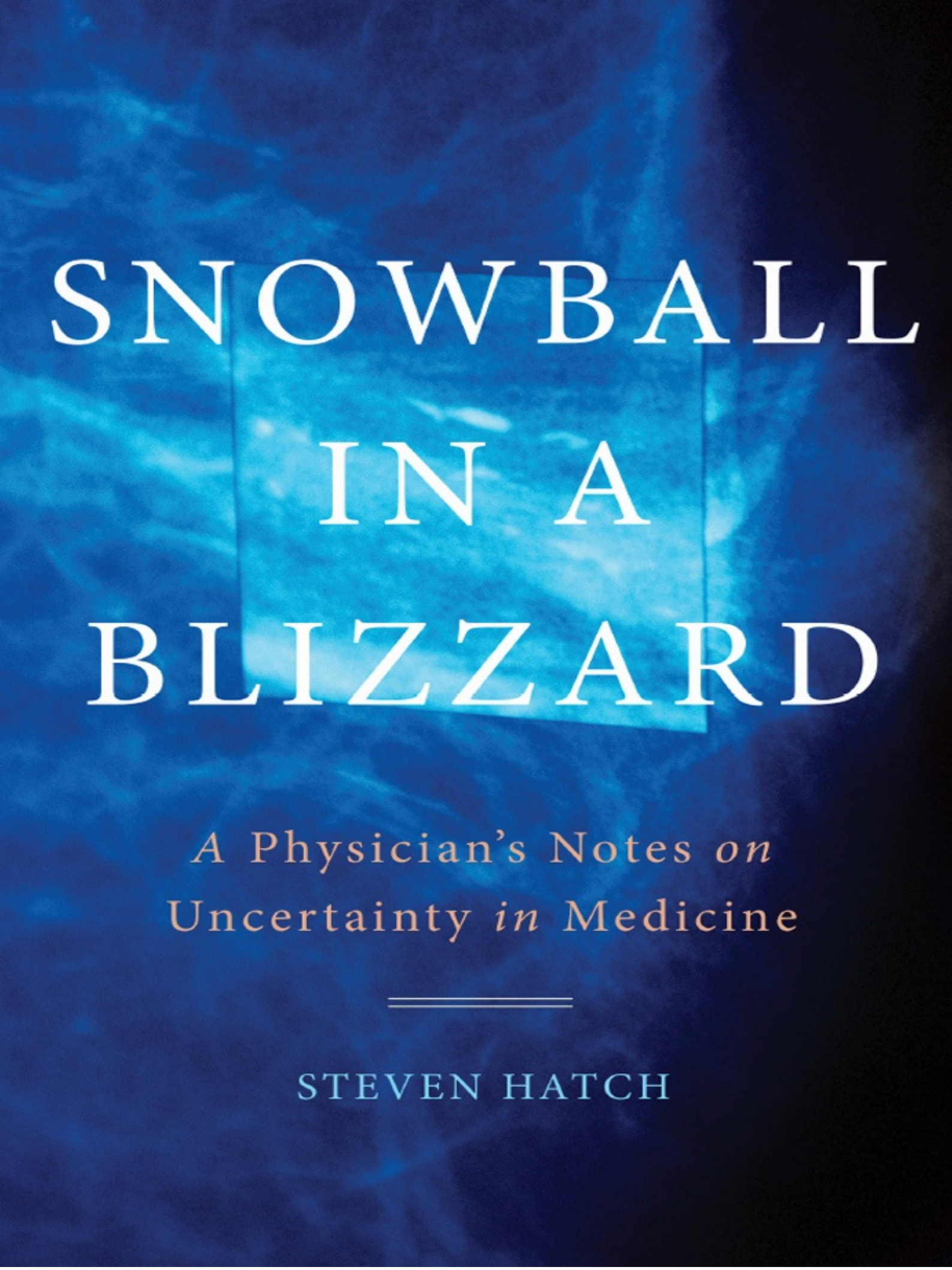
SNOWBALL
IN A
BLIZZARD
A Physician's Notes on
Uncertainty in Medicine
STEVEN HATCH

# SNOWBALL IN A BLIZZARD

# SNOWBALL IN A BLIZZARD

## A Physician's Notes on Uncertainty in Medicine

STEVEN HATCH, MD

BASIC BOOKS
A MEMBER OF THE PERSEUS BOOKS GROUP
*New York*

Copyright © 2016 by Steven Hatch

Published by Basic Books,

A Member of the Perseus Books Group

All rights reserved. Printed in the United States of America. No part of this book may be reproduced in any manner whatsoever without written permission except in the case of brief quotations embodied in critical articles and reviews. For information, addres Basic Books, 250 West 57th Street, New York, NY 10107.

Books published by Basic Books are available at special discounts for bulk purchases in the United States by corporations, institutions, and other organizations. For more information, please contact the Special Markets Department at the Perseus Books Group, 2300 Chestnut Street, Suite 200, Philadelphia, PA 19103, or call (800) 810-4145, ext. 5000, or e-mail special.markets@perseusbooks.com.

Library of Congress Cataloging-in-Publication Data
Names: Hatch, Steven, 1969–, author.
Title: Snowball in a blizzard: a physician's notes on uncertainty in medicine / Steven Hatch.
Description: New York: Basic Books, a member of the Perseus Books Group, [2016] | Includes bibliographical references and index. | Description based on print version record and CIP data provided by publisher; resource not viewed.
Identifiers: LCCN 2015042274 (print) | LCCN 2015041457 (ebook) | ISBN 9780465098576 (eb)
Subjects: | MESH: Diagnosis. | Uncertainty. | Health Policy.
Classification: LCC RC71 (print) | LCC RC71 (ebook) | NLM WB 141 | DDC 616.07/5—dc23
LC record available at http://lccn.loc.gov/2015042274

10 9 8 7 6 5 4 3 2 1

FOR MY MOTHER AND FATHER

*sorry, Pops, wish I coulda got it done sooner*

*Contents*

Confusion + Science = Answers*

*Answers may require years of studying (real studying, not humanities studying) to be understood an
will be expressed in terms of probability rather than absolute certainty.

—C. G. P. GRE

The diagnostic enterprise hinges on an optimistic notion that disease is part of a natural world th
only awaits our understanding. But even if this is true, nature gives up its secrets grudgingly, and ou
finite senses are in some ways ill-suited to extracting them.

—GARY GREENBER

# *Author's Note*

THIS BOOK IS A SURVEY OF THE LANDSCAPE OF UNCERTAINTY IN MODERN medicine. My goal is to give t
reader a sense of the challenges that can be found in all areas of medicine, which means that I cover
broad swath of topics ranging from cancer to women's health to cardiovascular disease to infectiou
disease and others besides. Because I want people to see the thread connecting these topics, I can
give comprehensive explanations about each of the issues I'll touch on. One could write a very lon
and engaging book about mammography; here I'm going to discuss it in a few thousand words just
give you a sense for the underlying data and why people have interpreted the utility of mammogram
in contradictory ways, which has led to dueling recommendations for its use.

Specialists reading this may throw their hands up in frustration over what they perceive to b
oversimplifications of particular studies, as well as an anemic bibliography. Perhaps I am guilty a
charged. My hope is that by actually taking data straight off the journal page and putting it in front
readers, but doing it in a selective manner so it is framed by explanations helping them to make sen
of it, they will have a sense of how the process works and will find medical research a little le
mystifying.

Too often academics are chided by their colleagues for attempts at popularizing their field, whic
by necessity requires stripping away some of the layers of complexity. I have found far too man
scholarly books whose topics look interesting but are written in Academicish, leaving lay readers
struggle with impenetrable language or heaps of detail that obscure the main point. I will endeavor
find that sweet spot where readability and scholarliness overlap. In doing so, I hope to provide reade
with a nodding acquaintance on human-subjects research, with the understanding that there is more
the story on any of the topics about which I'll write.

An additional disconnect between academics and the general public involves citations.
academia, you can't even take a pee without providing seven references on who was the first person
that restroom, what studies have been done on the traffic of the restroom, research on the flushin
dynamics, et cetera. Because our careers are tied to making observations that nobody else has mad
before, we're understandably a bit jumpy when people take credit for our work inappropriately, s
we're very careful to attribute every assertion.

My impression is that lay readers are far less interested in this citation game. Personally, I ha
reading a book with footnotes (especially when they're at the end of the chapter, which makes m
have to flip back and forth) only to discover that a given footnote is just a reference when I thought
might be an aside providing further illumination on the topic in question. However this *is* a book abo
a very highly academic field, so I've settled on a compromise where footnotes are brief digression
and references can be found in the bibliography. I won't, however, offer up specific citations to thos
references in the text. This may make the occasional academic apoplectic, but it can't be helped.

Throughout much of the book, I use the term "doctors" and "physicians" to describe man

different kinds of people, not all of whom *are* doctors or physicians. In many parts of the countr
nurses now have wide latitude in making medical decisions and some have as much independence
full physicians. Additionally, the rise of the physician assistant (PA)—a title that sounds like the
have *less* training than nurses when in fact they have more, occupying a true middle ground—h
introduced a whole new type of health-care provider to medicine, and they typically make medic
decisions indistinguishable from those of their physician colleagues. I therefore use "physician" a
"doctor" as convenient umbrella terms to refer to all these professionals in the interests of n
burdening the reader with a more accurate but distracting description. I apologize in advance to m
nursing and PA colleagues for the shorthand.

For the most part, this book is not a chronicle of my personal experiences as a physician, and
such it does not focus on patients I have encountered. The one exception is in the chapter on Lyme,
which I discuss a patient named David Marsh. David is not an "actual" patient but is rather
composite of many patients I have seen over several years as part of consultations on Lyme. N
former patient of mine should fear that I am exposing their lives in some easily identifiable manner
the printed page.

As noted in the Acknowledgments, I am grateful to many colleagues who have provided the
insights in areas beyond what modest clinical expertise I possess. If I have made any penetrating
illuminating observations in this book, the entirety of credit should go to them. But any inaccuracie
misrepresentations of fact, or failures of communication are due to me and me alone. I hav
endeavored to paint a picture of what I think is a critical problem in medicine today, but if I have n
succeeded in this task, I humbly ask the reader's forgiveness.

*Newton, Massachusetts, and Monrovia, Liberia, July 2015*

# *Foreword*

IT IS COLD AND RAINING OUTSIDE THE HOSPITAL—TYPICAL FOR THIS TIME of year. Rounds are about to sta in the Intensive Care Unit. It's going to be a long day, as the unit is full. There are many tests that wi need to be ordered and reviewed, many treatment options to consider, and many conversations wi patients and family members that will need to take place. The charge nurse calls for the team gather: the lead attending physician, the nurses, the pharmacist, the social worker, a medical reside The difficult business of tending to patients on the edge of life is beginning its daily cycle.

The first stop is the room of a seventy-year-old woman who came to the emergency room wi abdominal pain. Her symptoms began a little more than a day before she called the ambulance and g progressively worse during that time. By the time she came to the ER the night before, she was pal and her skin was cool and clammy. Her blood pressure was low, which is why she was sent to the ICU

Now, twelve hours later, her pressure continues to remain low, and she has been given speci medications called "pressors" to boost it. She is awake but drowsy, and she doesn't respond much questions. The team sweeps in and gathers around the bedside, looking over the paper chart, logging to the portable laptop computer to review the labs, Shuffling around to accommodate the group in th small space.

The patient's daughter and husband sit nearby. They are not asked to leave.

The medical resident summarizes the case for the team. Since coming in to the hospital, th patient has been given fluids and antibiotics. The resident explains that the on-call radiologi performed an abdominal ultrasound the previous evening.

"Why didn't we get a CAT scan?" the attending physician asks.

"Her creatinine was 1.4," the resident responds. "They wouldn't give her the contrast."

"So what did it show?"

"Normal bowel gas pattern, liver looked okay, not much else."

"Do we know why her kidney function is so low?"

"No, we don't," says the resident, who then offers a few thoughts as to what might be the cau and how it might be worked up. "I think if she doesn't improve, then we should call radiology an push for the CAT scan."

"We could throw her into ATN," the patient's nurse observes. "And it may not help us with th diagnosis."

None of this technical language is translated for the family, and the team doesn't stop to unpac the subtleties of the diagnostic dilemma. This is rounding as it's been done for generations medicine: a highly specialized, fast-paced discussion to consider what is going on and what mo needs to be done to restore a patient to health. What makes these rounds unusual is that this discussio is taking place directly in front of the family. There is no attempt to make it anything other than wh it is, so the family has a direct window on how the team "really" functions. And although they hav

understood little of the jargon being bandied about, they heard the phrase “no, we don’t” quite clear and understood exactly what *that* meant.

The discussion continues for several more minutes. They examine the patient, itemize the variou issues involved in her care, and formulate a detailed plan for the day. At the end, as the team readie itself for the next patient, the attending physician turns to the husband and daughter and explains, th time in the language of laypeople, the plan, which mainly revolves around finding the cause of th pain and the low blood pressure. Finally, he asks if they have any questions.

“So, you don’t know why she’s sick?” the daughter asks.

“Right now, I’m not sure.”

“And you think it’s a good idea to get this CAT scan, or not?”

“At the moment, I’m not sure. I want some more tests to return before I decide on that. Normal the CAT scan in this case is the best test we could order, but with her that carries some real risk mainly because of the fact that the contrast we use can damage the kidneys, sometimes irreversibly.”

“Do you think she needs antibiotics?”

“Yes. Of that, I’m pretty sure, at least until we have some other explanation that would clearl indicate we can safely stop them.”

And with that, the team leaves.

What this family just witnessed was a discussion in which they heard the phrases “we don’t know and “I’m not sure” more than once. To some laypeople, that may smack of clinical incompetence o cluelessness, but actually such phrases are common currency in medical rounds. Nothing about th example is particularly unusual. Patients with unknown conditions and diagnostic dilemmas like he are medicine’s daily bread. Yet, far from creating anxiety and distress, the husband and the daughte are *satisfied* with the care she is receiving, and the frank admissions of uncertainty leave them *mo* confident in the team than they would be if they had not been allowed to observe rounds in i unadorned state.

The example is fictitious.

But this ICU, where doctors and nurses and other health professionals openly confess uncertainty, in plain sight of patients and families, is real.

# INTRODUCTION

There are known knowns; there are things we know that we know. There are known unknowns, that is to say, there are things that we know we don't know. But there are also unknown unknowns; there are things we do not know we don't know.

—SECRETARY OF STATE DONALD RUMSFELD, 2002

*How* do we know that medicines work? How do we know that a blood test can unlock th mysteries of the body or that eating a particular diet may allow us to live longer? For instanc everyone knows with the kind of certainty that the earth revolves around the sun that smoking caus lung cancer, even though many of us have witnessed firsthand smokers who lived to old age as well a nonsmokers cut down by the disease. So why are we so confident of the harms of smoking? Wh allows public health officials to take to the airwaves and make that pronouncement with suc certainty? Certainty brings a sense of comfort, but we do not often consider how we arrived at it.

Many of us take for granted that we live in an age of medicine where, to put it quite simply, w know what we are doing. We can read about common treatments for ailments that afflicted people i previous centuries and think to ourselves *I'm sure glad I didn't live in that time*. We look back at th confidence that European doctors had in bloodletting, purgatives, and poultices of dung with horro we see the faith of healers around the world in herbal remedies that we know are no match for o knowledge of biochemical molecular mechanics, which forms the basis of what we now call ration drug design.

If you had to ask someone who knew a little of the history of medicine about when it becam modern, they'd say the transformation took place over about fifty years spanning the late nineteen and early twentieth centuries. They would cite early precedents that indicated change was soon come, like the creation of that ubiquitous tool of medicine, the stethoscope (1816), the dawn modern anesthesia at Massachusetts General Hospital (1846), John Snow's detective work on chole in London that basically founded modern epidemiology (1854), and so on. But the development biochemistry by the 1880s, with its increasingly sophisticated ability to identify, purify, and eve synthesize physiologically active compounds, really marked the turning point for medicine as scientific discipline. This was followed in quick succession by the discovery of X-rays in 1895 and th development of the EKG in the early 1900s, which we still use today almost exactly as we did the Everything that came before these advances was largely quackery, and everything after, large rational.

This is, of course, an imagined generalization, as well as an oversimplification, but I don't think stretches credulity to suggest that many people harbor some kind of notion like this about medicin

During the twentieth century, they would say, medicine could finally stand alongside its "harde brethren of physics and chemistry and claim to be modern without a trace of irony. The reason w would allow ourselves to be subject to the ravages of some phenomenally toxic treatments for, sa pancreatic or bone marrow cancer, and regard equally toxic treatments doled out in 1750 for dropsy something just short of manslaughter, is because we *know* that the cancer treatments can prolong lif We have science to shed light on the situation, and science not only separates the wheat from th chaff, but it invents new treatments by its intimate knowledge of the body at the molecular level, an not by running off into the forest gathering nuts and leaves helter-skelter, administering them patients in an equally random manner.

Make no mistake, this depiction of medicine has much truth behind it. The advent of biochemist really *did* allow for much more highly effective treatments, and early radiology set the stage for quantum leap in the quality of diagnoses over the next several decades. Moreover, this period saw th rise of regulatory agencies that forced drug manufacturers to market their products based only o narrow indications for the diseases they could prove to treat, and state laws gave physicians an apothecaries rigorously trained in the sciences an almost complete monopoly on the business healing. At the dawn of the Republic, pretty much anyone, anywhere in the United States, no matt their level of education and scientific training, could hang up a shingle, call themselves "doctor," an treat patients in whatever way they saw fit. Yet in the age of modern medicine, about the past hundre years, if one did this without possessing the proper credentials, one would likely face jail time.

Since the beginning of this modern period of medicine, the advances have come with eve increasing speed, in nearly every aspect of practice: breakthroughs in microbiology, in pharmacolog in surgery. In his signature work, *The Greatest Benefit to Mankind*, the eminent historian Roy Port attempts to compress the entire history of medicine into a single volume.* The first half of the boo fully 350 pages of dense text, is devoted to the first 5,000 years of the profession, including chapte on early Chinese and Indian medicine. The second half of the book, by contrast, covers just the pa *200*. It is an unmistakable message: *some* stuff was interesting in medical antiquity, but it was most a minor attraction until somewhere after 1800, and the show really got going the century after that.

## A fantastic book. An abysmally boring, stuffy title.

This characterization can be found in popular culture as well. A few years ago the BBC aired medical drama for two seasons. Known as *Casualty 1907* and *Casualty 1909* and marketed outside th UK under the title *London Hospital*, the show was a carefully constructed imagining of what life wa like as modern medicine was taking shape in earnest. As much as the show was meant to entertain, also clearly envisioned itself as a form of dramatic history lesson, in effect asking its viewers to thin about how much has changed, but also what has not. We see, for instance, a rigid sexual hierarchy th has since been (mostly) obliterated, with male surgeons and physicians dashing about in dapp Edwardian dress, giving unambiguous orders to female nurses clad in demure floor-length dresse color coded to their level of rank. We follow the patients' stories as they lie in large public ward instead of private rooms, many of them dying of diseases that we now dispatch with a spritz penicillin. On the surface, it's a very antiquated environment.*

## While I was writing this book, an American TV show called *The Knick* aired on the network Cinemax, which was similar in its preoccupations.

But those familiar with the inside of a hospital will find some of the similarities to today's healt care facilities uncanny: the aseptic technique of the OR, with gowned, gloved, and masked personne

is practiced; infectious outbreaks, despite the inability of the staff to use antibiotics because the weren't yet discovered, are monitored and rapidly quarantined; and a variety of what was the experimental scientific gadgetry is employed, the clear forerunners to our high-tech medic subspecialties such as radiology. Their technology wasn't as sophisticated as ours, but these docto and nurses, and the medical system they inhabit, is recognizably modern. They *know* what they a doing, at least in broad outlines. Moreover, they know what they know and they know what they don' and that there is more to be discovered in the years to come. You can almost sense they are aware tha modern doctors and nurses will be looking back at their work, knowing it was unsophisticated at on level but also aware that such work was on a trajectory. *We are like you*, these characters whisper. *W have solved the puzzle about* how *to know. It's a matter of details from here on out.*

Those characters, although invented in a contemporary writer's head, are saying something tru about early modern medicine. We really *can* draw a straight line between us and them; their too were crude, but we approach patient care and think about pathology in fundamentally the same wa The arrow of medical and scientific progress is quite real.

I work as a physician and was educated in this scientific method in the manner of tens thousands of my brothers and sisters over the past century. We were trained in places like Iowa, Addi Ababa, London, Tokyo, and Mumbai. We speak a common language and have similar ways o thinking such that I can travel to Monrovia in the heart of West Africa, get off the airplane, go straigh to the hospital and evaluate a patient there, offer drugs from their stockroom with which I am familia and teach nascent doctors about disease, in much the same way that I do in Worcester, Massachusett And I know that what we provide with our so-called Western approach can have a much mor significant impact on the diseases people face in all of those places compared to the offerings of tho who still traffic in folk remedies.

Yet, like all characterizations rooted in a powerful truth, our pride in our modernity has th potential to blind us to our own shortcomings and leave us overconfident in our abilities.

This book is in large part about those shortcomings and the resulting overconfidence it ca produce. The term we'll give to this phenomenon is *uncertainty*. In the coming pages, we'll careful consider uncertainty—specifically, the uncertainty that permeates the theory and practice of moder medicine. The book's premise is simple: namely, that doctors do not often "know" what they ar doing with the same kind of mathematical precision that we associate with rocket scientists chemical engineers. A diagnosis is, much more often than not, a conjecture, and a prognosis typically less certain than *that*. There is a good deal more haziness in the world of medicine than mo people—those both outside *and* inside that world—understand. The consequences of tho misunderstandings can be perilous for physician and patient alike.

Uncertainty lies at the heart of what physicians do on a daily basis. Sometimes they are entire aware of it, and sometimes they fail to appreciate it. Sometimes it prominently features in discussion between doctor and patient. And sometimes it is completely misunderstood. The purpose of this boo is to show the reader not only *that* this is so, but *how* it is so as well.

Many of the original thinkers on probability and uncertainty were card playing and gambling typ living in the eighteenth and nineteenth centuries. This isn't accidental, as these pastimes predispo one to bend one's thinking toward the statistical. It would take medicine a few centuries to catch on earnest, but the groundwork for incorporating uncertainty into medicine was being laid during th heyday of the Enlightenment. Today, the early deeds of these medical pioneers are typically intone with great solemnity at some occasion involving pomp and circumstance such as a White Co ceremony or a medical school graduation. Interestingly, such evocations of the past are done f

almost precisely the wrong reasons, with the protagonists being falsely depicted as bringers of tru and light to otherwise ignoramical colleagues. In Chapter 6, we'll see one of the most famou examples of a great medical hero who is typically portrayed as a towering genius, only l misunderstood the meaning of the very discovery he was credited with making.

Much of this book will discuss uncertainty by emphasizing the underestimated imperfection results. My goal will be to show that these results, whether those of an individual blood test or tho of a 10,000-person study five years in the making, need to be approached with varying levels caution. I will try to highlight some areas in which doctors or patients or both have gotten themselv into trouble by neglecting uncertainty when they interpret results, not realizing that a positive test ma sometimes be negative in reality or that a new miracle drug may not be so miraculous.

In the coming pages, I will attempt to survey the landscape of uncertainty in the diagnosis an treatment of human disease. One central assumption I make is that uncertainty, at least for th foreseeable future, is an irreducible feature of modern medicine and that understanding uncertainty a vastly better strategy than ignoring it. My aim here is to explain those areas in which medic problem solving is most profoundly misunderstood, precisely because such misunderstandings ca have, at the extreme, lethal consequences. This is as true for the physician who blithely an injudiciously prescribes a course of antibiotics for an elderly patient with a touch of a cough, wh subsequently develops severe antibiotic-associated *Clostridium difficile* colitis, as it is for the fami members of a patient in the ICU who keep pressing the medical team to perform invasive, high-ris tests that aren't likely to help with their loved one's outcome. This is as true for the policy makers an "disease advocates" who recommend screening tests that sometimes aren't very accurate as it is f the politicians who may take unscientific, and ultimately harmful, positions in the pursuit of curryin favor with a special interest group. In short, I intended to make this book a practical exercise, consideration of the consequences of uncertainty in medicine.

You might be wondering right now how uncertainty takes shape—that is, what does it actuall *mean* to say that doctors are either uncertain about what they are doing or are overly confident becau they haven't taken enough uncertainty into account? To better acquaint ourselves with ho uncertainty manifests itself, let's consider one of the most well-known doctor-patient scenarios medicine: the "cancer prognosis" talk. After all, when newly diagnosed cancer patients sit down wi their oncologists, they ask a reasonable question: *how long do I have to live?* Most of us would expe to hear a dispassionate prediction from the physician as they stare the patient squarely, sympathetically, in the eyes: *I'm sorry, but you have 8 months . . .* or *you have 2 years* or some oth hard number that will coldly and scientifically state the simple truth.

What moment in the physician-patient encounter could be more well-known? This conversatio forms the basis of plot lines in TV dramas and movies. Many or most patients and their fami members rightly assume that, given the staggering array of blood tests and body scans that a performed in the aftermath of a new cancer diagnosis, all of that information can be reviewed by a oncologist and lead to a fairly accurate prediction of survival time. Nobody thinks that oncologists ca predict someone's remaining time to the day or the week, but most assume that their predictions ar accurate to within at least a few weeks' time.

In fact, oncologists almost *never* make these kinds of predictions because, as a rule, they're n very good at them. Only as death approaches closely do oncologists become reasonably decent prognosticating survival length—and even then, the evidence that they predict survival tim accurately is mixed at best. One review found that, even among terminally ill patients whose media survival is only four weeks, doctors were correct to within a week of survival in only 25 percent

cases, and in another 25 percent their predictions were wrong by more than four weeks! This revie paper looked only at patients who were clearly at the end of their lives, and pretty much anyon whether they possess a doctorate in medicine or not, can look at such patients and make a predictio with the same level of accuracy. So oncologists are keenly aware that guessing the life span of patient with virtually any cancer, unless they are presenting at a very advanced stage, is an exercise folly.

What oncologists *can* do with much greater accuracy is talk about the behavior of *groups* of peop who have a given cancer that present at a given stage. Based on data collected about cancer patien over the past four decades, they can talk about the *odds* of survival. For example, we know that patient who has localized bladder cancer has about a 70 percent chance of being alive at five year We know this because cancer is a disease that is tracked by the federal government—physicians a required to submit each case to a national database we'll explore later—so that number is fair precise. But oncologists saying to patients that they have a 70 percent chance of survival at five yea is a very different thing than predicting they have about four years left of life, as some patients wi bladder cancer will decline very quickly, and others will live for many years to come. Suc discussions necessarily entail an honest admission by clinicians that they cannot look into the cryst ball, and such statements are only meant for patients and families to consider the odds, weighing th risks and benefits as they move forward and make decisions about their care because cancer treatme can often make patients very sick and reduce their quality of life.

Even here, however, the acknowledgment that a patient is subject to laws governed by probabili rather than certainty can sometimes prove misleading. If a patient has squamous cell cancer of th lung, a very common kind of cancer, and the cancer is staged accurately, a doctor's statement that th patient has a 40 percent two-year survival with aggressive treatment is likely to be very accurate. Th is because thousands of people each year develop this disease, and data from such a large cohort less subject to the vicissitudes of random statistical fluctuations. Thus, researchers can know wi reasonable precision how many people are likely to survive in a given time span.

But take a more unusual cancer, such as chondrosarcoma. This disease, a cancer of cartilage cell is quite uncommon: only about four hundred people are diagnosed with the disease each year in th United States. Moreover, chondrosarcoma strikes people at various stages in life, and the cancer ca appear at different parts in the body. It may turn out that an overall 40 percent survival is simpl because the average of the past two years was 10 percent followed by 70 percent. Thus, the rarity of given disease can cause even confident statements conceding inherent uncertainty to b untrustworthy! This is uncertainty in action. But it can be found everywhere in medicine, not ju cancer diagnosis or prognosis. My goal here is to introduce you to some of the most importa medical topics today in which uncertainty plays a starring role.

## Snowball in a Blizzard

I chose the title *Snowball in a Blizzard* in part because it provides a useful metaphor for uncertaint Picture a game in which we are testing you on your ability to recognize snowballs thrown through th air by some person, say, one hundred feet away, in the midst of a raging blizzard. You don't how man snowballs we're going to throw nor how often nor how fast or slow. You just have to look out into th whiteness and decide whether you see randomness or you have identified something as worthy attention.

It should not be too hard for readers to picture the difficulty in the task. In the first chapter, we'
see an example where a scientist fiendishly performed almost exactly this experiment, except instea
of using snowballs, he used schizophrenics while sane individuals served as the blizzard, and he tri
to see whether psychiatrists were, as people would generally assume, good at spotting the "snowballs
(Though, to be clear, he didn't throw the patients through the air but rather had them present
psychiatric hospitals for admission.)

*Snowball in a Blizzard*, then, underscores that uncertainty is a structural component of da
interpretation and is not merely some occasional and accidental feature of the system. Sometimes th
uncertainty lies in diagnosis: *Does this test really mean that I have this disease?* Sometimes it pertai
to treatment: *If I take this drug, am I really going to benefit from it?* Sometimes it concer
environmental risks: *Is it really okay for me to have coffee while I'm pregnant*? Rarely are the answe
to these questions a simple unqualified yes or no. Uncertainty is nearly always part of the discussio
the only real question is, to what extent?

Moreover, *Snowball in a Blizzard* has a special resonance in medicine, for it is a well-knov
phrase among one group of doctors, a sort of inside joke they have indicating their keen appreciati
of the complexities of data interpretation. I learned of it many years ago when I was a medical stude
at the University of Cincinnati, when I was rotating on the radiology service. One day we attended
lunch sponsored by the department, intended to be an overview for any of us who might be interest
in pursuing radiology as a career. One of the speakers was finishing up his fellowship in pediatr
radiology, and he had just accepted a position at a suburban hospital outside Philadelphia. "I'll b
doing mostly general radiology, a little bit of everything," he said, but quickly added, "though I'm n
going to do mammography. They have other folks for that. And I'm perfectly happy to avoi
mammography anyway."

"Why would you want to avoid mammography?" someone asked.

"Because it's like trying to find a snowball in a blizzard," he immediately replied.

The phrase hit me like a thunderbolt. I came to learn that the witticism wasn't his originally b
was a bit of grim humor passed around by radiologists as a commentary on the difficulties
detecting breast cancer—the "snowball"—in the "blizzard" of otherwise healthy breast tissue. (W
will have much to say about mammograms in the coming pages.) Many radiologists, this doctor note
have found themselves facing lawsuits for having missed tumors in women who went on to develo
cancer.

Thus, "snowball in a blizzard" compresses all of the challenges of uncertainty into one pith
phrase. In doing so, it also expresses something peculiar about medicine that is not quite the same
the uncertainty discussed in other recent books, such as Nate Silver's *The Signal and the Noise*
Nicholas Nassim Taleb's *The Black Swan*. Those books have tackled, for instance, the problem
associated with guessing which baseball team or political candidate will win, what will happen wi
the stock market, or when the next big earthquake will hit California. These are unknown futu
events, and the bare thesis of these books might be thought of as *predicting the future is n
impossible, but it's more difficult than you think*. Yet, when radiologists make cracks about findin
snowballs in blizzards, they are implying not only that the future is uncertain but that knowing what
going on *right now* and directly in front of one's nose can be equally uncertain!

Finally, it is fortuitous that the phrase "snowball in a blizzard" is used specifically with referenc
to mammography, for not only does it describe the technical challenges involved in accurate reading
of mammograms, it also serves as a metonym about the contentious debate that has evolved arou
the practice. The biggest killer in the Western world is, by far, cardiovascular disease, and yet it

mammography that is arguably the most hotly debated medical technology in public health polic particularly in the United States. Much has been written about mammography and the dimensions the public discussion; my goal in a later chapter will be to apply a small amount of mathematical rig to the debate to clarify the logic that guided the public health authorities when they issued ne guidelines on screening mammograms several years ago.

## The Spectrum of Certainty

I will turn throughout the book to the notion of the spectrum of certainty—just *how much* we kno about a given subject—and then make comparisons with other health matters. It is a compass which one can navigate the landscape of doctorspeak and the weighty decisions doctors or heal authorities sometimes ask patients and family members to make. For instance, we know with a gre deal of certainty that a sedentary lifestyle combined with a high-calorie, high-fat diet puts individual at high risk of a variety of unpleasant medical problems. But do we know whether eati dark chocolate once each day will help prevent Alzheimer's dementia? As I will show in Chapter the answer is, not so much. But let's sketch out the spectrum and then step back and see how it can b useful.

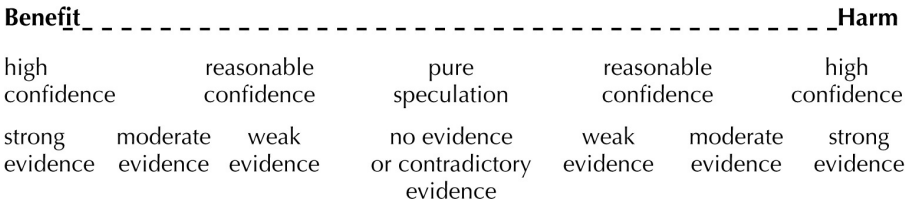


FIGURE 1.1. Spectrum of certainty.

At the left end of the spectrum, we encounter the idealized form of medical knowledge, where v have a high level of confidence that we really do know something, that this something indicates clea cut benefits, and that our knowledge will not be subject to massive revision.* Most people, and mar doctors, believe this is the state of much current medical knowledge, although I am a bit less sanguin that this is so. To be clear, I harbor no doubts whatsoever that red blood cells transport oxygen, fo instance, or that HIV causes AIDS or that antibiotics improve a patient's chances of survivin bacterial pneumonia. But there are a good many other aspects of medicine that remain in murki territory.

Readers shouldn't infer any political implications from this left-right-center scheme; it's totally arbitrary, whatever my political views.

The center-left side of the spectrum is what most would consider *reasonable* but not absolu confidence. Do drugs for diabetes save lives? Depending on the drug, the answer is yes—but sever diabetes medications come with some pretty serious side effects such that we can't assure *eve* patient that taking them will be beneficial. Many diagnostic technologies occupy this part of th spectrum, as we'll discuss in the first few chapters. This part of the spectrum is still a pretty goo place to find oneself, but there is room for improvement.

As we approach the middle of the spectrum, we enter the realm of pure speculation, whe evidence is either completely contradictory or lacking altogether. For instance, at present there much research devoted to the impact of the gut microbiome—that is, the many billions of bacteria th

live inside our intestines and the DNA that they possess—on human behavior and mental stat
Researchers have a sense that *something* is going on, though exactly *what* it is and how this ma
translate into drugs that might alter our perception of the world and how we interact with it
anyone's guess. (That hasn't stopped rampant speculation on the Internet about "mood altering" foo
regimens, however, an example of the profit to be made in creating the illusion of certainty. This is
problem that extends beyond the hawkers of fad diets: in Chapters 6 and 7, we'll look at what happe
when multinational conglomerates do essentially the same thing.)

As we start to move toward the right side of the spectrum, we begin to have greater confidence
our knowledge, but this time our increasing certainty is of the *harms* of some drug or innovation
diagnostic approach. Perhaps the most provocative argument I will make in this book is that th
practice of using mammograms to screen otherwise healthy women under the age of fifty is on th
center-right spectrum of certainty and that there is a minimal to moderate amount of evidence that,
currently performed, mammography in this population carries overall net harm.

Finally, the right side of the spectrum is where we're quite confident that some practice
harmful. For example, avoiding antibiotics is a bad idea when one has clear signs of a probab
bacterial infection. But it's also a bad idea to take antibiotics, especially for prolonged periods, whe
there is no evidence of bacterial infection. Occasionally, some groups have a vested interest in sowin
seeds of confusion and having people believe that some medical knowledge is in the middle of th
spectrum when in fact it is out toward the right end, as it is in this case. Chapter 5, which looks at th
treatment of Lyme disease, will explore one such group in depth.

The spectrum of certainty is a crucial tool to help make sense out of the sometimes overwhelmin
information with which a patient or family member can be bombarded when trying to understand
health issue. My argument is that uncertainty is the great unspoken secret of medicine and that b
ignoring this fundamental uncertainty we are doing real harm to ourselves. However, I don't make th
argument in a linear fashion. False certainty can lead us as doctors and patients to misinterpret da
and thus make bad choices; each chapter, in some way, adds evidence to this argument. But I cover
lot of ground and investigate many different disciplines. That's by design so that you can see just ho
pervasive uncertainty really can be. By utilizing the idea of the spectrum of certainty, readers ca
envision the broader claims of the book without having to "reinvent the wheel," as it were, as the
read each new chapter, struggling to connect each divergent story, hearing only the static and not th
signal.

A working notion of the spectrum of certainty also allows one to move past the binary constructio
of doctors either knowing everything or doctors knowing nothing at all (more on this latter vie
anon). It also provides readers with some perspective on how best one can probe a health-ca
provider, allowing one to ask the deceivingly simple question about what is or isn't known about
subject. Finally, it provides a framework by which we can apply some mathematical precision to
topic. For example, in Chapter 1 we'll look at the prostate specific antigen (PSA) test, a screening to
for prostate cancer; when one attempts to quantify the exact benefits of the PSA test, the often fiero
debates over the past ten to twenty years about its value seem fairly ridiculous.

Consider the Donald Rumsfeld quote that began the introduction. "There are known knowns, the
are known unknowns, and there are unknown unknowns"—his quip came as part of a tart reply to
reporter who had the temerity to question whether the Bush administration should have anticipated th
chaos that engulfed Iraq after the US armed forces deposed Saddam Hussein in 2002. His point,
rather dressed-up version of the observation "shit happens," was meant to convey the impossibility
knowing with certainty how a post-Hussein world would work. Whatever else one may think

Rumsfeld, the administration he served, or the planning and prosecution of the Iraq War, he left u with one of the more crisp and useful observations of the nature of epistemology: sometimes one certain of the state of the world, sometimes one can have a clue about it, and sometimes one is utter flummoxed by what's really out there.

This book is primarily concerned about the middle region of the spectrum of certainty: the know unknowns in medicine. Moreover, this book asserts something that may be a surprise to both patien and doctors alike: *most* of medicine functions in the world of known unknowns—as well as th unknown unknowns! That is, doctors often may know the general outlines of a problem but may n know, or even be able to know, with total certainty the specific problem in a given patient at a give time. This book is an attempt to describe that aspect of medicine where the light of knowledge is di and the mind can play tricks on itself, diagnosing things that turn out not to be there or creating ma hysteria over relatively trivial and distant threats such as exotic, tropical viruses while simultaneous ignoring the public menace of the double cheeseburger, a significantly more lethal object in th Western world and especially so in the United States.

The writer Michael Pollan wryly informed the readers of his book *In Defense of Food* that h opening seven words—"eat food, not too much, mostly plants"—were the boiled-down advice of h entire tome, and the chapters themselves were merely clarification and elaboration of that advice. medicine, too, we have an answer to the seemingly ferociously daunting question, how do I sta healthy? We've known the answer with increasing scientific certainty for several decades now, and mirrors the straightforwardness of Pollan's advice in the same number of words:

*Exercise more*,
*Eat less*, and
*Do not smoke*.

*This* is the far left of the spectrum of certainty, and not much else can be found out there excep one or two items that we'll take up during the course of this book. Unless you have some relative unusual disease such as lupus or primary biliary cirrhosis that is often genetically determined requires special medications, this is really all you need to know about maintaining your health. That because most Americans die from cardiovascular disease and diabetes (which is why you should e modestly and exercise) or emphysema and lung cancer (which is why you shouldn't smoke Everything else is, largely, commentary. Of course, there are important health stories that deserv coverage, but one could make a strong case that these seven words should begin and end *every* new item that deals with medicine and health. So, for those reading books on the economy class model, just gave away the secrets to healthy living at the outset, and you can feel free to read no further.

## The Road Map

Broadly speaking, there are three major portions of this book. The early chapters deal with problem relating to uncertainty in *diagnosis*—that is, when do we know that someone has a disease? Chapter "*Primum Non Nocere*" (an ancient Latin dictum meaning "first, do no harm" that continues to b regarded as a bedrock value of medicine to this day) looks at the conundrum of overdiagnosis. Wi increasingly sensitive ways of detecting disease by means of technological advances in radiology an biochemistry, we are able to find diseases earlier in their course and thus have a greater impact o mortality. But it's become clear over the past generation that there is a price to be paid for this, and has come in our finding "disease" that turns out *not* to be disease in the conventional sense of the ter

—namely, some biologic process that would lead to illness or death if left unattended. For instanc
we'll see how doctors have found more and more cases of cancer, even though finding these cance
earlier hasn't ended up saving any lives, which must mean that the cancers they've found aren't t
kind of cancers that actually kill people.

The problem is that we can only know such nondisease diseases exist at a population level; wh
confronted with an individual patient, it is impossible to know with much certainty that son
treatment will carry the expected benefit. Since all treatments carry risks, this means that we are qui
probably harming some patients as a consequence of overdiagnosis.

The second chapter, "The Perils of Predictive Value," briefly recounts the tale of the physicist an
author Leonard Mlodinow when he received a shocking diagnosis of a terminal illness as part of
standard insurance exam. Only the diagnosis was wrong, and we will investigate just how wrong
was. Mlodinow's story is a cautionary tale in the perils of what are known as "false-positive" test
which is exactly what it sounds like—tests that appear to indicate disease but do so wrongly becau
no test is 100 percent perfect. The consequences of false-positive tests—and what treatments docto
might suggest as a consequence of those tests—can range from mild anxiety to outright bodi
mutilation.

For reasons that I will discuss, false positives are a frequent problem in screening tests, and
such Mlodinow's story helps illustrate the core issue in the third chapter, "Snowball in a Blizzard
which looks at the thorny issue of mammography. Although mammograms continue to be regarded a
one of the most important ways in which women can have an enormous positive impact on the
health, the data suggest a more nuanced reality. In large part this is because the technology can dete
breast cancer before it becomes clinically apparent, but uncertainty creates false positives, and wome
whose mammograms are falsely positive can suffer serious harm. Thus, ascertaining the true value
mammography involves weighing these two opposing variables. I will demonstrate, by looking
some sample data, the relative size of the benefit, as well as the risk.

The middle chapters of the book are mainly concerned with uncertainty in *treatment*. Chapter
"The Pressures of Managing Pressure," looks at recent guidelines for treating hypertension and ho
uncertainty divided expert consensus in a fairly dramatic manner. Chapter 5, "Lyme's Fals
Prophets," investigates a different set of expert-driven recommendations, which formed a kind
mirror image of the hypertension guidelines: although the expert consensus about Lyme diagnosis an
treatment is absolute, the popular perception is that there is great controversy. "Lyme's Fals
Prophets" looks at how this public confusion arose through the Internet, various advocacy groups, an
at least one powerful politician.

Chapter 6, "The Origins of Knowledge and the Seeds of Uncertainty," considers how uncertain
forms a structural component of drug trials. I will explore two of the biggest blockbuster classes
drugs of the modern age: lipid-lowering statin drugs such as Lipitor and the antidepressant class
drugs known as SSRIs, such as Prozac. In both cases, I'll put them under a microscope to see what w
do and don't know about what these drugs can offer to patients and consider the impact th
uncertainty has on the term "effectiveness" in relation to drugs. Chapter 7, "The Correlation/Causatio
Problem," evaluates ways other than drug trials that we learn about (or fail to know about) a drug
usefulness. That is, although drug trials produce as a rule the most ironclad data about how good
drug can be, there are other methods for assessing a drug's effectiveness, and these methods a
subject to their own kinds of uncertainty. I'll consider some of the major challenges involved
interpreting "retrospective" data.

Finally, I will briefly look at the role media plays in shaping our attitudes about medicine either b

emphasizing or disregarding uncertainty. We live in an age of unfettered access to all sorts of medi and yet whether one is watching a local television newscast or reading the latest online health report, good number of stories follow broadly similar patterns, frequently leaving consumers overestimatin medicine's miraculousness on the one hand or overscared by the system on the other. But I'll als examine one crusader for health media and his organization's vision for how the media can provide more balanced picture of what modern medicine has to offer without too much fuss, if they wou only listen.

After we've gone on this tour, I'll consider ways in which the average person might benefit fro an increased understanding about these concepts because the topics driving health care today wi surely be different not long after the publication of this book. Lastly, in the Appendix, I will explain i a very nontechnical way some of the mathematical concepts that underpin the discipline biostatistics, using some of the studies we have looked at as models for understanding such concep without using equations.

Uncertainty pervades medicine: surgeons as well as psychiatrists must cope with its presenc whether they are aware of it or not. Problems that arise from uncertainty can be found in the hospit corridors, the pathology lab, the nursing home, and in urgent telephone calls from sick and worrie patients. Nearly all exercises in clinical judgment involve incorporating uncertainty into equations medical reasoning—a variable that, like Einstein's cosmological constant, cannot be stamped out r matter how much brainpower is brought to bear. By developing an appreciation for uncertainty, w can get at the heart of many of today's medical mysteries. By bringing uncertainty into ope discussion, we can assess the real value of mammograms, recognize the hype of so many medic reports, sense when to push a physician for more testing, or resist a physician's enthusiasm when oth tests or treatments are being offered.

Ultimately, appreciating the subtleties and parameters of uncertainty allows patients and famil members to be empowered. I am writing this book to help people understand uncertainty to help the navigate the swift currents and roiling waters of modern medicine. I cannot promise to translate th often inscrutable language of physicians and the medical research that is their touchstone, but I ca attempt to give people a tool by which real communication can take place.

## Nobody Knows Anything

It may be unsettling to a reader thus far unaccustomed to these concepts to be told that uncertainty central to modern medicine. A sense of despair can set in when discussions of probability an statistics take center stage in the doctor-patient interaction. Frank admissions of uncertainty can ofte be met with irritation, because the idea that a test doesn't provide an unassailable answer th describes a crystal-clear reality is so foreign to many people. Some may have the emotional urge conclude, after reading thus far, that these tests are pretty much worthless and that, in the immort words of screenwriter William Goldman, "nobody knows anything."

But this book is not a jeremiad. The nihilism of "nobody knows anything," although emotional satisfying on a certain level, is just that: an emotional response, a spasm of frustration with a healt care system that is mightily complicated enough, to say nothing of expensive, bureaucratic, an frequently impersonal. Only by stripping away the layers of misunderstanding about what medicine and how it works can patients and families begin to be their own best advocates. Uncertainty is f from the only area in which misconceptions exist, but I would argue it is a critical area, and graspin

it might just help people avoid some of the more unpleasant shocks that medicine is capable delivering.

Indeed, the *point* of highlighting all these various instances of the limits of our medical knowled is to demonstrate that these can be teaching moments—occasions where we can illustrate what's stake in a medical decision and how we think about a problem. Are the stakes high or low? Are th repercussions of a decision significant or trivial? And is the evidence supporting a given decisio overwhelming, minimal, or somewhere in between? By opening up about uncertainty, we a championing patient autonomy, rather than arrogantly flicking it away as an irritating feel-good idea

This book is *hopeful* in its outlook, which I ask readers to keep in mind if they find themselv thinking in the early chapters how deeply flawed our medical practices truly are, and how foolish o certainties. My goal is to offer you a vision: *read this book and you will learn something to impro your life and deepen your understanding of the process of medicine*. I want readers to see ho embracing uncertainty allows for more humane treatment, less anxiety, and better care. But to do th we will need to confront some sobering realities of our modern medical system. It may require t periodic deep breath and the awareness that acquainting yourself with this medical machine ca occasionally make for bleak reading. Have faith, for there are rewards in knowing and understandin There is a tangible and powerful light at the end of the tunnel.

## Narrative and Uncertainty

*Why* do people—physician and patient alike—have such difficulties coping with concepts probability and uncertainty? The answers can be found in the disciplines of evolution and psycholog and are largely beyond the scope of this book, but the power of stories, and the influence of narrativ on our thinking, is critically important. We think about ourselves, and of the universe around us, absolute terms of cause and effect. We don't regard our lives as being subject to mere chance; w assume that the variables are within our control and that our successes can be attributed to o strengths and our failures to our weaknesses. Medicine, too, is a story of sorts, and we resist the notio that chance plays a key role in the endeavor.

But this just isn't so. It is a trick of the mind, and it impedes us from understanding the mode world. Daniel Kahneman, a Nobel laureate in economics, refers to this as the "narrative fallacy writing that it inevitably arises "from our continuous attempt to make sense of the world," adding th "the explanatory stories that people find compelling are simple; are concrete rather than abstract . and focus on a few striking events that happened rather than on the countless events that failed happen." In medicine—both at the personal and at the policy level—succumbing to the narrati fallacy can be disastrous.

Take a look at nearly any news story on medicine, and you will see this devotion to narrative full view. Invariably, a story on a new diabetes drug or a fancy new surgical technique or a unfortunate reaction to a medication will begin with the saga of one (or more) patients. All to frequently statistics aren't even mentioned: Is this patient's story common or rare? Is the sto applicable to the many or the few? When these rather important details are sidestepped, th misunderstandings can be profound, with the result that patients and families often feel betrayed wh the state-of-the-art technology fails to deliver.

I think the reason people have so much difficulty coping with uncertainty is that these powerf narratives, from which the narrative fallacy arises, are both hidden and in plain sight. You can almo

sample content of Snowball in a Blizzard: A Physician's Notes on Uncertainty in Medicine

- download online Roads to Quoz: An American Mosey
- *read online Ferragus - La Fille aux yeux d'or*
- read online Bitters: A Spirited History of a Classic Cure-All, with Cocktails, Recipes, and Formulas
- click Complete Works of Victor Hugo here

- http://metromekanik.com/ebooks/Roads-to-Quoz--An-American-Mosey.pdf
- http://omarnajmi.com/library/Aristotle-Transformed--The-Ancient-Commentators-and-Their-Influence--Ancient-Commentators-on-Aristotle-.pdf
- http://yachtwebsitedemo.com/books/Bitters--A-Spirited-History-of-a-Classic-Cure-All--with-Cocktails--Recipes--and-Formulas.pdf
- http://creativebeard.ru/freebooks/Town-Tamers.pdf