Preface

THIS BOOK IS ABOUT THE STRUGGLE TO SAVE the lives of children who, because of a roll of the genetic dice, are born with any one of more than several thousand rare genetic disorders.

I have spent much of my life in medicine trying to help people who are afflicted with some of these disorders. In many cases, people are burdened with diseases carrying mysterious names that you will read for the first time in this book. Often physicians have no therapies to offer. Care is custodial, and the main goal is to relieve suffering. Although each genetic disorder is rare—often so rare as to be invisible—collectively these disorders touch hundreds of thousands of people . . . and of course their families.

Over the last three decades I have come to know many families burdened with such disorders. Over and over again, I have met mothers and fathers who I am certain are among the great, unsung *heroes* of our world. Each day they wake to face challenges that most of us cannot even imagine. You will meet a few of these amazing parents in this book.

I think, for example, of the parents of daughters with Rett syndrome. Apparently healthy for the first year or so of life, by the age of 6 or 7 many of these girls have lost all speech, cannot walk, have seizures (sometimes on a daily basis), and have abnormal breathing patterns that force some parents into a state of unrelenting fear that their child might die of respiratory arrest. When a child develops Rett syndrome, the family is changed profoundly and forever. So severe is the disorder and so needy is the child that parents often alter the very structure of their homes to provide daily care.

Children born with severe dystrophic epidermolysis bullosa (rDEB) do not have the proper form of a protein that holds the outer layer of the skin to its inner layer. The slightest trauma causes the skin to slough off. Sometimes, strangers mistakenly think that these children have been scalded with hot water. Parents often spend 2 hours each day bandaging

the children in a desperate effort to control chronic skin lesions. During childhood, despite the best medical care, some of these children lose the use of their hands and feet as chronic injuries cause the digits to fuse. The more severely affected live with unremitting pain. Then, sometime in midlife, many succumb to an unusually aggressive cancer of the skin.

Here is one more example. Until recently, children born with one of the many severe lysosomal storage disorders (diseases in which different genetic errors prevent cells from clearing certain metabolites, causing a buildup of toxic material that impairs many organ systems) were doomed to a slow and painful death. Best known among these may be Tay–Sachs disease, a disorder that manifests at about age 2, stopping a healthy child in his or her tracks, and leading inexorably to blindness, neurological decline, and death by age 4 or 5. There are about 50 rare genetic disorders like Tay–Sachs disease. Fortunately (as I discuss in Chapter 6) there are now therapies for *some* of them (but, alas, not yet for children with Tay–Sachs disease).

This book recounts the century-long effort of small groups of physicians and scientists to take on some of these genetic diseases. As you will see, in many cases just a few physician–scientists—whom I also regard as *heroes*—have made an immense contribution to blazing a path toward new therapies.

Clinical genetics occupies a tiny niche in the vast medical ecosystem. So, it seems right that I briefly recount how I came to spend much of my professional life in it. Although the son of a surgeon, I did not become interested in science and medicine until after college. I first became aware of striking advances in genetics in about 1972, and despite my inadequate training, had the good fortune to find a mentor who took me under her wing as I redirected my career. In the fall of 1973, I started graduate work in human genetics in the laboratory of a remarkable physician–scientist named Margery Shaw at the University of Texas Graduate School of Biomedical Sciences in Houston.

After 2 years studying with Margery Shaw and her colleagues, I decided to become a clinical geneticist. After earning my medical degree at Yale in 1981, I undertook a residency in internal medicine at Boston City Hospital. My real training in clinical genetics began in 1985 when I joined the Eunice Kennedy Shriver Center for Mental Retardation as a member (and later director) of the primary care group that cared for about 800 adults with severe neurological disorders who resided at the Walter E. Fernald State School, a large state-run institution near Boston.

The physicians at Fernald knew the cause of the disability in only about one-quarter of the population for which we cared. But, even then, my medical colleagues and I suspected that many of our patients were burdened with as-yet-undiagnosed genetic disorders that had harmed brain development. During the course of my time there (1985–2000), new procedures (such as improved cytogenetic testing, DNA testing, and MRI scanning) enabled us to diagnose an increasing, but still relatively small, number of patients. For example, we found that several adults had Fragile X syndrome and that several others had severe intellectual disability due to deletions or duplications in one of their chromosomes. But diagnostic success never led to therapeutic benefit.

As the years passed I became increasingly frustrated with how little we could offer most patients. Eventually, I decided that I would like to help catalyze efforts to develop new drugs to help children who were burdened with rare genetic disorders. In medicine, we often call such diseases "orphan disorders." This is largely because (until recently) the progress in biomedical research since World War II had largely bypassed them. When hundreds of thousands of people are dying each year from heart disease and cancer, it is hard to convince the National Institutes of Health or the pharmaceutical industry to allocate many millions of dollars to better understand and develop new drugs for diseases that afflict only a few thousand (or even fewer) people. The term "orphan disease" became firmly set in our lexicon in the mid-1980s after the federal government enacted legislation that offered special tax benefits and market exclusivity to companies that developed drugs for rare disorders. In the United States, to gain the benefits of that law, the drug under development must afflict less than 200,000 persons in the nation. This includes many cancers and almost all single-gene disorders.

In the summer of 2008, I had the good fortune to start work at a venture capital firm in Boston known as Third Rock Ventures. From 2008 to 2015, TRV created, built, and launched about 35 innovative biotech companies. One of the areas in which it has done much work is in starting companies to develop therapies for rare genetic disorders. Of course, my comments about any of these companies do not represent the views of anyone else.

Although I miss the practice of medicine, I view my current work as a determined response to a world in which there is still little to offer children and adults affected with most of these terrible disorders. I often have the privilege of interacting with parents of affected children, some of whom have started foundations that are dedicated to taking on the immense challenge of developing new therapies. Today, such groups are

quintessential partners in the struggle to develop new therapies for rare genetic disorders.

Despite the immense discord among peoples on this planet, we are united by our shared membership in the human gene pool. When I think about those who suffer and die from rare genetic disorders, I recall the great English poet, John Dunne, who wrote, "No man is an island, entire of itself; every man is a piece of the continent, a part of the main. If a clod be washed away by the sea, Europe is the less, as well as if a promontory were, as well as if a manor of thy friend's or of thine own were: any man's death diminishes me, because I am involved in mankind, and therefore never send to know for whom the bell tolls; it tolls for thee."