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Cover photos: (Top left) Egyptian stele (c. 1500 B.C.) depicting the priest Ruma, afflicted with paralytic poliomyelitis. Note the withered leg, high arched foot, and cane. Photo courtesy of the NY Carlsberg Glyptotek, Copenhagen. (Bottom) Ribbon diagram showing the binding of a candidate anti-enteroviral compound to the VP1 pocket of a human picornavirus (for details, see chapter 18). Photo courtesy of Dr. Edward Arnold, Center for Advanced Biotechnology and Medicine, Rutgers University.
To my wife, Sara,
and our kids,
Matthew, Emily, and Samuel,
who fill our lives with infectious smiles, contagious laughter,
and pandemic love

And to my mom,
who has her own germ theory but never published it
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In August of 1982 I had just completed my residency training in Pediatrics and was beginning my subspecialty fellowship in Infectious Diseases. I was called to the newborn intensive care unit at Children's Hospital of Denver to see an ill one-week-old baby with a rash. The prenatal course was unremarkable until 38 weeks gestation when the baby's mother developed abdominal and back pain, uterine tenderness, fever, and an elevated leukocyte count; she and several family members also had upper respiratory infections. The obstetrician induced labor for fear that the mother's symptoms heralded bacterial chorioamnionitis, an infection treated by prompt delivery of the infant and administration of antibiotics.

The first 4 days of little “Briana’s” life were entirely normal. On day 5, at home, she developed poor feeding and lethargy. By the time she was readmitted the next day, she was hypothermic, minimally responsive to external stimuli, and bleeding from both upper and lower gastrointestinal tracts. Laboratory studies confirmed disseminated intravascular coagulation, hepatitis, meningitis, pneumonia, and renal impairment. She was treated with broad-spectrum antibiotics and vidarabine (anti-herpesvirus medication) with the presumed diagnosis of overwhelming bacterial or herpesvirus sepsis.

Her pneumonia required assisted ventilation for more than 2 weeks. Her meningitis evolved into meningoencephalitis, with difficult to control seizures, profoundly abnormal brain waves by electroencephalography, and coma, but her neurologic condition stabilized and returned to normal by 4 weeks of age. Her renal disease gradually resolved. By 4 weeks of age Briana was breast-feeding, alert, and active. Her hepatitis, however, progressed to full-blown liver failure; she became progressively more jaundiced and edematous, continuing to ooze blood from multiple body sites. Although the jaundice gradually faded, the synthetic capacity of her liver never recovered and she died with massive ascites and pulmonary edema at 3 months of age.

Viral cultures of blood, cerebrospinal fluid, urine, and nasopharyngeal as-
pirate all grew echovirus 11, the same agent which undoubtedly caused her family’s upper respiratory infection symptoms and her mother’s lower abdominal pain. Early induction of labor may have precluded maternal antibody from developing in time to cross the placenta and protect the baby from transplacental enterovirus infection. Bacterial and herpesvirus cultures were negative.

It took 6 hospital days before we knew the cause of Briana’s overwhelming sepsis, but the slow laboratory diagnosis probably did not harm her, since there was nothing other than supportive care to offer for neonatal enteroviral sepsis. When the culture results were known, we administered plasma obtained from her mother in the hope that by then enough maternal antibody to echovirus 11 had formed to neutralize some of the virus in Briana; there was no sound evidence that such an approach would help, but we had nothing else.

There may be 2,000 or more babies like Briana who die of this infection every year in the United States, but she was the first that I had seen, and the impact on me was enormous. I watched her die from a virus that causes adults to cough and sneeze. Knowledge of the pathogenesis of such infections was rudimentary, diagnostic tools were inadequate, and there was no meaningful treatment. So we watched her die.

Now, 12 years later, understanding and awareness of human enterovirus infections have increased logarithmically. The genomes of these pathogens have been cloned and sequenced, virulence determinants have been mapped, atomic structures have been resolved, cellular receptors have been identified, and immune responses have been characterized. Diagnosis can now be made in a few hours, promising antiviral drugs are in the final stages of development, and the knowledge is in place for the design of new vaccines to protect us from both the polio and nonpolio enteroviruses.

This is a worthy list of achievements in a field already rich in scientific heritage. Indeed, the discoveries which preceded the current molecular era of enterovirus research include no less than the first propagation of animal viruses in continuous cell culture. That Nobel Prize winning accomplishment allowed the development of the vaccines which have now eradicated wild-type poliovirus infections from the Western Hemisphere.

The progress we have seen over the past 12 years in the field of human enterovirus infections is the result of a unique synergy between basic science and clinical medicine, reflected in the subject and spirit of this book. The chapter authors are the preeminent scholars in their fields, which assures the reader that the basic science contributions are written with an eye toward clinical implications and that the clinical chapters are steeped in relevant science. Necessarily, there is some overlap and some controversy between the chapters—both of which I hope will provide the reader with the fullest possible perspective on these important pathogens and the diseases they cause. Our goal in preparation of this monograph was that it be a definitive and current resource for scientists wanting clinical correlates, clinicians seeking explanations, and medical scientists pursuing cures.
Which brings us back to little Briana. Her picture is shown below as a reminder to us all of why we do what we do.

HARLEY A. ROTBART

October 1994

Briana
I am grateful to the contributing authors of this book, not only for their fine chapters but also for their collaboration and friendship over the years. I thank my colleagues and mentors Myron Levin, Lewis Pizer, and John Sninsky for their invaluable, longstanding support. Thanks also go to Patrick Fitzgerald and Pamela Wilks of ASM Press for their encouragement and efficiency.
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