SIDDHARTHA MUKHERJEE

In Conversation with Nicholas Wade

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LIVE from the New York Public Library

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PAUL HOLDENGRÄBER: Good evening. My name is Paul Holdengräber, and I am the Director of LIVE from the New York Public Library. I think all of you by now know that my motto is to make the lions roar. I actually had occasion to do a variation on that on Monday when I interviewed Jay-Z. I could say that I was making the lions rap. But in fact tonight we'll just go back to our old motto and say that we'll make the lions roar.

Another way of putting it is I try to make a heavy institution levitate. I've been here for many years now, and nobody has been able to answer this very simple question, which is how much does this library weigh? I would love to know at some point. Fifty-two million items later. Just before coming onstage now we had occasion to take Siddhartha Mukherjee and Nicholas Wade down—you may or may not know we have seven floors of books that go all the way under Bryant Park. It's rather mesmerizing. Someday you should ask for such a tour as well.

When this book was brought to my attention some months ago—Siddhartha Mukherjee's new book, *The Emperor of All Maladies: A Biography of Cancer* of course at first I was wondering, my goodness, this is quite a difficult subject, and for that very reason, and because of how extraordinarily this book is written with such insight and grace I felt that we had to present it. So I'm really delighted to have Siddhartha Mukherjee here tonight.

You will look at your menu of the last few events that are happening here at the Library. I asked our designer to design a new kind of announcement. I said I want a new menu, and in fact he gave me a menu, so you will see that we have coming up on Monday Zadie Smith—I will be interviewing Zadie Smith, and Derek Walcott will be talking about Hemingway in the Caribbean. Don't ask me what that means, but I heard about that today. And then we'll be ending the season with a tribute to the *National Lampoon*. I enjoy the movement from the beginning to the end. We started with an interview with Supreme Court justice Stephen Breyer and end with the *National Lampoon*. To start again in January with a tribute to Gypsy Rose Lee. You may or may not know that the

Library has Gypsy Rose Lee's archives, so come, please come for an evening of burlesque.

I would like to encourage all of you to join the New York Public Library. For just forty dollars a year, you become a Friend of the New York Public Library, which gives you great discounts and also might even make you feel good. After the event Siddhartha Mukherjee will be signing his book, which is sold by our independent bookstore, which we love—both that it's independent and still a bookstore—192 Books.

Nicholas Wade is a scientific reporter, editor, and author who currently writes for the Science Times section of the *New York Times*, after working for both *Nature* and *Science*, where he became a member of the editorial board of the *New York Times* in 1982, writing editorials on science, health, the environment, and military technology. He was science editor at the *Times* from 1990 to 1996 and has been a science reporter there since 1997. Wade is the author of several books, of which the most recent is *The Faith Instinct*, an account of how religious behavior evolved and why it endures.

In conversation with him, or maybe Nicholas Wade will interview Siddhartha Mukherjee I don't know if it will be more of an interview or more of a conversation. Siddhartha Mukherjee is a cancer physician and researcher at NYU Presbyterian Hospital and a professor of medicine at Columbia University. A Rhodes Scholar, he earned degrees from Stanford University, the University of Oxford, and the Harvard Medical School. Mukherjee studied in cancer medicine at the Dana Farber Cancer Institute of Harvard

Medical School and was on the staff of the Massachusetts General Hospital. His articles have appeared in *Nature*, *New England Journal of Medicine*, *Neuron*, *Journal of Clinical Investigation*, the *New York Times*, and the *New Republic*. His first book, which has come out just very recently and has gotten some extraordinary reviews, both in the *New York Times* and the *New Yorker* is called *The Emperor of All Maladies: A Biography of Cancer*. Please welcome them both to the stage.

(applause)

NICHOLAS WADE: Siddhartha and I came to discuss a rather forbidding subject about which he has written a surprisingly upbeat and lighthearted book. I get to start by asking him how it was he came to write this book and why his duties as a doctor didn't take up enough of his time that he needed, in addition to two small children, to take on writing the book as well?

SIDDHARTHA MUKHERJEE: First of all, Paul, thank you, it's incredible forum, and thank you for having both of us here. Thank you, Nicholas, for doing this. The book—I wrote this book—as a child I read this story about Edmund Hillary, who said that when he was asked why he climbed Mount Everest, he said, "I climbed it because it was there," and this book is not about climbing Mount Everest, it doesn't have any of that gravitas to it, but I wrote this book because it was not there. It seemed to me that there was an incredible vacuum in the scholarship, but also in the human history of this incredible, elemental disease that was engulfing our lives, that *is* engulfing our lives today, engulfing

our societies, has had a deep influence on our culture, and yet—you know, there are five thousand books on cancer and yet there was not a single book which addressed the history of this disease and its future to some extent in the way that I wanted it to be addressed and the way patients wanted it to be addressed.

So the book actually grew out of a very small—a question that a woman had asked me when I was a fellow in training, and she had had abdominal cancer, and she had relapsed and had another remission and another relapse and so forth. She was on targeted therapies and new therapies, and then finally she said, "Sid, I am willing to go on with all of this but I need to know what it is that I'm battling," and that was a very humbling moment for me and she was not the only one asking this question. I mean, patient after patient was asking variations of this question—"What is that I'm battling?"—"What is its origin? Where did it come from, what is happening to it, where is it going, what is its future?" And so therefore I started writing this book and then it grew into a six hundred-page answer to a question.

NICHOLAS WADE: I read the book with a great enjoyment, but I think it might be useful to the audience if you would give a quite brief summary of the book and then perhaps mention some of the themes you expect readers to take away from it.

SIDDHARTHA MUKHERJEE: Sure, sure. My book structurally has—it is quite complex, because it really has two, or perhaps even three stories that thread through the book. One of the stories is of course the story of my own coming to age as an oncologist,

as a cancer doctor in training, who learns to deal with this, as I said, this magisterial illness that is taking over the lives of my patients. So that's one thread of the story, but then intertwined in that story is of course the larger history of cancer, and so we begin this book with the story of Sidney Farber, and I'll tell you why Sidney Farber became the thread that sort of stitches the book together.

Sidney Farber was born in 1903—he was a pathologist, he trained at—he trained actually in—he trained in Germany. Part of the reason was that typically Jewish students were not allowed into Harvard Medical School, and had a really tough time, so often they had to train in Germany, ironically, before they would come back and complete their advanced training in Boston or New York. So Farber went to Germany, came back to Harvard, was trained there, and stayed on as a pathologist. And a pathologist, as you know, is in colloquial language you call them doctors of the dead. So these are people typically, particularly in the 1950s and 1940s, are people who are essentially looking at tissues after children have died. He was a pediatric pathologist, he was looking at children after they had died, so he had this tiny hospital, this tiny chamber, at the bottom of the hospital, a freezing series of icy corridors, and people would be wheeling in the kids who had died in the main wards, and he would perform autopsies on these children.

But Farber had a hunger, and he was interested in treating patients, and so he began to wonder how he could enter the world of clinical medicine even as a pathologist and his key insight, which launches the book, is that he, through a series of collaborations, stumbles upon a chemical which will turn off the growth of leukemic cells, and so the

book begins with that history. From that point of time, from that moment, we will come back to Farber as we speak a little more because he's such a central character in this book. From that point in time, in fact we leap back, having just launched chemotherapy, we leap back to ask questions about what the origins of cancer were, so here we are in the 1950s, and the Farber too is at this moment in which he's trying to find out what the history is of this disease that he's first encountering.

We leap back and ask the question of when does cancer arise, what was the first time that we ever know its history? And then we thread forward from about 2,500 B.C. up through the age of early discoveries in cancer, most famously through Galen. Galen the Greek physician who practiced among the Romans who had this fantastical theory of cancer. He said cancer is an overabundance of black bile. He characterized the body—he said, well, the body has four fluids which are kept in balance—blood, black bile, yellow bile, and phlegm, and so Galen assigned a disease to each one of these four fluids, and cancer was the disease of the excess of black bile—it was black bile that was in overabundance and boiled out—Galen literally imagined them boiling out into tumors.

So we go through Galen, the systemic theory of cancer, and then arrive at the age of surgery, the great nineteenth-century era of surgery when surgeons using anesthesia and antisepsis are first beginning to take out cancer, excavate cancer literally from the body, and we first learn the dictum which becomes one of the central themes of the book, which is that if something is good, then more of that something must be better, and so nineteenth-century surgeons then begin to not only excavate pieces of the body but they

wonder that if, since cancer still recurs, they invent larger and larger and more and more invasive dissections, launching the era of radical surgery, which remains with us until about 1950, and of course now we're brought back to Farber again, to 1950.

So I want to take a little break here because what happens in the book next is about the politics of cancer, so we go now from Sidney Farber, who has just invented chemotherapy, and he hooks up with this incredibly dynamic woman, a socialite, a person who, people often said of Mary Lasker, they said, "Well, meeting Mary Lasker was like having your self annihilated. Every resistance of your body would be annihilated." She would come into the room and she would say, "I would like you to change everyone in the room around such that, I would like you to reseat this auditorium," and you'd have to do it, because there was no answer, there was no no ever with Mary Lasker. So there was Mary Lasker, and Mary Lasker became interested in finding a solution to cancer, so she and Farber have about a three- or four-decade-long collaboration which launches the war on cancer, Nixon's war on cancer, so this book takes us through that collaboration, and that's a major theme in this book, how do you take science out of this fourteen foot by twenty foot laboratory and make it into the so-called war on cancer?

And from there—we move on, from 1971 the book then moves on to the major discoveries of cancer biology from 1970 to 1990 and all the intense disappointments and finally asks the question, well, what happens next? That's a long answer to your question, but that's the arc of the book, and that's why this book is something that you can use as a doorstop.

NICHOLAS WADE: No, it's a very good summary of a five-hundred-page book. I'd like to ask you about a tension that I perceived in the book between the generally sort of optimistic tone of the writing and the appearance of these heroic figures or these figures who are presented as heroic, like Sidney Farber and Mary Lasker, and yet that seemed to me to contrast with the actually quite pessimistic conclusion that one would find at the end of most chapters saying, well, this didn't work and this caused a lot of mystery. And I'd like one of us to read one of these paragraphs, which I found the most depressing of all, **(laughter)** which, you are summarizing many decades of radical mastectomies as it explains that the surgeons decided that cutting once was okay and cutting twice was even better, so they had this really appalling procedure of radical mastectomy which they put into place without asking themselves well, does it actually work, is it better than less aggressive courses of action? And as Sid explains, it was not. Are you going—or I can read this.

SIDDHARTHA MUKHERJEE: Go ahead.

NICHOLAS WADE: So here is the summary of ninety years of this horrendous operation. "Between 1891 and 1981, in the nearly one hundred years of the radical mastectomy, an estimated five hundred thousand women underwent the procedure to 'extirpate' cancer. Many chose the procedure. Many were forced into it. Many others did not even realize that it was a choice. Many were permanently disfigured; many perceived the surgery as a benediction; many suffered its punishing penalties bravely, hoping that

they had treated their cancer as aggressively and as definitively as possible. When radical surgery fell, an entire culture of surgery thus collapsed with it. The radical mastectomy is rarely, if ever, performed by surgeons today." So when you read paragraphs like that, you have to wonder were we living in the Dark Ages, why didn't someone blow the whistle sooner on the fact that this wasn't working?

SIDDHARTHA MUKHERJEE: So there are many questions in that question. One question is what is the mechanism by which we ever gain knowledge in medicine? There's a moment in the book in which we come upon that within the case of Carla, who threads the book. The incredible irony in medicine of course is that it pretends to have certainty, because every medical decision is about certainty, it's about telling someone, let's do this or that, because I expect this or that to occur, but yet it is a discipline fundamentally rooted in uncertainty and so every measure of progress furrows its way through the lives and bodies of patients. That's the sad story about medicine. And yet of course progress has to be made, if you don't go through the process, you never learn.

I mean, if Halsted, who invented the radical mastectomy, did not ultimately, surgeons did not commit themselves to these trials, and the book tells us how difficult it was to get these trials up and running, how terrible. Surgeons essentially said, "We know the procedure works. Why on earth should we try it? What are you trying to prove here, this is a procedure that works very well, what is the knowledge that you are trying to get?" And even the word *radical* mastectomy, even the word radical mastectomy is loaded, because if you're a patient in 1948, and if someone comes to you and says "I'll give you

a choice between radical mastectomy and a nonradical procedure," you have cancer, what would you choose?

And so part of the story here is the tortuous quality of progress, but importantly and impressively progress happens, and it happens through five steps forward, two steps back, so make no mistake, as you point out, make no mistake that things are moving forward even as they're furrowing their way through the lives and bodies and psyches of patients. So I think that's what gave the book, for me, that's what gave the book a kind of a propulsion, which is how can you describe uncertainty and this sort of queasy quality of it, two steps forward, three steps back, five steps forward and four steps back, and yet convince yourself—and I am convinced—that the whole field is slowly moving forward from out of the dark ages towards a deeper understanding.

NICHOLAS WADE: Well, it seems to me one has a particularly inflammatory situation in all of medicine, but in cancer in particular, between patients who are desperate and will try anything and doctors who with their sort of mixture of perhaps good and bad motives will also try anything, they want to help their patients, they're looking for medical glory, a place in the history books, and this is a very dangerous combination, because it leads to excesses of the kind you describe both with radical surgery and with chemotherapy. In retrospect I think if we could have advised those physicians from our position of knowledge, we would have said, "Don't go down this path, you're much better off with palliative care, you don't have the knowledge or technology to do anything useful except cause misery to your patients," and yet because of this—because of the fact that both

parties in a medical procedure want it to work and will try anything, we get led to excess. So my question would be don't you think this is still in operation right now? And how do we control it and be sure that we're not putting the public and patients through unnecessary, harmful procedures?

SIDDHARTHA MUKHERJEE: Particularly in cancer, I think, and this is why this becomes the subject of this book, particularly in cancer, you know this metaphor. Cancer is a metaphorical disease in a very deep way and we talk a little bit about it. The word cancer comes from "crab," and the reason is as the book will explain, the reason is Hippocrates, thought that cancer, he thought that these tumors which were sitting under the skin, with blood vessels around them, reminded him of a crab, of a crab crawling under the skin in its peculiar unnatural movement. The reason I bring this up, of course, is that the metaphor of war very quickly permeated cancer, even long before the phrase "the war on cancer" appeared, famously in the New York Times, in an advertisement that Mary Lasker—Long, long before that if you track back the history, the metaphor of war had already permeated cancer. Let me tell you a story that is illustrative, and I guess the long answer to your question is how is this metaphor of war eventually collides with this idea that you have to do the most in order to do the best by your patients, therefore leading to the invention of radical surgery and radical chemotherapy.

Let's pause for a second at this metaphor of war. I don't know how many people—one of the things that I discovered in this book was, of course, that the very first chemotherapies came from war gases and it's a fact that's sort of lost in—when, you know, you go to a

hospital and there's a sanitized cancer ward even still today no one tells you that in fact that "Ma'am or sir, this drug that we're going to inject into your body is actually a chemically variant of war gas," and the reason was during the bombings of Bari, for instance, the Bari harbor, pathologists discovered that war gases were able to decimate the white blood cells and leave the rest of the body injured but not decimated, and therefore there was the idea that if you could use that war gas in a slightly different manner, you could kill malignant white blood cells and so forth. That's just one example of how literally chemotherapy and anticancer therapy grows out of metaphors of war.

Now these metaphors, of course, then become very much part of the consciousness of the doctor and the patient. It's not just one—both doctors and patients want to fight the battle, right, and in that moment of fighting the war on cancer, fighting—battling your own body, of course it's very hard to say, "Now let's stop, let's retreat the front, let's move backwards," and therefore this dense idea of—this dense metaphorical idea of fighting cancer still permeates our culture. And can we move back from it? Yes, we have to some extent, I would say, even in the practice of oncology today, but it's really, really tough.

NICHOLAS WADE: Well, I'm just wondering of that sort of present-day examples that either now or in a few decades people might look back on and say, you know, we're still fighting a war in the wrong way. For example, there are several screening procedures that are sort of so marginally effective that each year there's a new study saying screening for breast cancer, mammography is successful or it's not successful, this age-group should do

it, this age shouldn't. For men there's the PSA test for prostate cancer. Some studies say that it's marginally effective, some say it's marginally ineffective. Aren't these examples of mass screening ones where we have gone too far, where we'd be better off waiting or not doing anything?

SIDDHARTHA MUKHERJEE: Well, it depends. It depends on the kind of cancer. It really depends on which kind of cancer one is talking about. The problem with screening of course is that I mean there's been so much reported recently about mammography, so let's just talk about mammography. The problem with mammography, as we know, is that it's not a great tool, but unfortunately it's probably the best tool we have right now for screening. Would we and can we invent better tools? Absolutely. Probably can invent better tools. Already coming up with better ways of visualizing, of visualizing tumors in the breast, for instance. The fundamental problem with mammography is that we need to find a way to restrict the population into a high-risk versus low-risk population, and that metric, how to find more intelligent ways of screening, just have not appeared so far, and that's been a constant trope that runs through the book.

The other problem with mammography, another story that's told in the book is how difficult it was to run the trials that finally proved that mammograms saved lives. And one particular story strikes me as very moving actually. And the story happens in Canada, a massive trial, a massive highly funded trial to prove whether mammograms saved lives or not, and there were manuals passed around asking people to—there was a protocol passed around in Canada saying, "Well, this is how you're supposed to do the trial," and

one small little thing happened in the trial, which no one really noted, which was that—the trial was randomized, so you'd have random assignment, so a woman would walk into the clinic and would be either randomly assigned into a nonmammographic screening or a mammographic screening, a perfectly fine way to do things, and the way it is they decided to randomize is that they would write names alternately in a notebook—they would take a little notebook and say, "Well, if your name is on the first line, you get the mammogram, and if your name is on the second line, you don't get the mammogram," and so forth. Seems like a reasonable way to randomize.

It turnd out that when they unveiled the randomization process in Canada, it was completely nonrandomized in the sense that, for some reason that they couldn't really figure out initially—women with high risk for breast cancer were put into the mammogram group, and women with low risk for breast cancer were put into the nonmammogram group, so they really started scratching their heads, and they did something very intelligent: they started asking the nurses, the secretaries, the assistants, "Well, how *did* you randomize?" And an amazing thing happens there what happens is when they went through some of these testimonials, they would say, "Well, this woman said to me, 'I have a high family history of breast cancer,' and I felt really bad for her and I thought I would put her in the mammogram group," **(laughter)** and this basically was, I think, I don't remember the exact number, I think this was a seventy-thousand-women study, a seventy-thousand women study, which was essentially undone by compassion.

So here is a study where you're trying to be as cold, as clinical as possible. And a tiny mistake was made, there was no reason to randomize, you know, using a notebook, this even other stories, some people said, "Well, I waited my turn in the notebook, I let other people pass by so that I would fall in the right line so that I would be screened by mammography," so once again, you know, number one, the road to hell is paved with best intentions in this case, and that entire study had to be redone, so just one more story from that book.

NICHOLAS WADE: So let me come back to this question of optimism and the war and how it's going. I was very struck that by after I read about sort of three hundred pages or so of the book you introduce the character of John Bailar who is a very distinguished biostatistician, and Bailar in response to all these sort of "wars" that were going on and the enormous funding boost that the war on cancer attained for cancer research. Bailar decided to look at the statistics and ask if the cancer rate in the U.S. was going down and he wrote a celebrated article, which Sid describes, and the answer was, "No, the rate is not going down, if anything it has increased, and we are not winning this war," he said, and then you read on another fifty pages or so and Dr. Bailar appears again ten years later, again with the same very gloomy message, I mean it's slightly more nuanced this time, but still basically he's saying, this is statistics up to, this was ten years ago, up to '97, so Bailar is still saying, "this war is not going well," so despite the few rare cancers against which we've had surprising success and the improvements of mammography and surgery and chemotherapy and all the rest, nonetheless, none of these procedures have actually made any difference to the bottom line as far as he can see. So I'd like to ask is

the picture still as gloomy? As far as I could see Bailar hasn't updated his—has anyone else done so and if so is the bottom line improving or not?

SIDDHARTHA MUKHERJEE: So a couple of thoughts. I called Bailar the "nation's reminder in chief of cancer," because every ten years he comes out of Chicago—that's where he studies—and he performs this kind of reminder act. He's sort of like the—he's the bean counter, he tells us—he's the moral conscience of epidemiology. I've met him. He's a wonderful, cantankerous, powerful, brilliant man, but Bailar's analysis, very important analysis and it really sort of in some ways threads the book. Let me tell you the bottom line, and I'll tell you a little bit more about it. The bottom line is that it is now quite clear that the more cancer-specific mortality in the United States, having risen continuously for several decades, has plateaued and is finally turning around, and finally turning around by a significant number. The most recent numbers I've seen is—you know, there are various ways you can compute this metric, but on the order of about people say, and as I say, there are various ways, about two hundred thousand to five hundred thousand lives saved, and by that I mean you can compute the number of lives that are potentially saved by the advances or changes in the cancer-specific mortality. That's a big number.

NICHOLAS WADE: Is this just people smoking less?

SIDDHARTHA MUKHERJEE: So it is not just people smoking less, although that it is a large contributor to it. It also contains a little bit of contribution from screening,

mammography in particular. It does have a contribution from chemotherapy, actually, tamoxifen in particular for estrogen-receptor-positive breast cancer, and chemotherapy, the kind of traditional chemotherapy, absolutely, has also contributed to a little bit of this plateauing, so a combination, and I quote Donald Berry, the statistician, who's a very close colleague of Bailar's, who says no one has labored in vain. These changes are not just skimming, these are deep, meaningful changes in lives saved.

So just backtracking a little bit, Bailar, one very interesting thing we find out about Bailar in this book is how tricky it is to measure progress in the war on cancer, so you might naively say, "What is progress in the war on cancer?" Well, you might say, "Well, I'm going to take—I'm going to measure, I'm going to measure, let's say for breast cancer, I'm going to measure the fraction of women who are alive at five years starting in 1970, comparing to 1990, comparing to 2010." And let's say you find the fraction increases from twenty percent to thirty percent to fifty percent. So you go home happy, you're very happy, because now you say, well now you've made, "twenty percent of women were surviving at five years in 1970, that number is fifty percent now, that must mean progress."

The problem, of course, as you know very well, is that screening has occurred, and so what might have happened really is that you've really shifted the diagnosis time of a woman backwards, such that instead of being diagnosed, instead of being diagnosed when she was sixty-five years old, she is now being diagnosed when she was fifty-five years old, and she seems to survive an additional ten years, but in fact all that you've

really done is moved the plot of diagnosis backwards, I don't know if that fully—you know, if that's obvious. But that is an incredibly tricky problem. Because now you have to take that problem and multiply it by every kind of cancer, right, and you have to then find a mechanism to analyze every kind of cancer, and then ask the question, "Well, you know, now is there increased survival?"

So that's one problem, and then the second problem, just as equally tricky, very interesting problem, too, is that the American population like any population is aging overall, and cancer is an age-related disease, so the population in 1990 is different from the population in 1970, the population in 2010 is different from the population in 1970. How do you then—how do you then compute? And what Bailar does is something very ingenious. He essentially—he ignores this idea of survival, he says, "I'm not interested in survival percentages, because that's going to be a sloppy metric," so what he does is he says, "I will only take cancer mortality, people who have died of cancer, regardless of when they were diagnosed, I will take only people who have died of cancer." That's one innovation. The second innovation that he makes is that he finds a mechanism to statistically shrink all these populations such that they become identical. So now you're identically comparing 1970, 1990, and 2010. Again, let me emphasize this is a very complicated process, but if you do all this, and you do it accurately, you come upon these curves, and these curves very clearly tell the message that the war on cancer was not—*is* not a dud, that there has been progress made, and it continues to be made, and it declined for I think about ten straight years off that upswing.

NICHOLAS WADE: One of the most successful approaches to cancer we've had has been with a disease called chronic myelogenous leukemia, for which we have a very specific drug called Gleevec, so I wondered if you'd like to tell the story of Gleevec, because I want to make a point about it. But I'll have you tell the story first.

SIDDHARTHA MUKHERJEE: So the story's in the book, it's sort of a late part of the book, it's in a chapter called, or a section called "The Fruits of our Long Endeavors." This is a letter that Mike Gorman wrote to Mary Lasker, the chapter's titled after that, in which he says—Mary Lasker dies late in the book, and just before she dies or soon before she dies, Mike Gorman writes her a very moving letter saying, "now at last we're seeing the fruits of our long endeavors." Just to remind us how tragic that was—this was a woman essentially who had to wait from 1970 to 1990 before she could see the fruits of her long endeavors. While she was waiting for all of this having put all of this energy into the project, meanwhile everyone was saying the war on cancer is a complete failure, it is a disaster, et cetera, et cetera, and Mary Lasker really retreated back and took herself out of these sidelines, until as I said the turnabout began.

So the story of Gleevec, fascinating story. So Brian Druker was a young fellow, recently finished his fellowship in the 1980s at the Dana Farber Cancer Institute, was looking for a project, and here he had leukemia, chronic myelogenous leukemia, which was lethal. Its only therapy was a variation of a drug that would cause all sorts of awful side effects and was barely effective, essentially, and then patients would die, and the other possibility was to do a bone marrow transplantation, and had awful side effects, and it was

successful, but in a limited number of cases, so that's the background of this leukemia, chronic myelogenous leukemia.

So far away in a company that eventually would become Novartis, a completely separate group of chemists was trying to find drugs that would—that could change—a certain family of proteins which are important in heart disease. So they were trying to find—actually they were trying to find clot busters, among other things, they were finding various drugs to thin the blood and change the way heart disease was managed, and they had one very critical insight, and that is that this family of proteins that they were trying to target with this group of chemicals happens to have—there is one chemical that was actually targeted, and sea bacteria for some reason make a poison that would kill this family of protein.

So these chemists, sitting in Basel in Switzerland were taking this very primeval molecule that they'd extracted from sea bacteria , a terrible poison, actually, a terrible poison, and they were trying to make little variants, it was like playing merry-go-round, they were trying to make little molecular variants around this bacterial poison trying to see, "Well, what will hit only some of these proteins and not others such that they could not kill a patient but only affect the heart cells?" So in the process of doing this, they found one molecule that would effect one protein, but of course unfortunately this protein wasn't very active in the heart, so they had essentially abandoned this project. But Druker, who was an oncologist, figured out that a cousin of that same protein was active in chronic myelogenous leukemia, and so he called up—he essentially called up—he

called up these chemists in Basel and said, “You’ve got this freezer full of useless chemicals, and I’ve got this ward full of dying patients, could we not find a way to get these chemicals into these patients, because you haven’t found your drug, but maybe somewhere in that big freezer is lurking the drug that we really need for these patients.”

And it turns out that one of those drugs is an exquisite poison to the gene that drives chronic—the protein that drives chronic myelogenous leukemia, the protein happens to be called bcr-abl, and it’s a very beautiful phrase in the book, chemists describe it, chemists are incredible poets, and he says, “Gleevec was like driving an arrow into the heart of bcr-abl,” because he crystallized it, he crystallized that protein, and he could see the drug sort of sitting in the heart of this protein, this protein that drives this leukemia. And so Druker is interviewed in this book, Druker tells me that the first time he introduced this drug into patients, he thought they were going to die, because there was no way to know whether this would only poison that one protein, or if it would poison the rest of the body, you don’t know. So he sat—he said he has this very wonderful memory. He says he sat by the bedside of the first patient—he was a train conductor from Seattle, who was terribly ill—and Druker sat by his bedside giving him—inching up dose by dose, he gave him twenty-five milligrams, and waited, and said, “Well, okay, he survived, I’ll now give him fifty milligrams,” and he crept up dose by dose by dose and by the end of the day the man was still alive and, of course, a week later he had gone into the most profound remission ever in the history of CML. So and then subsequently this drug has become the exemplar of a new kind of cancer medicine, and, you know, that’s the story of Gleevec, the background.

NICHOLAS WADE: And let me add a few details so I can make my point—the story starts even earlier as you describe in your book—it starts I think in 1962 with the first observation that people with leukemia had a very curious chromosome, it's called the Philadelphia chromosome, which consists as they worked out of one protein, one chromosome that had got broken and then it'd had been knitted back in the wrong place, it had been knitted back to another chromosome, making a very odd-shaped structure that you could see in the microscope, and this—this wrong joining in fact fuses these two genes, the bcr gene and the abl gene, together in a way that cuts off a vital part the cell uses to restrain this protein so that research sort of—and everything that Sid and I have been describing to you took place over about sort of fifty years and resulted in this very precise therapy, which itself is not perfect, because people unfortunately after these miraculous remissions do then become resistant to Gleevec, but we understand this cancer so well that we now have several backup chemicals that also hit the cancer. So for these patients, it's not a very common disease, in fact it's so rare a disease that Novartis originally didn't want to put money into this drug—for these, for this small number of patients we've got a really good solution.

SIDDHARTHA MUKHERJEE: Can I talk to you for one second about that because it's an interesting—so you know, I sort of talked about this, so you know what's interesting about Gleevec, this is in general an interesting epidemiological observation. So there's small numbers of patients, but if you give—if they're on Gleevec, of course their life span increases, and therefore the prevalence of patients increases in the

population. So in fact there was a time when you could rarely see a patient with CML, because they were dying so quickly, so you would meet and they would be dead in three or four years, it was a rapidly accelerating leukemia, it's called "chronic," but it's chronic only by the standards of leukemia, which is a very rapidly escalating disease. And then slowly as Gleevec comes into the world, I mean, Druker describes this, you'd all of a sudden start hearing of patients—"I have chronic myelogenous leukemia," "my grandfather has chronic myelogenous leukemia, or my neighbor." And it's because essentially what's happening is these patients are living longer and longer. And the prevalence is rising.

What's amazing about the prevalence is that prevalence is estimated to rise to about two hundred and fifty thousand patients in the world, so essentially there's a metric that says each one of us knows about a thousand people, essentially within a couple of years every one of us in this room will have one person in their social network who is being kept alive by a new-generation, molecularly targeted cancer drug. So, you know, that's change.

NICHOLAS WADE: Wouldn't you agree that there is quite a big contrast in two approaches that you describe a lot in your book, and one approach is the sort of brute force approach of radical surgery, very high-dose toxic chemotherapy, the other approach sort of starts very small, looks at the cancer cell in a very fundamental way, and produces much more satisfactory cures. Does this tell us anything about research policy or the practice or medicine? Doesn't it perhaps tell us that you are more successful sort of

holding off on sort of brute force approaches that you don't really understand? You're better waiting until you really understand the system at a fundamental level?

SIDDHARTHA MUKHERJEE: I think the sad story there and which is also a very deep tension in the book is you cannot tell a patient, "Hold off, I'll get back to you in five years, when I know the solution to your breast cancer." You can't go to someone and say, "Well, let me go back, take your problem to the laboratory." Of course this is happening, scientists are doing this actively while this process is happening. As an oncologist, you can't go and tell a patient, "Hold on for five years, I'll get back to you, stay on the line." Because that's not how medicine works. There's an urgency, there's a potency, there's a propulsion in medicine that needs to be answered *now*. Part of the tension, of course, is absolutely, you know, figuring out the molecular mechanism of the cancer cell would eventually become the fruits of long endeavors in this book, and yet for patients who were in the 1960s and 1970s there was no other option but Cisplatin, which is, by the way, a remarkably effective drug in some kinds of cancer, or, you know, injecting chemical variants of war gases, you know, and doing so "by brute force," as you describe it.

NICHOLAS WADE: Let me ask about some—I'll make one more point on this issue. Being an oncologist must be a terribly difficult job—you make very difficult decisions. You refer to it in your book as a "dismal discipline."

SIDDHARTHA MUKHERJEE: It can be.

NICHOLAS WADE: I was reading today of how many people are still undergoing chemotherapy on the last days of their life, a very high percentage. I know you can never—no physician can ever project when a patient will die, but it seems to me an absurd situation that people should be submitted to these very fierce treatments when (a), they are hopeless, and (b), the patients have a finite amount of time to live. You have a very moving chapter where you describe the growth of the hospice movement and Cicely Saunders. Shouldn't oncologists be more aware of the fact that surely that a right time comes to say, "Now you should go home or to a hospice and not submit yourself to these fierce treatments"?

SIDDHARTHA MUKHERJEE: Absolutely. And make no mistake about it, the invention of the hospice system was the invention of a radical new kind of technology. It is as much technology, as much—it was the product of as much intellectual depth and thinking outside the box as the invention of Gleevec, to some extent, and I actually make this point in the book to remind us that there is nothing fluffy about palliative care—it's actually the most difficult kind of care that oncologists and actually the experts in palliative care, nurses, provide to patients.

The story is incredible—the story, which—I got the story from looking at Cicely Saunders's papers. Cicely Saunders was a British nurse. She trained as a nurse, and then in the middle of her life, actually decided to retrain as a physician because she—at a time when it was very, very hard to be a decision maker as a nurse, in particular in Britain.

And she had tended to a man, a man from Poland, who was dying from cancer. And instead of going through these surgeries and chemotherapies, the man, in collaboration with Cicely Saunders, had decided to opt for palliative care. And the man had left her five hundred pounds and a letter which said, "I want to be a window in your home," and that was his last wish, he said, "take these five hundred pounds and make me a window in your home."

And for Cicely Saunders that phrase took on a kind of an incredibly amazing meaning, because she then went into the wards in England, typically in the East—she describes them in the East End, where these cancer patients were essentially pushed aside to windowless rooms, there was no place for them, they had become the pariahs of oncology. They had become—the rhetoric of—the rhetoric of progress didn't fit them, clearly, they were not making progress. In fact I very self-consciously called—there's a middle section of the book, which is probably one of the largest sections of the book, I quote one of these women who said, who said to her doctor, it's a chilling quote, "will you throw me out if I don't get better?" she says at a time, because if I don't get better, I'm not meeting your expectations in the so-called war on cancer, will you now remove me from the wards?

Saunders, Cicely Saunders, says to herself, "Well, wait a second, what I will do is that if oncologists cannot fit these patients into their rhetoric of progress, I will physically remove the dying from the wards, I will take them to a different place, and she did so by inventing the hospice system; she called it—she coined the term "palliative care." And

there's a lovely line that I quote from her, a lovely paragraph that I quote from her in the book, which says, "This is—palliative care is not the negative of treatment, it's not as if—it's not the antimatter to the matter of therapy, but, in fact, it is part of treating patients, and if you don't learn it, then you will not learn something about cancer," and so, as I said, I made a very concerted effort to put it right bang in the middle of the book just to—and named a major section of the book after it just to remind us of the role it has played in this incredible history. So, and I often tell people palliative care is as much an invention as Gleevec, make no mistake about it.

NICHOLAS WADE: I was struck by a passage at the end of the book where you mention a discovery that was probably being made at the end of the writing, about the theory of cancer stem cells, so this is the theory that just as each organ in the body has its sort of dedicated population of stem cells that sort of throw off the mature cells of which the tissue is made, that maybe this is true of cancer as well, and if so it has rather important implication, which is that most chemotherapeutic drugs are designed to target the mature cells, so if in fact the cancer is being caused by the stem cells, which are quite different in nature, then all chemotherapy has been targeted at the wrong place, and now this theory is still sort of being tested and may be true or not true or sort of partially true, but when someone comes out with a theory like that implying that, you know, the previous hundred years' worth of research has been focused on the wrong target, you begin to see how very little we still know about this disease.

SIDDHARTHA MUKHERJEE: Yes. Absolutely. And, you know, the cancer stem cell theory, I've written about it, it's in the book, is really a kind of evolving frontier, we know so little about it, but if it's true it really means revisiting much of what we know about what cancer is, and one feature that emerges in the book and again it's a kind of a metaphorical feature or a poetic feature, is that every time you go back to look at what cancer is, it turns out to become—it turns out to resemble normalcy more and more. So the resemblance between the development of normal organisms, normal organs, is being recapitulated in a very profound sense in a cancer cell.

Now, I think that tells us something relatively profound about the human body as a multicellular organism. It also tells you something profound about our mortality, I think. It tells us something about the fact that the very genes that keep us going, that allow us to behave and live as multicellular organisms, distorted versions of those very genes can cause cancer or, another way to put it is that the very processes, such as stem cells, that allow regeneration to occur, when distorted, can allow cancers to live and survive. And I think, of course, that that is a scientific fact, that one of the things, I think an important feature in the book is the link between science and metaphor, the link between science and a more profound way of thinking about the human body is so close that you can't think about cancer without very quickly thinking about this alternative way of thinking about cancer, which is, you know, "Is cancer the night side of our life?" The book opens with Susan Sontag's quote, "Illness is the night side of life," and by the end one of the questions that I raise in the book is although there's a large heterogeneous body of diseases that we call cancer, they happen to share these incredible phenomena—could it

be that cancer is the night side of our mortality? And that's a question that's sort of raised in the book and, of course, that's a question that's far beyond this book and also far beyond cancer itself.

NICHOLAS WADE: Is the very aggressiveness of the cancer cell shows how robust our ordinary cells are and they've been evolving over three billion years, they're very hardy creatures, and it's only because they're so well behaved in our normal body that we don't appreciate how sort of vital and eager to survive they are.

SIDDHARTHA MUKHERJEE: And of course the important feature for all of this is that's just scratching the surface. Right? Outside the cancer cell sits the host, and the host has the immune system, blood vessels, a psyche, a personality and so forth, and so how does one take, how does one build complexity out of this—out of simplicity? One very important feature in the book, and I think for me a very important feature in writing the book, was to remember at the same time, to look at the microscopic, the cancer cell, but also place it in the context of the macroscopic. One thing we talked about a little bit before was one really driving, propelling force in this book was to find the stories of patients. Who was patient zero for X disease?

And one story that I know we talked briefly about, is I became—the book is dedicated to Robert Sandler, this child who lived from 1945 to 1948, and I just wanted to tell you a story about how I came about Robert Sandler. Robert Sandler was one of the first children to be treated with chemotherapy, he was one of Farber's first patients, and when

I was reading—when I was writing this book, I was trying to write about who these patients were, but, of course, I didn't know—there was no sign of Robert Sandler, he died three and a half months after he'd first been detected to have acute lymphoblastic leukemia in Boston, and he—I knew he was in Boston, but the only thing I knew is his name was R.S.—that's it, because in the paper, it says R.S., nothing more. So I became obsessed with finding R.S. Finding R.S. became my mission in writing this book. So I started sending out e-mails on various listservs—I would post stories saying, I knew he had a twin, I knew Robert Sandler had a twin. But I knew nothing more about him. "If you had a twin," I would say, contact me, "who died of leukemia in 1948, who was treated at the Dana Farber Cancer Institute, contact me," nothing, no replies.

So I got kind of dejected and I went to my—I went on vacation to my parents' house in India, and someone said to me, "You know, there is a biographer of one of the colleagues of Sidney Farber's who lives a few doors down from you," a few blocks down from the house, my parents' house, and so, "Fine," I said, "what do I have to do? I'll go and meet this biographer." So I go to meet this biographer, now we're a thousand miles away from Boston, I go to meet this biographer and he said, "Well, you know, in 1960, I traveled to Sidney Farber's institute and I have a roster of his patients he was treating, and in fact I have these cuttings, I have these articles that I cut out from 1948, and in fact I have a picture of a boy called Robert Sandler."

So there I was, a thousand miles away from Boston, where this story occurred, trying to—becoming obsessed with finding Robert Sandler, and yet through a mixture of

peculiar serendipities, I found a picture. And then, I was just telling Paul, one nice thing about having libraries and the reason that we love libraries, is that I could then go to the Boston Public Library and look through the records of deaths, and I could look through the entries, because now I knew his mother's name. There's a picture of Robert Sandler in the book, incidentally, that same picture that I got from the biographer, his mother's name, and I could find where he lived, and then fifteen or twenty minutes later, having gone around the world, fifteen or twenty minutes later I could drive to the home where the first child with leukemia was treated, thereby launching this history.

So for me that became a metaphor for writing the book—that there are ways in which you can write books about a disease. We began this conversation about oncology being a dismal discipline, but its history is furrowed, if you will, not only by dismal things that are done on human bodies but by these incredible stories of hope which come and flicker away and then sort of lead to these enormous things, including famously the war on cancer.

NICHOLAS WADE: Well, I've had great fun grilling Siddhartha without putting much of a dent in his basic optimism. I don't know if anyone else would like to share the fun. Shall we go to questions, Paul? You sir, from the front.

Q: It's said that prostate cancer is not the most prevalent cancer in men, it's the second most, after lung cancer, and finasteride allegedly is a drug that will inhibit prostate cancer and yet it's widely underutilized and it does have that effect, I've read that. There's also

another drug which will also inhibit the developing cancer, and it's also not utilized, and I've forgotten what that is. But could you comment on why there is that underutilization?

SIDDHARTHA MUKHERJEE: The trouble is, and Nicholas—the *Times* has covered this story—the trouble is that although if I remember correctly that although finasteride does inhibit the growth of some prostate cancers, when prostate cancers do grow out of men in which finasteride has been used they can be often highly resistant, so we don't know if we're doing good or harm in that situation. So we essentially need to run a large trial looking at mortality with the use of preventive—finasteride as a preventive. The problem is the trial has been plagued with this observation—are we essentially—might we be actually doing more harm?

Q: You say, when the prostate cancer breaks through—

SIDDHARTHA MUKHERJEE: Well, we don't know if it's breaking through or not, we do not there are occasions, or occurrences, of resistant prostate cancers, in fact, more fatal, more aggressive variants, based on pathological variants of prostate cancer that emerge in patients that have been treated with finasteride as preventive therapy. This goes back to the case of mammography, you know. How does one run a preventive trial which carries deep risks? You know, does one, how does one even give informed consent to a preventive trial that carries a risk?

NICHOLAS WADE: There's a question here.

Q: Did you ever find anything about Robert Sandler's twin?

SIDDHARTHA MUKHERJEE: A lovely question, no, never found him. There's a website called—he lives on Dougal Avenue, so I when I finished the book I sort of wrote a little note to myself, and a little sort of e-mail saying, I finished this book, if you ever find it, read it—I have a picture of him, I have a picture of the twin as well . . .

Q: If he didn't get this disease and he has the same identical genome **(inaudible)**

SIDDHARTHA MUKHERJEE: Absolutely, yeah. There are many such cases of twins that do and don't develop various forms of cancer, leukemia being one of them. The simplest reason, that we know of so far is that cancer is a disease in which based on the interaction of various—based on the interaction of mutations and cells, so even though you have the same background genome, mutations in one can cause cancer, the other genome might be normal and therefore you can have identical genomes, but cancer evolves in one and not the other.

Q: In terms of your of that the cancer ones are a better version or a normal—I have the impression and which I don't have any data to back up, but other people have had the same impression that smart people get brain cancer at a higher rate than not-smart people. Now, there's an obvious thing that you don't hear stories about, "Well, yes, and this person's brain was destroyed by cancer, but actually nobody really noticed because it

wasn't very good to begin with," but it seems to fit if the people with good brains had more, you know, regeneration, had more glions growing in there or something like that, does this—and I mean it's very, very hard to find something like that in Google because they haven't figured out the right words for it. Do you have any impression about that?

SIDDHARTHA MUKHERJEE: I have no impression, but let me tell you a story which is kind of interesting. There was a massive trial in England, followed by one in Scandinavia asking the question do cell phones cause brain cancer? Remember this trial? Very interesting story. So they actually did something very interesting. They said, "Well, we'll ask whether you developed brain cancer on the left side of your brain and you happened to use cell phones on the left side of your brain." And in fact when they first ran this trial, the trial was strikingly positive. So people who used—people who had cancer on the right side of their brain happened to use cell phones on the right side of their ear, and therefore the association was so striking. Then the investigators did something interesting, they said, "Okay, well, let's ask those same people if they also happened to use cell phones on the left side of their brain," and what they found is that there was a decrease in people who had cancer on the right side of their brain with cell phone use on the left side.

Now, what this really means if you think about it—the book goes through this—what's actually happening is they're recalling incorrectly. They're saying to themselves—if a patient has a brain cancer, for deep reasons, you know, for deeply moving reasons, they think, "Oh, my God, I really use, I constantly use the right side of my ear, that must be

the link." And, you know, it's of course moving and funny, but this is how deep epidemiological biases can run. So when they reran the trial, and they asked the question more accurately, it turned out there was no link, at least with the cell phones that were in use right now. I can't comment on your question about smartness, I don't know if that exists or not, but I think we have to move on to another question. Sorry about that. Yes.

Q: You said something which made my heart jump. You said something about multicellularity, and then I started thinking about the evolutionary tree of life and about phylogeny. I was thinking—when did cancer evolve in the tree of life, do sponges get cancer, is it just a disease of multicellularity, or are there some organisms that don't get cancer? And if they don't, then have people been doing research on using them as a paradigm for thinking about how to cure cancer?

SIDDHARTHA MUKHERJEE: That's a fascinating question—what's the most primeval organism that gets cancer? So it turns out that fish certainly get cancer. Len Zon, among other people, at Harvard has launched this incredible series of experiments in which he is analyzing the growth of melanoma in fish. This is a disease that is very lethal, and to have a simple animal model for this was a real challenge for a long time. The problem is, of course, as move back further and further in evolutionary phylogeny, you start getting organisms that are what I would call loosely multicellular. By "loosely multicellular" I mean that, unlike the human body in which every cell cooperates and collaborates to create the multicellular organism, by the time you get down very early in phylogeny, it's more like a republic, as it were. These animals have cells that are very—

they are often self-preserving and they have gotten together, as it were, to create an organism, but really the organism is a loose confederation of many cells that happened to have come together because it gives them a certain series of evolutionary advantages.

Now, somewhere between that phylogeny and the true multicellular organism is probably where cancer really begins to arise, and it arises, again, because, and this is what's amazing about the development of cancer—if a tumor was so quick in evolutionary—in the history of an organism—that it would instantly eliminate that organism, then it immediately would be selected against. Such a tumor or such a gene would never survive evolution. So a cancer has to live, then, in this peculiar situation in which it does not annihilate the host before the host's reproductive fitness is completed, but I mean that very loosely, of course. I mean that the genes that cause cancer cannot be so easily disruptable such that in early embryonic biology the embryo begins to explode with cancer, such a gene would be immediately selected out, but the gene essentially may retain enough vulnerability that many years later, after the organism has reproduced, it can still have the capacity to break out into cancer. I don't know if that really answers your question.

Q: I think you covered an enormous field of endeavor, from discovery, early detection, to treatment, to targeted therapy to palliative care; it's a wonderful exercise. I happened to have known Sidney Farber, and have been in the field myself for fifty-five years. My take on his role in it is somewhat different than yours, but that's really not important. What is important is the number of people who were involved in the discoveries that brought us

the cure of leukemia, and I think it's a lesson. Mr. Wade has covered this from many different angles in medicine. But it takes so many different discoveries to bring us to a cure, and I think what's so encouraging to me is that now we have the genetic code. We know something about the genes, we know something about ability to target—fine molecules that target specific genes that drive an arrow into the heart. I think that we're going to see rapid acceleration of this progress in the near future, so I'm very encouraged about that.

NICHOLAS WADE: I think it does agree with the prediction we just heard that there will be substantial progress in the past.

Q: I think would you agree that one of the goals now of cancer therapy is to make it from an acute disease into a chronic disease, more or less as we're doing with AIDS—not to say that we shouldn't cure it altogether, but if that's not possible . . . ?

SIDDHARTHA MUKHERJEE: Absolutely. I think this is very much part of the evolving frontier of cancer. I think, I would make the argument that for estrogen-receptor-positive breast cancer in some cases it has become a somewhat chronic disease. That doesn't mean that we should stop focusing on curing cancer, particularly various forms that have no curative regimens right now, but it is true, and if you're around in the world, culturally, you can sense it. And I said to you, as we talked before, one of the results of the conversion of a disease from an acute disease to a chronic disease is that ironically its prevalence begins to increase in the world, and so the cultural shadow of

cancer is of course increasing, it is dilating, because it is becoming, in many cases, a chronic disease for many people—people are surviving fifteen, twenty, thirty years.

I have a very interesting memory from my own residency days of the beginnings of the moment—I trained when the AIDS epidemic, particularly in America, was reaching its sort of tail, as it were, moving of course out, whirring out into a global epidemic of a completely different character. I have a very vivid memory, I have actually written about it, I have a very vivid memory of the first patient with AIDS who came into the hospital with a complaint that had nothing to do with AIDS. He was having a myocardial infarction, he was having an MI, he was having a heart attack, like any of us will at some point in time in our lives given the statistical prevalence of heart disease. **(laughter)**

For me that was a very moving experience to come to walk into the bedside and record on a piece of paper. When you take a patient history, you have a little part that says "past medical history," and you record other things that the patient also happens to have but are not particularly pertinent to this diagnosis. So I remember writing, you know, "patient has presented, sixty-year-old man presented with a heart attack, needs x, y, or z therapy," and I remember very vividly, poignantly recording in his past medical history a history of HIV positivity since the last ten years. That was for me kind of a moment in which I sort of took a step backward and said, "something has changed so dynamically, so dramatically in this," and, you know, in the practice of oncology, you can do that with children with acute lymphoblastic leukemia, you can say, you know, "here's a child with

acute lymphoblastic leukemia, cured in 1968, living in our midst," very, very moving moment.

Q: Thank you for all of this very important work, and I'm also harking back to—I heard Atul Gawande recently, there's some parallels between you're both doing and geting away from the diseases known as cancer. Is there such a thing, or should there be such a concept as the philosophy of cancer, the psychology of cancer? Is there some complementary, the mind/body connection element to this that would be useful to humankind?

SIDDHARTHA MUKHERJEE: Again, variations of this question are very important and get asked all the time, you know, "What role does the mind play in cancers?" The quick simple answer to the question is well, when you're a patient and you're going through therapy, there is no more, there is no greater reservoir of resilience than your mind. So that people who say, "The mind has nothing to do with cancer," that's absolutely wrong, we know that it does, in this sense, in this sense that you know, the way your psyche deals with illness is a profound and deep way in which human beings mobilize, they resurrect the deepest parts of their soul—Sontag talks about this several times in her book *Illness as Metaphor*.

Now, the other question is, "Well, what does mind or stress have to do with the development of cancer?" The quick answer to that question is we don't know yet. We've never done—we haven't done sophisticated enough studies to know. The single study

which I think is the most provocative study about this is the recent study, in which, and again, I think has very profound consequences, was a study in which mice were either put in what was called a “stimulated environment” or a “nonstimulated environment.” And the development of tumors that were injected already in the mice was observed in the mice that were in the highly stimulated versus the nonstimulated environment. And, very surprisingly, the mice in the stimulated environment—surprising maybe not for some other people, but experimentally very surprisingly—the mice in the stimulated environment developed cancer—they developed smaller tumors, and often they actually developed no tumors. This is a very artificial model, and, in fact, the researchers could track back a single hormone, actually leptin, the single hormone, and could make the argument that leptin was controlling whether the mice in the nonstimulated environment versus the stimulated environment had larger or smaller tumors.

So I think that’s opened up an enormous field—this is a very busy field right now which is asking that kind of question, but it’s asking it in an experimental way, and that’s very key I think. One thing we’ve talked about so often is that in a field where there’s so much hope and so much optimism, it’s counterproductive very quickly—that hope and optimism becomes counterproductive, you get false hope and false optimism, and this has been a marker in the field of stress and cancer. This has become—this has plagued the field linking stress and cancer. But if you now go backwards and start unpacking it, with very carefully performed experiments, you can reinvent the field, and that’s what happening, I think, now with these experiments.

Q: You've written not just one book but many books within a book, and one of the threads in the book that you haven't yet had a chance to touch on in this forum is the intersection of politics and public policy with cancer research and cancer science and the ways in which these two very kind of different worlds exist in a kind of dialectic with one another. If you were in a position, you know, to do so almost kind of by fiat, how would you—how would you think about reorienting or altering the sort of public policy framework that exists in a kind of conversation with cancer research?

SIDDHARTHA MUKHERJEE: Well, that's a very important question and of course has to do with Mary Lasker's mission in some sense, right? Mary Lasker was this force, she *was* the fiat, and if you didn't believe it, you'd better believe it. But the question is what happens now, what happens today? And I think one of the things that the National Cancer Institute has begun to realize is that you require—the role of the translational science has become more important in cancer biology. There is now money being poured into creating a person who literally can move from the clinic to the laboratory and from the laboratory to the clinic to translate the incredible wealth of knowledge that is coming out of the human genome and the cancer genome and various cancer scientific projects and accelerate the translation of that into real medicines.

One big problem here is that the conversation that we have—the public conversation that we have with the pharmaceutical industry has broken down in a very fundamental sense. I do think that there are—it is almost as if there are two pharmaceutical industries. There's a pharmaceutical industry that peddles drugs that are toxic, often that are with

hidden under bad data, and eventually lives with spasms of guilt, but lives for about five years until that secret is discovered and essentially packs up its bags and leaves. That is a pharmaceutical industry, we have seen that pharmaceutical industry, we have seen that in Vioxx, we have seen that in various other drugs.

But there is another pharmaceutical industry, which is responsible for the birth of Gleevec, as I detail in the book, was responsible for the birth of receptin, was responsible for the birth of tamoxifen—major, major changes in the way we treat cancer patients, was the basis of you know the birth of important palliative care medicines which allowed—the antinausea medicines. So how then does one reconcile these two pharmaceutical industries and reconcile their conversation with scientists, with public policy, in a way that we can reject with some kind of specificity the pharmaceutical industry that is perverted and ghoulish with the pharmaceutical industry that is inventive and resilient? I think that really is the front of public policy especially for the evolution of therapy.

One last point, of course, is that there's a big chapter on cancer prevention and I think a major emphasis at the National Cancer Institute is to also reinvent the way we think about prevention, which has not been done for a while. Prevention research was based on a kind of epidemiological model, a very powerful epidemiological model, as I talk about in the book, and that's been changed to a kind of molecular model, a molecular way of thinking about prevention. That will definitely change the way we think about cancer prevention.

Q: I just have a question. I'm right here. Later in the book you talk about Queen Atossa of Persia, and I was curious, I know that she was the first woman diagnosed with breast cancer, and I was just curious if you could talk a little bit more about what you detail on her and why her story is important.

SIDDHARTHA MUKHERJEE: Atossa is the first woman that we know of who may have had a disease that might have been breast cancer. And the reason I say that with so many caveats is because the language doesn't have a word for cancer yet. And this is Herodotus writing in his histories and he describes this case of a queen, a Persian queen, who develops, as he puts it, a mass in her breast and instead of approaching her own physicians, she hides in shame, of course this becoming a theme that will run through the book, so she hides in shame until we are told that a Greek slave of hers named Democedes cures her, probably by cutting out the tumor. Now whether that was a tumor, whether that was an abscess, we don't know, the book acknowledges as such, but by many descriptions, many surgeons have really imagined that this was the first description of breast cancer.

The twist to the story, of course, is that Democedes was from Greece, he had been captured and brought to Persia, she was the Persian queen, and so then Atossa having recovered from her surgery asks her husband instead of invading Scythia, which is on the eastern side of the border, to invade Greece instead so that Democedes can be brought home and in fact this is true, this is what was changed from the Eastern phase of Persia to the Western phase, launched the Greco-Persian wars and therefore it really radically

changed the early history of the West. So that's Queen Atossa, and I say in the book cancer even in its most clandestine form manages to leave this indelible fingerprint on human civilization, a single case of cancer in 440 B.C.

One last point is that we return back to Atossa at the end of the book because Atossa becomes for us a way, a kind of device to perform a thought experiment. The thought experiment is imagine Atossa as cancer's Dorian Gray, so her illness is frozen in time but she moves across time, so she returns back in 1609 and 1709 and 1809 and 1909 and so forth all the way to 2009. And we ask the question "what has changed, what has changed in Atossa's history?" And this goes back to Nicholas's question—what is the arc of that history? And I think what we do find is that Atossa's diagnosis, her management, her prevention, the medicines she's treated with, the apparatus around her treatment, the psychological, the psychiatric care of her cancer changes radically over time, and it becomes, I think, a story, a thought experiment that allows us to understand what really has happened.

Now, does she survive longer? We don't know because we can't—this is a thought experiment, but I think and I make this point in the book reasonable people would say that if she had estrogen-receptor-sensitive breast cancer she probably has extended her survival from ten to twenty years, that is meaningful. If she had pancreatic cancer, and here comes the chill, if she had pancreatic cancer, her prognosis from 1609 to 2009, she has metastatic pancreatic cancer, which is not surgically amenable, her prognosis from 1609 to 2009 has not changed. That's the history.

Q: Like the business of cancer so there's really no, I guess from a business perspective, reason to cure it. What do you—I'm sure you've come across that, too, in your research.

SIDDHARTHA MUKHERJEE: Well, I think it's a little bit nihilistic to say there is no business reason to cure cancer—I think that would be a strong statement to make about the—

Q: From a dollars-and-cents perspective, you just talked about the apparatus and the medicine and the therapy and the—all these businesses that would go out of business, all these people who would get unemployed if cancer was cured.

SIDDHARTHA MUKHERJEE: I think that's—I mean, you know, you could say that, I think that pushes the nihilism too far for me. I think that's a particularly nihilistic way of looking about the way this sort of apparatus works. Fair enough, I mean, you know, if we cure all illnesses, medicine would go out of business and we would all be happy. I would have no job and I would be happier for it. But that is not happening, and unfortunately I think that even the best efforts to cure cancer, whether they were driven by more perverse incentives, have not worked out, so we are now stuck with whether you like it or not for some cancers, cancer as a chronic disease and we need to manage it. Now, I agree, and you could imagine that there are perverted incentives there. I'm not the biggest fan of that way of looking at it. For me, particularly, it deflates what I do. I mean, Nicholas, what's your sense about—do you have a sense that—you cover this area very

much, you've covered it for many years. Do you have a sense that there has been, that there is a machinating process in the background here?

NICHOLAS WADE: A machinating process? You mean a conspiracy.

SIDDHARTHA MUKHERJEE: Well, Not a conspiracy. Is there a disincentive for a pharmaceutical industry to create a curative therapy or is there a disincentive for a hospital or a doctor to find a curative therapy because then the so-called cancer world would collapse?

NICHOLAS WADE: I don't think so. I think the incentives are the opposite. We have a vigorous pharmaceutical industry in this country because competition is encouraged and because if you do make a successful drug, you hit the jackpot. And you could argue that the Europeans have regulated their pharmaceutical industry sort of so tightly that they've stifled innovation. You know, our system thrives on people seeking their self-interest.

Q: There are—it's well known that there are certain ethnicities in the world that have a lower—in fact have a lower degree of heart disease because of their diet, such as the Mediterranean diet or people who live in Japan, you know, who don't eat meat, they eat fish. And my naïve question is are there any ethnic groups in the world that have a lower incidence of cancer than other ethnic groups, which, and possibly the answer is yes or no, but if the answer is yes, then the next logical question would be, "why?"

SIDDHARTHA MUKHERJEE: So the answer is yes, but it depends on what kind of cancer, that's the unfortunate piece of it. So it's not as if there are ethnic groups that are cancer-immune, as it were. There's a spectrum. There is clearly an increased incidence among African Americans for instance of multiple myeloma, one form of cancer, we don't know why. The question you're asking is a very deep question with epidemiology. How do you take that statistic and convert it into what the reason is, what's the background behind it, and we don't know.

In some cases we did know. We know, for instance, that the increased instance of liver cancer in Asia likely has to do with the hepatitis B virus. So eliminating that virus, targeting that virus and eliminating it has led to a dramatic reduction of that disease. We do know that in certain parts of Japan there was an endemic infection with a stomach bacterium, there was a great story in that book, in which that discovery occurs and the man, Barry Marshall, who subsequently won the Nobel Prize for the discovery. For the longest time people said gastritis was because of stress. There's a line in which he quotes someone saying, "You go to the doctor and say, 'you know, Doctor, I have this ulcer in my stomach, I have this gastritis,' and he would say, 'that's nothing, dear, it's just too much stress, take an anti-stress tablet.'" It turned out of course that it was a bacteria. It's a bacteria called *helicobacter pylori* which causes this kind of inflammatory reaction in the stomach.

But this was so hard to accept, this was so difficult to get people to accept that Barry Marshall when he was discovering it performed what I call the ultimate experiment. He

took *helicobacter pylori*, scraped it off a dish when no one was looking and he swallowed it. He created, he re-created gastritis in his stomach, he could treat it with antibiotics, and essentially he provided biopsies from his own stomach to prove that there was a direct link, a causal link, between bacteria and stomach cancer, or stomach inflammation that leads to cancer. That said, no one does experiments like the Australians do, **(laughter)** and so that said, but he really put that idea on the map, and now there's an exploration about, you know, how to tend to these various ethnic clusters. So some of them are bacterial, some of them are genetic, some of them are carcinogens that are unique to those areas, and some of them are completely mysterious and we don't know why.

PAUL HOLDENGRÄBER: Do we have one last excellent question before I ask one?

SIDDHARTHA MUKHERJEE: The questions have all been excellent.

Q: I'm just curious to know whether in this country—what is the current situation in this country in, for example, taking in consideration Eastern medicine approaches to cancer. I know that Columbia—I work at Columbia, and I know that Columbia has a program now on alternative medicine and I was wondering if that was really taken into account in the war on cancer. I don't believe there is a conspiracy, you know, plot, by the pharmaceutical companies, but I do believe that there may be a lot of products over the counter that in theory may be potential small molecule inhibitors.

SIDDHARTHA MUKHERJEE: Absolutely. As Barry Marshall proves, alternative medicine is alternative until it stops being that way. So we have to be humble about what alternative medicine is. Of course, if you look back at the Gleevec story, right? The drug Gleevec was, you might say the drug Gleevec was invented by Novartis and then brought to its full being by Brian Druker, but in fact its original variant was invented by a sea bacterium. Right? That's what the reality is. And if you look at our pharmacopeia, a vast number of substances come from plants. Plant medicines, extracted in various forms, form the molecular spine of our current pharmacopeia, there's no denying it. And where there is wealth in evolutionary diversity, particularly biodiversity, there is a place for plants, these plant medicines to be brought into the human pharmacopeia.

My only plea is the following. My only plea is I think alternative medicine is incredible, but the ways that we test medicine in clinical trials happens to have evolved very highly in this part of the world. There are probably other ways of testing medicines that we don't know about, but this happens to be a relatively good way of testing medicines. So my only plea is let's find a way to bring these small molecules into the same kind of rigorous testing mechanisms so that we don't fall plague to the very biases that we talked about that happened to have been problems in the history of cancer.

PAUL HOLDENGRÄBER: One more eager person there.

Q: Hi. I wanted to ask a quick two-part question. One, I've read that chemotherapy is most effective against certain kinds of cancers, testicular, non-Hodgkin's lymphoma, and

I forget the third. And if that's the case how come the push for chemotherapy is so widespread? And the second part is I read that in Germany they do chemotherapy sensitivity tests and how come we don't do that as much here?

SIDDHARTHA MUKHERJEE: So the two part question. Number one, how come chemotherapy is used in other forms of cancer where it's less effective? The quick answer is there's nothing better that we have. To return back to the case of breast cancer, although we can use other examples here, chemotherapy applied after surgery for breast cancer saves lives, there is no doubt. There have been multiple trials in multiple countries run. Now, does it cure breast cancer? It does not cure metastatic breast cancer, but this form of chemotherapy, called adjuvant chemotherapy, in breast cancer and several other forms of cancer saves—extends lives significantly and, in fact, one reason that this dip has occurred post the 1980s or 1990s, there is a small contribution, if you measure it, there is a small contribution of chemotherapy in breast cancer to that, so let's not minimize that, and unfortunately we don't have another alternative.

The second part of the question is why don't we test—part of the reason I think is that we don't have the mechanisms that allow us to discriminate between what can and cannot work in the laboratory and the clinic. Even in Germany, where these tests are being run, I would say the tests are in their very crude infancy, and we've never done properly a kind of study that you're asking for, which is could we ask the question in the most rigorous manner possible where they're testing for a particular spectrum of drugs and then

applying that drug to a patient will or will not help that patient extend survival. That's the kind of study that needs to be done. We haven't done it yet.

PAUL HOLDENGRÄBER: I have a two-part question, I didn't want you only to have a two-part question, so I have a two-part question, and it's not two parts, it's two questions, but I'll say they're two parts. The first one has to do with a comment you made very quickly en passant, but which is very important. You mentioned that chemists are poets, and from my own past, I remember my father, who studied medicine, trying to teach me chemistry when I was failing terribly and he was saying "the C loves the O," and he was making it very lovable and very poetic indeed. And so I'm interested in how you went about writing this book because the subtitle is "A Biography of Cancer," and indeed cancer becomes a personage, a protagonist, and it's a book written one would say by a writer and I'm quite struck by many of the metaphors you use and how you sat down and wrote the book, the very daily work, when you found the time and how you went about writing it.

The second question, which is totally unrelated really, comes from a quotation from Susan Sontag, you refer to her quite often, and you quote this passage from one of her books: "The purpose of my books," Susan Sontag wrote, in the conclusion of *Illness as Metaphor*, "is to calm the imagination, not to incite it," and I'm wondering if your project is any way similar.

SIDDHARTHA MUKHERJEE: So those are lovely questions to end this conversation with. The answer to the first question what went into writing the book? A little bit about my writing process. I said to you before that I wrote the book as an answer to a question, and that already gave it a certain kind of internal propulsion. I had to start at the beginning and end at the end, I had a sense of what was going on. Two important features: Number one is that when I wrote the book I did not know whether Carla would live or die at the end of the book. So it was for me a kind of a peculiar moment of writing, because it was like writing a novel in which—or actually even more frighteningly—writing a work of nonfiction in which I literally did not know the end. If Carla had died at the end—she does not—if Carla had died at the end, this book would end on a very different note. And so one of the most complex things about the book was I was driving without a destination while writing this book.

So I took that and rather than saying to myself, "Well, here is the end I'm driving towards," I said instead, "I'm going to concentrate very deeply on process," because there was no destination. And what I would do, essentially, is I would write in very short bursts, five and ten minutes squeezed here and there. I was often keeping a diary, because I was writing while I came back from work, so I would come back from work, and I would think about the day and I would keep a little diary and say "well, here's something that can enter the book," and then I would forget about it, and then it would enter again in a different way. And I think that allowed me to deal with it. I mean, this manuscript was about three times its length. Nan Graham, who edited it, had to wrestle with a manuscript

that was literally three times its length. There are many people who don't get into the book because no one would read an eighteen-hundred-page book on cancer.

So that was very much the process and I told this to Chip McGrath, who came to do a lovely review of the book from the *Times* I said I mastered the idea of profound indiscipline, what I would do was rather than say I was going to work from nine a.m. to ten a.m. on the book and shut everything out, I would rather work in five-minute bursts, I would say "I'm going to write from 9 to 9:05 and then stop," and "I'm going to start at you know 10:15 and write till 10:30." So that was one feature.

And the third feature—those are the three salient features in terms of what I remember about writing the book. The third feature is that I wrote in a very linear manner, by that I meant that I started at the beginning and I ended at the end. I didn't—Many writers told me, "Well, it's, you know, we work nonlinearly, we put in chapters later, come back, switch them around, et cetera, et cetera." It didn't work for me. I can't write like that. I'm a profoundly linear writer, so I write start at the beginning. The advantage, because everything has a little advantage, the advantage of that is when I would get stuck I would become obsessed with projects, so when I got stuck with the Robert Sanders story, it seemed to me that if I didn't find Robert Sanders this book could not be written, **(laughter)** because I was so stuck, because he here was, I was at Sidney Farber in 1948 and in a very peculiar way and for me a very heartfelt way, it allowed me to discover things that I hadn't discovered before and I would never have discovered them if I didn't get stuck in this way.

And so then I would move on, and then I said to myself, “Well, I have got to find the first survivor of childhood leukemia, now that I’ve found the first child who had leukemia, now I have got to find the first long-term survivor of childhood leukemia,” so I’m going to tell you the story very quickly, but so I again went back I was looking all around to find the first survivor of—because this was the beacon for me, this man or woman who had survived from 1960s, these trials of 1960s, would become therefore the emblem of what was successful and not successful in the war on cancer. And then I was looking on—I was buying a textbook on cancer on Amazon, and in the reviews of the textbook, someone had written, a woman had written “something something something, I had leukemia in 1964, and I thought this book was very nicely written,” or something.

And because I was so habituated to looking for those names and their numbers I said, “wait a second, 1964, the woman is now these many years old, she has got to be a long-term survivor of chemotherapy,” and there was a little address that said on the side, she had a little Facebook address or something, so I called her up, and I said, “Can I come see you?” And so I drove out to Maine, I actually took a bus out, because we were in somewhere far away, I had to take a bus out and then a car and finally I have this very vivid memory of arriving at her door, and she was like, “Why are you here?” **(laughter)** But I couldn’t explain to her, I said, you know, “If you weren’t there, if I hadn’t found you, I wouldn’t be able to write this book, you see, you are my book.” **(laughter)**

And so then she brings out these pictures from 1964, she brings out these pictures of herself as a preteen from the Boston ward, and we tell this story, this was a time when there were no antipsychotic drugs, and she was treated with the highest doses of steroids, and she went crazy, and they had nothing to do, and the only thing they could do was restrain her, and we go through the story, and they tied her up so they could give her chemotherapy, and she survives, you make of that what you will. So that's the process of writing the book.

The last question you said was—remind me—about inciting the imagination. Of course, yes, this is a lovely line from Susan Sontag who says, "my purpose was not to inflame the imagination but rather to calm it." I felt if this book is successful it would demystify one of the fundamental mysteries of illness that happens to be a part of our times. I think cancer in some ways is a defining plague of our generation just the way that tuberculosis has been for a prior generation, just the way that actually the plague was for a prior generation, and AIDS famously was for another generation that is becoming a prior generation. I felt that as if if this book is successful, it will succeed if it is able to demystify something that is mysterious and in that sense it will calm the imagination. And so if the book succeeds I hope we are able to take—because it's only by understanding that our imagination will calm.

PAUL HOLDENGRÄBER: Nicholas Wade, Siddhartha Mukherjee.

(applause)