategy sounds obvious—and nobody makes it sound more so than Lander, the charismatic founding director of the Whitehead Institute's Center for Genome Research in Cambridge, Mass., and a leader of the Human Genome Project. The "Prince of Nucleotides," as FORTUNE once called him, sketches the biological route to cancer cures as if he were directing you to the nearest Starbucks: "There are only, pick a number, say, 30,000 genes. They do only a finite number of things. There are only a finite number of mechanisms that cancers have. It's a large number; when I say finite, I don't mean to trivialize it. There may be 100 mechanisms that cancers are using, but 100 is only 100."

So, he continues, we need to orchestrate an attack that isolates these mechanisms by knocking out cancer-promoting genes one by one in mice, then test drugs that kill the mutant cells. "These are doable experiments," he says. "Cancers by virtue of having mutations also acquire Achilles' heels. Rational cancer therapies are about finding the Achilles' heel associated with each new mutation in a cancer."

The principle is, in all likelihood, dead-on. The process itself, on the other hand, has one heck of an Achilles' heel. And that takes us back to the six-foot poster showing the taxonomy of genomes. A mouse gene may be very similar to a human gene, but the rest of the mouse is very different.

The fact that so many cancer researchers seem to forget or ignore this observation when working with "mouse models" in the lab clearly irks Robert Weinberg. A professor of biology at MIT and winner of the National Medal of Science for his discovery of both the first human oncogene and the first tumor-suppressor gene, Weinberg is as no-nonsense as Lander is avuncular. Small and mustachioed, with Hobbit-like fingers, he plops into a brown leather La-Z-Boy that is somehow wedged into the middle of his cramped office, and launches into a lecture:

"One of the most frequently used experimental models of human cancer is to take human cancer cells that are grown in a petri dish, put them in a mouse—in an immunocompromised mouse—allow them to form a tumor, and then expose the resulting xenograft to different kinds of drugs that might be useful in treating people. These are called preclinical models," Weinberg explains. "And it's been well known for more than a decade, maybe two decades, that many of these preclinical human cancer models have very little predictive power in terms of how actual human beings—actual human tumors inside patients—will respond." Despite the genetic and organ-system similarities between a nude mouse and a man in a hospital gown, he says, the two species have key differences in physiology, tissue architecture, metabolic rate, immune system function, molecular signaling, you name it. So the tumors that arise in each, with the same flip of a genetic switch, are vastly different.

Says Weinberg: "A fundamental problem which remains to be solved in the whole cancer research effort, in terms of therapies, is that the preclinical models of human cancer, in large part, *stink*."

A few miles away, Bruce Chabner also finds the models lacking. A professor of medicine at Harvard and clinical director at the Massachusetts General Hospital Cancer Center, he explains that for a variety of biological reasons the "instant tumors" that researchers cause in mice simply can't mimic human cancer's most critical and maddening trait, its quick-changing DNA. That characteristic, as we've said, leads to staggering complexity in the most deadly tumors.

"If you find a compound that cures hypertension in a mouse, it's going to work in people. We don't know how toxic it will be, but it will probably work," says Chabner, who for many years ran the cancer-treatment division at the NCI. So researchers routinely try the same approach with cancer, "knocking out" (neutralizing) this gene or knocking in that one in a mouse and causing a tumor to appear. "Then they say, 'I've got a model for lung cancer!' Well, it ain't a model for lung cancer, because lung cancer in humans has a hundred mutations," he says. "It looks like the most complicated thing you've ever seen, genetically."

Homer Pearce, who once ran cancer research and clinical investigation at Eli Lilly and is now research fellow at the drug company, agrees that mouse models are "woefully inadequate" for determining whether a drug will work in humans. "If you look at the millions and millions and millions of mice that have been cured, and you compare that to the relative success, or lack thereof, that we've achieved in the treatment of metastatic disease clinically," he says, "you realize that there just has to be something wrong with those models."

Vishva Dixit, a vice president for research in molecular oncology at Genentech in South San Francisco, is even more horrified that "99% of investigators in industry and in academia use xenografts." Why is the mouse model so heavily used? Simple. "It is very convenient, easily manipulated," Dixit explains. "You can assess tumor size just by looking at it."

Although drug companies clearly recognize the problem, they haven't fixed it. And they'd better, says Weinberg, "if for no other reason than [that] hundreds of millions of dollars are being wasted every year by drug companies using these models."

Even more depressing is the very real possibility that reliance on this flawed model has caused researchers to pass over drugs that *would* work in humans. After all, if so many promising drugs that clobbered mouse cancers failed in man, the reverse is also likely: More than a few of the hundreds of thousands of compounds discarded over the past 20 years might have been truly effective agents. Roy Herbst, who divides his time between bench and bedside at M.D. Anderson and who has run big trials on Iressa and other targeted therapies for lung cancer, is sure that happens often. "It's something that bothers me a lot," he says. "We probably lose a lot of things that either don't have activity on their own, or we haven't tried in the right setting, or you don't identify the right target."

If everyone understands there's a problem, why isn't anything being done? Two reasons, says Weinberg. First, there's no other model with which to replace that poor mouse. Second, he says, "is that the FDA has created inertia because it continues to recognize these [models] as the gold standard for predicting the utility of drugs."

"People obsessed with cures, cures, cures are being—I hate to use the word—selfish by ignoring what could be done in terms of prevention."

"WE HAVE A SHORTAGE OF GOOD IDEAS"

IT IS ONE OF THE MANY chicken-and-egg questions bedeviling the cancer culture. Which came first: the FDA's imperfect standards for judging drugs or the pharmaceutical companies' imperfect models for testing them?

The riddle is applicable not just to early drug development, in which flawed animal models fool bench scientists into thinking their new compounds will wallop tumors in humans. It comes up, with far more important ramifications, in the last stage of human testing, when the FDA is looking for signs that a new drug is actually helping the patients who are taking it. In this case, the faulty model is called tumor regression.

It is exciting to see a tumor shrink in mouse or man and know that a drug is doing that. A shrinking tumor is intuitively a good thing. So it is no surprise that it's one of the key endpoints, or goals, in most clinical trials. That's in no small part because it is a *measurable* goal: We can see it happening. (When you read the word "response" in a newspaper story about some exciting new cancer drug, tumor shrinkage is what it's talking about.)

But like the mouse, tumor regression by itself is actually a lousy predictor for the progression of disease. Oncologists can often shrink a tumor with chemo and radiotherapy. That sometimes makes the cancer easier to remove surgically. If not, it still may buy a little time. However, if the doctors don't get every rotten cell, the sad truth is that the regression is not likely to improve the person's chances of survival.

That's because when most malignant solid tumors are diagnosed, they are typically quite large already—the size of a grape, perhaps, with more than a billion cells in the tumor mass. By the time it's discovered, there is a strong chance that some of those cells have already broken off from the initial tumor and are on their way to another part of the body. This is called metastasis.

Most of those cells will not take root in another tissue or organ: A metastasizing cell has a very uphill battle to survive once it enters the violent churn of the bloodstream. But the process has begun—and with a billion cells dividing like there's no tomorrow, an ever-growing number of metastases will try to make the journey. Inevitably, some will succeed.

In the end, it is not localized tumors that kill people with cancer; it is the process of metastasis—an incredible *90% of the time*. Aggressive cells spread to the bones, liver, lungs, brain, or other vital areas, wreaking havoc.

So you'd think that cancer researchers would have been bearing down on this insidious phenomenon for years, intently studying the intricate mechanisms of invasion. Hardly. According to a FORTUNE examination of NCI grants going back to 1972, less than 0.5% of study proposals focused primarily on metastasis—trying to understand, for instance, its role in a specific cancer (e.g., breast, prostate) or just the process itself. Of nearly 8,900 NCI grant proposals awarded last year, 92% didn't even *mention* the word metastasis.

One accomplished researcher sent an elegant proposal into the NCI two years ago to study the epigenetics (changes in normal gene function) of metastases vs. primary tumors. It's now in its third resubmission, he says. "I mean, there is nothing known about that. But somehow I can't interest people in funding this!"

M.D. Anderson's Josh Fidler suggests that metastasis is getting short shrift simply because "it's tough. Okay? And individuals are not rewarded for doing tough things." Grant reviewers, he adds, "are more comfortable with the focused. Here's an antibody I will use, and here's blah-blah-blah-blah, and then I get the money."

Metastasis, on the other hand, is a big idea—an organism-wide phenomenon that may involve dozens of processes. It's hard to do replicable experiments when there are that many variables. But that's the kind of research we *need*. Instead, says Weinberg, researchers opt for more straightforward experiments that generate plenty of reproducible results. Unfortunately, he says,"the accumulation of data gives people the illusion they've done something meaningful."

That drive to accumulate data also goes to the heart of the regulatory process for drug development. The FDA's mandate is to make sure that a drug is safe and that it works before allowing its sale to the public. Thus, the regulators need to see hard data showing that a drug has had some effect in testing. However, it's hard to see "activity" in preventing something from happening in the first place. There are probably good biomarkers—proteins, perhaps, circulating in the body—that can tell us that cancer cells have begun the process of spreading to other tissues. As of yet, though, we don't know what they are.

So pharma companies, quite naturally, don't concentrate on solving the problem of metastasis (the thing that kills people); they focus on devising drugs that shrink tumors (the things that don't).

Dozens of these drugs get approved anyway. At the same time, many don't—and the FDA is invariably blamed for holding up the War on Cancer. The fault, however, is less the umpire's than the players'. That's because many tumor-shrinking drugs simply don't perform much better than the standard treatments. Or as Rick Pazdur, director of oncology drugs for the FDA, puts it, "It's efficacy, stupid! One of the major problems that we have is dealing with this meager degree of efficacy." When it's clear that something is working, the agency is generally quick to give it priority review and/or accelerated approval, two mechanisms that speed up the regulatory process for compounds aimed at life-threatening diseases. "We have a shortage of good ideas that are likely to work," agrees Bruce Johnson, a Dana-Farber oncologist who runs lung-cancer research for institutions affiliated with the Harvard Medical School, a huge partnership that includes Massachusetts General Hospital, Brigham and Women's Cancer Center, and others.

That is also the devastating conclusion of a major study published last August in the *British Medical Journal*. Two Italian pharmacologists pored over the results of trials of 12 new anticancer drugs that had been approved for the European market from 1995 to 2000, and compared them with standard treatments for their respective diseases. The researchers could find no substantial advantages—no improved survival, no better quality of life, no added safety—with any of the new agents. All of them, though, were several times more expensive than the old drugs. In one case, the price was 350 times higher.

WHY THE NEW DRUGS DISAPPOINT

FLAWED MODELS FOR DRUG development. Obsession with tumor shrinkage. Focus on individual cellular mechanisms to the near exclusion of what's happening in the organism as a whole. All these failures come to a head in the clinical trial—a rigidly controlled, three-phase system for testing new drugs and other medical procedures in humans. The process remains the only way to get from research to drug approval—and yet it is hard to find *anyone* in the cancer community who isn't maddeningly frustrated by it.

In February 2003 a blue-ribbon panel of cancer-center directors concluded that clinical trials are "long, arduous," and burdened with regulation; without major change and better resources, the panel concluded, the "system is likely to remain inefficient, unresponsive, and unduly expensive."

All that patients know is that the process has little to offer them. Witness the fact that a stunning *97%* of adults with cancer don't bother to participate.

There are two major problems with clinical trials. The first is that their duration and cost mean that drug companies—which sponsor the vast majority of such trials—have an overwhelming incentive to test compounds that are likely to win FDA approval. After all, they are public companies by and large, with shareholders demanding a return on investment. So the companies focus not on breakthrough treatments but on incremental improvements to existing classes of drugs. The process does not encourage risk taking or entrepreneurial approaches to drug discovery. It does not encourage brave new thinking. Not when a drug typically takes 12 to 14 years to develop. And not with $802 million—that's the oft-cited cost of developing a drug—on the line.

What's more, the system essentially forces companies to test the

most promising new compounds on the sickest patients—where it is easier to see some activity (like shrinking tumors) but almost impossible to cure people. At that point the disease has typically spread too far and the tumors have become too ridden with genetic mutations. Thus drugs that might have worked well in earlier-stage patients often never get the chance to prove it. (As you'll see, that may be a huge factor in the disappointing response so far of one class of promising new drugs.)

The second problem is even bigger: Clinical trials are focused on the wrong goal—on doing "proper" science rather than saving lives. It is not that they provide bad care—patients in trials are treated especially well. But the trials' very reason for being is to test a hypothesis: Is treatment X better than treatment Y? And sometimes—too often, sadly—the information generated by this tortuously long process doesn't much matter. If you've spent ten-plus years to discover that a new drug shrinks a tumor by an average of 10% more than the existing standard of care, how many people have you really helped?

Take two drugs approved in February for cancer of the colon and rectum: Erbitux and Avastin. In each case it took many months just to enroll the necessary number of patients in clinical trials. Participating doctors then had to administer the drugs according to often arduous preset protocols, collecting reams of data along the way. (ImClone's well-known troubles with the FDA occurred because it had not set up its trials properly.)

And here's what clinicians learned after years of testing. When Avastin was added to the standard chemotherapy regimen, the combination managed to extend the lives of some 400 patients with terminal colorectal cancer by a median 4.7 months. (A previous trial of the drug on breast cancer patients failed.) Oncologists consider the gain substantial, considering that those in advanced stages of the disease typically live less than 16 months.

And Erbitux? Although it did indeed shrink tumors, *it has not been shown to prolong patients' lives at all*. Some certainly have fared well on the drug, but survival on average for the groups studied didn't change. Still, Erbitux was approved for use primarily in "third line" therapy, after every other accepted treatment has failed. A weekly dose costs $2,400.

Remember, it took several years and the participation of thousands of patients in three stages of testing, tons of data, and huge expense to find out what the clinicians and researchers already knew in the earliest stage of human testing: Neither drug will save more than a handful of the 57,000 people who will die of colorectal cancer this year.

You could say the same for AstraZeneca's Iressa, another in the new class of biological wonder drugs—compounds specifically "targeted" to disrupt the molecular signals in a cancer cell. Not a single controlled trial has shown Iressa to have a major patient benefit such as the easing of symptoms or improved survival—a fact that the company's upbeat press releases admit as if it were legal boilerplate. Even so, the FDA okayed the pill last year for last-ditch use against a type of lung cancer, citing the fact that it had shrunk tumors in 10% of patients studied.

"Very smart people, with a lot of money, have done trials of over 10,000 patients around the world—testing these new molecular targeted drugs," says Dana-Farber's Bruce Johnson. "AstraZeneca tested Iressa. Isis Pharmaceuticals and Eli Lilly tested a compound called Isis 3521. Several different companies ended up investing tens of millions of dollars, and all came up with a big goose egg."

The one targeted drug that clearly isn't a goose egg is Novartis's Gleevec, which has been shown to save lives as well as stifle tumors. The drug has a dramatic effect on an uncommon kind of leukemia called CML and an even more rare stomach cancer named GIST. Early reports say it also seems to work, in varying degrees, in up to three other cancers. Gleevec's success has been held out as the "proof of principle" that the strategy we've followed in the War on Cancer all these years has been right.

But not even Gleevec is what it seems. CML is not a complicated cancer: In it, a single gene mutation causes a critical signaling mechanism to go awry; Gleevec ingeniously interrupts that deadly signal. Most common cancers have perhaps as many as five to ten different things going wrong. Second, even "simple" cancers get smarter: The malignant cells long exposed to the drug (which must be taken forever) mutate their way around the molecular signal that Gleevec blocks, building drug resistance.

No wonder cancer is so much more vexing than heart disease. "You don't get multiple swings," says Bob Cohen, senior director for commercial diagnostics at Genentech. Use a drug that does not destroy the tumor completely and "the heterogeneity will evolve from the [surviving] cells and say, 'I don't give a rat's ass! You can't screw me up with this stuff.' Suddenly you're squaring and cubing the complexity. That's where we are." And that's why the only chance is to attack the disease earlier—and on multiple fronts.

Three drugs, four drugs, five drugs in combination. Cocktails of experimental compounds, of course, were what doctors used to control HIV, whose rapidly mutating virus was once thought to be a death sentence. Virtually every clinician and scientist interviewed for this story believes a similar approach is needed with the new generation of anticancer drugs. But once again, institutional forces within the cancer world make it nearly impossible.

"If you look at the millions of mice that have been cured of cancer, and compare it to humans, you realize there just has to be something wrong with those models."

Combining unapproved drugs in clinical trials brings up a slew of legal and regulatory issues that cause pharma companies to squirm. While many drug-company oncologists are as committed to the public's well-being as government or cancer-center researchers, they have less flexibility to take chances on an idea. Ultimately, they need FDA approval for their investigational compounds. If two or three unapproved drugs are tested in concert, it's even harder to figure out what's working and what isn't, and whether one drug is responsible for side-effects or the combination. "It becomes much more challenging in the context of managing the databases, interpreting the results, and owning the data," adds Lilly's Pearce.

Over dinner at Ouisie's Table in Houston, M.D. Anderson's Len Zwelling, who oversees regulatory compliance for the center's

800-plus clinical trials, and his wife, Genie Kleinerman, who is chief of pediatrics there, have no trouble venting about the legal barriers that seem to be growing out of control. It takes no more than ten minutes for Kleinerman to rattle off three stories about trying to bring together different drug companies in clinical trials for kids with cancer. In the first attempt, the trial took so long that the biotech startup with the promising agent went out of business. In the second the lawyers haggled over liability concerns until both companies pulled out. The third, however, was the worst. There were two drugs that together seemed to jolt the immune system into doing a better job of targeting malignant cells of osteosarcoma, a bone cancer that occurs in children. "Working with the lawyers, it was just impossible," she says, "because each side wanted to own the *rights* to the combination!"

CHANGING THE WAY WE THINK ABOUT CANCER

STRANGE AS IT MAY SEEM, much of our failure in fighting cancer—and more important, much of the potential for finally winning this fight—has to do with a definition. Some 2,400 years ago the Greek physician Hippocrates described cancer as a disease that spread out and grabbed on to another part of the body like "the arms of a crab," as he elegantly put it. Similarly, medical textbooks today say cancer begins when the cells of an expanding tumor push through the thin protein "basement" membrane that separates them from another tissue. It's a fancy way of saying that to be cancer, a malignant cell has to invade another part of the body.

Michael Sporn, a professor of pharmacology and medicine at Dartmouth Medical School, has two words for this: "Absolute nonsense!" He goes on: "We've been stuck with this definition of what cancer is from 1890. It's what I was taught in medical school: 'It's not cancer until there's invasion.' That's like saying the barn isn't on fire until there are bright red flames coming out of the roof."

In fact, cancer begins much earlier than that. And therein lies the best strategy to contain it, believes Sporn, who was recently named an Eminent Scholar by the NCI: Let's aggressively find those embers that have been smoldering in many of us for years—and douse them before they become a full-fledged blaze. Prevent cancer from ever entering that deadly stage of malignancy in the first place.

Sporn, who spent more than three decades at the NCI, has been struggling for many years to get fellow researchers to start thinking about cancer not as a state of being (that is, an invasive group of fast-growing cells) but as a *process*, called carcinogenesis. Cancer, as Sporn tells it, is a multistage disease that goes through various cell transformations and sometimes long periods of latency in its progression.

Thus, the trick is to intervene earlier in that process—especially at key points when lesions occur (known to doctors as dysplasias, hyperplasias, and other precancerous cell phases). To do that, the medical community has to break away from the notion that people in an early stage of carcinogenesis are "healthy" and therefore shouldn't be treated. People are not healthy if they're on a path toward cancer.

If this seems radical and far-fetched, consider: We've prevented millions of heart attacks and strokes by using the very same strategy. Sporn likes to point out that heart disease doesn't start with the heart attack; it starts way earlier with the elevated blood cholesterol and lipids that cause arterial plaque. So we treat those. Stroke doesn't start with the blood clot in the brain. It starts with hypertension. So we treat it with both lifestyle changes and drugs. "Cardiovascular disease, of course, is nowhere near as complex as cancer is," he says, "but the principle is the same." Adds Sporn: "All these people who are obsessed with cures, cures, cures, and the miraculous cure which is still eluding us, they're being—I hate to use this word, but if you want to look at it pragmatically—they're being selfish by ignoring what could be done in terms of prevention."

The amazing thing about this theory—other than how obvious it is—is that we can start applying it *right now*. Precancerous cell changes mark the progression to many types of solid-tumor cancers; many such changes are relatively easy to find and remove, and others are potentially reversible with current drugs and other treatments.

A perfect example is the Pap smear, which detects premalignant changes in the cells of the cervix. That simple procedure, followed by the surgical removal of any lesions, has dropped the incidence and death rates from cervical cancer by 78% and 79%, respectively, since the practice began in the 1950s. In countries where Pap smears aren't done, cervical cancer is a leading killer of women.

Same goes for colon cancer. Not every adenomatous polyp in the colon (a lesion in the organ's lining) goes on to become malignant and invasive. But colon cancers have to go through this abnormal step on their way to becoming deadly. The list of other dysplasia-like conditions goes on and on, from Barrett's esophagus (a precursor to cancer there) to hyperkeratosis (head and neck cancers). Obviously, doctors are already doing this kind of testing with some cancers, but they need to do it much, much more.

Some complain that the telltale biomarkers of carcinogenesis, while getting more predictive, still are far from definitive, and that we should wait until we know more. (Sound familiar?) Researchers in heart disease, meanwhile, have taken an opposite tack and been far more successful. Neither high cholesterol nor hypertension guarantees future cardiovascular disease, but they're treated anyway.

A few cancer researchers have made great strides in finding more early warning signs—looking for protein "signatures" in blood, urine, or even skin swabs that can identify precancerous conditions and very early cancers that are likely to progress. For instance, Lance Liotta, chief of pathology at the NCI, has demonstrated that ovarian cancer can be detected by a high-tech blood test—one that identifies a unique "cluster pattern" of some 70 different proteins in a woman's blood. "We've discovered a previously unknown ocean of markers," he says. And it's potentially a mammoth lifesaver. With current drugs, early-stage ovarian cancer is more than 90% curable; late stage is 75% deadly. Early results on a protein test for pancreatic cancer are promising as well, says Liotta.

Yes, the strategy has costs. Some say wholesale testing of biomarkers and early lesions—many of which won't go on to become invasive cancers—would result in a huge burden for the healthcare system and lead to a wave of potentially dangerous surgeries to remove things that might never become lethal anyway. But surely the costs of not acting are much greater.

Indeed, it is an encouraging sign that Andy von Eschenbach, director of the NCI, and Elias Zerhouni, who leads the NIH, are both believers in this strategy. "What our investment in biomedical research has led us to is understanding cancer as a disease process and the various steps and stages along that pathway—from being very susceptible to it, to the point where you get it, and ultimately suffer and die from it," says von Eschenbach, a former urologist who

has survived prostate and a pair of skin cancers. So, he says, he wants to lead the NCI on a "mission to prevent the process from occurring in the first place or detect the occurrence of cancer early enough to eliminate it with less morbidity."

HOW TO WIN THE WAR

THERE HAS BEEN TALK like this before. But the money to fund the assault never came. And several cancer experts interviewed for this story worry that the new rhetoric from the NCI, while encouraging, has yet to move beyond lip service.

For the nation finally to turn the tide in this brutal war, the cancer community must embrace a coordinated assault on this disease. Doctors and scientists now have enough knowledge to do what Sydney Farber hoped they might do 33 years ago: to work as an army, not as individuals fighting on their own.

The NCI can begin this transformation right away by drastically changing the way it funds research. It can undo the culture created by the RO1s (the grants that launched a million me-too mouse experiments) by shifting the balance of financing to favor cooperative projects focused on the big picture. The cancer agency already has such funding in place, for endeavors called SPOREs (short for specialized programs of research excellence). These bring together researchers from different disciplines to solve aspects of the cancer puzzle. Even so, funding for individual study awards accounts for a full quarter of the agency's budget and is more than 12 times the money spent on SPORE grants. The agency needs to stop being an automatic teller machine for basic science and instead use the taxpayers' money to marshall a broad assault on this elusive killer—from figuring out how to stop metastasis in its tracks to coming up with testing models that better mimic human response.

At the same time, the NCI should commit itself to finding biomarkers that are predictive of cancer development and that, with a simple blood or urine test (like PSA) or an improved molecular imaging technique (PET and CT scans), can give patients a chance to preempt or control the disease. For that matter, as a nation we could prevent tens of thousands of cancers—and 30% of all cancer deaths, according to the NCI—by getting people to stop smoking. This all-too-obvious observation was made by every researcher I interviewed.

Alas, this is not a million-dollar commitment. It's a billion-dollar one. But the nation is already investing billions in research, and that doesn't even include the $64 billion a year we spend on treatment. To make the resource shift easier, Congress should move the entire federal war chest for cancer into one bureaucracy, not five. Cancer research should be managed by the NCI, not the VA and Pentagon.

Just as important, the cancer leadership, the FDA, and lawmakers need to transform drug testing and approval into a process that delivers information on what's working and what's not to the patients far faster. If the best hope to treat most cancer lies in using combinations of drugs, we're going to have to remove legal constraints and give drug companies incentives to test investigational compounds together in shorter trials. Those should be funded by the NCI—in a process that's distinct from individual drug approval. One bonus for the companies: If joint activity showed marked improvement in survival, the FDA process could be jump-started. *continued*

"It's going to require a community conversation to facilitate this change," says Eli Lilly's Homer Pearce. "I think everyone believes that at the end of the day, cancer is going to be treated with multi-

MIRACLE CURES THAT WEREN'T

Decades of breakthroughs have raised hopes again and again for people with cancer—but have failed to deliver on expectations.

Radiation therapy Soon after Wilhelm Roentgen's discovery of X-rays in 1895, some doctors predicted that the high-energy waves from exotic "cyclotrons" could be used to kill most cancerous tumors. A century-plus later, targeted radiation is a critical weapon in the oncologist's arsenal but not the magic bullet many thought.

Interferon In 1980, the world was afrenzy about the big "IF"—an immune-system booster produced by the body in tiny quantities—as word spread that this natural virus fighter could also shrink tumors. Though still in use in some cancer therapies, IF has not fulfilled its early promise.

Interleukin-2 Like Interferon, this protein helps activate the body's immune system. And like IF, IL-2 was once thought to be the "cancer breakthrough" we were waiting for (see FORTUNE's 1985 cover, lower right). But after years of testing and tweaking, the therapy has led to only scattered remissions in patients.

Endostatin After a flurry of early hype, this first of many compounds designed to fight tumor angiogenesis failed dramatically in human tests. The jury is still out on its next-generation kin.

Gleevec The little yellow pill from Novartis has wondrous effect in a few rare cancers involving simple mutations, although the disease can grow resistant to this "targeted" biological drug.

ple targeted agents—maybe in combination with traditional chemotherapy drugs, maybe not. Because that's where the biology is leading us, it's a future that we have to embrace—though it will definitely require different models of cooperation."

When clinical trials begin to offer patients more than incremental improvements over existing drug treatments, people with cancer will rush into the studies. And when participation rates go up, it will accelerate the process so that we can test more combinations faster and cheaper.

To see which drugs truly have promise, however, we need to do one thing more: test them on people in less advanced stages of disease. The reason, once again, comes back to cancer's genetic instability—a progression that not only ravages the body but also riddles tumors with mutations. When cancer patients are in the end stage of the disease, drugs that might have a potent effect on newer cancers fail to show much progress at all. Our current crop of rules, however, pushes drug companies into this can't-win situation, where the only way out is incremental improvements to existing therapies. Drugs that might well help some cancer patients are now getting tossed by the wayside because they don't help people whom they couldn't have helped in any case. This has to stop.

"It's like a Greek tragedy," says Intel's Andy Grove. "Everybody plays his part, everybody does what's right by his own life, and the total just doesn't work."

Witness what has happened with the new class of drugs developed to fight the process called angiogenesis ("angio" refers to blood vessels, and "genesis" to new growth)—compounds designed to block the development of capillaries that supply oxygen and nutrients to tumors. Avastin is the best known, but there are some 40 anti-angiogenesis drugs in clinical trials.

This, by the way, is one of those big ideas that the cancer culture didn't take seriously, and would barely fund, for decades. The concept was pioneered 43 years ago by Judah Folkman, now a surgeon at Children's Hospital Boston. While studying artificial blood in a Navy lab, he was struck by a simple and seemingly obvious idea: Every cell needs oxygen to grow, including cancer cells. Since oxygen in the body comes from blood, fast-growing tumors couldn't develop without access to blood vessels.

Folkman later figured out that tumors actually recruited new blood vessels by sending out a protein signal. If you could turn off that growth signal, he reasoned, you could starve the tumors and keep them tiny. The surgeon submitted a paper on his experiments to various medical journals, but the article was rejected time and again. That is, until an editor at the *New England Journal of Medicine* heard Folkman give a lecture and offered to publish it in the *Journal's* Beth Israel Hospital Seminars in 1971—ironically, the year the War on Cancer began.

After decades of resistance, the cancer culture has finally come around to Folkman's thinking—as the reception greeting Avastin makes clear. Still, the biggest promise of anti-angiogenesis drugs will be realized only when doctors can use them to treat earlier-stage patients. That's because the drugs designed to choke the tumor's blood supply often take a far longer time to work than traditional toxic chemo—time that people with advanced disease and fast-growing cancers may not have. Doctors also need the freedom to administer such drugs in combination. Tumors recruit blood vessels through several signaling mechanisms, researchers believe, so the best approach is to apply several drugs, cutting off all routes.

Who knows? A new paradigm in treatment may emerge from Folkman's 40-year-old idea. Yet to make this simple and seemingly obvious shift, the entire cancer culture must change—from the rules governing drug approval to tort law and intellectual property rights. Science now has the knowledge and the tools; we need to act.

THE GOOD DOCTOR

IN THE WEEKS SINCE I finished my reporting and began writing this story, one image has stuck with me: a drawerful of letters. The letters belong to Eric Winer, a 47-year-old physician at Dana-Farber. He and I had been talking for close to an hour when he showed me the drawer.

It was late on a Friday evening, and Winer, still in the clinic, was describing the progress we were making in this war, his reedy voice cracking higher every so often. He was telling me of his optimism. That's when he mentioned the drawer: "That enthusiasm is very much tempered by the fact that we have 40,000 women dying of breast cancer every year. Um, and you know, I've got a file full of letters that are almost entirely from family members of my patients who died…."

I asked to see it, and then asked again, and there it was, in the bottom drawer of his filing cabinet—two overstuffed folders of mostly handwritten notes. Once the letters go in, Winer confessed, he never looks at them again. "I don't go back," he said sheepishly. "My excuse initially was that if anyone wanted to say I was a bad doctor, I'd hold on to these things that people said about me. And I could prove that I wasn't."

If the walls of his office are any indication, there is no way Winer is a bad doctor. They are covered with loving mementos from patients. There is a picture of Tolstoy from a woman whose breast tumors were initially shrunk by Herceptin, but who died within five years. (Winer had once mentioned to her to that he had majored in Russian history at Yale.) There's a photo of the Grand Canyon taken by a young nurse who was determined to take a trip out West with her 10-year-old son before she died. The daughter of another patient even cornered Lance Armstrong and begged him to sign a neon-yellow jersey for Winer, who is an avid cyclist. It is the most prominent thing in his office.

No, it isn't just the patients in this War on Cancer who need renewed hope. It is the foot soldiers as well. F

ADDITIONAL REPORTING *Doris Burke*

FEEDBACK *cleaf@fortunemail.com*