Near the end of the first decade of the 21st century, the National Cancer Institute, fearing that it was locked in a losing battle, decided to reach beyond its usual pool of expertise. For almost 40 years, cell biologists, physiologists, geneticists, and other medical researchers had made small advances in the war on cancer. But for all the improved treatments and diagnostic techniques, the death toll had barely budged. The field was desperate for new ideas. Beginning about two years ago, scientists from a dozen different fields began arriving in Washington for a series of brainstorming sessions. What emerged were some startling new ways to think about cancer.

Maybe the most terrifying thing about a malignancy is knowing that something alien is growing inside you -- like a new organ suddenly sprouting in the wrong place. Or, even more disturbing, a vicious, misshapen embryo. And one that is mobile. Once it has sacked the resources in its immediate vicinity -- your stomach, your colon, your uterus -- it moves on, metastasizes, to new ground. Its universe is your body and it is determined to seek out and exploit every nook. If a cancer is like a beast in a Darwinian struggle -- continually mutating, evolving, and out-competing more timid tissues -- then maybe evolutionary biologists and even wildlife ecologists have something to contribute to the fight.

Encouraging medical researchers to confer with their distant cousins in the life sciences is unusual enough. But the Cancer Institute was determined to reach even further. To an information theorist, biological cells are little computers, and a tissue or an organ is a communications network. Through the exchange of chemical signals, normal cells cooperate, growing and dying in synchrony. A cancer cell is one that has learned to hack the cellular machinery. Computer scientists study how complex information networks can be sabotaged from within. Now they are also considering the biological cyberattacks behind cancer.

Mathematicians are beginning to play their own role, particularly experts in game theory -- the analysis of rules of engagement that developed during the Cold War. In the game of life, cancer cells are cheaters and bluffers whose strategies might follow predictable rules.

As more minds flocked to the problem, the metaphors multiplied. To a physicist specializing in thermodynamics, a cell is a temporary back eddy in the universal energy flow, a fragile bubble in a sea of chaos. It can be analyzed and understood in terms of entropy and information. Other physicists have suggested that cells are like harmonic oscillators, tuning forks. In a healthy tissue they vibrate

harmoniously. What then causes the cancerous dissonances, the banging on the piano keys? Addressing questions like that brings complexity and chaos theory onto the table.

So many of the old dogmas are coming into question. It has long been assumed that the series of mutations that causes a cell to become malignant is random -- a string of bad luck. But some researchers suggest that there may be a pattern, that the mutations might be predictable. Look deep enough and randomness can be order too deep to perceive. At one workshop, the physicist Paul Davies proposed that cells are “bags of quantum nanophysics” -- structures that are subject to the counterintuitive rules of quantum mechanics. It is a strange idea. Tiny as they are, the parts of a cell are generally considered too large to be affected by the quantum weirdness that governs subatomic particles. But are they? Everything suddenly seems up for grabs.

After gathering these and other wild ideas, the Cancer Institute began funding what could turn out to be the next stage in the war on cancer. At a dozen new research centers, physicists, mathematicians, engineers, nanotechnologists, and other specialists have begun collaborating with biologists to understand how a single cell gone crazy can cause a whole body to die.

I began thinking about cancer six years ago when my wife, Nancy, found a lump on the inside of her right groin. Cat scratch fever, we decided, after seeking reassurance from the Web. The human mind, ever hopeful, has a talent for absorbing aberrations. But the bump didn't go away. Her doctor thought it might be a hernia and recommended a consultation with a surgeon. He took one look and immediately ordered a biopsy.

There are those moments we all know when you are sitting in a hospital waiting room surrounded by people idly flipping through magazines or staring into their cellphones. Just when you think you cannot wait a minute longer, the surgeon walks in, her mask hanging around her neck, smiling, pleased to be giving you the good news. This time that didn't happen. "We may be looking at a carcinoma," she said.

A few days later the pathology department confirmed the hypothesis. Somehow cancerous cells had gotten into my wife’s lymphatic system and lodged inside a lymph node, creating the lump in her groin. But where in her body had the cells come from? It would be weeks before we knew. “Metastatic carcinoma with an unknown primary" -- it seemed like the worst possible diagnosis. A tumor was

single-mindedly growing, shedding cancerous seeds, metastasizing. But no one knew where.

After all the scans and tests and consultations, the doctors finally formulated a story. How at some moment in the last few weeks -- she might have been driving to the store or rehearsing her part for a choral performance -- a single cell in her uterus had started insanely multiplying. Rapidly overtaking the surrounding tissue, the cancer marched down a ligament from her uterus to her groin, replacing the bulk of the fatty tissue. A Stage 4 cancer.

I remember that year in flashes. In the next one, we're sitting in a restaurant, two nights before surgery, when she notices another lump, this one in her left groin -- a mirror image of the first. The cancer cells, a rare and unusually rabid type called papillary serous carcinoma, had already jumped through the lymphatic system to the other side of her body. The operation, a hysterectomy and lymphectomy, took six hours.

Then came the chemo and the radiation -- an onslaught designed to be as aggressive as the attacker -- and the long recovery from the cure. Worst of all was the waiting to see if, after all of that, a single mutant cell had escaped.

At the onset, the five-year survival rate for papillary serous carcinoma seemed bleak. We have gotten to the sixth year with good reason to believe the cancer will remain in remission, but there is always the possibility that it will stir from slumber and start growing again.

It was during those first months that I began learning how a cell can acquire the precise combination of mutations that leads down the path to cancer. Every time a cell divides it must duplicate its DNA and pass the replica along to its progeny. Most mutations occur from copying errors. Others might be caused by a carcinogenic chemical or exposure to ultraviolet light, x-rays, or gamma rays. Sometimes a sequence of mutant DNA is inserted into your genome by an invading virus. And there are the mutations you inherit readymade from your parents.

Most of these aberrations, by far, are harmless. The handful that might give you cancer occur in the genes that regulate cell growth. The tiniest mutation -- a G where there should be a C in the genetic encoding -- can lead to the overproduction of chemical signals that order a cell to grow and divide. Or a different mutation can cause the molecular receptors that respond to the signals to

become hypersensitive. Set on a hair trigger they prematurely fire. Either defect can cause a cell to start multiplying more quickly than its neighbors.

In fact these kinds of errors happen all of the time. We usually don't get cancer because other genes react to sudden bursts of activity by unleashing signals that rein in the growth. But a mutation in these tumor suppressor genes can cause that safeguard to fail. If there are mutations in both the growth-promoting and growth-restraining genes, the cell has two strikes against it. It is balanced on a razor's edge ready to tip.

Just as vulnerable is the cell cycle clock, which regulates the rhythm by which a cell divides. It is dependent on cascades of enzymes: cyclins and kinases and proteins called p16 and p53 -- gears in a delicate clockwork and more things that can go wrong. And they do. All of the time. But the mistakes are almost always caught and corrected. As cells divide, proofreading enzymes scan the newly copied DNA for errors to repair. If that backup fails, a cell can sense the danger and send itself a suicide signal, killing itself for the common good through a procedure called apoptosis. But another mutation can cause apoptosis to fail.

The longer a cell has lived the more likely it is to have mutated to the brink of cancer. It produces too much growth stimulant and not enough tumor suppressor. Its cell cycle clock is out of order along with the safeguard of cellular suicide. That leaves the final barrier against runaway growth: a chemical computer that keeps track of how many times in its life a cell has divided. Caps on the ends of the chromosomes, called telomeres, get shorter with each division. Once they fall below a certain size they trigger signals that halt further proliferation. The cell enters a benign state called senescence. But for every fail-safe, something can arise to circumvent it. With the right mutation a cell can develop the ability to replace its own shrunken telomeres, to reset the clock and become what biologists call immortal. Copying itself again and again it produces a mass of mutant offspring. A tumor.

And that is still not enough to give you cancer. A tumor can grow only so large, about 1 or 2 millimeters in diameter, the size of the spherical tip of a ballpoint pen, before its outer cells are starved of nutrients or drown in their own waste. For the tumor to continue expanding it must find a way, through mutation, to stimulate the formation of new capillaries, hooking itself into the body's circulatory system.

When that happens the cells start multiplying more rapidly than ever, dramatically increasing the chance of more mutations -- or adaptations, if you take

the skewed point of view of the cancer cell. The phenomenon is what computer scientists call "random generate and test." With all the restraints removed, the genome spins out one variation after another -- hopeful monsters -- some of which will gain an upper hand. Some cells might stumble upon the ability to oxidize glucose more efficiently, others to tolerate harsher environments. Finally the fittest of the cells may learn to metastasize. Breaking away from the tumor, they carry their genetic instructions through the bloodstream, lodging in a distant capillary and starting another growth.

When I think about all of this I am pulled between opposite reactions: With so many checks and balances, a person must be extraordinarily unlucky to get cancer. Then again, with so many things that can go wrong, it is amazing that cancer doesn't happen all the time.

What I propose is a book that explores cancer from both the perspective of the host -- the victim -- and the perspective of the disobedient cells. The field work will take me to research centers in the United States and Europe where scientists are rethinking the old certainties. At a recent National Cancer Institute workshop, a Princeton biophysicist made the disturbing suggestion that cancer is not a disease in the familiar sense but a natural part of the evolutionary process. It is a mechanism that nature, on the largest scale, uses to eliminate phenotypes -- human bodies -- that are receptacles of defective genes. That is not much consolation if you are one of the phenotypes. But these kinds of struggles -- the part against the whole -- are endemic throughout the biosphere. What is good for the tumor is bad for the host. But what is good for the host -- surviving the tumor and possibly bequeathing more cancer-causing genes -- may be bad for the species.

No one is suggesting that we give up and bow to nature's own program of eugenics. But this change in perspective might help explain why the war on cancer has been such a bust. Except for certain childhood leukemias and testicular cancer in young men, there is rarely anything that can be called a cure. And once most cancers have metastasized to another organ, the odds of long-term survival rapidly approach zero. What is hailed as a new miracle drug might interrupt the process for half a year at the cost of $10,000 a month. And then the cancer will start growing again.

For all the talk of prevention there may be nothing you can do -- short of quitting smoking or avoiding nuclear materials -- to keep from getting cancer. Exercise, vitamins, anti-oxidant cereals -- none has been proven beneficial. For

most cancers even the value of early screening is dubious. The most dangerous tumors grow too fast for early detection to matter, while the ones most likely to be discovered during a routine checkup grow too slowly to cause harm.

There is so little we really know. Surely toxic chemical waste dumps should be avoided. But a 20-year followup of residents who lived near Love Canal showed that their overall cancer rate was no worse -- in fact it was slightly better -- than that of the public as a whole. The survey showed a slight elevation in kidney and bladder cancers, so slight that the effect may have been caused by chance.

For all these surprises and setbacks, there is no shortage of hope. Maybe with new ways to think about cancer, scientists will find a commonality among all types, a unified theory that can be exploited to bring the phenomenon under control. Maybe as more is learned about manipulating the machinery inside an individual cell, an arsenal of weapons can be developed, each zeroing-in on a particular mutation. Or maybe we will never win the war on cancer. But along the way science will deepen its understanding of the complexity and the randomness and maybe even the meaning of life. I want this to be a book, a big one, that brings readers to the cutting edge of the field, that takes a broader, more panoptic view than has been taken before.

The more I think about cancer I start seeing malignancy and metastasis everywhere. In the ecosystem of our backyard garden, conglomerations of cells that have mutated to outcompete the flowers are called weeds. Over the years I have watched them adapt to me, the gardener. Or so I imagine. A horrible mutant dandelion called western salsify seems to have "learned" to set seed almost immediately -- before I can spot the yellow blooms and pull up the weed by its roots. At the small ranch where my wife keeps her horses, I've become locked in a battle with a particularly nasty invader called salsola tragus, or tumbleweed, which crowds out the grasses and metastasizes with every windstorm, creating acres of new malignancies. As I chop the weeds with my hoe --my scalpel -- and apply my own chemotherapy (no radiation yet) I think how the human race has become the earth's malignancy. We co-opt our host, suppress the competition, and spread, locked into a logic where progress, metastasis, is necessary for survival. Edward Abbey wrote that "growth for the sake of growth is the ideology of the cancer cell."

Ultimately a story about cancer is about coming to terms with randomness. What caused *you* to get the triple or quadruple strike of mutations? Not enough sun screen or vegetables? Too much red meat, or radon leaking from the crawl space beneath your house? Something in the water? A cell damaged by an errant cosmic

ray?

In my collection of old scientific instruments is a device called a spinthariscope (from the Greek word for spark). Inside a brass tube is a piece of radium next to a scintillation screen. As the radium decays it randomly shoots out alpha particles, clusters of protons, which are registered as tiny flashes of light. On the other end of the spinthariscope is a lens through which you can watch the show. Sometimes when I cannot sleep I pick the device up from the bedstand and watch the light bursts -- microscopic nuclear explosions, quantum randomness. I think about the randomness of the genetic mutations that cause cancer, and about the fact that I am holding something radioactive so close to my eye. The alpha particles are safely contained inside the instrument, but if I scraped out a speck of the radium and swallowed it, I might die from stomach cancer. How can life be so robust and yet so delicate?

As with *Fire in the Mind* my intent is to make unexpected connections and to tame big themes into a good book. I also hope to expand my readership to another level. This year cancer is expected to surpass heart disease as the world's No. 1 killer. It is something that touches everyone.