



Dead, your majesty. Dead, my lords and gentlemen. Dead, Right Reverends, and Wrong Reverends of every order. Dead, men and women, born with Heavenly compassion in your hearts. And dying thus around us everyday.



The Heretic in the Lab

In his new book *The Truth in Small Doses*, journalist Clifton Leaf takes a long and critical look at the war on cancer. Part of his critique stems from the research of Michael Sporn, a professor of pharmacology and toxicology and of medicine at the Geisel School of Medicine, who for years has advocated an unorthodox approach to addressing cancer, one that would include a prominent role for preventive treatment. In this excerpt, Leaf discusses how his encounters with Sporn made him rethink how best to battle cancer.

By Clifton Leaf

When I first met Michael Sporn, in January 2004, he was dressed in a dark green peacoat, green sweater, green check shirt, olive-green pants, and green knit hat with a green pom-pom dangling from a string. He looked like a leprechaun girded for winter.

I had driven up to Hanover, N.H., to speak with him for an article for *Fortune* magazine. And when he saw me standing outside the local inn on the morning of our interview, he bounded through the snow from his Subaru Forester to greet me. The car was his “eighth straight Subaru,” he volunteered just after saying hello, the corners of his mouth lifting into an unbroken grin.

Somehow, it was hard to picture this good-natured smirk of a fellow—a man who had owned eight straight Subarus—as being any kind of a revolutionary. But that he was. Mike Sporn, graying, twinkling, was then a month shy of his 71st birthday. And if anything, he was more subversive than ever.

Like John Bailar III, the NCI statistician who had, in 1986, famously questioned the government’s claims of progress in the war on cancer, Sporn had also challenged the gospel. He had sent his first broadside against what he calls “the cancer establishment” in 1996, when he was invited to write an essay for the venerable British journal *The Lancet* to mark the silver anniversary of the National Cancer Act. (The NCI director at the time had said the long campaign

deserved a “birthday present” of a “pat on the back.”) Sporn opened his own commentary with an epigraph from Charles Dickens’s *Bleak House*:

Dead, your majesty. Dead, my lords and gentlemen. Dead, Right Reverends, and Wrong Reverends of every order. Dead, men and women, born with Heavenly compassion in your hearts. And dying thus around us everyday.

“This magnificent quotation,” the scientist began, “provides a unique summary on the total success of the ‘war on cancer’ during the past 25 years.” The salvo was quintessential Sporn.

In his innumerable writings and lectures since then, he has found analogies to the failures of the U.S. cancer program in Camus’s *Plague*, the Lernaean Hydra, the guillotines of the Reign of Terror, and the intricate design of Byzantine mosaics. Where other scientists fill their PowerPoint presentations with charts and tables, Sporn prefers Renaissance paintings and classical sculpture. Elegant as the imagery is, though, the message behind it is often as blunt as the *Bleak House* passage. As Sporn told me several years after our first meeting, “The NCI clucks when the death rate goes down one or two points, but more people are dying than ever. Nothing is being done to stop this.”



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What makes the criticism sting, in particular, is that Sporn, who now holds an endowed professorship and runs a laboratory at Dartmouth, has long been a prominent member of the cancer research club. After receiving his medical degree from the University of Rochester, he went to work at the National Institutes of Health, where he shone for 35 years before heading to Dartmouth. Along the way, he served as chief of the National Cancer Institute's Lung Cancer Branch and later ran one of the NCI's most storied labs. Like Bailar, he worked and thrived within the cancer establishment for decades.

But unlike Bailar, Sporn has largely gotten away with his truth-telling unscathed. That, for the most part, is due to the kind of researcher he is. Sporn is the sort of basic scientist other basic scientists look up to, one who has to date authored or coauthored more than 500 research studies, perspectives, and reviews. But more telling than even the huge size of this output is its impact on the research efforts of colleagues: Sporn is among the most "cited" authors in the cancer field, a metric of peer approval that matters more than almost anything else in the culture of modern science. His writings, according to the official arbiter of such matters, Thomson Reuters's "Web of Knowledge," have been referenced in the published work of fellow scientists 67,000 times.

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Sporn's impact, moreover, has been as broad as it is deep. While over a dozen of his research papers have, individually, received over 1,000 references from colleagues (a remarkable achievement), nearly 170 have been cited at least 100 times each. Sporn's fellow scientists have cited his collective work no fewer than 1,000 times per year, every year, since 1985.

Following the citation trail is itself a tour through cancer discovery, beginning with his seminal work on retinoids. Inspired by experimental work that had been done half a century earlier by Harvard's Burt Wolbach and Percy Howe, Sporn showed in the mid-1970s how cancer progression could be halted in some cases—and proper cell differentiation restored—by vitamin A and its chemical cousins. Such analogs of the vitamin, which Sporn termed retinoids (for their steroid-hormone-like signaling ability), could be synthesized in the lab to be thousands of times more active than the naturally occurring vitamin.

Since then, a number of leading investigators from all over the world had joined the quest and studied the effect of retinoids on cancer and other diseases, with varying degrees of success. Sporn, though, moved on.

Just as famously, Sporn's NCI laboratory, along with another group at the Mayo Clinic, was the first to discover a protein "growth factor" called TGF- β , which would prove from the start to be monumentally important in normal cell development, the healing of wounds, and cancer progression. Through the 1980s and '90s, he and his revered NCI collaborator Anita Roberts raced against a handful of rival labs to reveal the stunning complexities of this molecule, showing how it helped to suppress carcinogenesis in some contexts and foster it in others. In the end, the discoveries attributed to this duo of "TGF- β pioneers" would be striking in number and significance.

With another accomplished scientist, George Todaro, Sporn formulated a hypothesis of "autocrine secretion" that laid out, as early as 1980, a clear framework for how cancer cells could produce the very protein growth factors, hormones, and other signaling molecules that inevitably allowed them to escape from normal growth controls.

The work would have been enough to distinguish any research scientist's career, earning Sporn the Medal of Honor from the American Cancer Society, the prestigious Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research, the Komen Brinker Award for Scientific Distinction, and prized lectureships at the American Association for Cancer Research's annual gathering of cancer researchers. In 2004, even the NCI named its sometimes dissident alumnus its first-ever "Eminent Scholar."

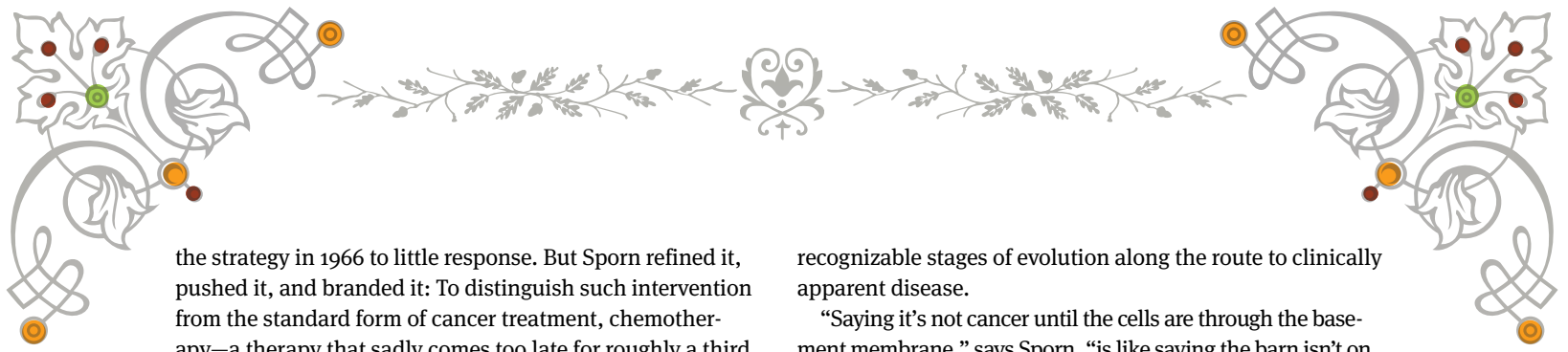


For all his contributions to biology, biochemistry, and pharmacology, though, Sporn is still better known for something else. Rather than any one molecular discovery, it is an idea.

The notion is so straightforward—so damned obvious, really—that it is easy to forget how revolutionary it was when he first proposed it in the mid-1970s: cancer, Sporn contended, could (and should) be chemically stopped, slowed, or reversed in its earliest *preinvasive* stages.

That was it. That was the whole radical idea.

Sporn was not the first to propose such an idea. Lee Wattenberg at the University of Minnesota had suggested



the strategy in 1966 to little response. But Sporn refined it, pushed it, and branded it: To distinguish such intervention from the standard form of cancer treatment, chemotherapy—a therapy that sadly comes too late for roughly a third of patients to be therapeutic—he coined the term “chemoprevention” in 1976. The name stuck.

On first reading, the concept might seem no more than a truism. But to grasp the importance of chemoprevention, one has first to dislodge the mindset that has long reigned over the field of oncology: that cancer is a disease state. “One has cancer or one doesn’t.” Such a view, indeed, is central to the current practice of cancer medicine: oncologists today discover the event of cancer in a patient and respond—typically, quite urgently. This thinking is shared by patients, the FDA, drug developers, and health insurers (who decide what to pay for). This is the default view of cancer.

And, to Sporn, it is dead wrong. Cancer is not an event or a “state” of any kind. The disease does not suddenly come into being with a discovered lump on the mammogram. It does not begin with the microscopic lesion found on the chest x-ray. Nor when the physician lowers his or her voice and tells the patients, “I’m sorry. The pathology report came back positive. . . . You have cancer.”

Nor does the disease begin, says Sporn, when the medical textbooks say it does: when the first neoplastic cell breaks through the “basement membrane,” the meshwork layers of collagen and other proteins that separate compartments of bodily tissue. In such traditional thinking, it matters little whether a cell, or population of cells, has become immortalized through mutation. Or how irregular or jumbled the group might look under the microscope. Or how otherwise disturbed their genomes are. As long as none of the clones have breached the basement membrane, the pathology is not (yet) considered “cancer.”

For more than a century, this barrier has been the semantic line that separates the fearsome “invader” from the merely “abnormal.” It is the Rubicon of cancer diagnosis. From the standpoint of disease mechanics, the rationale is easy to understand, because just beyond this fibrous gateway are fast-moving channels (the blood and lymphatic vessels) that can conceivably transport a predatory cell, or cells, to any terrain in the body. Busting through the basement is therefore a seeming leap past the point of no return, a signal that a local disturbance is potentially emerging into a disseminating mob.

But while invasion may define so-called clinical cancer for legions of first-year medical students, it is by no means the start of the pathology. Cancer is not any one act; it is a process. It begins with the first hints of subversion in the normal differentiation of a cell—with the first disruption of communication between that cell and its immediate environment. There is, perhaps, no precise moment of conception in this regard, no universally accepted beginning—which makes delineating the process that much harder. But most, if not all, types of “cancer” have their own somewhat

recognizable stages of evolution along the route to clinically apparent disease.

“Saying it’s not cancer until the cells are through the basement membrane,” says Sporn, “is like saying the barn isn’t on fire until there are bright red flames coming out of the roof. It’s absolute nonsense!”



ong before a cancer cell becomes invasive it goes through a continuum of development, a process known as carcinogenesis. The precise molecular and physical changes vary from cell to cell, from one cell type to another, and from one tissue of origin to the next. But in the case of the major epithelial cancers (which account for the vast majority of all cancer deaths), the path to transformation seems to conform to one general rule: a group of normal cells gets stranger-looking as the progression wears on.

The first infinitesimal changes can be seen in a small number of cells in a particular organ, as they take on an irregular shape and orientation. In some cases, their nuclei bulge in comparison to the cytoplasm around them. Normal cells of the same lineage, in the same old tissue, look generally uniform under the microscope. In the case of mild dysplasia (the word means “abnormal growth”), a smattering of cells do not.

Most often, mild dysplasia corrects on its own, replaced by a generation of well-proportioned cells. Occasionally, though, the progression continues, and a slight disturbance of order morphs into a moderate one. The boundary between such phases is a matter of judgment. (It is surprisingly common for two practiced pathologists to disagree on how atypical cells in any specimen are.) But dysplasia is often thought to be moderate when half the cells in a tissue look abnormal. The clumping appears stranger than in mild dysplasia. Nuclei, now packed with chromosomal material (chromatin), turn to dark blotches when stained on a glass slide.

Severe dysplasia is the next step in the continuum. Here, the entire layer of epithelial cells appears “disorganized,” any semblance of order gone. Cells are frequently of different sizes and shapes and scrambled together every which way, their nuclear centers engorged with chromatin.

The border between this phase and the next—carcinoma in situ—is thin, if it exists at all. For under the microscope, the tissue has all the makings of a malignant lesion except that it has not yet invaded through the basement membrane. It is a “cancer in waiting,” so to speak, though the wait might conceivably last forever. No one knows.

Given how blurry such dividing lines are, the entire spectrum of developmental phases is typically lumped together under a single rubric called intraepithelial neoplasia, or IEN. But that’s as far as the agreement goes. Pathologists argue over histology, the parameters of disorder, and the risks projected by each presumed degree of tissue irregularity. They speak in a babel of diagnostic tongues—with each organ site having



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its own unique argot. When it comes to IEN of the larynx, for example, no fewer than 20 classification systems have been put to the test over the years. Three are still in use today. Each breaks down the disease progression in a different way.

For all this fervent debate over the nature and inherent risk of IEN, though, all sides agree on one matter: the genesis of cancer is not merely a process (and a perpetually uncertain one at that), it is most often a slow-motion process, too.

The physical metamorphosis from one phase of dysplasia to the next is shaped and driven by an accumulation of changes at the molecular level, each of which is the result of an alteration

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in the coding or expression of a specific gene (or genes). Biologists and geneticists have spent the better part of four decades cataloging such molecular triggers. Many dozens of oncogenic pathways have now been plotted to a minute degree. But the factor implicated in carcinogenesis more than any other, it turns out, has little to do with genes or the proteins they encode. Cancer’s great enabler is time. Time provides the opportunity for accidents, erosion, and random destruction. Time offers the chance for the orderly to break down. Time lets the damage from environmental carcinogens and mutagens accrue and compound.

A lethal cancer can manifest at any age—even in infancy, which is when many cases of neuroblastoma are seen. But childhood cancers aside, the odds of developing an invasive malignancy increase with a person’s age, as a rule, simply because there is more time for genetic accidents to happen,

more time for entropy to run its course, more time for the continuous cycle of injury, repair, reinjury, and re-repair to go awry.

This is the long-enshrined “stochastic,” or random, view of how most cancers form: the disease as a kind of Russian roulette of genetic injury. (When it comes to the relatively uncommon heritable cancer syndromes, mutations, typically in one copy of a critical gene, are carried from birth, sharply raising that person’s risk of an early-onset malignancy.)

Over time, genomic damage and instability from all causes add up—to the point where four in ten Americans can be sure of a cancer diagnosis during their lifetime. While half of these cases will not be diagnosed until patients are at least 66 years old (the median age of cancer “incidence” in the United States), it is folly to think that the process, in nearly every case, has not been under way for years, if not decades.

The parallels with coronary heart disease and hypertension, and virtually every other ailment of advancing age, are hard to miss. A heart attack on the golf course is nearly always the culmination of a drawn-out process, a decades-long buildup of arterial plaque that may have begun, in some cases, in teenage years. Likewise, the diagnosis of an invasive cancer is the late recognition of a progressive disease long in development. If such is the case, Sporn reasons, it only follows that cancer ought to be interrupted or slowed or controlled early in that progression. That, after all, is precisely the strategy that has reduced the burden from heart disease and stroke so “miraculously” over the past half century.

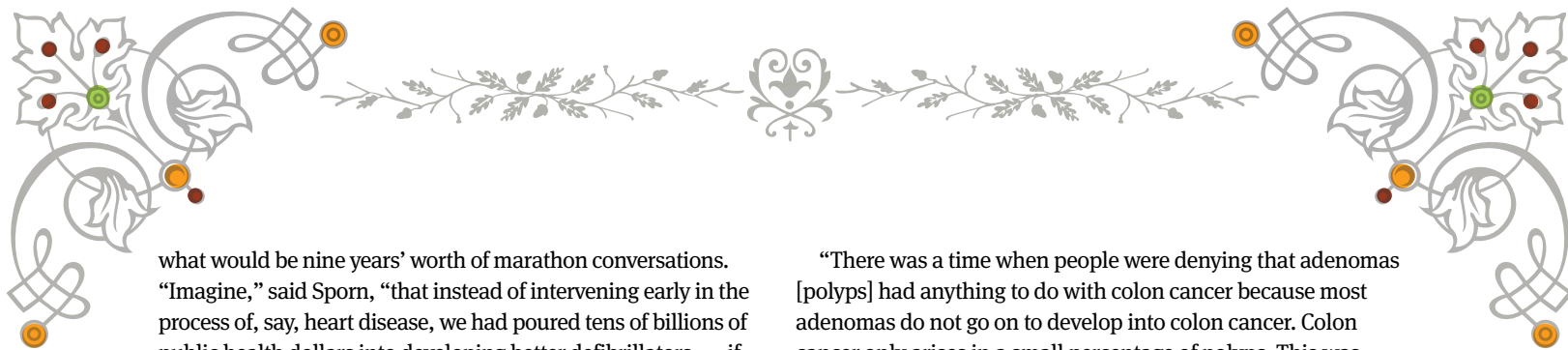
“We do not generally wait until a person is in the midst of cardiac arrest to treat him or her,” says Sporn. “We treat the patient at the first sign of early disease.”

Statins are used to lower artery-clogging cholesterol in millions of people, even though not everyone with elevated levels of low-density lipoprotein (“bad cholesterol”) is destined to die of a heart attack. Beta-blockers and other drugs are routinely, perhaps even too aggressively, used to counter high blood pressure. Blood thinners and anticoagulants are used to prevent clotting in those who are deemed “at risk.” Irregular heart rhythms are stabilized, sometimes with risky surgery. Stents and other procedures are frequently employed in later stages of disease progression to prevent the heart muscle from being damaged. The approach is hardly passive; this prevention is interventionist in nature.

For nearly every major pathology other than cancer, a vigorous preemption strategy has governed. Doctors attack *pre*-disease not only through chemoprevention, but also by having those with such risk markers as high LDL levels, blood sugar, or blood pressure make immediate, substantive changes in their diets and lifestyles.

One can only wonder what the result might have been had we tried a different tack 50 or 60 years ago.

That, indeed, is the what-if Sporn put to me as he drove me back to the hotel in his trusty Subaru, after the first of



what would be nine years' worth of marathon conversations. "Imagine," said Sporn, "that instead of intervening early in the process of, say, heart disease, we had poured tens of billions of public health dollars into developing better defibrillators . . . if we had treated heart disease like an event to react to rather than a long process to stop at the beginning (or even in the middle)? What if we had approached this leading killer, in other words, the way we have approached cancer—how many millions of people would have died too soon?"

Mike Sporn's heresy is that he began asking such questions in 1976. And that he cannot bring himself to stop. . . .

Cancer could (and should) be chemically stopped, slowed, or reversed in its earlier preinvasive stages.



Over a period of nine years I have spent dozens of hours in conversation with Michael Sporn and exchanged hundreds of emails and letters with the man. His thoughts and memories unfold a history of cancer biology, one of improbable geniuses and the sometimes uncelebrated discoveries they made. Here is the story of optimism, of modesty, of hope, in the wisdom of the men and women of science. And at the end of the timeline is heartbreak.

Sporn has joked about the perennial lack of funding for prevention research ("We're still a minority viewpoint, but in terms of grant money, we're a superminority!"); he has cheerfully pressed his case for chemoprevention in one scholarly article, speech, and government testimony after another. But he has been deflated by the mindset, even among scientists and health-policy officials, that people in the midst of active carcinogenesis are healthy.

"People do not wake up one day as 'healthy,'" he says, "and the next as 'having cancer!' Were the 20,000 women told they had ovarian cancer this year healthy the year before, when they had no symptoms to speak of?"

"There was a time when people were denying that adenomas [polyps] had anything to do with colon cancer because most adenomas do not go on to develop into colon cancer. Colon cancer only arises in a small percentage of polyps. This was a very, very big argument. And the modern corollary to this, to people who don't want any chemoprevention, is that you can't treat healthy people. 'Healthy people, healthy people. Dr. Sporn, how can you go treating healthy people?'"

"Was Anita healthy in 2003?"

Anita Roberts had come to his NCI laboratory as a post-doctoral fellow in 1976. She had become his full partner in research, going on to earn fame for her pioneering work studying the protein TGF- β , and had assumed command of Sporn's lab after he left. The pair published hundreds of papers together over a three-decade collaboration. On ScienceWatch's list of the 50 most cited researchers in the life sciences from 1983 to 2002, Roberts was one of only two women; Sporn was also on the list, naturally.

In March 2004, the 62-year-old Roberts was told that she had an aggressive Stage IV gastric cancer. By May of 2006 she was dead.

The loss of his longtime friend and partner devastated Sporn. It was also a heartrending reminder of the cost of a mindset. For even if doctors could have identified a precancerous lesion in Roberts's stomach five or ten years earlier, they would not have treated it. She would have been considered "healthy," after all—even colleagues at the NCI, who knew carcinogenesis was a process, would have sighed relief at the biopsy of a mere dysplastic lesion. "Thank God it's not cancer," many would have said.

The view is so deeply etched into cancer culture that it affects everything from the drug-approval process to clinical trial design, and reimbursement rules from insurance companies and Medicare. Current regulatory standards make it almost impossible to test chemopreventive drugs, let alone develop and market them. According to one pharmaceutical-industry database, only 1.5 percent of all drugs in active development as of 2004 had a prevention indication of any kind. The mindset has frozen the science of chemoprevention in place, leaving even the growing ranks of believers in a kind of suspended animation. Theirs will continue to be a world of "task forces" and "working groups" and poorly funded "consortiums" until the risk equation is fundamentally rethought.

If we are ever to face the cancer burden head-on, the threshold for intervention can no longer be framed as one of risk versus benefit alone. The more important tradeoff to consider here is risk versus risk: it is the uncertain risk of action versus the sure and devastating risk of inaction; it is the age-old contest between the sin of commission and the sin of omission. In this case, almost certainly, the sin of omission is the greater transgression.

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