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BOOKS

CANCER WORLD

The making of a modern disease.

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Targeted therapies hold out the promise of a new era in cancer treatment, but will we fear cancer any the less?

This is how it starts. Carla wakes up one morning feeling that something is wrong. She has been having headaches, but not of the normal, take-a-pill-and-relax type. These headaches come with a sort of numbness, and now she notices some other things that aren't as they should be. There are bruises on her back that she can't explain; her gums have been going pale; and she's very, very tired. She goes to her doctor, but he can't tell her what's wrong. Try some aspirin, he says; maybe it's a migraine. The aspirin doesn't help, so she finally asks for some blood tests and soon she winds up at Massachusetts General Hospital, in Boston, where a young and talented physician gives her the preliminary diagnosis: acute lymphoblastic leukemia (A.L.L.). Carla knows nothing about lymphoblasts, or why she's going to have to have a bone-marrow sample taken, but she knows about leukemia. It's cancer of the blood. She's terrified, and she may not be in a state of mind to take in the oncologist's reassurance that A.L.L. is "often curable."

Carla now enters not just a cancer ward but a cancer world. The ward is what the sociologist Erving Goffman once called a "total institution," like asylums, armies, prisons, monasteries, and Oxbridge colleges—an institution that strips you of your identity and equips you with a new one. She's given a case number, a bracelet, a hospital gown. Some of her physicians will know her name and what she was before becoming a cancer patient, and some will not. Her chemotherapy ward is an environment made sterile in order to protect her soon to be therapeutically devastated immune system from infection, so her relations with family and friends are reconfigured along with the rhythms of her days and weeks. She's now a case.

The oncologist in the story is Siddhartha Mukherjee, the author of "The Emperor of All Maladies: A Biography of Cancer" (Scribner; \$30), a history of the disease and of the attempts to describe it, explain it, manage it, and cure it, or just to reconcile its victims to their fate. It is a personal story, too, an account of the author's own "coming-of-age as an oncologist," and its

historical narrative is crosscut with Mukherjee's present predicaments. He is sure that he can do much more for his patients than the physicians of the past, yet he recognizes his fellowship with his medical ancestors; he knows that he shares many of their hopes and frustrations. At the same time, he wants to understand what his patients share with their ailing forebears and what is peculiarly modern about their predicament. He sees that cancer is a world unto itself; that Carla is now part of this world; and that he is part of it, too. For cancer patients and their physicians, the cancer world seems to expand to the whole of experience. As one victim of a muscle sarcoma told Mukherjee, "I am in the hospital even when I am outside the hospital."

Cancer has always been with us, but not always in the same way. Its care and management have differed over time, of course, but so, too, have its identity, visibility, and meanings. Pick up the thread of history at its most distant end and you have cancer the crab—so named either because of the ramifying venous processes spreading out from a tumor or because its pain is like the pinch of a crab's claw. Premodern cancer is a lump, a swelling that sometimes breaks through the skin in ulcerations producing foul-smelling discharges. The ancient Egyptians knew about many tumors that had a bad outcome, and the Greeks made a distinction between benign tumors (*oncos*) and malignant ones (*carcinomas*). In the second century A.D., Galen reckoned that the cause was systemic, an excess of melancholy or black bile, one of the body's four "humors," brought on by bad diet and environmental circumstances. Ancient medical practitioners sometimes cut tumors out, but the prognosis was known to be grim. Describing tumors of the breast, an Egyptian papyrus from about 1600 B.C. concluded: "There is no treatment."

The experience of cancer has always been terrible, but, until modern times, its mark on the culture has been light. In the past, fear coagulated around other ways of dying: infectious and epidemic diseases (plague, smallpox, cholera, typhus, typhoid fever); "apoplexies" (what we now call strokes and heart attacks); and, most notably in the nineteenth century, "consumption" (tuberculosis). The agonizing manner of cancer death was dreaded, but that fear was not centrally situated in the public mind—as it now is. This is one reason that the medical historian Roy Porter wrote that cancer is "the modern disease *par excellence*," and that Mukherjee calls it "the quintessential product of modernity."

At one time, it was thought that cancer was a "disease of civilization," belonging to much the same causal domain as "neurasthenia" and diabetes, the former a nervous weakness believed to be brought about by the stress of modern life and the latter a condition produced by bad diet and indolence. In the eighteenth and nineteenth centuries, some physicians attributed cancer—notably of the breast and the ovaries—to psychological and behavioral causes. William Buchan's wildly popular eighteenth-century text "Domestic Medicine" judged that cancers might be caused by "excessive fear, grief, religious melancholy." In the nineteenth century, reference was repeatedly made to a "cancer personality," and, in some versions, specifically to sexual repression. As Susan Sontag observed, cancer was considered shameful, not to be mentioned, even obscene. Among the Romantics and the Victorians, suffering and dying from tuberculosis might be considered a badge of refinement; cancer death was nothing of the sort. "It seems unimaginable," Sontag wrote, "to aestheticize" cancer.

Cancer is "the modern disease" not just because we understand it in radically new ways but also because there's a lot more cancer about. For some cancers, the rise in incidence is clearly connected with things that get into our bodies that once did not—the causal link between smoking and lung cancer being the most spectacular example. But the rise in cancer mortality is, in its way, very good news: as we live longer, and as many infectious and epidemic diseases have ceased to be major causes of death, so we become prone to maladies that express themselves at ages once rarely attained. At the beginning of the twentieth century, life expectancy at birth in America was 47.3 years, and in the middle of the nineteenth century it was less than forty. The median age at diagnosis for breast cancer in the United States is now sixty-one; for prostate cancer it is sixty-seven; for colorectal cancer it's seventy. "Cancer has become the price of modern life," an epidemiologist recently wrote: in the U.S., about half of all men and about a third of women will contract cancer in their lifetime; cancer now ranks just below heart disease as a cause of death in the U.S. But in low-income countries with shorter life expectancies it doesn't even make the top ten.

The cancers of the past were visible on the body's surface; now we have visual access to the enemy within at a micro level. Modern technologies—advances in microscopy, histological staining, biopsies, X-rays, computed tomography (C.T.) and magnetic resonance imaging (M.R.I.) scans—have given us new possibilities for understanding cancer, but also a new vocabulary of fear. In "The Illness Narratives," the psychiatrist and anthropologist Arthur Kleinman recorded conversations between cancer victims and their physicians. A dying patient with metastasized rectal cancer told his doctor about his feeling that "there is something not me in me, an 'it,' eating its way through the body. . . . These cancer cells are me and yet not me." The more science tells us about the cancer cell, the more it resembles us. It wants to grow and multiply, as we do, but it doesn't know how to stop. "Cancer's life is a recapitulation of the body's life, its existence a pathological mirror of our own," Mukherjee writes. "Down to their innate molecular core, cancer cells are hyperactive, survival-endowed, scrappy, fecund, inventive copies of ourselves." Researchers, in their more detached moments, can't help admiring the cancer cell, the way that

Sherlock Holmes admired Moriarty, as a worthy opponent. Toward the end of his book—surveying the patterns thrown up by modern cancer genetics—Mukherjee pauses before judging those terrible patterns “quite beautiful.”

The story of cancer as a distinctively modern—and even specifically American—entity starts with the marriage, in 1940, of Albert Lasker, a wealthy and well-connected advertising executive whose accounts included Lucky Strike cigarettes, and Mary Woodard, a dress designer and Radcliffe graduate, who had social aspirations. Mary Lasker needed a philanthropic cause, and found one in harnessing the tremendous power of medical research to cure all manner of disease. Her husband was soon converted to Mary’s vision and urged her to think very big. “There are unlimited funds,” he said. “I will show you how to get them.”

The big, new idea was to unleash these funds not just through charitable giving but through political action. By the time that Albert died, horribly, of colon cancer, in 1952, Mary Lasker and her supporters (by then known as the Laskerites) had begun to develop a focussed target and a strategy: cancer was the enemy, and Washington was to be the battlefield. “You were probably the first person to realize that the War against Cancer has to be fought first on the floor of Congress,” the breast-cancer activist Rose Kushner later wrote to Lasker, and the military language stuck. This was a colossal fight, needing huge amounts of money, and engaging the enemy through overwhelming force.

If medical research was to be the weapon, the Laskerites needed a medical researcher to give the campaign credibility and to identify strategic targets. When Lasker met the cancer researcher Sidney Farber, in Washington in the late nineteen-forties, it was, Mukherjee writes, “like the meeting of two stranded travelers, each carrying one-half of a map.” In 1947, working at Boston’s Children’s Hospital, Farber had had striking success in treating child-leukemia patients with a group of chemicals known as folic-acid antagonists. Cancers were understood to be malignant neoplasms, caused by uncontrollably dividing cells, and Farber was looking for substances that could target and check that division. There had been recent signs that the chemical-warfare agent nitrogen mustard could do this with non-Hodgkin’s lymphoma, and now it seemed that antifolates could be effective with certain cancers of the blood. Farber’s success was limited, but, given the current state of cancer therapy, it was stunning. He was getting significant remissions through systemic intervention. It was the origin of modern chemotherapy.

In Farber, Lasker found her field commander: she capitalized on his expertise and authority, and she eventually lifted his sights from voluntary fund-raising to political action. Working together for two decades, the pair learned how to mobilize, organize, and focus scientific and technological assets. By 1970, as the Vietnam War ate away at the nation’s soul and resources, Richard Nixon came to think that a Presidentially promoted War on Cancer could be much more popular and more likely to end in unambiguous victory. It could be another Manhattan Project or Apollo program. In 1971, the combined forces of Lasker, Farber, and Nixon pushed the National Cancer Act through Congress, tapping vast federal resources specifically targeted at cancer research and control. Administratively and financially, cancer was now set apart from other dread diseases; it was institutionally special, with a special political base and a special scientific and clinical agenda. The modern cancer world came into being thanks to a new configuration of federal politics, popular activism, finance, corporate activity, and science. Lasker’s realization that the cure for a disease could proceed through political action changed the rules of the game.

There are basically three ways to treat cancer: you can cut it out surgically; you can burn it up with radiation; and you can poison it by suffusing the body with cytotoxic chemicals that knock out cancer cells without such extensive damage to normal cells that the attempted cure kills. The therapeutic triad can be combined in any number of ways. The fight is hard and the assessment of progress is not easy, but it would be understandable for a modern oncologist to celebrate recent progress and condescend to the knowledge and the therapies of his forebears. Mukherjee mainly resists that temptation, and his sympathy for failed therapies matches his compassion for the patients they could do so little to help.

If there are heroic figures in his story, they are the chemotherapists and the biomedical scientists whose researches seek ever more specific targets for drug action. Mukherjee’s story gives comparatively little space to the surgeons, and the only genuinely unsympathetic figure is the surgeon William Stewart Halsted, who began to perform radical mastectomies at Johns Hopkins Hospital in the eighteen-nineties. They were called “radical” because the aim was to remove the “root” of cancers. Disdainful of what he called “mistaken kindness,” Halsted proceeded to excavate more and more tissue—digging out the muscles of the breast cavity, the lymph nodes and glands above and underneath the collarbone—playing a macabre game of surgical chicken with women’s bodies.

It didn’t work: the survival rate depended not on the width of the surgical margin but on the cancer’s metastatic reach before surgery. If you really needed to take out a lot of tissue, the cancer had, in all probability, already spread through the system; and, if it had not spread, the women were disfigured for no reason. But Halsted, working within an ingrained culture of surgical showmanship, saw success as the absence of “local recurrence.” Historians these days seek to understand how predecessors thought they were right even when we know they weren’t, but some retain the privilege of judging those who were hubristically

wrong, who ignored evidence that was then available. Mukherjee reckons that Halsted looked the facts in the face and then looked away.

Over time, surgeons learned more about what to cut out and what to leave. The far less extensive “lumpectomy” operation for breast cancer, pioneered in the nineteen-twenties by the English surgeon Geoffrey Keynes, was given its name as a sneer—to American Halstedians, it seemed insufficiently aggressive. But by the nineteen-eighties it was accepted that outcomes among patients receiving “simple mastectomies” were statistically identical to those for patients undergoing the radical operation. The latter group paid heavily in disfigurement and ancillary ill health, but, Mukherjee writes, they “accrued no benefits in survival, recurrence, or mortality.”

In chemotherapy, too, the lines between cruelty and cure have not always been obvious, nor have consciences always been untroubled. Experience with chemotherapy led to the conviction that the ingenious adaptability of the cancer cell had to be combatted by using varied “cocktails” of cytotoxins, by continuing chemo long after signs of remission, and by delivering doses that might cause excruciating pain to patients and also constitute an independent danger to their lives. The blood cancer that killed Susan Sontag was caused by the aggressive chemo she was given for her breast cancer.

Chemotherapists have also faced the dilemma of whether their chief responsibility is to minimize an individual patient’s suffering or to further the search for an eventual cure. When risks to a given patient may mean benefits to future sufferers, the boundary between experiment and care can blur. Mukherjee, describing experimental chemo regimens of the early sixties, recounts the controversial decisions made to concoct terrifyingly toxic cocktails for child-leukemia patients, while the physicians in charge did what pathetically little they could to make the kids more comfortable. Years afterward, and with the clearer conscience of substantial success, one oncologist recognized the dangers of what they had done: “We could have killed all of those kids.” From its postwar origins to the present, the chemotherapist’s predicament is the precarious balance between best-practice care and the crying need to improve current practice. In the eighties, AIDS patients started to insist on being “guinea pigs,” and terminal-cancer sufferers soon followed their lead. In the current world of end-stage cancer, care and experiment can often be much the same thing.

This is an enduring fault line in the nature of medicine itself—is it a future-oriented science or is it a present-rooted, caring practice? How can you balance the need to understand the fundamental mechanisms of a disease, and the need to treat sick patients now, with whatever knowledge and therapies are at hand? Sidney Farber, for one, embraced the notion of the War on Cancer as a means of insisting on the pressing priority of present care: aspirin, after all, had relieved headaches long before anyone understood how it did so; perhaps cancer could be cured without physicians being able to specify the mechanisms of curative action. Absent secure knowledge of fundamental mechanisms, cancer medicine in the sixties and seventies deployed the “full armamentarium of cytotoxic drugs,” Mukherjee writes, “driving the body to the edge of death to rid it of its malignant innards.” For practical purposes, cancer therapy and cancer science then belonged to virtually distinct worlds.

This situation found its political moment in the opening moves of the War on Cancer. Nixon not only wanted a winnable war; he also wanted a rod with which to discipline the nation’s scientific community and get it to “shape up.” Scientists didn’t “know a goddam thing” about how their own activities should be organized and directed. The War on Cancer was meant as a visible token of the future course of American science—not an “endless frontier” of basic research but an enterprise energetically focussed on solving identifiable, and politically approved, national goals.

But it’s hard to wage a war against a poorly defined enemy. If the enemy doesn’t define itself, then you can configure the enemy you need for the war that you want to fight. That’s what happened with the War on Cancer. It gave definite form, Mukherjee says, to an adversary that was essentially formless: “Cancer, a shape-shifting disease of colossal diversity, was recast as a single, monolithic entity.” In this way, the War on Cancer resembles less, say, the war on Nazi Germany than the War on Terror.

Most cancer researchers in the nineteen-seventies already understood that cancer is diverse, and the research and clinical care of the following decades gave that diversity greater clarity and texture, implicating a bewildering range of underlying mechanisms. Knowing that all cancers were malignant neoplasms could take cancer care only so far. Turning the patient’s body into something like a free-fire zone wasn’t working, and, by the eighties, it was widely recognized that what the oncologist Guy Faguet has called the “cell-kill paradigm” of chemotherapy had reached its limits. What was needed was a way to engage not just rapidly dividing cells but specifically cancerous cells. You could not get to that goal without a far better understanding of underlying cellular and genetic disease mechanisms. Cancer science and cancer therapy could no longer be kept separate.

Mukherjee’s book has the vividness of an insider’s account. It evokes what it feels like to be at the forefront of modern biomedicine and to bring new knowledge and technologies into the clinic. Take Mukherjee’s account of Sidney Farber in 1947, waiting for his first supply of the antifolate drug aminopterin and watching a two-year-old leukemia patient’s condition deteriorate as another drug failed: The patient “turned increasingly lethargic. He developed a limp, the result of leukemia

pressing down on his spinal cord. Joint aches appeared, and violent, migrating pains. Then the leukemia burst through one of the bones in his thigh, causing a fracture and unleashing a blindingly intense, indescribable pain.” Mukherjee can also summon up the texture of previous systems of understanding, even of what it must have been like for Halsted to feel that he was right. It’s hard to think of many books for a general audience that have rendered any area of modern science and technology with such intelligence, accessibility, and compassion. “The Emperor of All Maladies” is an extraordinary achievement.

Mukherjee is an able guide through the conjunction of science, politics, and charitable fund-raising exploited by the Laskerites and their successors. But there are important aspects of the modern American cancer world that he scarcely mentions. Modern cancer care is big business, and cancer drugs are envisaged as the future cash cows of Big Pharma. The expense of developing cancer drugs, and their cost to patients and insurers, would clearly be worth it if the drugs promised cures or even deep remissions, but the vast majority of new drugs achieve far more modest results. A drug called Tarceva extends the life of pancreatic-cancer sufferers by just twelve days, at a cost of twenty-six thousand dollars. The issues to be confronted here definitely include those of the “What’s a life worth?” sort, but they also encompass questions about our best and most effective means of reducing the over-all toll taken by cancer.

The book also has little to say about prevention, aside from the campaign against tobacco. When Mukherjee talks about knowing the “causes” of cancer, he means genes and cellular mechanisms gone wrong, not the environmental agents that might induce changes in those genes. Compare this with the historian Robert Proctor’s “Cancer Wars” (1995), which bluntly states, “The causes of cancer are largely known—and have been for quite some time. Cancer is caused by chemicals in the air we breathe, the water we drink, and the food we eat.” The epidemiologist Devra Davis, in “The Secret History of the War on Cancer” (2007), goes further, alleging that political inaction over environmental carcinogens has its root in the influence of industrial chemical companies—both those that profit by making “pesticides and other cancer causing chemicals” and those that profit by making cancer drugs. Depending on how you parse the notion of cause, fighting cancer can mean either more genetics or more environmental cleanup, dietary reform, and green politics.

Nevertheless, Mukherjee shows judicious skepticism in considering the long history of unfulfilled oncological promises. As a former head of the National Cancer Institute once said, “Human beings seem to have this endless ability to think they are at the end of history.” Mukherjee doesn’t think anything remotely like that. So how are we now doing in combatting cancer? His answer is a qualified “better.” He knows that many of his colleagues have concluded that “we are losing the war on cancer”; that therapeutic progress against some forms of cancer is matched by mounting mortality rates in others; and that thousands of symptom-free people have to be screened—with attendant uncertainties, costs, and risks—to prevent even one death. Yet Mukherjee allows himself to hope, and recognizes that some form of hope is, and has to be, negotiated between the physician and the patient.

And Carla? She’s fine. Five years after Mukherjee confirmed her first remission, he drives to her house, bringing her flowers and good news. Her latest bone-marrow biopsy is negative. Oncologists are sparing with the word, but she has his permission to count herself as cured: five years in total remission is as good as good news gets.

Basic cancer science, Mukherjee believes, has revealed not another false dawn but a light at the end of the historical tunnel. We now see a way out of the “cell-kill paradigm” and toward the development and deployment of highly targeted, nontoxic chemical therapies based on genetic science. The much touted anti-leukemia drug Gleevec here appears as the hero of modern, genetics-based cancer therapy, a “rationally designed” drug specifically directed against a known cancer gene. In development since the late eighties, Gleevec has been stunningly successful against a form of blood cancer called chronic myeloid leukemia (C.M.L.), achieving such deep remissions that oncologists talk of a “pre-Gleevec era” and a “post-Gleevec era,” and tell patients that they can look forward to “their functional life span”—on the condition that they take Gleevec “for the rest of their lives.” C.M.L. is just one, not very common, type of cancer, but, as one oncologist said, “It proves a principle. It justifies an approach.”

Whether Gleevec will come to count as the proof of a new and powerful principle or, rather, as yet another broken promise remains to be seen. (Resistance to Gleevec has developed in some patients, and research continues on new drugs to overcome that resistance.) But let’s indulge the hopefulness for a moment and assume that we really are entering a golden age of rationally designed, targeted drugs. What will the cancer world of the near future look like?

Perhaps it will indeed be a long-hoped-for state in which cancer becomes just another chronic disease, along the lines of diabetes, hypertension, and even—if an adequate supply of anti-retroviral drugs can be obtained—AIDS. But what of those who have not been diagnosed with cancer? The fortunate patient taking Gleevec forever constitutes only one of two new kinds of being in the modern cancer world; it’s also populated by legions of the screened and the tested, who become more and more aware of the dangers battering away at their cells from the external environment and lurking inside, encoded in their genes. This is the world of the cancer “risk factor”: of the Pap smear; the annual mammogram; the prostate-specific antigen test; the colonoscopy; the wait for the results of biopsies of polyps removed in the colonoscopy; the daily dose of Prilosec taken because

frequent heartburn is thought to be a risk factor for esophageal cancer; even the world of knowing one's personal genome and the world of the prophylactic mastectomy.

The risk-factor world holds out hope for avoiding cancer while recruiting masses of us into the anxious state of the "precancerous." The physician and historian Robert Aronowitz offers an acute illustration of the problem: a fifty-eight-year-old woman diagnosed with breast cancer has a lumpectomy, followed by local radiation and months of chemo. After that, she is put on the anti-estrogen Tamoxifen for five years. As she finishes that course of treatment, she weighs the decision whether to go on a different type of hormonal therapy and what type and frequency of M.R.I. or mammogram to get. She is an active member of a breast-cancer-survivor group, and she closely monitors the latest developments on the Web. Meanwhile, another woman, the same age, has not received a breast-cancer diagnosis. She has, however, taken supplementary estrogen pills for several years in connection with menopause, and her doctor now tells her to stop, because estrogen may constitute a risk factor for breast cancer. She has been getting annual mammograms since she was forty, and four years ago an abnormal mammogram was the occasion for an aspiration biopsy. This proved negative, but her anxiety increases. She surfs the Web for information about risk factors, and she is struck by direct advertisements for Tamoxifen to prevent the development of breast cancer, for which she now believes she is at serious risk. The first woman had cancer; the second woman does not have cancer. But their experiences eerily resemble each other.

"Cancer," Carla told Mukherjee, "is my new normal." A world in which cancer is normalized as a manageable chronic condition would be a wonderful thing, but a risk-factor world in which we all think of ourselves as precancerous would not. It might decrease the incidence of some forms of malignancy while hugely increasing the numbers of healthy people under medical treatment. It would be a strange victory in which the price to be paid for checking the spread of cancer through the body is its uncontrolled spread through the culture. ♦

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