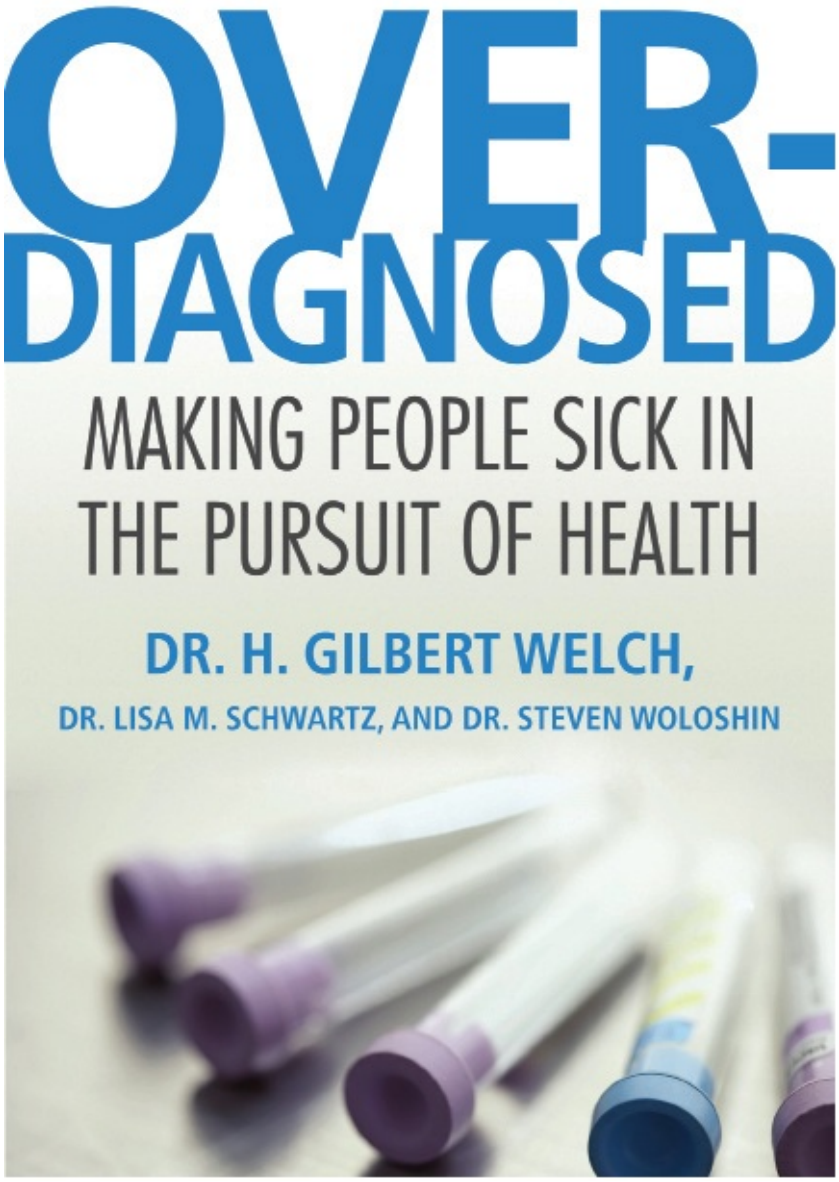
OVER-
DIAGNOSED
MAKING PEOPLE SICK IN
THE PURSUIT OF HEALTH
DR. H. GILBERT WELCH,
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Overdiagnosed

Making People Sick in the Pursuit of Health

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Beacon Press • Boston

To my mother,

Katharine Smith Welch

(1920–2010)

Contents

Introduction: Our Enthusiasm for Diagnosis

My first car was a ’65 Ford Fairlane wagon. It was a fairly simple—albeit large—vehicle. I could even do some of the work on it myself. There was a lot of room under the hood and few electronics. The only engine sensors were a temperature gauge and an oil-pressure gauge.

Things are very different with my ’99 Volvo. There’s no extra room under the hood—and there are lots of electronics. And then there are all those little warning lights sensing so many different aspects of my car’s function that they have to be connected to an internal computer to determine what’s wrong.

Cars have undoubtedly improved over my lifetime. They are safer, more comfortable, and more reliable. The engineering is better. But I’m not sure these improvements have much to do with all those little warning lights.

Check-engine lights—red flags that indicate something may be wrong with the vehicle—are getting pretty sophisticated. These sensors can identify abnormalities long before the vehicle’s performance is affected. They are making early diagnoses.

Maybe your check-engine lights have been very useful. Maybe one of them led you to do something important (like add oil) that prevented a much bigger problem later on.

Or maybe you have had the opposite experience.

Check-engine lights can also create problems. Sometimes they are false alarms (whenever I drive over a big bump, one goes off warning me that something’s wrong with my coolant system). Often the lights are in response to a real abnormality, but not one that is especially important (my favorite is the sensor that lights up when it recognizes that another sensor is not sensing). Recently, my mechanic confided to me that many of the lights should probably be ignored.

Maybe you have decided to ignore these sensors yourself. Or maybe you’ve taken your car in for service and the mechanic has simply reset them and told you to wait and see if they come on again.

Or maybe you have had the unfortunate experience of paying for an unnecessary repair, or a series of unnecessary repairs. And maybe you have been one of the unfortunate few whose cars were worse off for the efforts.

If so, you already have some feel for the problem of overdiagnosis.

I don’t know what the net effect of all these lights has been. Maybe they have done more good than harm. Maybe they have done more harm than good. But I do know there’s little doubt about their effect on the automotive repair business: they have led to a lot of extra visits to the shop.

And I know that if we doctors look at you hard enough, chances are we’ll find out that one of your check-engine lights is on.

A routine checkup

I probably have a few check-engine lights on myself. I’m a male in my mid-fifties. I have not seen a doctor for a routine checkup since I was a child. I’m not bragging, and I’m not suggesting that this is a path others should follow. But because I have been blessed with excellent health, it’s kind of hard to argue that I have missed out on some indispensable service.

Of course, as a doctor, I see doctors every day. Many of them are my friends (or at least they were before they learned about this book). And I can imagine some of the diagnoses I could

accumulate if I were a patient in any of their clinics (or in my own, for that matter):

• From time to time my blood pressure runs a little high. This is particularly true when I measure it at work (where blood pressure machines are readily available).
Diagnosis: borderline hypertension
• I'm six foot four and weigh 205 pounds; my body mass index (BMI) is 25. (A "normal" BMI ranges from 20 to 24.9.)
Diagnosis: overweight
• Occasionally, I'll get an intense burning sensation in my midchest after eating or drinking. (Apple juice and apple cider are particularly problematic for me.)
Diagnosis: gastroesophageal reflux disease
• I often wake up once a night and need to go to the bathroom.
Diagnosis: benign prostatic hyperplasia
• I wake up in the morning with stiff joints and it takes me a while to loosen up.
Diagnosis: degenerative joint disease
• My hands get cold. Really cold. It's a big problem when I'm skiing or snowshoeing, but it also happens in the office (just ask my patients). Coffee makes it worse; alcohol makes it better.
Diagnosis: Raynaud's disease
• I have to make lists to remember things I need to do. I often forget people's names—particularly my students'. I have to write down all my PINs and passwords (if anyone needs them, they are on my computer).
Diagnosis: early cognitive impairment
• In my house, mugs belong on one shelf, glasses on another. My wife doesn't understand this, so I have to repair the situation whenever she unloads the dishwasher. (My daughter doesn't empty the dishwasher, but that's a different topic.) I have separate containers for my work socks, running socks, and winter socks, all of which must be paired before they are put away. (There are considerably more examples like this that you don't want to know about.)
Diagnosis: obsessive-compulsive disorder

Okay. I admit I've taken a little literary license here. I don't think anyone would have given me the psychiatric diagnoses (at least, not anyone outside of my immediate family). But the first few diagnoses are possible to make based solely on a careful interview and some simple measurements (for example, height, weight, and blood pressure).

More are possible if a doctor were to order any one of a number of diagnostic tests for me. Even routine blood work—a complete blood count, an electrolyte panel, and liver function tests—involves more than twenty separate measurements. The chances are good that I would have at least one abnormal value.

And then there's imaging. Lots of people have "abnormal" findings on X-ray studies. If I had a chest X-ray, I wouldn't be surprised if a lung nodule was seen. If I had an abdominal CT scan, I wouldn't be surprised if a cyst on my kidney was found.

Further inspection could reveal more. A colonoscopy might show that I have polyps—as about a third of people my age do. A prostate biopsy might demonstrate a small cancer—which many men have, even if their PSA (prostate-specific antigen) screening tests are normal. And it's a safe bet that my genome contains all sorts of genetic variants.

To be fair, most doctors wouldn't order any imaging studies; some might have skipped the

routine blood work. Nonetheless, several of these diagnoses could have been made.

Would I be better off if I were given these diagnoses? I don't think so. Would I be put on prescription medications? Probably. Would I consider this good medical care or bad? I'd say bad. But enough about me. This book is about the millions of Americans who have access to what some would call the best medical care in the world. Of course, there are millions of other Americans whose access is severely limited—the uninsured. This is a real problem, but not the topic of this book. The problems described here are actually less likely to happen to the latter group, simply because they receive less medical care. This book is about the relentless expansion of medicine and our increasing tendency to make diagnoses.

Americans have been trained to be concerned about our health. All sorts of hidden dangers lurk inside of us. The conventional wisdom is that it's always better to know about these dangers so that something can be done. And the earlier we know, the better. That's why we are so enthusiastic about amazing medical technologies that can detect abnormalities even when we think we are well. That's also why we welcome the identification of risk factors, disease awareness campaigns, cancer screening, and genetic testing. Americans love diagnosis, especially early diagnosis.

Not surprisingly, we get more diagnoses today than we did in the past. In fact, we are in the midst of an epidemic of diagnosis. Again, the conventional wisdom tells us that this is good: finding problems early saves lives because we have the opportunity to fix small problems before they become big ones. What's more, we believe there are no downsides to looking for things to be wrong.

But the truth is that early diagnosis is a double-edged sword. While it has the potential to help some, it always has a hidden danger: overdiagnosis—the detection of abnormalities that are not destined to ever bother us.

Living longer, yet sicker?

Consider the generation of which I am a part—the baby boomers. This is the generation born in the period of increased birthrates that followed World War II. They went on to become leaders in the major social movements of the 1960s—civil rights, feminism, and the Vietnam War protests. They also spawned the counterculture of that era: sex, drugs, and rock and roll. As they aged, they became the dominant culture: they gained political power and amassed large sums of money. Now television ads promise them that they will engage in a new kind of retirement, one in which their dreams won't retire. Just think of the Ameriprise ad featuring the late Dennis Hopper saying, "'Cause I just don't see you playing shuffleboard—know what I mean?" (while the powerhouse organ riff from the classic rock hit "Gimme Some Lovin'" blares in the background). Brings back fond memories of high school. I love it.

But then I saw a piece in the *Washington Post* suggesting that the boomers might indeed need to prepare for a different view of retirement—because they are falling apart.[1] Large national surveys reported that while 57 percent of those born before World War II reported excellent health as they approached retirement, only 50 percent of boomers described themselves in this way. About 56 percent of those born before World War II reported having a chronic condition at retirement; about 63 percent of boomers reported having a chronic condition at the same age. Could boomers be in worse shape than their parents were?

A few weeks later I attended a medical meeting at which one of the participants reported on the Department of Health and Human Services' midcourse review of the program called Healthy People 2010. This is the federal government's effort to increase both the length and the quality of life.

Length of life was measured using life expectancy—the average number of years Americans live. Quality of life was measured using healthy life expectancy—the average number of years Americans live free of disease (such as heart disease, stroke, cancer, diabetes, hypertension, and arthritis). The speaker showed a table with data from 1999 to 2002, during which life expectancy had increased by about six months, from 76.8 to 77.2 years. But surprisingly, the healthy life expectancy had *fallen* by a little more than a year, from 48.7 to 47.5.

It looked like the program was getting it only half right: the quantity of life was increasing (people were living longer), but the length of healthy life was decreasing (people were having fewer disease-free years). Could we be living longer, yet be sicker? That is hard to believe. But there is an alternative explanation: we live longer, we are healthier, but we are increasingly more likely to be *told* we are sick.

Some may view diagnosing more people (and treating more people) as the price that has to be paid for most of us to achieve an extension of life. This assumes that early diagnosis and treatment is the only explanation of a longer life span. But because other things are more important (such as not smoking, nutrition, exercise, and medical care for the acutely ill), it's likely that most of this life extension would occur regardless of whether or not there was more diagnosis. And since for many, length of life is not the only goal, questions about whether the health-care system introduces disease and disability into the population become more relevant.

What this book is about

My mother thinks she knows what this book is about. She is almost ninety and has advanced dementia. A few months ago she picked up my first book and read the title out loud: *"Should I Be Tested for Cancer?"* And then she answered with a resounding *"No!"* (Note: her response is a vast oversimplification of the book's content.)

She asked me what my next book would be about. I attempted to explain it to her. She suggested that it be titled *Should I Be Tested for Anything?* Not that great a title, but it gives you the idea. This book examines the possibility that American medicine now labels too many of us as "sick."

As I've noted, the conventional wisdom is that more diagnosis—particularly, more early diagnosis—means better medical care. The logic goes something like this: more diagnosis means more treatment, and more treatment means better health. This may be true for some. But there is another side to the story. More diagnosis may make healthy people feel more vulnerable—and, ironically, less healthy. In other words, excessive diagnosis can literally make you feel sick. And more diagnosis leads to excessive treatment—treatment for problems that either aren't that bothersome or aren't bothersome at all. Excessive treatment, of course, can really hurt you. Excessive diagnosis may lead to treatment that is worse than the disease.

More specifically, this book is about overdiagnosis. While the term sounds like it means simply "excessive diagnosis," it actually also has a more precise meaning. Overdiagnosis occurs when individuals are diagnosed with conditions that will never cause symptoms or death.

So while I diagnosed myself with a number of conditions a few pages ago, some were not overdiagnoses, since I had symptoms: heartburn, cold hands, and so forth (although they may well constitute excessive diagnoses, given that my symptoms were trivial). But the diagnoses related to slight elevations in blood pressure and weight were not associated with symptoms. They could reflect overdiagnosis. So too could all the diagnoses I might have gotten following subsequent testing. In other words, overdiagnosis can occur only when a doctor makes a diagnosis in a person who has no symptoms referable to the condition. While this can happen when a doctor stumbles

onto unexpected diagnoses in the course of an evaluation of unrelated conditions, generally it happens because doctors seek early diagnoses—either as part of an organized screening effort or during routine exams. Thus, overdiagnosis is a consequence of the enthusiasm for early diagnosis.

The trouble is that we doctors don't know if an individual has been overdiagnosed unless that person forgoes treatment, lives the rest of his or her life symptom free, and dies from some other cause. But we do know that if we make more and more diagnoses in a healthy population, we are more likely to overdiagnose.

Overdiagnosis is a relatively new problem in medicine. In the past, people didn't go to the doctor when they were well—they tended to wait until they developed symptoms. Furthermore, doctors didn't encourage the healthy to seek care. The net result was that doctors made fewer diagnoses than they do now.

But the paradigm has changed. Early diagnosis is the goal. People seek care when they are well. Doctors try to detect disease earlier. More people have findings of early disease than of late disease. So we make more diagnoses—including diagnoses in those who have no symptoms. Some of these people are destined to develop symptoms. Others are not—they are overdiagnosed.

So the problem of overdiagnosis stems directly from the expansion of the pool of individuals in whom we make diagnoses: from individuals with disease (those with symptoms) to individuals with abnormalities (those without symptoms). The problem is further aggravated as the definition of what constitutes an abnormality gets increasingly broad.

The objective of this book is to lay out the data on how overdiagnosis occurs, explain why it can be harmful, and explore its root causes. My hope is to help you critically consider the desirability of being turned into a patient prematurely.

Let me be clear about why you should care about overdiagnosis. Since doctors don't know who is overdiagnosed and who is not, overdiagnosed patients tend to get treated. But an overdiagnosed patient cannot benefit from treatment. There's nothing to be fixed—he will neither develop symptoms nor die from his condition—so the treatment is unneeded. An overdiagnosed patient can only be harmed. And the simple truth is that almost all treatments have the potential to do some harm.

What this book is not about

This book is not about what you should do when you are sick. It is not for the few who are severely ill (those for whom medical care offers a lot), but for the many who are (or used to be) basically well—or those who have one illness and are at risk of being told they have others. Nor is this book an apology for sloppy diagnosis in the sick. Diagnosis is always important when people are suffering, and it's important that it be done well. None of my comments should be construed as suggesting you are better off not being diagnosed when you are sick. Finally, this book is not a condemnation of all of American medicine, nor a call for alternative medicine. I'm conventionally trained in Western medicine, and I believe doctors do a lot of good. If you are sick, you should see one.

A final note about people and language

Before moving on, I feel obliged to make a few comments about names and words. There are stories in this book: stories about my patients, my friends, and people I've met along the way. The stories are accurate; the names are not. While I have not altered information relevant to the clinical narrative (such as the individual's gender, age, symptoms, and experiences), I have altered

information that could potentially identify individuals (such as whether a person is from New York or New Jersey—as my daughter might say, "Like it matters").

Then there is the word *disease*. Although the word has a wide range of interpretations, its origins are quite specific. *Dis-* means "without," and *ease* requires no explanation. A synonym for *disease* might be *discomfort*. Although there are other perfectly legitimate definitions, in this book *disease* will refer to a condition that a person experiences—a sickness, an illness, a disorder that produces symptoms.

The word *abnormality* will serve a distinct purpose. I will use it to describe findings that are considered abnormal in the medical profession yet are not experienced by the individual. Some of the most familiar abnormalities—high blood pressure, high cholesterol—will sometimes be referred to as *conditions* to distinguish them from *diseases*.

Although occasionally I use the broad term *health-care provider*, for simplicity, I tend to use the term doctor. This is not meant to exclude other caregivers. On the contrary, it is important to acknowledge that physician assistants and nurse-practitioners are assuming larger and more important roles in medicine—particularly in the delivery of primary care (where a lot of diagnoses are made).

Finally, some quick notes about pronouns. The most familiar are *he* and *she*. Of course, a patient can be either male or female, as can a doctor (there are now more women than men enrolled at Dartmouth Medical School). I don't know of a satisfactory way to handle the absence of a gender-neutral singular pronoun. *He* or *she* gets pretty awkward after a while; using *they* would upset my mother too much. So when the situation allows (some diseases are gender specific), I alternate between the two.

Then there's *we*. *We* will generally refer to "we doctors" or "we health-care providers." (I'd guess *generally* means "roughly 90 percent of the time"—although I'm not going to bother to calculate it.) I use *we* in an attempt to represent the professional perspective of doctors: what we are taught in medical school, how we are trained as residents, what we learn in practice. In short, I'll try to give you a sense of how we think. Not that we all think alike, but we do all share a common experience, about which you should have some insight.

Occasionally *we* will refer to "we the public." Just like you, I am a member of society and a potential patient. And all of us will face some decision about how we want to interact with medical care. Sometimes I modify the *we* with something like "we the public" when I am attempting to communicate this perspective.

I will represent me—the author. But it should be another *we*, as this book is really a collaboration of three authors: Dr. Lisa Schwartz, Dr. Steven Woloshin, and myself. But to avoid the confusion with the other *we*'s requires this sleight of hand. To be clear, our voice encompasses two viewpoints. All three of us are academic physicians: we see patients, we teach students, and we do research. But we are also people, and therefore potential patients. As people, we are concerned about the relentless expansion of the medical profession and the subsequent drive to turn people into patients. It is the melding of these two viewpoints—medical and personal—that provides the motivation for this book.

Chapter 1: Genesis

People Become Patients with High Blood Pressure

Might as well begin at the beginning. And the beginning of overdiagnosis lies in the diagnosis and treatment of a common condition—hypertension (high blood pressure).

Only one paragraph in and I can already sense the unease in my physician and public health colleagues (*Is he really going to start by suggesting we stop diagnosing hypertension? We're not doing enough to diagnose and treat hypertension now!*). In fact, detecting and treating high blood pressure is one of the most important things we doctors do. And it's true that we don't do enough of it. There are some people with undetected hypertension who would benefit tremendously from treatment.

But it's also true we do too much of it. Some people are diagnosed and treated needlessly—they are overdiagnosed. Hypertension was arguably the first condition for which regular treatment was started in people without symptoms.[1] Prior to the late twentieth century, physicians generally prescribed medicines only to patients with symptoms of disease. But hypertension changed that. Suddenly people with no health complaints—who perceived no health problems—were being given a diagnosis and prescribed treatment. People became patients—it was really a remarkable paradigm shift. Seeking diagnoses of hypertension in those without symptoms provided the opportunity to prevent symptomatic disease in some, but at the cost of making the diagnosis in others who were not destined ever to develop symptoms or die from hypertension. In other words, at the cost of overdiagnosis.

A condition that warrants treatment

I work at a small Department of Veterans Affairs hospital in White River Junction, Vermont. Earlier in my career, I'd spend one or two months a year taking care of patients who were sick enough to be admitted to the hospital. One evening I admitted a fifty-seven-year-old man who came to the emergency room complaining of severe chest pain. Mr. Lemay told me he had been having increasingly frequent episodes of chest pain; sometimes he had the chest pain when he was walking or otherwise exerting himself, and sometimes he had the chest pain when he was doing nothing at all.

The phrase *chest pain* has almost magical qualities in medicine. It is a powerful catalyst for action; it can trigger a cascade of tests and interventions. That is because chest pain sometimes signals a heart attack—the number-one cause of death in the United States. A patient's mere mention of chest pain impels us to do a number of things very quickly, like provide supplemental oxygen, administer an aspirin, and check an electrocardiogram. Mr. Lemay's electrocardiogram was markedly abnormal. It showed that part of his heart wasn't getting enough oxygen, a sign of an impending heart attack.

But something else was markedly abnormal. His blood pressure was 202/117. Blood pressure is measured using two numbers. The top number (in this case, 202) is called the systolic blood pressure. It reflects the highest pressure in your arteries—the pressure created immediately

following the contraction of the heart. The bottom number (in this case, 117) is called the diastolic blood pressure. It reflects the lowest pressure in your arteries—the pressure immediately prior to the contraction of the heart—that is, when your heart is most relaxed. If a doctor is asked, "What is a normal blood pressure?" she'll typically give the numbers 120/80. But doctors see blood pressures higher than this all the time. The question is: At what level is blood pressure abnormal? Most doctors would agree that a systolic pressure over 160 or a diastolic pressure over 90 is abnormally high. And we all would agree that 202/117 is abnormally high. Really high. In fact—really, really high.

Because an impending heart attack was a genuine concern, I admitted Mr. Lemay to the intensive care unit. We gave him medicines to lower his blood pressure, and his chest pain quickly went away. He did not have a heart attack. Well, maybe by today's standards he did. This was in the early 1990s, before we routinely checked troponin levels (a very sensitive indicator of heart damage). Then we made the diagnosis by combining electrocardiogram findings with relatively crude laboratory measurements. My guess is that today we would diagnose Mr. Lemay as having had a small heart attack—a subendocardial myocardial infarction. But all the same, a couple of days later, he went home. That was over fifteen years ago. And he has not been in the hospital since.

Mr. Lemay is now seventy-two. I see him in clinic about twice a year. He's been very healthy. I've done very little for him, except one thing: I've made sure his blood pressure is controlled. It's not glamorous. It's not difficult. It certainly doesn't require a physician (nurses, nurse-practitioners, and physician assistants can do it just as well). But for patients like Mr. Lemay, it's pretty close to being the difference between life and death. While one can never be sure, I am confident that he would have died years ago had his hypertension not been diagnosed and adequately treated. Of course, he came to the emergency room not for the high blood pressure but for the chest pain it caused. But even if he had had no symptoms, simply a sustained blood pressure of 202/117, I would say that treatment saved his life. Let me tell you why I can confidently say that.

Discovering the effects of hypertension

Although physicians have been able to measure blood pressure for well over a hundred years, they were slow to recognize the dangers of hypertension. President Franklin D. Roosevelt, for example, was known to have high blood pressure—it was recorded as being higher than 200/100 at the time of his reelection in November of 1944—but it is unclear whether his doctors recognized it was a problem. Six months later he developed a hypertensive crisis: a severe headache followed by a loss of consciousness and a measured blood pressure of 300/190. He died shortly thereafter of a massive hemorrhage in his brain [2].

As late as the 1950s, some expert physicians considered high blood pressure to be essential for some patients: essential to deliver enough blood to vital organs. Insurance companies, however, did recognize the dangers of hypertension at the time—they observed that people with high blood pressure were more likely to die, and they often refused to sell them life insurance policies.[3]

In the mid-1960s, the Veterans Administration (now the Department of Veterans Affairs) decided to study the value of treating people who had hypertension but no symptoms of it. It initiated a VA cooperative study; *cooperative* because these studies involve veterans from multiple VA hospitals. This study identified men (almost all veterans at the time were male) who had been found to have high blood pressure when they were hospitalized for other reasons. The investigators tracked the men's blood pressure after they left the hospital and recruited those whose average outpatient diastolic blood pressure—the bottom number—ranged from 115 to 129 (that is, those

who had what we would now call severe diastolic hypertension). Because the idea of giving people medicine for a condition that produced no symptoms was so unusual, the investigators decided to make sure that study participants would actually take the medicine prescribed for them. So before any patient could be enrolled in the study, he had to pass a test to demonstrate that he would take a medicine regularly even if he felt well.

Here's what the test involved. Each prospective participant was given two containers of pills (two because the investigators correctly anticipated that treated patients would require two drugs) along with instructions of how to take each. One pill was an inert sugar pill; the other was vitamin B2—also known as riboflavin. Two weeks later, the participants met with study personnel, and they counted the pills left in each container. If the correct number remained, the investigators presumed that the medicine had been taken correctly. But they had a second way to check whether prospective participants had taken their medicine: a simple urine examination. Riboflavin imparts a bright yellow color to urine that fluoresces brilliantly under UV light. Nearly half of the prospective participants failed the test and so were not enrolled in the study, as they could not be relied upon to take their medications regularly.

This finding highlights how much of a paradigm shift this was. At that time, people simply didn't take medicines in the absence of symptoms. Now it is the norm. In contemporary studies of hypertension therapy, typically less than 20 percent fail a test of medication adherence.[4]

This VA study was a true experiment: The enrolled participants were divided into two groups, and the group to which each subject was assigned was determined purely by chance. One group received treatment for hypertension (the drug hydrochlorothiazide combined with either reserpine or hydralazine); the other group received placebos (inert sugar pills). The VA cooperative study of the treatment of severe hypertension is considered one of our classic randomized trials. Because discussions of randomized trials will appear throughout this book, figure 1.1 illustrates their basic design. Randomized trials are studies in which enrolled patients are assigned to either receive treatment or not simply by chance. We typically describe this allocation process as being like the flip of a coin; operationally, however, it is accomplished by computer. The word *randomized* is used because the group an individual is assigned to is randomly chosen.

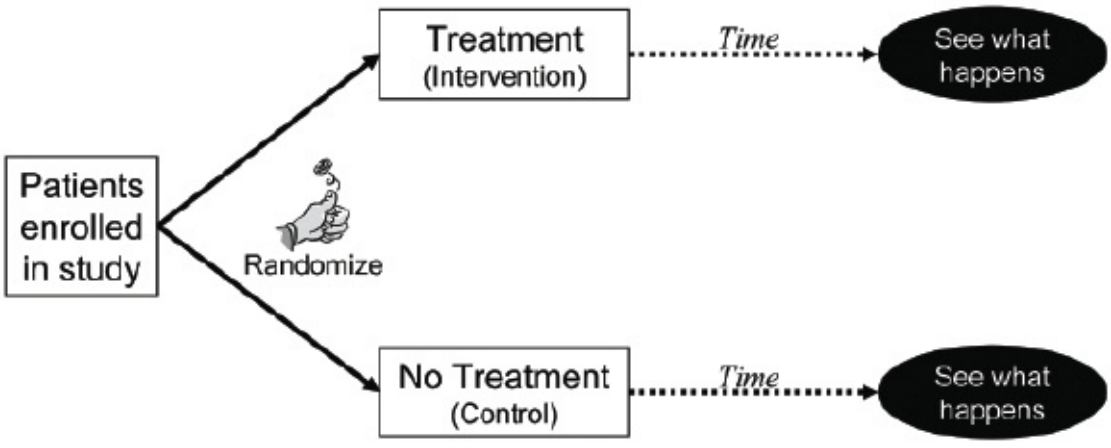

Figure 1.1 Basic Design of a Randomized Trial

The randomized trial was developed in the 1940s by British epidemiologists, who used it to demonstrate that pertussis vaccine prevented whooping cough and that a drug called streptomycin cured tuberculosis.[5] Unfortunately, the concept was slow to catch on, and we still don't do enough of them. Why do I say this? Because randomized trials are the most reliable way to determine what

works in medicine.[6] If members of two groups are similar to each other in every way except one—whether or not they get treatment—then any differences observed at the end of the trial must be the result of the treatment.

For over two decades we were misled by observations that postmenopausal women who took hormone replacement therapy did better (in terms of just about everything) than those who did not. But when women were finally allocated to hormone replacement therapy or placebo in a randomized trial, we learned the therapy caused more problems than it solved.[7] It is tempting to compare people who take a particular medicine with those who do not, but these groups differ in many important ways other than the fact of treatment. In particular, people who take medicine (that is, those that have access to doctors, can afford the prescription, and choose to take it) tend to be better educated, wealthier, and more attentive to health in general (for example, they exercise more; they smoke less). So while this kind of comparison is easy, it is not fair. People who take preventive medicines are bound to do better than those who don't simply because they are healthier to start with—even if the medicine doesn't help one bit. To avoid this problem, we need to do true experiments: randomized trials.

The VA randomized trial of treatment for severe hypertension

The VA trial was pretty small by current standards: there were only about 140 enrolled participants. About 70 were treated, 70 were not.[8] The trial was also fairly short by current standards: around a year and a half long. Table 1.1 is the tally sheet showing the number of participants who had bad health events (what we call outcomes) over that period—separated by whether they were randomized to the No Treatment group or the Treatment group.[9]

Outcome	No Treatment (Control)	Treatment (Intervention)
Death	4	0
Stroke	4	1
Heart failure	4	0
Heart attack	2	0
Kidney failure	3	0
Eye hemorrhage	7	0
Hospitalized for high blood pressure	3	0
Treatment complication	0	1
Total	**27**	**2**

Table 1.1 Outcomes in the VA Randomized Trial of Treatment for Severe Hypertension

Small study, short follow-up—yet powerful results. You see an awful lot of zeros in the Treatment group. And the bottom line is stark: 27 bad events in the No Treatment group versus 2 in the Treatment group.

To see how powerful this is, consider that there are a total of 29 participants who had bad events. If treatment made no difference, you'd expect the 29 events to be roughly split between the two groups. Now imagine flipping a coin 29 times and getting heads 27 times and tails only 2. What are the chances of that? If it's a fair coin, about two in a million. In other words, there is almost no

way to get a difference like this in two similar groups (groups created by randomization) unless the treatment worked.

It is important to point out just how common these bad events were in the No Treatment group. Among 70 patients, 27 had something bad happen over the course of a year and a half. People don't usually think about the likelihood of any particular event happening over a period of 1.5 years (or, for that matter, over 3.3 or 4.7 years); we usually think about the chance of something happening over one year. The one-year chance of one of these bad events happening was about 26 percent. In other words, more than a quarter of the men with untreated severe diastolic hypertension had something very bad happen within one year (bad like a stroke, heart attack, or death). The corresponding risk for the Treatment group was less than 2 percent. There's a huge difference between 26 percent and less than 2 percent. It means that the treatment really helped. This is about as good as it gets in medicine. If I had severe diastolic hypertension, I'd definitely want to be diagnosed and treated.

Because most people with hypertension get treated for years, it helps to take a longer view into the future. You're probably concerned about strokes, heart attacks, and death not only for the next year but also for a longer time period. Looking at just the one-year time frame minimizes the risks you face; risks accumulate over time. So doctors often look at the chances of people experiencing bad health events over five or ten years. Based on the above data and assuming the rate of bad events is constant, the five-year risk of something bad happening to a person in the No Treatment group is around 80 percent. (For those wondering why it would not be more than 100 percent, remember that as time passes—and more bad events happen—fewer and fewer men are available to experience a first event. After five years, 80 percent of men with untreated severe diastolic hypertension have experienced a bad health event; after ten years, 95 percent; and after fifteen years, 99 percent. Now you see why I'm so sure that Mr. Lemay probably would have died years ago had he not been treated.)

Of course, the risk accumulates in the Treatment group as well: over five years, the likelihood of a bad event is 8 percent; over ten years, it's 15 percent, and over fifteen years, it's 21 percent.

So we can compare No Treatment versus Treatment using different amounts of time:

After five years, the chance of a bad event is 80 percent for the No Treatment group versus 8 percent for the Treatment group

or

After ten years, the chance of a bad event is 95 percent for the No Treatment group versus 15 percent for the Treatment group

or

After fifteen years, the chance of a bad event is 99 percent for the No Treatment group versus 21 percent for the Treatment group.

Regardless of which comparison you choose to look at, my guess is that you would choose treatment. I know I would.

There are other ways to think about the benefit. Let's stick with the five-year time frame. If you are not treated, you have an 80 percent chance of something bad happening over that period. If you are treated, that chance falls to 8 percent. So the likelihood that you will benefit from treatment—that is, avoid something bad because you have received treatment—is 72 percent (80 percent – 8 percent). And here's one more way to think about it. If one person has a 72 percent chance of

benefiting, that means we need to treat fewer than two people (on average) to make sure one person will benefit. The exact number of patients we must treat is simply the reciprocal (or 1 divided by the number) of the chance of benefit. In this case, the number we want the reciprocal of is 72 percent, which is 0.72 in decimal form. The reciprocal of 0.72 is 1 divided by 0.72 (a calculator is handy here): 1.3888, which for simplicity's sake I'll round up to 1.4. Doctors call this the "number needed to treat": we need to treat an average of only 1.4 patients for five years to be sure that one person will benefit.

Table 1.2 summarizes these three ways to think about benefit.

Measure	Definition	Example [Severe Diastolic Hypertension]
Five-year risk in each group	The chance of having a bad event in each group over five years	No Treatment group: 80 percent Treatment group: 8 percent
Chance of benefit (over five years)	Subtraction of the risk in the Treatment group from the risk in the No Treatment group = the chance of being helped by treatment	80 percent – 8 percent: 72 percent of people benefit from treatment
Number needed to treat (over five years)	The reciprocal of the chance of benefit; the number of people that must be treated to ensure that one person benefits	1 / 0.72 ≈ 1.4 people

Table 1.2 Measures of Benefit

Benefit across the spectrum of hypertension

The benefit of treating very high blood pressure—severe hypertension—is great. But hypertension varies in degrees of severity, from almost normal blood pressure to very high. And the benefit of treatment is affected by the degree of hypertension. I'd like to examine the benefit of treatment for different degrees of hypertension.

Table 1.3 shows the results of multiple randomized trials, each one looking at a different degree of hypertension.

Degree of Hypertension	Five-year Risk of Bad Event		Chance of Benefit	Number Needed to Treat
	No Treatment	Treatment		
Severe [Diastolic BP 115–129]	80%	8%	72%	1.4
Moderate[10] [Diastolic BP 105–114]	38%	12%	26%	4
Mild [Diastolic BP 90–104]	32%	23%	9%	11
Very Mild[11] [Diastolic BP 90–100]	9%	3%	6%	18[12]

Table 1.3 Benefit across the Spectrum of Hypertension [10] [11] [12]

Each successive row represents a study of patients with a progressively milder degree of hypertension (that is, lower diastolic blood pressures) than the preceding group. For each study, I made sure that a bad event meant roughly the same thing: death or serious problems with body organs (for example, a heart attack, a stroke, kidney failure). Note that in the No Treatment group (the second column), the likelihood of having a bad event falls as the level of blood pressure falls. This reflects a basic principle: *milder abnormalities are less likely to cause problems than severe abnormalities are.* You might have guessed that. But it's really an important point to remember. And you may even need to remind your doctor about it.

The third column is a little surprising. You might think that all the numbers should be about the same, that all people who are treated will end up with the same chance of a bad event. But these are real data, and real data aren't as tidy as we would like. These numbers bounce around a bit, probably reflecting differences in the patients studied and the drugs used—plus the fact that different studies will always produce somewhat different answers. So all of these numbers are only an approximation of the truth. The point is the big picture.

The chance that you will benefit from treatment (the fourth column) falls as the degree of hypertension becomes milder. This reflects a second basic principle: *people with milder abnormalities stand to benefit less from treatment than those with severe abnormalities.* The fifth column is another way of saying the same thing. While almost everyone treated for severe hypertension will benefit, eighteen people with mild hypertension have to be treated for one to benefit.

Because the second principle is so important in understanding the remainder of this book, I think it's useful to illustrate it with the drawing in figure 1.2:

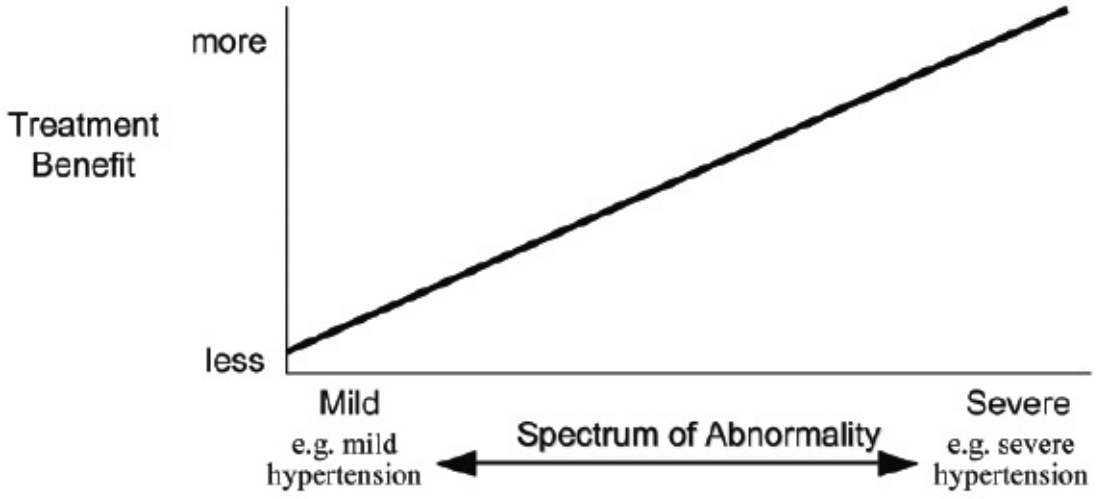

Figure 1.2 Relationship between the Spectrum of the Abnormality and Treatment Benefit in Hypertension

The bottom of the drawing shows the spectrum of the abnormality. Most conditions, like hypertension, exist on a spectrum: from very mild to severe forms. In general, treatment benefit rises with the severity of the abnormality. Of course, the two principles above are closely related. The reason people with milder abnormalities stand to benefit less from treatment is that milder abnormalities are less likely to cause problems (symptoms or death) than severe abnormalities. In other words, milder abnormalities are more likely to represent cases of overdiagnosis. Most people are not destined to have anything bad happen to them as a result of their mild abnormalities. And those who are overdiagnosed cannot benefit from treatment—there's nothing to fix.

At this point you might be thinking, *So what? If there's any chance of benefit, why not take the*

medication? One reason is money. Some people have to spend a lot of their income on these medications; in order to afford the medicine, sometimes they'll have to spend less on necessities, such as food. Another reason not to take the medications is what I call the hassle factors: you have to make appointments with your doctor, get your prescriptions filled, get lab tests, make phone calls for refills, and fill out insurance forms. And finally, all other things being equal, some people prefer not to have to take daily medication.

But let's take all these reasons off the table. Suppose treatment is free, there's no hassle involved in getting it, and you are perfectly happy to take a daily medication. In that case, everybody would want to be treated, regardless of the severity of his or her hypertension and regardless of how small the benefit, right?

Unless, of course, there were downsides, some sort of harm associated with treatment.

When the treatment is worse than the disease

Most of my clinical work has not involved the care of inpatients (patients in the hospital), but the care of outpatients (patients in the clinic). Many of the regular patients I see in clinic might be described as old-time Vermonters—rugged, elderly men who have spent most of their lives outdoors. (And because I work for the Department of Veterans Affairs, all of my patients have spent some portion of their lives in the military.) One such patient, Mr. Bailey, is an eighty-two-year-old man who lives alone on a farm about twenty-five miles away from the hospital. He spends most days working outdoors: clearing brush, tapping maple trees, shoveling snow, rebuilding stone walls, tending livestock, or fixing his house. I can't reach him on the phone unless I call him after dark. (Adding to the challenge is the fact he doesn't have an answering machine.)

Luckily I haven't had to contact Mr. Bailey much, because he has been fairly healthy. Over the past decade, we have seen each other in clinic once or twice a year, and mostly we just talk. Honestly, I haven't done much for him. He's never been admitted to the hospital. The only regular medicine I've given him is for benign prostatic hypertrophy—a common condition in middle-aged and elderly men in which the prostate enlarges, compresses the urethra (the tube that drains the bladder), and interferes with the normal flow of urine (much like a clamp on a garden hose). We have contemplated treatment for his intermittent depression, but it has never been severe enough for me to argue strongly for it. Moreover, he has never been inclined to take medicine for it. He's fairly conservative about medical intervention in general.

It's probably worth digressing here to say that, although many of my patients actively seek medical intervention (believing that medical care can only help them feel better), a substantial portion of my patients fall into Mr. Bailey's category. They avoid elective surgery. They are hesitant about taking medicines for what they perceive to be minor problems. And they are predisposed to be skeptical about preventive interventions, interventions for conditions that aren't problems now but might become so in the future. I call it the "if it ain't broke, don't fix it" school of thought. I attribute their membership in this school to the fierce independent streak of many rural Vermonters—they are raised to be self-reliant (and may have regretted excessive mechanical interventions on their tractors).

A couple of winters ago, Mr. Bailey's name appeared on a list given to me by clinic administrators identifying which of my patients had blood pressures that the VA considered somehow suboptimal. His diastolic blood pressure had been fine, in the 70 to 90 range. But his systolic blood pressure had been high at his last two visits—both measurements in the 160s. Honestly, I can't tell you whether or not I knew this before I got the list. When I was in medical

school, treatment decisions were based solely on the diastolic blood pressure. Now there is a growing recognition that among older individuals, systolic blood pressure elevations are probably more important than diastolic blood pressure elevations. I most likely saw the high systolic readings and simply didn't have any reaction. But now it was clear somebody else knew about them and had reacted.

I'd like to tell you that this fact in and of itself wouldn't influence my practice. But I can't. No doctor wants to be identified as being out of step with practice norms. I had mixed feelings about the importance of treating his mild systolic hypertension—I could make an argument either way. But seeing Mr. Bailey's name on the list was enough to get me to pursue treatment.

So I started Mr. Bailey on one twenty-five-milligram tablet of hydrochlorothiazide every morning. Hydrochlorothiazide is a diuretic: it makes a person urinate more, which lowers the amount of fluid in the body (part of the reason it lowers blood pressure). Mr. Bailey had no ill effects from the medicine. His blood pressure came down and was normal throughout the spring. Then we had a spell of hot, humid weather. That sort of thing doesn't stop Mr. Bailey. One day he was outside rebuilding a stone wall, lifting heavy rocks and dripping with sweat. And since he's not the kind of guy to tote a water bottle around with him, he got dehydrated. His blood pressure got too low and he collapsed.

When he woke up, he called me. (I'm easier to get on the phone than he is.) He hadn't hurt himself when he fainted, but he could have. And what if he had been using his chain saw? I told him to stop the medicine, drink more water, and see me in clinic.

When I saw him a few days later, he seemed fine. I told him that I suspected that the combination of sweating, not drinking water, and the blood pressure medicine had made him faint. He wanted to know whether he really had to take the medicine at all. A perfectly reasonable question. Because I'm a researcher, I thought I'd look for some numbers so he could consider the question more carefully.

While the treatment of diastolic hypertension dates back to the 1960s, the treatment of systolic hypertension is much more recent. The study that changed our practice was a randomized trial published in 1991.[13] The trial enrolled elderly patients (like Mr. Bailey) whose diastolic blood pressures were normal but whose systolic blood pressures were over 160, a condition called isolated systolic hypertension. The study was big—almost five thousand patients. And the follow-up was long—almost five years. For those familiar with clinical research, these details are a clue about the size of the effect researchers expected to find. Remember the VA randomized trial? It was a small study with a short follow-up that found a huge effect. If a huge effect exists, it will be found using a small number of people in a short amount of time. If a study is really large and has a long follow-up, that's a clue that the effect the researchers are looking for is small.

In the study of isolated systolic hypertension, the researchers were looking for the same outcomes that were found in studies of diastolic hypertension: death and problems stemming from damage to the blood vessels supplying the heart and brain. Because the patients in the study were relatively old (in their seventies and eighties), these events were fairly common in the No Treatment group—18 percent had bad events over five years. The Treatment group did somewhat better—13 percent had bad events over five years.

I shared the numbers with Mr. Bailey. Since the life expectancy of an eighty-two-year-old white male is about seven years,[14] the five-year time frame seemed appropriate. I told him the chance of something bad happening in the next five years was 18 percent without treatment and 13 percent with treatment. That means 5 percent of patients will benefit from treatment (18 – 13). Twenty

patients will have to be treated for one to benefit (1 / 0.05). He was perplexed. To him, the benefit seemed really small. Why on earth would he choose treatment?

No sale. Mr. Bailey didn't focus on the possibility that he might be the one person in twenty who benefited. He worried he would be one of nineteen who did not. He was worried about overdiagnosis. And he had a problem with the medication now; he had already experienced a harmful side effect. He chose not to be treated.[15] Perfectly rational.

The management of hypertension represented a true paradigm shift in medicine: from treating patients experiencing health problems now to treating people who may develop problems in the future. It marked the beginning of treatment for people without symptoms—people who felt well but who were more likely than the average person to develop disease.

While treatment does save lives, it doesn't save everyone's life. It doesn't prevent every heart attack and stroke. And some people with hypertension aren't destined to experience these problems even without treatment. They face a different problem: overdiagnosis. There are downsides to being treated for hypertension, some more serious than others. I don't want to overemphasize the physical side effects of medical treatment, but they are there. Some medicines can cause fatigue, others can cause cough, still others can impair sex drive. All of them can make your blood pressure too low, leading to light-headedness, fainting, and falls. And for the elderly, major falls can be the start of a chain of events that lead to death. The balance between the potential benefit of treatment and the risk of overdiagnosis is closely related to where a person falls on the abnormality spectrum—in other words, how high his or her blood pressure is—and to how aggressively we choose to lower it.[16] If you have severe hypertension (systolic or diastolic), treatment is a no-brainer. But as the degree of hypertension falls, the decision to treat becomes a much tougher call. And theoretically, at least, there is some point where the benefit of treatment is so small and the chance of overdiagnosis so high that the decision once again becomes a no-brainer: there's simply no point to diagnosis and treatment.

This raises the question: Where should we draw the line? In other words, when should something be considered a condition that warrants treatment?

Chapter 2: We Change the Rules

How Numbers Get Changed to Give You Diabetes, High Cholesterol, and Osteoporosis

As you saw in the previous chapter, hypertension is defined by a numerical rule. If your blood pressure is above a certain number, you have hypertension. If it isn't above that number, you don't. But hypertension isn't the only condition defined by a numerical rule. There are many conditions that you can be labeled with simply because you are on the wrong side of a number, not because you have any symptoms. Diabetes is defined by a number for blood sugar; hyperlipidemia is defined by a number for cholesterol; and osteoporosis is defined by a number for bone density (called a T score). Of course, in each of these conditions doctors are trying to get ahead of symptoms—we are trying to make diagnoses early in order to prevent bad events such as leg amputation and blindness from diabetes, heart attacks and strokes from high cholesterol, and wrist and hip fractures from osteoporosis. But whenever we make diagnoses ahead of symptoms, overdiagnosis becomes a problem. Some people diagnosed with diabetes, high cholesterol, and osteoporosis will never develop symptoms or die from the conditions. And this is most likely the case for those in whom the condition is mild.

The numerical rules used to define conditions are really important. They typically involve a single number: if you fall on one side of the number you are defined as well; if you're on the other, you are defined as abnormal. These numbers—called cutoffs or thresholds—determine who has a condition and who doesn't. They determine who gets treatment and who doesn't. And they determine how much overdiagnosis occurs.

Cutoffs are set by expert panels of physicians. I wish I could say that their determinations result from purely scientific processes. But they are more haphazard than that: they involve value judgments, and even financial interests. The experts who select the cutoffs have particular sets of beliefs about what is important. Because these doctors care greatly about the conditions they specialize in, I believe they sometimes lose a broader perspective. Their focus is to do everything they can to avoid the bad events associated with the condition; their main concern is not missing anyone who could possibly benefit from diagnosis and treatment. So they tend to set cutoffs that are expansive, leading many to be labeled abnormal. They tend to either ignore or downplay the major pitfall of this strategy: treating those who will not benefit.

Over the past few decades many cutoffs have been changed in a way that dramatically increases the number of individuals who are labeled with these conditions. It means that the threshold to make a diagnosis has fallen. Even if this is done with the best of intentions—to avoid more bad events—it can lead to an undesirable consequence: more overdiagnosis.

How bad things happen when we try to do good

This is not a happy story. Mr. Roberts was a seventy-four-year-old man whose major medical problem was ulcerative colitis—an inflammatory condition of his colon (the large intestine). It's a disease that causes symptoms such as severe abdominal pain and diarrhea (and it also increases the

risk of colon cancer). Because his disease was so severe, he had part of his colon surgically removed. Although this led him to have frequent bowel movements, he learned to deal with his situation quite well.

One day, in a routine lab test, Mr. Roberts was found to have an elevated blood sugar. It wasn't that high, but the finding prompted more testing. And more testing confirmed the diagnosis: diabetes. He had type 2 diabetes—the form of the disease that typically occurs in older adults (as opposed to type 1, which usually starts in childhood). Although he had no symptoms of diabetes, over the past few decades doctors had gotten much more aggressive about treating it early, so his primary care physician started him on glyburide—a drug that lowers blood sugar. The medication worked well.

Six months later he blacked out while driving on the local interstate. His car went off the road and rolled over. He fractured his sixth and seventh cervical vertebrae—in other words, he broke his neck. The paramedics on the scene measured his blood sugar. It was very low. The medication had worked *too* well. I'd hate to have been the doctor who prescribed him glyburide.

But I was that doctor. I'm not sure what happened. I had used the standard starting dose of medication. He had tolerated it well for almost half a year. Maybe he hadn't eaten normally that day; maybe he had the flu, or some stomach virus. I don't know.

Mr. Roberts was in the hospital for over a month. When I next saw him in clinic he was wearing a halo brace. The halo is a metal ring that encircles the head, much like the brim of a hat, except the halo doesn't sit on the head—it is secured to the skull with pins. Attached to it are two metal rods that extend to the shoulders and are connected to a tightly fitted plastic jacket. With this apparatus, the neck is both immobilized and stretched so that the fracture can heal. I felt terrible. And—maybe it goes without saying—I didn't restart the glyburide.

Mr. Roberts is now ninety and is still a patient of mine. He has not been treated for diabetes since the accident, nor has he had any complications from diabetes. I think he was overdiagnosed. But he was lucky. There was no permanent injury. He has recovered fully from the problems caused by his unneeded treatment. But I'm not sure I have.

Who has diabetes?

Diabetes can be a very serious disease. Some patients with the disease—usually children—first come to medical attention because they lose consciousness. They are in a diabetic coma: their blood sugar may be ten times normal, their potassium stores are extremely low, and their body fluids are dangerously acidic (we call it a metabolic acidosis). Without treatment, they die.

Treating a patient in a diabetic coma is one of the most rewarding experiences in medicine. The patient comes in near death, and generally about two days later he feels fine. All the patient needs is lots of intravenous fluids, some potassium, and the hormone that was lacking—insulin. Insulin is the hormone that allows sugar to move from the blood into the cells. Giving it, along with the fluid and potassium, normalizes the blood sugar and the acid-base balance. More important, the patient wakes up. It's really something to see.

But what I have just described is actually the less common form of diabetes—type 1. Patients with type 2, the much more common form, are usually adults and have plenty of insulin. Their problem is that the insulin doesn't work because the body has become resistant to it. These patients are frequently overweight (and the best treatment is losing weight). While it does not tend to lead to a diabetic coma, this type of diabetes can still be a very bad disease. Either type can lead to severe complications, including blindness, kidney failure, heart disease, impaired healing of wounds, and

leg infections requiring amputation. But type 2 diabetes can also be a totally asymptomatic condition. So just like hypertension, there is a spectrum of abnormality in diabetes. Some people with the diagnosis will develop the aforementioned complications; others will not. Although we are never sure exactly who these others are, they have been overdiagnosed.

So how do we decide who has diabetes? When I was in medical school, our numerical rule was this: if you had a fasting blood sugar over 140, then you had diabetes. But in 1997 the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus redefined the disorder.[1] Now if you have a fasting blood sugar over 126, you have diabetes. So everyone who has a blood sugar between 126 and 140 used to be normal but now has diabetes. That little change turned over 1.6 million people into patients.[2]

Is that a problem? Maybe, maybe not. Because we changed the rules, we now treat more patients for diabetes. That may mean that we have lowered the chance of diabetic complications for some of these new patients. But because these patients have milder diabetes (relatively low blood sugars between 126 and 140), they are at relatively low risk for these complications to begin with.

So just like people with relatively mild hypertension, people with mildly abnormal blood sugar levels have less to gain from treatment.

Figure 2.1 illustrates the effect of broadening the numbers defining diabetes—moving down the spectrum of the abnormality—on the benefit of treatment. My editor noticed that it's pretty much the same figure as the one in the first chapter. And, of course, it is. But that's the point. Furthermore, the relationship depicted in the figure applies equally well to the other disorders in this chapter: just replace the "mild diabetes" and "severe diabetes" poles of the spectrum with "near normal cholesterol" and "very high cholesterol" or "mild osteoporosis" and "severe osteoporosis," and you'll get the picture.

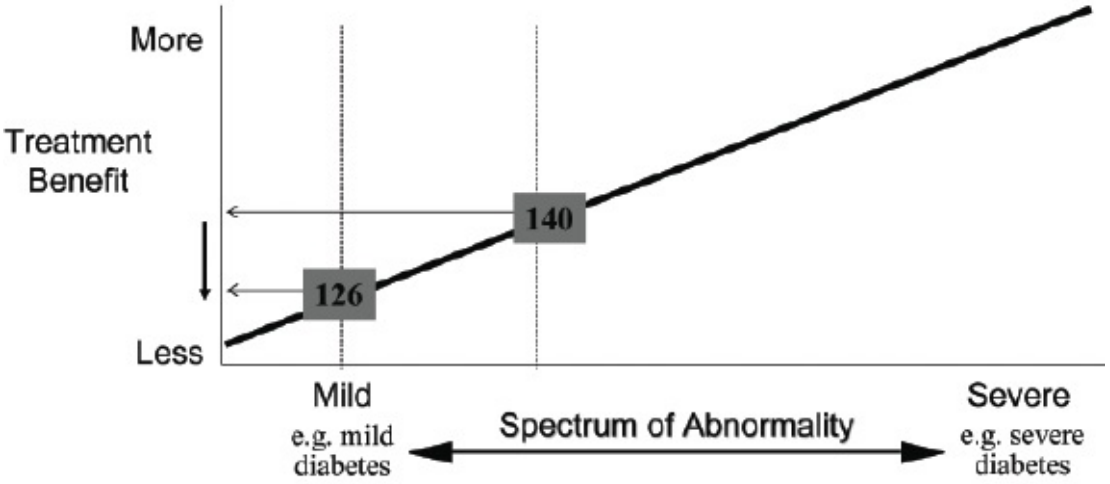

Figure 2.1 Effect of Changing the Rules in Diabetes

In fact, the relationship applies to all of medical care. As we expand treatment to people with progressively milder abnormalities, their potential to benefit from treatment becomes progressively smaller. So the redundancy is purposeful—I really want you to write this concept to your hard drive.

Severe abnormalities are different. Just like it's bad to have really high blood pressure, it's bad to have really high blood sugar. You want to take action to lower both. But remember: it's also bad to have a blood pressure that is too low. And it's bad to have a blood sugar that is too low—just ask Mr. Roberts.

The general problem was dramatically demonstrated in a recent randomized trial from the

National Institutes of Health.[3] The trial was designed to determine whether intensively lowering blood sugar reduced the risk of having or dying from a heart attack or stroke. The trial enrolled over ten thousand patients with diabetes at high risk for these events. About five thousand were randomized to receive standard diabetes therapy—therapy to lower their average blood sugar to a more acceptable, although not normal, range. The other five thousand were randomized to receive intensive drug therapy—therapy to make their blood sugar normal. And half of these patients achieved the goal: the average blood sugar level was below 140.[4] Because the average includes blood sugars measured right after eating (which tend to be high), it is safe to assume that their fasting blood sugars were considerably lower.

The trial started in 2003 and was supposed to continue to 2009. But on February 6, 2008, the National Heart, Blood, and Lung Institute issued a press release saying they were "changing" the intensive therapy regimen "due to safety concerns."[5] *Changing* wasn't the most accurate word to describe what they were doing; *stopping* would have been a better choice. And the safety concern was that patients receiving intensive therapy were dying more often than patients receiving standard therapy. After three years, 5 percent of patients receiving intensive therapy had died, compared with 4 percent of those receiving standard therapy. It was about a 25 percent increase in the risk of death, and the researchers were confident that it was not a statistical fluke. There was little doubt: intensive treatment was worse than standard treatment.

You might wonder how making people's blood sugar normal could end up killing them. It's probably because we can't simply dial a patient's blood sugar to a specific number; our therapies aren't that precise. Instead, blood sugar bounces around, and if we try to have blood sugar bounce around normal, sometimes it will bounce too low. And having your blood sugar too low increases your risk of death. The investigators might argue that hypoglycemia (low blood sugar) was not the cause of the increased risk of death. But by their own admission, they were not sure what explained the increased mortality. In the official report, lead author Hertzel C. Gerstein wrote: "Despite detailed analyses, we have been unable to identify the precise cause of the increased risk of death in the intensive blood sugar strategy group . . . Our analyses to date suggest that no specific medication or combination of medications is responsible. We believe that some unidentified combination of factors tied to the overall medical strategy is likely at play." My view is that if the trial had shown a mortality benefit, the authors would have been quick to ascribe that benefit to intensive control of blood sugar (as I think would have been correct in that case). But since the trial showed a mortality harm, that must also be ascribed to intensive control of blood sugar. That's the point of a randomized trial.

What does this study tell us about where to set the threshold to diagnose diabetes? My take is this: if it's not good to make diabetics have near normal blood sugars, then it's not good to label those with near normal blood sugars diabetics. Why? Because doctors will treat them. People with mild blood sugar elevations are the least likely to gain from treatment—and arguably the most likely to be harmed, as Mr. Roberts was.

Beyond diabetes

This isn't only about diabetes. The tendency to lower the threshold of diagnosis has been repeated in a number of other common conditions, including, as we've seen, hypertension. Prior to 1997, many physicians did not treat patients with mild hypertension. Although the Joint National Committee on High Blood Pressure recommended treating these individuals, they acknowledged that reasonable doctors might disagree with this recommendation "in the absence of target organ