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Foreword: How It All Started, 40 Years Ago

Like any expectant mother, Abbey Meyers hoped above all to have a healthy child.

Neither she nor her husband Jerry, then a military officer, had any family history of genetic diseases or any reason to expect anything unusual.

And when their son David was born in 1968, everything seemed fine.

Around the time David turned two, however, he started to show some odd symptoms, like stuttering, rapid blinking, and uncontrollable movements of his arms, legs, or head.

Her pediatrician called them "tics" and said, "Don't worry. He'll outgrow it."

But Abbey's concerns grew as David's disruptive behaviors worsened year by year. He experienced repetitive muscle tics, uncontrollable head shaking, wildly flailing arms and legs, involuntary noises, hyperactivity, and other behaviors that made daily life very difficult. In nursery school, his teacher wouldn't tolerate his behavior.

His pediatrician still had no answers, and his disease remained undiagnosed.

Finally, one day when David was eight, Abbey was reading a Sunday newspaper magazine when she came across an article about a teenager with a strange neurological disease.

The article described a boy with a disease called Tourette's syndrome. A neurological disorder first described in a paper by Georges de la Tourette in France in 1885, it was characterized by an onset in childhood, frequent tics, uncontrollable movements, and compulsive behaviors—and was often misdiagnosed as a psychiatric disorder.

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Abbey Meyers vividly recounts the exchange that followed with her husband in her memoir, *Orphan Drugs: A Global Crusade,* "I sat in my chair mesmerized. I could not believe what I was reading... 'Jerry,' I screamed. 'Come here, I found out what's wrong.' Jerry rushed into the room and picked up the article. He started reading. 'This is beyond belief,' he said. 'Whoever heard of a diagnosis made possible by a Sunday magazine?' But he agreed; the article listed David's symptoms. What to do now?"

Her answer to that question would trigger the start of the orphan drug revolution.

Abbey first took the article to her pediatrician, who agreed she might be right and referred her to a specialist, Dr. Arthur Shapiro, at New York's Mount Sinai Hospital.

Dr. Shapiro was studying Tourette's and, after examining David, confirmed the diagnosis. He prescribed Haldol, a powerful tranquilizer used for schizophrenia. But as another Tourette's parent had bleakly put it, Haldol "makes a zombie out of people," and the Meyers quickly had to take David off it.

When David turned nine, Dr. Shapiro found a way to get him a drug called pimozide that blocked dopamine receptors in the brain and appeared to help other Tourette's patients. It was approved for sale in Europe but not yet approved in the United States; however, Dr. Shapiro was participating in a clinical trial for Tourette's patients, and the Meyers were able to enroll David and he did well on the drug, and at school, with hardly any side effects.

The drug was being tested by McNeil Laboratories, a division of Johnson & Johnson—the giant healthcare company with an image of caring for babies and families.

But McNeil was developing the drug primarily for conditions like schizophrenia, with millions of potential customers, and executives there saw Tourette's only as an add-on. When they decided to discontinue developing trials for schizophrenia—in 1979, just a year after David began taking it—McNeil also ordered pimozide stopped in Tourette's.

Despite desperate pleas, David and other Tourette's patients could no longer get any.

As Abbey Meyers summarized the situation, "The pharmaceutical industry simply ignored orphan drugs. Even when an academic scientist

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had already discovered a treatment for a rare disease, no pharmaceutical company would manufacture it."

"My journey in the orphan disease world began not because my son was sick, not because he had a rare disorder, but rather because the medication that eliminated his symptoms and gave him a chance to live a 'normal' life was suddenly unavailable to him—discontinued by the manufacturer because it was deemed not profitable enough due to the small potential number of patients who would buy the medication".

Meyers wrote that companies then viewed rare disease patients as "disposable, like a paper plate that is relegated to a garbage bag after the picnic is completed"—a view sadly borne out when results later confirmed that pimozide worked in Tourette's disease.

To redress that wrong, Abbey Meyers set out to build a coalition.

"By working together, ordinary people were able to plug an enormous hole in the healthcare system when the 'free market' did not address their needs. To accomplish this, they needed to attract to their cause other patients, physicians, politicians, business leaders, government employees, and millions of others throughout the world."

This is their story, and the story of those who have joined them in plugging that hole.

Why should people care?

Most people know the names of just a handful of rare genetic diseases that have somehow been given extraordinary publicity by celebrity entertainers or athletes.

Muscular dystrophies became familiar to Americans in the 1950s through comedian Jerry Lewis's popular telethons—and to Europeans through similar television appeals, continuing successfully in France and Italy today. ALS, amyotrophic lateral sclerosis, became famous first as Lou Gehrig's disease when it cut horribly short the life of the legendary baseball player, and again in 2014 when a fundraising "ice bucket challenge," championed by popular college baseball star Pete Frates, went viral. Cystic fibrosis is known to many through the work of NFL star Boomer Esiason and his son Gunnar.

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But the great majority of genetic diseases are very little known. To most people they remain arcane, hard to understand, a little scary, and often better ignored.

Even their names can be intimidating. Many invoke an obscure, long-dead discoverer, like the nineteenth century doctors Gaucher, Fabry, or Duchenne. Others reflect nearly unpronounceable pathologies, from mucopolysaccharidosis (MPS) and familial hypercholesterolemia (FH) to metachromatic leukodystrophy (MLD) and facioscapulohumeral dystrophy (FSHD). In total they cover the alphabet comprehensively, from Aagenaes syndrome to Zuska's disease.

Rare diseases are also called "orphan diseases," so named because they were long abandoned (or orphaned) by a profit-driven pharmaceutical industry. Officially these are defined by laws as diseases affecting up to a certain number of patients: in the United States 200,000; in the European Union one in 2000; and comparable numbers in other countries.

And most people think if there's no family history of a disease, there's no need to worry.

So why a book about orphan drugs, which by definition treat only rare diseases? Did they really trigger a revolution important enough to care about? And if so, why is that so little known?

In fact, orphan drugs have revolutionized society, for reasons ranging from the deeply personal to the broadly cultural and political.

Rare diseases deserve our attention because they're merciless, causing families often far worse human suffering than common diseases.

And unlike many common diseases, few can be prevented or treated by a good diet or exercise.

Perhaps most importantly, a rare genetic disease could someday strike any family—and an orphan drug become of utmost urgency to anyone with a child or grandchild, niece or nephew.

Most genetic diseases are monogenic, resulting from a defective mutation in a single gene. And although they can of course "run in families," one can equally have no prior family history.

The reason lies in the ways genetic diseases are inherited.

We each carry two copies of any gene. Someone who has one mutated copy of a gene is a carrier. When two parents each carry a mutation in one of those two copies for a recessive condition, neither shows symptoms of

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the disease, but each of their children has a 25% chance of inheriting the disease and a 50% chance of becoming a carrier. If one parent carries a mutation for an autosomal dominant disorder, each child of that parent has a 50% chance of inheriting the mutated gene and suffering from the condition.

In autosomal dominant diseases, such as Huntington's or polycystic kidney diseases (PKD), a single copy of a disease-causing mutation is sufficient to cause the disease. Although a parent with that mutation usually shows symptoms of the disease, many are asymptomatic until long after having children, and a new variant mutation can sometimes occur in births with no family history of the disorder.

Autosomal recessive diseases, such as cystic fibrosis and sickle cell disease, are transmitted through recessive or "masked" genes. They are "sleeping killers," in which two copies of a gene must be mutated to cause a disease; their effects are usually hidden in two asymptomatic carrier parents.

Finally, X-linked disorders, like hemophilia, Duchenne muscular dystrophy, and Rett syndrome, are caused by genetic defects on the X chromosome, one of the two sex chromosomes. Because women have two X chromosomes, most mothers are, again, usually disease-free carriers.

So, it is not at all uncommon for a baby to be born with a genetic disease to two parents with no family history of it.

And by the nature of genetic variability, all of us likely carry one or more mutations that can cause a genetic disease. Because we rarely know in advance when both parents carry the same defect, many devastating genetic diseases are no more predictable than, as Phil Reilly put it in *Orphan: The Quest to Save Children with Rare Genetic Disorders*, "an unlucky roll of the genetic dice," which could strike any family at any birth.

In fact, according to recent estimates, we each carry an average of one to two mutations that can cause severe genetic disorders. We all know how badly we'd hope for a therapy if our family was affected.

A few of these diseases can develop unexpectedly in adulthood—one example above is FSHD —but most do strike at birth or within the first months of life. Without a swift therapeutic intervention many can lead

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to an early death, lifetime incapacity, or an inexorably worsening disability. About one in every three children affected by a genetic disease dies before reaching their fifth birthday.

Moreover, these diseases collectively affect far more families than most people imagine. A recent article in the *American Journal of Human Genetics* summarized their collective toll:

> In aggregate, clinically recognized (single gene diseases) compose a substantial fraction ... of known human diseases ... ~8% of live births have a genetic disorder ... eight million children born worldwide each year with a ... condition that is life threatening or has the potential to result in disability. In the US alone, Mendelian disorders collectively affect more than 25 million people .... Each year, more than three million children under the age of 5 years die from a birth defect, and a similar number survive with substantial morbidity. (And) each child with a genetic disorder has been estimated to cost the healthcare system a total of $5,000,000 during their lifetime.

In some cases, the costs can be even higher. Approved hemophilia therapies can cost up to $600,000 per year for an adult in the United States, or more than $20 million over the course of a lifetime.

More than 6000 distinct monogenic diseases have now been identified, and recent analyses estimate the ultimate total to top 10,000. Although each is rare, together they afflict an estimated 25 to 30 million Americans, almost one in 10. Around the world genetic diseases collectively are thought to afflict around 300 to 350 million people, comparable to the population of the entire United States.

But despite those staggering burdens, genetic diseases are routinely misdiagnosed for years.

One recent analysis found that only 11% of children with rare genetic diseases were accurately diagnosed at first. The "diagnostic odyssey" is often excruciatingly prolonged; in a European survey of how long it took to diagnose eight rare diseases, 25% of families waited between five and 30 years for a correct diagnosis, and the initial diagnosis was incorrect in 40% of all cases.

And today, 40 years into the orphan drug revolution, an estimated 95% still lack a therapy.

So, we all have a primary stake—self-interest—in seeing the orphan drug revolution flourish.

But people should also care for other important reasons.

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First, orphan drugs have already transformed life for hundreds of thousands of people in the United States and around the world. Others now in development show promise to treat millions more.

Since the Orphan Drug Act's passage in 1983, drugs have been approved by the U.S. Federal Drug Administration (FDA) for more than 900 orphan conditions versus fewer than 10 in the ten years earlier. These drugs can collectively treat more than a million people in the United States alone—keeping children alive, out of hospitals, off ventilators, and out of wheelchairs, and sparing families the hardships of 24-hour care.

By helping patients live healthier lives, these therapies have also enabled both them and their extended families to contribute productively to society economically and in many other ways.

Per the long-established principle in medicine to "treasure your exceptions," the orphan drug revolution has also taught us much about non-rare diseases—larger indications, as they're often called—and has had an important, and still growing, impact on finding ways to treat them.

Parkinson's disease, Alzheimer's disease, high cholesterol, and many other conditions that afflict millions of people are being revealed to have individual monogenic, or single-gene, subtypes, opening doors to treating more genetically complex forms afflicting millions of people.

Insights from rare disease studies are also enabling more effective use of common medicines, allowing them to be tailored to individuals who will actually benefit from them and furthering the long-sought goal of "personalized medicine."

As the authors of one recent survey of "lessons learned from the field of rare diseases" concluded: "A large percentage of medicines do not work for the patient populations they are intended to treat. Increased knowledge regarding genomics (can help identify) groups of likely responders and non-responders."

Technologies honed in pursuit of orphan drugs have also had much broader applications—an impact shown vividly when RNA technologies developed in treating rare diseases allowed the creation of COVID-19 vaccines with unprecedented speed. As Walter Isaacson wrote in his study of gene editing, *The Code Breaker*, "I began ... thinking that biotechnology was the next great scientific revolution. (Seeing COVID-19) made me realize that I was understating the case."

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The orphan drug revolution has also transformed the culture of medical science.

Academic scientists who 40 years ago would never have dreamed of going "into industry" now routinely join start-ups or cofound companies. In parallel, industry-sponsored research, which was long oriented narrowly toward the development of individual drugs, has helped illuminate basic scientific principles applicable across broad fields of medical research.

Young scientists and physicians considering such paths may take special interest in the stories of others taking research not only from bench to bedside but all the way to regulatory approval.

The final reason we should care is that sustaining this revolution requires our active support.

Every year sees new laws that greatly impact both the number of new drugs developed and the number of patients able to get the ones they need. Policies supporting innovation and access can expand both, whereas misguided policies aimed at the wrong problems can constrain both.

The Orphan Drug Act came into being only because patients and families fought for it. The last section of this book explores what people who care can do to ensure it remains vibrant today.

Why 40 years?

This book traces the start of the orphan drug revolution to three catalyzing events that occurred in the early 1980s.

The first and most widely recognized was the transformational U.S. Orphan Drug Act (ODA), introduced in 1981 and enacted in 1983, for the incentives it provided and activity it triggered.

The preceding decades had brought hints of new attitudes toward people born with disabilities.

Marie Kilillea's best-selling 1952 memoir *Karen* told the true story of a family who refused to take their doctor's advice to put a daughter with cerebral palsy into an asylum and forget about her. The popular "Jerry's kids" telethons had raised money for children with muscular dystrophy. Eunice Kennedy Shriver's much-publicized Special Olympics, founded in 1968,

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put her family behind changing society's mindset from sidelining people with disabilities to celebrating them.

Nevertheless, as late as 1980, drug companies still balked at even trying to develop drugs that could help desperate patients suffering from crippling but rare genetic diseases.

A coalition of patients and advocates affected by rare diseases including Huntington's disease, Tourette's, myoclonus, narcolepsy, and rare cancers set out to do whatever it took to change that.

The group first tried to get a law passed that would force companies to make the drugs needed. A report from a commission chaired by Marjorie Guthrie, founder of a Huntington's disease patient support group, on pharma's lack of interest in diseases affecting relatively small numbers of people led Senator Edward Kennedy in 1978 to propose a new National Institutes of Health (NIH) center to have the government develop "drugs of limited commercial value" itself. When those ideas met fierce industry resistance, they considered the idea of offering incentives to attract private investment.

That approach found a supporter in California congressman Henry Waxman, who had been approached in parallel by a constituent named Muriel Seligman, whose son Adam suffered from Tourette's and needed the same drug David Meyers had been taking. Muriel had learned the drug was available in Canada and arranged to have a friend bring some back for him, but customs agents had seized the medication at the airport because it wasn't approved in the United States.

Waxman recounts, "As a constituent, she was calling to demand my help. 'They took the drug that my son needs,' she said. 'What are you going to do about it?'" Her call, he says, "set in motion a chain of events that culminated in legislation that addressed not only Adam's plight but those of millions of other Americans just like him who were silently suffering from rare diseases."

Waxman learned "the situation was especially tragic ... because scientists who discovered promising new treatments for orphan diseases could not interest profit-minded drugmakers."

But, "from the outset, we met stiff resistance. Drug company executives didn't want to appear before Congress for fear of looking mean-spirited (and) representatives of the industry's trade group,

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the Pharmaceutical Manufacturers Association (PMA), claimed that, contrary to all outward appearances, drug companies in fact had no problem at all developing treatments for orphan diseases, and would oppose any legislation aimed at making them do more."

In parallel, Bill Corr and others on Waxman's staff undertook a major survey of drug companies, agencies, and scientists to learn what it would take to stimulate treatments for rare diseases.

Committee staff drew on a number of ideas proposed in a white paper drafted by an interagency committee led by the FDA's Dr. Marion Finkel, who would later go on to be the first director of the FDA Office of Orphan Products Development. They learned in talking with executives that getting companies to invest would require both a tax credit, to offset the cost of early high-risk investment, and a period of market exclusivity, to allow some return on those investments.

The effort still stalled several times for lack of popular support, but continued advocacy from families led Waxman to hold a hearing. Waxman himself was moved by what he saw and heard:

> One by one, victims of these diseases and their family members described lives of helpless isolation, driven by the unending and often futile search for answers about their condition and medical care to treat it. Most had nowhere to turn. The sights, sounds, and personal stories brought many of us to the point of tears. It was as if someone had pulled back a curtain to reveal an entire segment of society that no one knew was there ... . In my thirty-five years as a congressman, I have never witnessed a more powerful scene.

Almost no one else had come to the hearing, but an aftermath had an unexpected impact.

A short news report in the *Los Angeles Times* came to the attention of Jack Klugman, then the star of the highly popular TV medical drama *Quincy*. Klugman's producer brother Maurice suffered from a rare form of bone cancer, and, after talking with Meyers, they decided to focus an episode on the plight of patients with rare diseases—featuring a Tourette's patient modeled on David. At the end of the episode, which highlighted the orphan drug gap, a message told viewers that the story was based on real events and invited them to write in if they wanted to help.

Abbey Meyers described what happened next: "Literally thousands of people who saw the program wrote to Klugman about the rare disease they

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or their loved ones had, asking if he knew of any treatments for them, and offering their support to solve the orphan drug dilemma.

The Quincy show staff put those letters into large mail sacks and sent them to me. When the postman arrived, he looked like Santa Claus unloading sacks of toys from his sled … . The first thing I did was create a mailing list of all the people who wrote to Jack Klugman about the orphan drug problem. When we needed letters going to Congress, these people would be able to write or phone their elected officials to urge passage of orphan drug legislation."

Abbey Meyers

Photo courtesy of Abbey Meyers.

In October 1966, Abbey Meyers (who was from Brooklyn) was scheduled to marry her fiancé Jerry (who was from Queens) in New York City, just before Jerry was scheduled to ship out for a tour of duty in Vietnam. But only days before the big day, Jerry called from Fort Devens military hospital in Massachusetts, with a diagnosis of routine mononucleosis but orders not to leave the hospital. Fearing he'd be shipped to Vietnam before they could get married, Abbey left promptly for Fort Devens, and they got married in the hospital chapel. But Jerry was instead sent to Korea; Abbey was able to accompany him, and they were "grateful that we had a healthy son born" at a missionary hospital there in 1968. Jerry was then shipped to Vietnam after all; on his return they moved to Long Island, where, Abbey hoped, "Finally we could live a 'normal life.'"

But "around this time, I first noticed that some of David's behaviors were unusual even for a young child." Following David's diagnosis with Tourette's and the discontinuation of the drug he was taking, and after moving to Connecticut, Abbey joined with others on the path to take on the pharma industry. In her crusade to help David, Abbey would, in addition to cofounding the National Organization for Rare Disorders (NORD), go on to serve on countless orphan disease commissions and boards at the national and international levels and speak and write often on the subject. She has been honored by the FDA with an FDA Commissioner's Special Citation, by the U.S. Department of Health and Human Services, and by leading patient organizations in both the United States and Europe.

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Still lacking widespread support for the bill in Congress, Waxman invited Klugman to testify at another hearing. Because in those days having TV celebrities appear before Congress was rare, "On the appointed day, *The New York Times* ran a front-page story on Klugman and the orphan disease problem. While our first hearing, nine months earlier, had taken place before a nearly empty room, this time we arrived to find it jam-packed with cameras and reporters."

That public support created crucial momentum that drove the bill to swift passage in the House.

Needing a cosponsor in the Senate, Waxman found an unlikely ally in health committee chair Orrin Hatch, a conservative Republican. But Hatch took out the key tax credit provision. That led Klugman to film a second episode, showing him visiting a heartless senator blocking the bill.

In the show's pivotal scene, the senator dismisses the need for orphan drugs, telling Klugman, "Nobody cares about this bill." A righteous Klugman fires back, "Look outside." Peering down from his window, the senator sees a large crowd chanting and holding signs reading "We Want the Orphan Drug Act"—shot with hundreds of extras, all rare disease patients and supporters.

Hatch gave in, and agreement was reached on the remaining issues, with the final point being a compromise that the cost of clinical trials for orphan drugs would be subsidized by a 50% tax credit, a 50% tax deduction, and a much smaller $12 million research grant program.

The bill, with the credits, passed unanimously in both the House and the Senate just before Christmas 1982—and Hatch would later become with Waxman one of the first two members of Congress designated a "Rare Diseases Hero" by the FDA.

The bill still needed President Reagan's signature. But the families involved got word he'd been advised to veto it over an unrelated provision inserted at Hatch's insistence calling for government studies of possible links between radiation exposure and cancer.

Reagan left for a Christmas vacation in Palm Springs intending to veto the bill. Knowing that his wife Nancy and all her friends read the local paper, advocates posted an open letter in it signed by many rare disease families. Noting in stark black type and with "deep despair" that a veto

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would leave desperate families without hope, the letter urged Reagan not to be "the Grinch who stole Christmas" by vetoing the bill.

Despite noting his "grave reservations" over the potential costs of the radiation provision, Reagan signed the Act into law on his return to Washington, D.C. on January 4, 1983.

The ODA provided carefully targeted incentives. If the FDA designated a disease as rare, a company pursuing a therapy would be eligible for a range of benefits, including enhanced agency consultation, reduced filing fees, clinical trial tax credits, and seven years of postapproval market exclusivity, intended to allow a return on development costs for drugs with limited patent life protection.

The initial act didn't actually specify what qualified as an orphan drug. Only in a 1984 amendment did Congress specifically define orphan diseases as those affecting fewer than 200,000 people in the United States—a number described in a 2001 review as "an arbitrary ceiling based on the estimated prevalence of narcolepsy and multiple sclerosis"—rough estimates indeed.

Little remembered today, the original ODA covered only unpatentable drugs. Patentable drugs, which have been key to its impact ever since, were included only in a 1985 amendment.

Equally critical, the initial bill applied only to chemical drugs; biological drugs, which would give rise to an entire new industry, were only added in the 1985 amendments as well.

The ODA addressed a very practical need. The high costs, risks, and times required to discover and develop new medicines presented prohibitive barriers for diseases affecting few patients. By substantially reducing those barriers, the bill and its later amendments triggered first a trickle and then a flood of investment into a then-unimagined diversity of rare disease therapies.

In his memoir Waxman hailed the patient advocates behind "a law that, twenty-five years later, has helped transform not only the lives of families like the Seligmans, but the entire way in which the drug industry approaches the development of new medications for orphan diseases."

And the coalition that drove its passage would evolve into the National Organization for Rare Disorders (NORD), which has played a key role in maintaining support for it since.

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The second catalyst arrived through the tragic onslaught and aftermath of the AIDS epidemic.

The first case of acquired immune deficiency syndrome, or AIDS, was reported in 1981. Over the next few years, as industry and FDA action on expediting therapies lagged, an unprecedented wave of patient activism galvanized new approaches to both drug development and patient access.

That wave spilled over into the rare disease world in 1982, with the first person with hemophilia reported to be infected by HIV from tainted blood products. The horrific consequences of the epidemic to follow would further transform the worlds of both hemophilia and patient activism.

The third and final catalyst was the emergence of the biotechnology industry.

The first biotech company to capture broad public attention was San Francisco–based Genentech, whose 1980 IPO is often marked as the industry's liftoff. Showcasing the power of genetic engineering, Genentech would go on to develop successful products for children with growth disorders, safer insulin for diabetics, and many cancer therapies.

In 1983 two other early biotechs went public—Amgen in California and Biogen in Massachusetts—developing therapies for many diseases, from chronic kidney disease to multiple sclerosis, that had been untreatable by traditional pharmaceuticals. A biotech era was under way.

A much less-heralded company called Genzyme was also founded in 1981, with an initial focus on more pedestrian activities like manufacturing reagents and enzymes. But after hiring Henri Termeer away from Baxter's hemophilia operations in 1983, Genzyme would over the next 30 years launch therapies for more rare diseases than any other company.

In doing so it would become the model for literally hundreds of orphan drug companies that have followed.

Why now?

Some of the most exciting technologies, programs, and start-ups in the history of the orphan drug revolution are just emerging as this is written.

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Applying the latest scientific breakthroughs, they show the promise of widely discussed tools like gene therapy and gene editing and hint at new diseases that may become treated in the coming years.

The last section of this book addresses two questions that have loomed over the orphan drug field from the outset—the affordability of its drugs and its own social responsibilities—which have both taken on a new urgency in light of recently publicized developments.

Addressing affordability calls for helping people understand why orphan drugs cost so much to develop, how patients can afford to pay for them, and how societies can afford them all—including headline topics of drug pricing and insurance coverage. Industry's social responsibilities center on ways to help ensure greater access to its drugs around the world, but increasingly also include broader goals of diversity, inclusion, and equity.

Every year society makes important decisions affecting the future of orphan drugs. This book identifies both threats to those innovations and ways we can expand them, and reminds us that one of the most important healthcare revolutions of our time can easily come to an end if we take its remarkable contributions for granted.

And why this author?

I first stumbled into the orphan drug world in 1981, with no idea a revolution was beginning.

Armed with degrees in psychology and law, but no knowledge of business, I'd unexpectedly been invited to join Bain and Company, a strategy consulting firm with a Fortune 500 client list. (Mitt Romney, then a young partner, valued the study of law, whereas founder Bill Bain wanted a psychologist; as the only applicant they saw who'd studied both, I was an unlikely compromise.)

Bain's work ranged across industries, from steel to services, trash to telecoms. I was drawn to the firm's major healthcare client, an innovative, diversified medical products company then called Baxter Travenol. Joining a team working on strategies for hemophilia products at Baxter's Hyland Therapeutics division, I was moved by how they transformed patients' lives.

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I also found a different culture than at most other Fortune 500 companies. Many executives were scientists or physicians, who knew Baxter needed to meet financial goals but cared less about profits than about patients—and to succeed, the company needed them engaged.

That window into the orphan drug world led a few years later to my becoming immersed in it by joining Genzyme. Over the now 40 years since, I've had the privilege to serve in many different roles —as a consultant, an international executive, a founding CEO, a strategic adviser to big pharma, an entrepreneur-in-residence at a venture fund, and today as a director and chair of emerging biotechs.

This book seeks to share some of the most noteworthy stories of those 40 years—stories of transformational therapies, of scientists and entrepreneurs who defied conventional wisdom, of often dramatic setbacks, and of the ways teams overcame or are still trying to overcome major abstacles.

As Walter Isaacson wrote of the digital revolution in *The Innovators*, these "are among the most important inventions of our era, but few people know who created them." And as he adds, "There were a lot of fascinating people involved [but] how teams collaborated is actually more important in understanding how [this] revolution was fashioned. It can also be more interesting."

The reason an orphan drug revolution hasn't been more widely proclaimed may lie in another of Isaacson's points—that "[h]istorians of science are sometimes wary about calling periods of great change revolutions, because they prefer to view progress as evolutionary." (Or in a lighter vein, "There was no such thing as the Scientific Revolution, and this is a book about it.")

Aspects of this story have been told earlier with thoughtful insights, in Monica Higgins' look at biotech's early leaders, *Career Imprints: Creating Leaders Across an Industry*; Phil Reilly's history of medical genetics, *Orphan: The Quest to Save Children with Rare Genetic Disorders*; John Hawkins' biography of Henri Termeer, *Conscience and Courage: How Visionary CEO Henri Termeer Built a Biotech Giant and Pioneered the Rare Disease Industry*; and Peter Kolchinsky's *The Great American Drug Deal*: *A New Prescription for Innovative and Affordable Medicines.*

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The Promise of Patient-Centered Biotechnology. Click here for more information on how to buy the book.

Others have written across a spectrum from the highly technical to the profoundly personal. At one end, Britain's Royal Society of Chemistry's *Orphan Drugs and Rare Diseases* provides in-depth accounts aimed primarily at specialists interested in the field. At the other, Abbey Meyers' *Orphan Drugs: A Global Crusade* offers a compelling first-person account anyone can relate to.

I've drawn on each of those, and many others, and hope to have added to their contributions.

This history is very much as seen by one participant and could be told in many other ways. Much is regrettably left out. I've tried to provide enough specificity on case studies of diseases and technologies to fully engage scientific and medical readers—and those aspiring to be entrepreneurs themselves—but to do so in a way that remains accessible to the general reader.

Although each case is unique, there are some common themes. They are stories of some of the finest minds of our time working as teams to learn from adversity in the service of a shared mission. No company in this book succeeded based on the plans it initially laid out or even went public on. All changed tack multiple times in the course of their journeys.

The orphan drug revolution was propelled by physicians, scientists, entrepreneurs, and families —passionate leaders who embody anthropologist Margaret Mead's famous words, "Never believe that a few caring people can't change the world, for, indeed, that's all who ever have."

It's been, as a colleague once called it, a "rare privilege" to work with so many exceptional people. Their successes, and setbacks, brought this revolution to life, and their stories deserve to be known.

My hope in telling their stories is to thank them for inspiring me, and perhaps inspire others.

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