Introduction

I SPENT SEVERAL YEARS AS A PRACTICING PHYSICIAN overseeing the care of hundreds of mentally retarded (that is how we described them in the 1980s and 1990s) adult patients who resided at the Walter E. Fernald State School, a large, century-old, state-operated institution in Waltham, Massachusetts. For the most part, these folks were cut off from the world we inhabit. Most of them had almost no use of language, and many had severe behavioral problems. Virtually all of them required round-the-clock custodial care. One building at Fernald was home to patients who were profoundly mentally retarded and deaf and blind. They were among the last group of individuals born (in the early 1960s) with severe congenital rubella, just before rubella vaccine became a routine part of health care. The rubella virus had devastated them while they grew in their mothers' wombs. Scattered among the different housing units were about 60 older patients with Down syndrome, people with untreated phenylketonuria, men afflicted with Fragile X syndrome, and persons with rare genetic disorders with unfamiliar names such as Rubenstein–Taybi syndrome and Cornelia de Lange syndrome. But the largest diagnostic group by far (~75%) included those for whom the cause of their disability was *unknown*.

Despite the best efforts of the staff, the living conditions at the school were grim. Although it happened 25 years ago, I still recall the sense of despair I felt one hot summer afternoon when I elected to check on a patient in one of the buildings. In a large room filled only with plastic furniture that reeked of urine, I found the woman alone, rocking herself, and softly uttering sounds that carried no message for me. When I approached, she turned away. Although I was the medical director of the program, it was beyond my power to make her life better in any way. I remember reflecting over the following weeks about therapeutic futility. It was that summer that I began a journey that, among other things, led me to write this book.

Rare genetic disorders—a group of disorders that we often call "orphans"—are, collectively, quite common. About four million babies are born each year in the United States. About 120,000 (3%) will be diagnosed with a disorder that is caused (or heavily influenced) by a mutation in a single gene. Some babies will be diagnosed within 2 or 3 days. In the United States virtually all babies are screened at birth for (depending on the state) about 25 to 50 severe single gene disorders. Screening will identify about 5000 affected babies in time to start treatment. But there are more than 1000 well-described genetic disorders and many more that are poorly described. We do not yet have the means to screen for most of them. Many genetic disorders manifest in mid-childhood (some muscular dystrophies), others in late childhood (Friedreich's ataxia, some forms of retinitis pigmentosa), and still others in adulthood (Huntington disease). Many thousands of children afflicted with ultrarare disorders will receive a correct diagnosis only after their parents spend a year or more on a diagnostic odyssey that is frustrating and expensive. A few will go undiagnosed for decades.

Rare genetic disorders touch almost every family. If there is no child with a genetically driven disability in your extended circle, you are among the lucky minority. About one-half of all pregnancies end (usually very early) due to chromosomal or genetic abnormalities, about one in a 1000 children is diagnosed at birth with spina bifida, about one in 300 infants is born with a heart defect, and about one in 100 children will be diagnosed with autism spectrum disorder. About 3% of children have significant intellectual disability. There are many thousands of people in the United States with phenylketonuria, muscular dystrophy, cystic fibrosis, β-thalassemia, sickle cell anemia, hemophilia, Marfan syndrome, Huntington disease, and an ever-growing list of newly described genetic disorders. One hundred years ago the wards in children's hospitals were full of patients suffering from pneumonia and related infectious diseases. Today, a sizable percentage of the in-patient population carries a primary diagnosis of a genetic disease.

This book recounts some of the important milestones in the fight to help children with rare genetic diseases. In most cases I tread softly over the more technical aspects of the accomplishment, instead trying to tell stories that stress the human element. The chapters are links in a chain, a coherent story of the heroic efforts by parents, physicians, and scientists to help children born with mysterious and, frequently, untreatable genetic disorders. I do not use the word "heroes" lightly, but heroes do stride through the pages of this book. Many stories are painful, but some do have happy endings. I am pleased to say that I think that there will be many more happy

endings in the future. I hope the stories in this book lead you to share my optimism.

Above all else, I wrote this book to convey a message of *hope*. The history of efforts to help children with genetic disorders provides irrefutable evidence that disorders that scientists and caregivers once viewed as beyond their therapeutic reach can be overcome. Sometimes, the therapeutic answer seems profoundly simple. As you will see in Chapter 1, the development of a special diet to treat children with phenylketonuria (PKU) by greatly reducing the amount of phenylalanine they consume has converted a severe form of mental retardation into a manageable, albeit chronic, disorder compatible with living normally. Today, rigorous control of diet (to avoid elements in foods that most of us eat safely each day) comprises the essential therapy for several genetic diseases.

In Chapter 3 I focus on blood. Until World War II most of the hundreds of thousands of children in the world who were born with β-thalassemia (in which the cells fail to produce enough hemoglobin to transport oxygen to the body's organs) died in childhood of profound anemia. The advent of blood banks and transfusion medicine in the early 1950s opened a new approach to treatment that converted (for those children who had access to such care) a fatal disorder into a chronic, but manageable, disease. Until not so long ago, children born with classical hemophilia (those whose cells could not make enough of the clotting protein called Factor VIII) rarely survived to adulthood. The purification of cryoprecipitate (which carries Factor VIII protein in great concentration) in the 1960s revolutionized the care of children with hemophilia.

Beginning four decades ago, a few intrepid physicians began to advocate for bone marrow transplants to treat certain single-gene disorders. This heroic intervention succeeded in some diseases, but failed in others. In the 1980s, a few scientists, especially at the National Institutes of Health, pushed the boundaries of biochemistry to create the new field of enzyme replacement therapy (ERT). The industrialization of the production of some crucial enzymes opened up a new era of therapy and helped to accelerate the growth of the biotech industry. Under the steady hand of CEO Henri Termeer, a company called Genzyme developed several ERT therapies that greatly improved the lives of children and adults with some of the lysosomal storage disorders. Today, as I discuss in the second half of the book, the burgeoning biotech industry is embracing a growing array of new technologies, including gene therapy, exon skipping, gene editing, and the delivery of structural proteins to take on the challenges posed by rare genetic disorders.

It is extremely difficult to meet the scientific, clinical, and regulatory challenges of drug development, but each year more groups determine that they will take on those challenges. Today, there are new partners in the mix of groups that develop novel drugs. Parents of children with rare genetic disorders have emerged as influential players at the biotech table. Foundations created by parents who refuse to surrender to rare disorders develop patient registries, support natural history studies, contribute to discussions about what constitutes approvable clinical end points, raise money to fund research, lobby regulatory agencies to be more innovative in how they oversee clinical trials, and push hard to have Congress earmark more research dollars for their diseases. As anyone who has had close contact with families that include children with severe genetic disorders knows, there are countless mothers who rise each day determined to move mountains.

When I was a medical student, the median life expectancy of a child with cystic fibrosis was about 12 years; today an affected child can expect to live into his 50s. Even a decade ago, most experts could not conceive of a means to attack the fundamental cause of cystic fibrosis. In 2012, after nearly two decades of effort, Vertex, a biotech company in Boston, won approval of a small-molecule drug to partially correct the molecular defect in one form of the disease. This has opened a door that may lead to the development of similar drugs for other molecular forms of cystic fibrosis. Further, it has established a new paradigm for drug development in general. Vertex's triumph required great vision, access to immense resources, and incredible tenacity. Victory came in no small part because the Cystic Fibrosis Foundation poured tens of millions of dollars into the effort. Unfortunately, in many cases the road to approval of a new drug will be long. However, some new technologies, especially gene therapy and gene editing, offer the hope that as our experience with them grows, the development pathway will be considerably shorter. I discuss them in two of the later chapters.

No tale about efforts to treat rare genetic disorders should sidestep the impact of the ever-growing power of diagnostic technologies, which I cover in Chapter 4. For decades, our ability to assess risk for genetic disorders has exceeded our abilities to treat affected individuals. Since the early 1970s pregnant women have had the option to undergo testing to determine if the fetus is burdened with a chromosomal disorder. Also since the 1970s members of certain groups have had the option to determine if they carry a mutation that (if they marry another carrier) puts them at risk for bearing a child with a severe genetic disorder such as sickle cell anemia, Tay–Sachs disease, and β-thalassemia. For a few disorders, abortion and avoidance of

entering into at-risk marriages became an important option. Today, we are on the verge of being able to offer individuals *vastly* greater amounts of genetic risk information in regard to their reproductive planning. But for most genes we still have a great deal to learn, so large-scale DNA testing will for some years pose difficult questions of how to interpret some test results.

In several of the later chapters I discuss emerging technologies that allow us to hope that the dreams they have for their children will be realized. Our ever-deepening knowledge of human biology is expanding the boundaries of therapeutic possibility.

The final chapter confronts the fact that *we are all orphans*. Each one of us carries many mutations across many genes that will (interacting with environmental forces) affect our overall health, how we will age, and when we will die. Do we want to confront this information? In that chapter, I also confront the difficult fact that the cost of developing new therapies for a small number of patients demands that the price of these drugs be extraordinarily high. As medical therapy becomes more personalized (as is rapidly becoming the case with cancer therapies), society will have to determine what, if any, restraints it should place on pricing. Yet, if limits are imposed, drug discovery may cease in certain areas. Indeed, the more important problem may be how to find ways to encourage drug development to save the lives of children with ultrarare disorders, of which there are thousands.

The title *Orphan* is meant to convey two messages. The first is that there are a vast number of genetic disorders that burden *only a few* people, but for which we must find a way to harness our biomedical research engine to develop cures. The second is to emphasize what we all know—that nothing is more precious than our children, and we must not let a bad ticket in life's genetic lottery leave them and their families desperate and alone.

When I reflect on the range of my experiences as a physician—from toiling in the 1980s in the back wards of a state institution housing hundreds of severely disabled people to the last 7 years during which I have helped to create several new biotech companies that intend to translate cutting-edge science into breakthrough therapies—I feel a great sense of privilege. One of the main reasons is that I have met so many people whose stories have touched me. I retell some of those stories here. They will touch your lives.