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# The Edge of Medicine

## The Technology That Will Change Our Lives

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The medical cases included in this book do not refer to individuals but are composites used to illustrate a wide range of diagnoses, treatments, risks and benefits associated with a variety of medical technologies. Names and characteristics are used fictitiously. Resemblance to any real person is unintended and entirely coincidental.

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# CONTENTS

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The idea for this book actually evolved from an unsuccessful concept for another book, one that, to be fair, would have been much less fun to write. Fortunately, while she passed on that first idea, Airie Stuart, senior vice president and publisher at Palgrave Macmillan, took the time, as she describes the way she sees her job, "to reshape and develop the proposal with an eye toward the larger trajectory of an author's career." After gently telling me on a conference call with my agent, Eric Lupfer from the William Morris Agency, that a book about health care's stupidities, however good, would be a downer, she suggested that I send her an alternative proposal for a book about health care's promises. I am grateful to Airie for her philosophy and to Eric for his thoughtful stewardship throughout the process. My editor, Luba Ostashevsky, has helped me to do what my sons' teachers would describe as "my best work," using, variously, blunt talk, patience, curiosity, humor and a light touch on the reins.

My siblings Chris, John, Beth and Ellen have all been cheerleaders along the way, and Beth, in particular, has acted as a rational sounding-board at every step. While several people helped focus how I have thought about the material, a few deserve particular mention. Richard Perlman and Jim Price were generous enough to lend me some of their boundless optimism and enthusiasm early on as I began, and Meg Davis provided some timely observations during the home stretch. I have also been fortunate enough to work with a number of bright, passionate, far-seeing people at several great academic institutions over the years.

I owe my greatest debt to the four people besides myself who have lived most closely with, been most impacted by and been the most enthusiastic

about the project: my wife, Beth, and my three sons, Addison, Watson and Callaghan. Appropriately, one of the themes that cropped up repeatedly as I researched material is the way that strong families anchor and nourish their individual parts, which brings me to one last debt—the one I owe to my parents. I've made an inadequate attempt to discharge this debt, the most fundamental one, in the closing chapter.

# INTRODUCTION

It is impossible to spend any time observing the world without concluding that curiosity is common to both humans and animals. Where we once believed that the use of tools was an exclusively human activity, we now know that various animal species manufacture and use tools in a variety of ways. The practice of medicine, as far as we know, is one of the oldest exclusively human industries. Although we don't know precisely when, at some point primate social activities such as mutual grooming and nit-picking transitioned into the beginnings of early human medicine. The first medical tools people used were their senses of sight, touch, smell, taste and hearing. And early humans weren't just observant; they acted on their observations.

Trepanation, a medical procedure in which a hole is bored in the skull, is typically used today to drain collections of blood from around the brain. Archeologists have found trepanned holes in skulls dating back to the Stone Age. We don't know what the indications were for the procedure back then, but some of the skulls were fractured, suggesting that the procedure may have been performed to treat brain injuries. Some of the trepanned Stone Age skulls show evidence of bone that healed, indicating that the patients survived the surgery in many instances.

The father of medicine, Hippocrates, diagnosed diabetes mellitus based on a patient's complaints of thirst, hunger and frequent urination. In fact, the word diabetes derives from the Greek word for siphon, because according to ancient Greek physicians, diabetics passed water like a siphon. Using his own senses as a diagnostic tool, Hippocrates tasted the urine to see if it was sweet.

One way to think of the five human senses is as dimensions of sensation. The loss of one sense would, then, be analogous to going from a five- to a four-dimensional world. The ability to see gives us the capacity to have a bird's-eye view of the lower-dimensional world, and to readily look for and find things in an area that we'd otherwise be forced to explore in a slower, less efficient fashion. Without sight, our human explorations could be confined to feeling around with our hands and listening for sound cues—which is actually a pretty good analogy for what we sometimes do in medical research: We grope around in a systematic fashion for new knowledge and new treatments using the research tools we have available in a given era.

Every once in a while, however, a new research technology comes along that effectively gives us a new sense with which to explore our world, and a burst of medical advances ensues. For example, Anton van Leeuwenhoek developed powerful microscope lenses in the mid-1600s and used them to systematically explore the world around him, thereby discovering what amounted to a new world. He put everything he could think of under the microscope and discovered bacteria, protozoa, even spermatozoa on what must have been a very surprising day.

The microscope lens augmented our ability to see and thereby extended our diagnostic capabilities. Today's CT and MRI scans are the remote descendants of the lens. In fact, the lineage of many of today's medical instruments can be traced to antiquity. Hippocrates used his sense of taste as a tool, and he also smelled diseases. He described the smells of liver and kidney diseases on the breath of his patients; in my lab today, we are working with an "electronic nose" to identify the smells of pneumonia, sinusitis and cancer on the breath of our patients.

Leeuwenhoek's microscope revealed a whole new, previously unsuspected world to scientists of his time, one that was so astonishing that many of them didn't believe his observations at first. Lenses of one sort or another have now been developed to see out into the universe and down to the individual atom. We have actually developed tools to shatter the atom in our relentless search for the most fundamental particles. In fact, the first chapter of this book will describe the lengths we have gone to in order to find the elusive Higgs boson—a critical missing piece to the model physicists currently believe best explains the nature of time and space. The pursuit of fundamental particles has already paid huge medical dividends. In fact scientists and doctors have found ways to conscript advances in almost every area of human investigation for the service of medicine; and we now have more tools than ever before to do something about what we find.

We have tamed the atom and used it for radiation-based treatments. We've designed molecular machines for medical diagnosis and treatment. We've enlisted robots and smart computers in the war on disease. We've identified the cellular equivalents of Adam and Eve. We're now able to look at and manipulate human DNA—the machine inside the man; and we're decoding the human genome.

Today, we are entering an era in which genetic information, stem cells and nanomolecular engineering will transform the world of medicine, providing us with many new dimensions of data and treatment. In this book we'll explore the evolution of medicine from past to present, showing how we got to where we are, and where we're headed in the future.

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# CHAPTER 1

# DEUS EX MACHINA

My father was a physician whose career spanned the four decades from the early 1950s to the early 1990s, and many things changed during his lifetime. For example, in the 1950s, the RJ Reynolds Tobacco Company actually ran a campaign with the slogan "More doctors smoke Camels than any other cigarette," and many of the pictures in my father's medical school yearbook show him and classmates with cigarettes in hand. However, the really big changes occurred during the latter part of his career (when my own career was just beginning), during which medicine began to evolve from a mom-and-pop, cottage industry into the highly competitive, rapidly advancing, multinational *business* it is today.

In the late 1970s and early 1980s, I worked at the same medical center that I do now, in an office that was then called Data Processing—the hospital division that managed patient's bills and accounts payable. There was exactly one computer in the entire hospital—in the basement—and it dined exclusively on IBM punch cards (those heavy, rectangular paper cards formerly used for census-taking, school examination registration, time cards and, perhaps most notoriously, for voting in Florida during the U.S. presidential election in 2000—the piece punched out of the card is, of course, a chad). Punch cards were used to keep track of the medical bills. There were data entry clerks who punch-typed the charges onto the cards, which were then sorted into piles secured with a rubber band. Periodically, the computer would be fed a pile of punch cards upon which it would chew noisily for some time and eventually spit out a ream of data on a teletype machine.

I was the hospital's only data analyst, and in order to get lunch every day, I walked down a creaky corridor lined with cases of memorabilia, past the administrative offices of the hospital and down the steps into the cafeteria. The hospital library was one flight up those same stairs, and the medical staff would go there to pass some leisure time browsing through medical journals. Less than ten people worked in hospital administration—the chief operating officer, the chief financial officer, the chief nursing officer and a few support people. It was the job of the folks in this office to keep the books, buy things that were needed and make sure the bills got paid—nothing more. The concept of engaging in overt competition to attract patients was inconceivable: The patients just came to us, and the hospital's officers did pretty much what they were told by the doctors who sat on the hospital's board.

As I drove to work in the early 1980s, I passed plenty of billboards, none of which advertised hospitals or doctors. In fact, the thought of self-promotion was abhorrent to the medical profession at that point. There were no signs on the city buses asking "Have you been misdiagnosed?" There were very few regulatory agencies, and magazines didn't publish lists of the best doctors and hospitals. Medical benefits were a little employee perk in the same category as parking and free company business cards.

In short, medicine back then was a pretty sleepy, gentlemanly affair, and some hospitals were like the fat, slow-moving dodos from the island of Mauritius. Today, however, a mere 25 years later, we are in a medical evolutionary arms race. Computer chips are ubiquitous—there are probably 20 in my office alone, what with desktops, laptops, telephones, cell phones, a camera and other gadgets. Data analysts have found their own ecological niche; and 30 *percent* of health care workers are administrators. In fact, upwards of 30 percent of health care dollars go toward medical administration. Hospitals now have powerful CEOs, many of whom have advanced degrees in health care administration, an educational track that teaches how to control costs, grow product lines and capture market share.

Successful hospitals rank highly on performance and patient satisfaction scores and garner certificates of excellence. Some of the certifying organizations could be described as parasitic: They grow their business *de novo* by defining excellence in some new way, trademarking their brand and then, for a fee, determining whether individual hospitals meet their standards. Malpractice lawyers are everywhere, having found a vast new food source, and rummage around largely untrammeled because their fellow lawyers tend to make the laws. In the medical profession, we have our own lawyers to make sure we stay current with rapidly changing laws and regulations. Looking back, it's as if an alien ship landed on the medical world of thirty years ago, bringing with it innovation as well as unintended disease, and things began to change almost immediately thereafter for better and for worse.

Every city and country still has its medical dodo hospitals, but medical evolution has proceeded quite rapidly where environmental changes have compelled change. The development of specialty hospitals (such as centers for the treatment of obesity in the United States) and private hospitals in countries with public health systems are but two examples of successful evolutionary adaptations by doctors and hospitals in resource-constrained environments. Of course today's profitable obesity center may become tomorrow's dodo hospital due to changes in regulations and reimbursement or, ideally, to the disappearance of obesity as a problem.

The current landscape of medicine and its place in the larger society is, at best, very confusing when viewed from the ground. We are in what Clausewitz described as the fog of war. On the one hand we hear a steady stream of dire predictions about the all-engorging growth of health care in every modern country in the world, while on the other, there is a competing flow of information about tantalizing new therapies, such as proton beams, that can cure or extend life. Some of the latter will represent major breakthroughs while others will turn out to be no better than or even worse than their less costly predecessors.

For centuries, medical knowledge was as closely held as the secrets to magic acts, but today we suffer from a surfeit of electronic information that often leaves us more confused than before. The biggest problem right now, both for those of us who treat medical problems and for our patients, not to mention policy makers and payers, is that things are changing so rapidly.

Proton beam therapy is a perfect example of the technologies and treatments that are at the leading edge of medicine and that you'll find in the hospital of the future. Developed by physicists, in their search for fundamental particles, this therapy is technologically sophisticated; even as a critical element of a treatment assembly line, it can be programmed to give treatments precisely calibrated to the specific needs of each individual patient.

Physicists and physicians are both engaged in a seemingly relentless quest to build bigger machines to interact with ever-smaller targets with greater precision; the two fields are inextricably interwoven. Nobel Prize–winning physicist Marie Curie discovered radioactive elements and forms of radiation that are fundamental to the practice of medicine; this same radiation killed both Marie and her equally talented daughter. In 1959, Nobel Prize winner Richard Feynman described nanotechnology and nanoscale medical devices that are now in the process of revolutionizing medicine. The World Wide Web was originally created as a tool for interaction among particle physicists at the European Council for Nuclear Research, commonly known as CERN; the Web is now, among many other things, a wide-reaching vehicle for the dissemination and practice of medicine, as we'll see in a later chapter. Another extraordinary physicist, Stephen Hawking, has amyotrophic lateral sclerosis; it is only by virtue of advances in the treatment of that disease that he is able to continue using his energies to further our understanding of arcane concepts pertaining to black holes and the nature of space and time.

The Higgs boson is the elusive, highly sought after, as yet theoretical fundamental particle that physicists desperately need in order to tidy up one of their theories of how all things work. The boson is the last unobserved member of the particle family belonging to the standard model of physics. Physicists describe it as a rumor crossing a crowded room because it, too, causes transient clustering and massing in the wake of its passage. In essence, the boson is believed to be the fundamental particle that gives all other things—planets, people and protons—mass.

If a large hadron collider, or LHC, sounds to you like something out of a science fiction movie, you're not too far off. It is actually the gigantic nuclear particle accelerator and collider located outside of Geneva, Switzerland, at CERN, with which modern physicists plan to find the Higgs boson, using what amounts to an enormous ray gun. The LHC was built with the collaboration of more than two thousand scientists and hundreds of separate universities and took ten years to construct. The collider and its associated particle detectors, electron magnets and laboratories are housed in a 26.5-kilometer-long tunnel that is a little less than 4 meters in diameter and crosses the serpentine border between France and Switzerland several times. It lies at average depths of between 50 and 175 meters underground to minimize its impact on the environment and to prevent harmful radiation exposure to people walking on the land above. The discoveries made within that hidden tunnel will likely change our world above it irreversibly.

This giant machine is designed to fire one beam of protons traveling clockwise at another traveling counterclockwise—both beams at almost the speed of light—in hopes that information about debris from the resulting collision will explain some of the still-unanswered fundamental questions in physics. This a time honored way of finding things out that was invented by and has been practiced for centuries by boys. Fortunately, the proton is a generally well-behaved member of the hadron family (a class of particles composed of quarks), which also includes neutrons and mesons, and the large hadron collider is based on the design of older linear particle accelerators, or atom smashers, upon which, in turn, some of today's medical radiation devices are modeled.

Over 1,600 superconducting magnets cooled with liquid helium are used to accelerate and steer the proton beams in the LHC. The energy developed in each of the circling proton beams is equivalent to that of a high-speed train traveling at 150 kilometers an hour. When the two beams of protons collide, an unimaginable amount of energy is released—in fact, the temperature at the contact point is a hundred thousand times hotter than the center of the sun. On the other hand, the cooling system for the magnets in the tunnel—the cryogenic distribution system—keeps parts of the collider at temperatures lower than that of outer space; we'll see in a later chapter how our understanding of cryonics may one day allow us to travel to outer space.

The protons in the beams make over 11,000 circuits of the tunnel every second, and the attendant forces are so powerful that there is at least a theoretical possibility that the proton collisions will produce microscopic black holes. This sounds really ominous but physicists reassure us that, if formed, these small black holes will deflate, like balloons, by blowing off energy through a process called Hawking radiation, named after the aforementioned physicist Stephen Hawking.

Hadron, or proton beam therapy describes the use of a beam of particles, exactly like the ones flying around the 26.5-kilometer hadron racecourse in Switzerland, to treat cancer in humans. Proton beam therapy is only available in a few places in the world. It differs from traditional radiation therapy in its use of beams of particles rather than x-ray waves for treatment. Unlike x-rays that deliver radiation to all the tissues along the path of the beam, causing a little bit of damage all along the way, proton beams pass harmlessly through the skin and overlying tissues to deliver their radiation into the target without injuring the surrounding tissues.

The first suggestion that protons might be used medically to treat tumors came from Robert R. Wilson, one of the physicists who worked on the Manhattan project with Albert Einstein, Richard Feynman and Robert Oppenheimer. A multidimensional scientist like Feynman (who sketched, painted, kept an office in a topless bar and played practical jokes), Wilson was also a sculptor, human rights advocate and a little bit of a rebel. Wilson described the potential for proton therapy in 1946. Having observed that proton beams fired from an accelerator give off a burst of radiation just before they come to a stop, he realized that a beam could be tuned to deliver energy to a very precise area, even one deep within the body.

Wilson proposed that bursts of protons could be trained, like horses, to gallop up to a tumor in formation and then stop on a dime (or on a pinpoint in the case of protons) to deliver their payload of radiation. It is instructive to contrast this elegant medical treatment with what happens in the hadron collider in Switzerland, where two columns of protons are smashed violently into one another at nearly the speed of light, shattering what we once thought were *the* fundamental particles—neutrons, protons and electrons—into still-smaller particles with names such as charm quark, strange quark, muon, gluon and baryon. In fact, all of the early proton treatments for medical disease were performed in particle accelerators originally built for physics research, such as the one at the Harvard Cyclotron Laboratory, which Wilson helped design, as well as devices in the Soviet Union, Switzerland, Japan and Sweden. The first accelerator built specifically for medical therapy wasn't constructed until 1988.

Highly targeted proton therapy is particularly useful when a tumor lies in close proximity to critical nerves or organs, such as the brain, prostate, esophagus, lungs and eyes. Because of the proximity of the tumor to its neighbors, the dose of radiation that can be safely administered is limited by the potential for unacceptable injury to critical normal tissue nearby. Proton beams act like smart weapons. The oncologist uses the coordinates of the tumor, based on imaging data from a CT or MRI scan, to design a course of radiation in which the beam is shaped to conform to the silhouette of the lesion. The protons are then energized to the exact level needed to deliver their radiation precisely into the tumor.

I recently had the opportunity to walk around a proton beam accelerator under construction at the Roberts Proton Therapy Center, in the Perelman Center for Advanced Medicine at the Hospital of the University of Pennsylvania. When complete, the center will be part of the largest proton therapy institute in the world, and after having seen the innards of the accelerator before the walls were installed, I can see why this $150 million piece of machinery is called the world's most expensive and complex medical device. While Geneva's large hadron collider is the world's largest *scientific* instrument, designed to answer big fundamental questions about the universe, its medical counterpart is a worthy little sibling.

The proton therapy cyclotron in the Roberts Center is a 220-ton device at the heart of a football-field-sized building, part of a beautiful medical center designed by the architect Rafael Viñoly. Viñoly specializes in the design of seemingly gravity-defying buildings such as the Frederick P. Rose Hall, home of Jazz at Lincoln Center in New York, the Kimmel Center for the Performing Arts in Philadelphia, Princeton's Carl Icahn Laboratory of the Lewis-Sigler Institute for Integrative Genomics and a lattice-work concept for the World Trade Center site, from which two beams of white light vanish into the night sky.

The proton beam generated in the Roberts Center cyclotron can be split into five separate independent sub-beams that are directed to patients by a series of bending, focusing and routing electromagnets. Each of the five beams is