By the early 1930s, pediatric drug knowledge had advanced little beyond Abraham Jacobi’s nineteenth-century declarations that children were not just miniature adults. When J. P. Crozer Griffith and A. Graeme Mitchell published their state-of-the-science *The Diseases of Infants and Children* in 1933, they lamented the weaknesses of nineteenth-century metrics for pediatric dosing. The authors, prominent pediatricians at Children’s Hospital of Philadelphia, nonetheless recommended these proportion-based rules in the absence of any more meaningful rubric. They considered the risks to children from the drugs available so great, and their potential benefit so minimal, that their use could not be justified. Griffith and Mitchell cautioned that for most children “little medicine of any sort is required, and the careful attention given to hygiene and diet is sufficient.”¹

Other pediatricians, particularly those trained and teaching at elite medical schools, agreed. Famed Harvard University pediatrician Charles A. Janeway noted that when he graduated from medical school in 1935, “there were only about six drugs I needed to know how to use; all the others were basically ineffective.”² Similarly, pediatrician Thomas E. Cone, who would become professor of pediatrics at Harvard and chief of ambulatory services at Boston Children’s Hospital, later recalled, “I didn’t feel that what I was doing was that
much different than thirty years before. . . . We had little to work with. We tended to be therapeutic nihilists, I think,” and trusted in “[t]he old aphorism about the healing power of nature.”

As a more nuanced understanding of children’s physiological and pathological differences from adults evolved in the 1910s and 1920s, the paucity of pediatric drug and dosing information became more glaring. By 1933, leading members of the venerable Philadelphia Pediatric Society (PPS) were particularly concerned that the standards for drugs, the United States Pharmacopeia (USP) and the National Formulary (NF), had no pediatric representation, especially since many of the drugs listed were “employed extensively in treating disease in infants and children.” The Philadelphia doctors’ worry was especially acute because so few American children in the 1930s ever interacted with a pediatrician. Many did not see a doctor regularly at all and, when ill, received care from a general practitioner who often had little or no training in pediatrics.

The PPS doctors wanted to discover whether pediatricians around the country shared their concern that “the committees of the USP and NF have never felt it sufficiently important to secure the advice of pediatricians.” The results of the survey they sent to a carefully selected group of their colleagues throughout the United States, showed near-unanimous agreement with the PPS position. Next, the Philadelphia pediatricians sent their findings to the newly founded American Academy of Pediatrics (AAP). The PPS sought the AAP’s assistance in securing pediatric representation on the committee that oversaw the decennial USP revisions, next scheduled to be published in 1940. The PPS also wanted the USP to appoint a permanent pediatric panel to strengthen the evidentiary base for pediatric practice.

Looking for opportunities to develop its activism as a voice on behalf of children, the AAP was immediately supportive of the PPS idea. Leaders saw this endeavor as a way to shore up pediatricians’ role as the primary, if not sole arbiter of whether a child should receive medication. Pediatricians wanted all recommendations for children’s drug treatment under their professional domain and away from public health nurses or pharmacists, both of whom frequently made such suggestions to parents. The AAP’s inaugural president, Isaac Arthur Abt, was especially enthusiastic about making sure that physicians oversaw all medication-related decisions. He had worked in an apothecary as a teenager in the late nineteenth century and remained troubled that the store’s clerk had dispensed medical advice along with drugs. His primary goal, as stipulated in comments in the Journal of Pediatrics in 1934, was that the AAP, through USP representation, could “reestablish the use of drugs and remedial agents prescribed by physicians in place of the use of proprietary products. A further purpose is to put dosage for children on a sound and satisfactory basis.”
The AAP formed a Committee on the Revision of the Pharmacopeia, and Abt appointed himself chairman. Because of the professional rivalries and tensions between pharmacists and physicians, the USP allowed a set number of representatives from each group. The AMA selected the physician members. Thus, in order for the AAP to seat its own representative, the AMA would need to agree to cede one of its slots, diminishing its authority. It was certainly improvident that Abt was the individual who approached the AMA to discuss the issue, for he had been one of the leaders of the AMA breakaway group that had chartered the AAP several years before. When he broached the topic with Olin West, secretary and general manager of the AMA, West, clearly rankled, was not receptive to the idea. Perhaps he was still miffed about the AAP rejection of the AMA several years before, or feared that doing so might result in other specialty groups seeking a place at the table, which could lead to a dilution of AMA authority. Whatever the reason, West was not about to help. Abt dejectedly noted West’s response, “I am inclined to the opinion that if the pediatricians of the country really desire to be represented in the Pharmacopeia convention, that they may of their own effort, obtain such representation through the procedure of bringing the necessary pressure to bear upon the officers of the Pharmacopeia convention.”

West’s advice to the AAP was disingenuous, however, since the USP was unlikely to change the balance of power between physicians and pharmacists by adding a new physician. The powerful AMA Council on Pharmacy and Chemistry considered itself the medical profession’s single voice on all matters related to drugs, and the USP had little wish to alienate the group. The council’s “New and Nonofficial Remedies,” published as a regular Journal of the American Medical Association (JAMA) section, represented the chief source of physician knowledge about drugs, dosing, and toxicity for every drug on the market, and drug companies competed with one another for the council’s financially advantageous Seal of Acceptance. The AMA did usually include a pediatrician as part of the council, but the AAP wanted to oversee the selection process, and the wall of interprofessional politics among physician groups was impossible to overcome.

Faced with defeat, the AAP Committee on the Revision of the Pharmacopeia looked for other ways to become relevant on matters pertaining to children and drugs. The group decided to gather in one place all the pertinent data related to pediatric pharmacology. This resource would include “a study of vehicles and other means of administering therapeutic remedies, with the thought of improving unpleasant-tasting remedies for use in infants and children, . . . a study of dosing standards by age [and] body weights, . . . [resulting in a] manual that serves as supplement to USP and NF with indications for the use of such drugs [and] method of administration.” Their goal was to assure that physicians caring for children would have ready access to state-of-the-science
pharmacology information. This initiative was especially ambitious because it aimed to make suggestions for every age range, from infancy to adolescence, and for all drugs—from each of the many pediatric laxatives on the market, for example, to the powerful heart stimulant digoxin. Support from the AAP executive board was tepid, however, perhaps because such a plan represented an entirely different agenda from the Committee on Revision’s original charge. The board may also have believed there were other, more important, issues facing children during the height of the Great Depression, especially considering the paucity of drugs pediatricians considered useful in children. With these obstacles and lack of board support, the Committee on Revision soon disbanded.15

The federal Children’s Bureau, a group that might have been a strong ally in the AAP’s efforts to secure a place for the 1940 USP revision, seems to have been silent. The work of the AAP, the FDA, and the Children’s Bureau overlapped in multiple areas: promoting food and milk safety, developing growth standards for children, and promulgating the importance of good nutrition, vitamins, and immunizations. Given the prevailing opinion among pediatric leaders that even sick children rarely benefited from drug therapy, perhaps the bureau saw little reason to devote time and energy to an idea that would presumably benefit only a few youngsters.

It is more likely that the long-standing tensions between leading academic pediatricians, who were more likely to view medicine as a private business enterprise, and the Children’s Bureau’s social workers, nurses, and physicians, who favored governmental involvement in health care delivery, also played a role. The bureau’s leadership may have felt that the AAP was attempting to undercut its role as a voice for children, not just within the federal government, but within society as well. Finally, more than just philosophical differences regarding government’s role in the delivery of health care may have prevented cooperation between the bureau and the AAP on this issue: gender may also have been a factor. Children’s Bureau physicians were almost all women and the early AAP leadership was almost exclusively male. Women physicians in this era faced a number of barriers within medicine, such as limited access to training at elite hospitals that served as pipelines for medical school professorships. While some male physicians were involved in the Children’s Bureau, it became a key organizational voice for female pediatricians who lacked other avenues to rise to positions of power.16

Despite the efforts of FDA reformers, pediatricians, and the AMA Council on Pharmacy and Chemistry, the patent medicine industry flourished in the 1930s.17 A growing consumer movement, nurtured by the FDA and accompanied by New Deal activism, offered hope for legislative reforms to rein in proprietary drug manufacturers. The FDA, for example, sponsored lectures and a series of exhibits at agricultural and state fairs around the country aimed
at building public support for new food and drug laws in the United States. At the same time, the nonprofit organization created to provide the American public with reviews of a wide variety of commercially available products, Consumers’ Research, Inc., published a monograph entitled *100,000,000 Guinea Pigs*. Its central argument was that Americans were at risk because of weak federal regulations for foods, drugs, and cosmetics.\(^{18}\)

In 1933, Senator Royal S. Copeland, a homeopathic physician from New York, placed a muscular bill on the docket of the U.S. Senate Commerce Committee, which he chaired. The proposed law placed strict new regulations on patent manufacturers’ labeling and branding practices. Like earlier drug industry reformers, rather than emphasize its regulatory features, Copeland stressed the way his proposed law would provide a measure of protection for vulnerable “women, babies, and children.”\(^{19}\) But his bill and subsequent related legislation stagnated over the next few years amid intense opposition. The Proprietary Association and the Institute of Medicine Manufacturers, representing the patent drug industry, convinced congressional Republicans that the proposed law placed undue burdens on the American free enterprise system.

Meanwhile, the FDA kept up its pressure tactics. In 1936, FDA information officer Ruth deForest Lamb published the polemical book *American Chamber of Horrors*. Demonstrating an astute understanding of how to use children to play on public sympathies, Lamb included a letter from a ten-year-old child, Hazel Fay Brown, to President Franklin Roosevelt. In her letter Hazel informed the president that her mother had been blinded by the dye in a brand of mascara. She pleaded with the president to “help my mother” and “to get the law across.”\(^{20}\)

The Sulfonamides and Children: Promise and Peril

A dramatic challenge to the notion that drugs offered a great deal of risk, but dubious benefit, to children occurred in 1936. At the International Congress of Microbiology in London, Eleanor A. Bliss and Perrin H. Long, researchers at the Johns Hopkins University medical school, heard riveting reports of a new agent’s ability to cure postpartum infection or “childbed fever.” The drug, Prontosil, worked amazingly well against the streptococcus bacteria in researchers’ experiments. After returning home, Long and Bliss procured a supply from DuPont and Company and began investigations with streptococcus-infected mice, confirming that the drug worked on almost all the mice treated. The two researchers were naturally eager to try Prontosil on a human subject, and later that fall their opportunity arrived in the form of a seven-year-old child at the Johns Hopkins Hospital’s pediatric center, the Harriet Lane Home, very ill with a high fever from a raging streptococcal skin and tissue infection known as erysipelas.\(^{21}\)
The child had not improved with conventional supportive therapy, in which nurses sponged her with tepid water to reduce her fever, elevated the infected area to reduce swelling, and encouraged her to drink to prevent dehydration. Doctors disappointedly noted that the little girl also did not improve with serum therapy. Serum worked in one of two ways. Some, such as diphtheria antitoxin, worked against the poisons produced in the body by bacteria; others contained antibodies that destroyed the bacteria itself. The production of antibacterial serum therapy was labor intensive and expensive. First, it required a laboratory for identification of the bacteria afflicting the ill person. Next, a skilled technician needed to inoculate an animal (typically a horse or rabbit) with the bacteria, then harvest the resulting antibodies from the blood, which would then be injected into the child to help fight the infection. Additionally, the serum was highly perishable and often produced serious side effects, including fever, joint pain, rash, and even fatal allergic reactions.

Because serum was administered subcutaneously, intravenously, or intraspinaly (.injected into the spine), it was an uncomfortable procedure. The treatment also posed challenges unique to the pediatric patient. Its administration almost certainly frightened young children who could not understand what was happening to them, which undoubtedly was upsetting to their parents as well. Moreover, infants and very young children who experienced an allergic reaction to serum could become critically ill much more rapidly than adults. Their smaller blood vessels also made serum administration more challenging than for adults. Bliss and Long arranged for the child to receive Prontosil. Despite the fact that she was critically ill, within twelve hours of her first dose, the child’s doctors and nurses reported excitedly that her fever had disappeared. The New York Times noted the “triumph” in a feature story entitled “Conquering Streptococi.”

Bliss and Long next sought to try the drug on a different streptococcal infection, scarlet fever. Baltimore’s Sydenham Hospital, a municipal infectious disease facility affiliated with Johns Hopkins, offered a ready supply of children suffering from the condition. According to physician trainee Elinor Fosdick Downs, Long arrived one day in late 1936, explaining to the young doctors that Sydenham’s sickest youngsters with scarlet fever were to receive the Prontosil he carried with him in a small glass bottle, mixed in orange juice to disguise its taste. Children received the drug four times a day until the limited supply was exhausted. Everyone was “incredulous” when, “within a few hours,” the youngsters’ fevers disappeared. Five days later, children were “smiling” and well enough to go home.

Research soon began using Prontosil’s therapeutically active component, sulfanilamide. Prontosil’s expense, set by its manufacturer, Germany’s I.G. Farbenindustrie, led a number of investigators to create a new, more cost effective formulation. The first American pediatric trial of sulfanilamide occurred in
a youngster with streptococcal meningitis, a bacterial infection of the membrane that protects the brain and spinal cord, at Sydenham Hospital. Before serum therapy, almost all of the children with this type of meningitis at the Harriet Lane Home or Sydenham Hospital died. Through bedside trial and error, by the 1930s Sydenham doctors developed a serum treatment protocol they believed worked best. Children received repeated doses of serum both intravenously and intraspinally. Doctors regularly drew spinal fluid and continued serum injections until the fluid was free of bacteria. This approach lowered the mortality rate to about 30 percent. But serum was no panacea because children often suffered life threatening allergic reactions and treatment progressed slowly. Many of the youngsters who received serum for meningitis and survived subsequently developed hearing loss, brain damage, or other aftereffects of protracted infection.

Because of meningitis’s high fatality rate and serum therapy’s side effects, Johns Hopkins and Sydenham pediatrician Francis F. Schwentker was ready to try sulfanilamide for meningitis. Although the mortality rate had decreased using serum, one fatality for every three of his pediatric patients was too many. Another reason was that he was having difficulty procuring the same quality serum for Sydenham as was available at the Harriet Lane Home, possibly because Sydenham, as a public hospital, had less money to spend on the product. After obtaining a small supply of sulfanilamide from two chemical companies, DuPont and Winthrop, Schwentker readied a supply for testing in Sydenham children with meningitis.

The first child with meningitis to receive sulfanilamide arrived at Sydenham Hospital on December 4, 1936, with a high fever, headache, and stiff neck, all suggestive of bacterial meningitis. Laboratory tests confirmed the deadly diagnosis: streptococcal meningitis. The child received serum, with no response. Death seemed imminent until she received sulfanilamide, at which point her doctors noted with amazement that she “showed rapid clinical improvement.” Not only did sulfanilamide have the potential to be more effective than serum, Schwentker concluded that it could be administered orally after an initial intraspinal, intravenous, or intramuscular injection. It had the added benefit of being much less expensive and less perishable than serum. The little girl returned home on Christmas Day, the first person ever to survive at Sydenham from streptococcal meningitis.

Because 80 percent of Sydenham Hospital’s patients were children, the institution provided a ready population of youngsters with bacterial infections on which to study the new class of drugs. When, in February 1937, Schwentker presented his latest research to the Medical Society of Kings County, New York, he also reported on sulfanilamide therapy for meningitis patients infected with a different bacterium, the meningococcus. Meningococcal meningitis was even more fatal than streptococcal meningitis. Eleven Sydenham
New Drugs, Old Problems in Pediatrics

patients with meningococcal meningitis received treatment with sulfanilamide. Only one patient, an adult African American male desperately ill on admission, died. The other ten, seven of whom were children, survived, much to the astonishment of the physicians.32

Notably, the records indicate that Schwentker and his colleagues were more concerned with distinctions among infectious organisms than with patients. They included more children in their research because these comprised the bulk of the hospital’s population, and they did not privilege access to the sulfonamides according to race. This by no means implies that Sydenham offered equal access to black and white children. The historical record is clear: between 1909 and 1924 no African Americans were admitted to Sydenham, despite the fact that infant and child infectious disease mortality in Baltimore was much higher in black children than white during these years.33 The institution maintained racial exclusion until it moved to a new and larger location in 1924. Physicians’ interactions with one another document the normative racism that framed their clinical thinking. For example, on his return from a trip to study public health infrastructure in other Southern areas, physician and Sydenham superintendent Myron G. Tull explained to a colleague his surprise when he learned that every “colored” child in Jacksonville, Florida, had been immunized against diphtheria. Tull concluded that the success was because “the Negroes do what they are told in the south,” not that the African American physicians and nurses overseeing the effort had done a better job than their white counterparts. But with regard to the early pediatric sulfonamide studies at Sydenham, there is no evidence that Schwentker and his colleagues used race as a criterion for receiving the drugs. Rather, they sought children of any race harboring the particular bacillus they were testing for response to sulfa drugs.34

Sulfanilamide quickly spread to other leading pediatric centers of care, and the results were similar to those at Sydenham. Physicians at Boston Children’s Hospital, for example, praised sulfanilamide as a “remarkable substance,” one that was clearly in a new category of therapeutic agent, since it was “neither a vaccine, nor a serum, but is a chemical drug.”35 Recognizing that they were practicing at a historically significant moment, one Children’s Hospital pediatrician noted that sulfanilamide’s “efficacy . . . has definitely changed the entire procedure which we were accustomed to use in the treatment of meningococcal meningitis. No longer is it necessary to subject children to repeated and painful lumbar puncture and to the injection of a foreign serum.”36

But even as Schwentker and his colleagues in Boston marveled at sulfanilamide’s curative potential, they, like their counterparts who treated adults, began documenting its troubling adverse reactions in some recipients: rash, fever, anemia, and kidney complications. Some side effects were dose-related, presenting a particular problem for the pediatric patient, since infants
and children came in so many different sizes that estimating how much sulfanilamide to administer represented a challenge. Nonetheless, they calculated that sulfanilamide’s risks were worth taking because serum therapy’s cure rate was so much less and its side effect profile was even greater.

The race was now on to decipher sulfanilamide’s metabolism and excretion in children of different ages and sizes to determine dosing protocols. This effort also provided clues that there were important differences in the way infants and young children processed drugs relative to adults. In one of their earliest publications about sulfonamides, Long and Bliss observed with surprise that children with severe infections sometimes needed a higher proportional dose than adults to achieve the same serum concentration of the drug. Their observations suggested that dosing requirements for the sulfonamides were not necessarily linear according to children’s size, a finding that would later have great clinical significance. Sulfanilamide also provided a stark example of how using age or weight as the sole rubric for calculating children’s dosages was profoundly inaccurate. This concern notwithstanding, Sydenham publicized its achievements with the new class of drugs now known as sulfonamides. As child after child survived after receiving sulfanilamide, the Baltimore Sun exulted about the victory over the “child-killing” bacteria and happily concluded that “Medical Science Conquers a Foe.”

While Schwentker, Bliss, Long, and Boston Children’s Hospital doctors successfully employed Prontosil and then sulfanilamide on youngsters in 1936 and early 1937, those working on drug law reform on Capitol Hill grew increasingly frustrated. Opposition to Senator Copeland’s bill to expand the FDA’s powers kept it from progressing through the legislative process. But in the fall of 1937 reports of more than one hundred fatalities from sulfanilamide treatment brought drug safety questions in the United States onto the pages of American newspapers. In one November article that spurred panic, for example, the New York Times proclaimed that a particular sulfanilamide brand was not a life saver, but rather a “Death Drug.” The crisis began because some adults, and almost all young children, had difficulty swallowing sulfanilamide in pill form. A sweet-tasting liquid formulation of the drug produced by the S. E. Massengill Company, called Elixir Sulfanilamide, seemed an ideal solution, especially for the pediatric patient. A Massengill pharmacist had discovered that diethylene glycol dissolved sulfanilamide, and the company rushed the drug into production and distribution. Because no one owned a proprietary stake in sulfanilamide, any company could manufacture its own version. Getting to market quickly and differentiating one’s product from others was essential to making a profit. Massengill considered diethylene glycol’s sweet taste a bonus, one that would make its addition to sulfanilamide more palatable for the pediatric patient.
Unfortunately, however, diethylene glycol was also a highly poisonous substance, analogous to antifreeze, that could cause severe kidney damage, agonizing pain, and death. Many of Elixir Sulfanilamide’s 107 victims were children. As Daniel Carpenter and Gisela Sin have shown, the public face of the disaster became a white child, Joan Nidiffer. The congressional report in response to the investigation of the Elixir Sulfanilamide disaster included a letter written to President Roosevelt from the girl’s mother:

Two months ago I was happy and working, taking care of my two little girls, Joan age 6 and Jean age 9. Our byword through the depression was that we had good health and each other. . . . [Joan] was given the Elixir of Sulfanilamide. Tonight our little home is bleak and full of despair. All that is left us is the caring of that little grave. Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain. . . . [I]t is my plea that you will take steps to prevent such sales of drugs that will take little lives.

The document included Mrs. Nidiffer’s full letter to President Roosevelt, as well as a smiling picture of the little girl.

The specter of children dying spurred new energy for legislative reform. Although the AMA was supportive, ultimately it was the FDA-mobilized advocacy of women’s and consumer groups that made the difference. Working together under the umbrella organization the Women’s Joint Congressional Committee, sixteen women’s groups—including the National League of Women Voters, American Medical Women’s Association, American Nurses Association, and National Congress of Parents and Teachers—joined FDA officials, sympathetic congressmen, and consumer organizations to mobilize public and congressional support for better drug laws. The resulting 1938 Federal Food, Drug, and Cosmetic Act amplified the FDA’s mission and expanded its regulatory powers. Not only did the statute codify and formalize many FDA procedures that had evolved since 1906, it also mandated drug safety testing before the sale and marketing of any drug. Going forward, whenever manufacturers developed a new medication, they were mandated to submit “full reports of investigations which have been made to show whether or not such drug is safe for use.” Additionally, companies needed to provide clear information about drug dosing, administration, and other important recommendations regarding its use. The 1938 law also created a regulatory category known as “new drugs,” meaning those that needed physician oversight. New drugs such as the sulfonamides required a physician prescription to be purchased. But neither the law nor its subsequent regulations provided clear guidance for how to determine a drug’s category of prescription or nonprescription.
With regard to children, Copeland’s original bill addressed drug safety for youngsters specifically. The final approved bill did not include any child protection language for the new drug category, for reasons that remain unclear. Most likely reformers and policymakers believed that the broad language regarding safety included youngsters, so there was no need to mention them by name. It may not have seemed necessary because although the Elixir Sulfanilamide crisis involved a number of children, the problem was not dose-related (or even drug-related, since it was the additive, not the therapeutically active compound that caused the problem), nor did the event spotlight the unique challenges involved in determining pediatric drug safety. Moreover, when the law was finalized, sulfonamides had been in use for slightly over two years, and their therapeutic benefits were still unfolding. The notion that medications would be recommended regularly was just emerging, even among physicians. And, as the Philadelphia Pediatric Society had noted years earlier, there was no stakeholder involvement in the policymaking or advisory process charged to represent children’s drug-related interests, or to point out that the trial and error process for determining the best administration route, dose, and length of treatment was riskier and took much longer in children because they lacked adults’ relative size uniformity.

**Sulfapyridine and the Pediatric Patient**

With the 1938 law, the United States entered a new era in drug regulation. The FDA now needed to sanction a drug’s safety before it could be sold, and efforts were underway to determine what kind of documentary evidence the agency needed to make those judgments. Three months after President Roosevelt signed the Federal Food, Drug, and Cosmetic Act, Merck and Company approached the FDA for permission to distribute its new sulfonamide, sulfapyridine, and the agency decided to use it to design the evaluation standard to which all new drug applications would be held.

Sulfapyridine held particular promise for the treatment of a major pediatric killer, pneumonia, for two reasons. First, despite the success of sulfanilamide in killing some bacteria, that drug had a limited effect on the one that caused many pediatric pneumonias, the pneumococcus. Second, the serum therapy that had reduced pneumonia’s morbidity and mortality in adults and older children by the 1930s was of limited value in infants and young children, for whom pneumonia was especially fatal. The disease was also a prime reminder of the fundamental ways, beyond size, in which infants and children differed from adults. Babies and young children often suffered from “mixed” pneumonias, meaning they harbored more than one bacterial subtype. As a result, they needed multiple types of sera, exponentially increasing the risk of an allergic reaction or other side effect. Given their small size, allergic reactions were
more likely to result in a medical emergency or death. Moreover, even identifying the microorganism when the patient was an infant or toddler posed a challenge because obtaining a sputum culture to confirm the causative bacteria required patient participation. Most adults could follow instructions to cough up a sample of sputum for laboratory testing, but young children could not. The most common method for obtaining sputum from young children, aspirating stomach contents in the morning before the youngster had eaten, was notoriously unreliable. For all these reasons, physicians were reluctant to employ serum therapy in infants and young children with pneumonia even as its use in adults grew, deeming the benefits “questionable.”

As a result, for infants and young children, pneumonia therapy remained what it had been in the 1910s and 1920s before serum therapy: ice caps and baths in an effort to reduce fever; steam heat to make breathing easier; and, if a child was unable to take fluid orally, hydration with subcutaneous or peritoneal fluid injections known as clysis. Where available, supplemental oxygen helped them breathe. The pharmacological remedies discussed in the pediatric medical literature through the 1930s addressed comfort rather than cure: codeine or phenobarbital for severe coughing, digitalis or whiskey for a weak or irregular pulse, opium-laced Dover’s powder to promote rest and sweating, and regular enemas to manage the resulting constipation.

Merck’s new drug application to the FDA for sulfapyridine included data from Great Britain, where the drug had been developed, as well as its preliminary testing on animals. As part of its evaluation, the FDA sought to obtain more data from investigators who were using it in trials with their patients in the United States. Companies were allowed to distribute new drugs to researchers and clinical investigators for testing before their product received FDA approval in order to generate safety data. Among the early subjects who provided pediatric data were a number of very ill Sydenham children who received it under the oversight of Sydenham’s new head pediatrician, Horace L. Hodes. One of the first Sydenham youngsters to receive the drug was a thirteen-month-old African American infant admitted Christmas Eve 1938 with post-measles pneumonia. Her high fever and labored breathing made her situation a dire one. But within twelve hours of receiving “sulphapyridine,” she “improved very rapidly . . . [Her] temperature came down to normal and remained normal until discharge.” In case after case, children recovered dramatically. For example, another severely ill thirteen-month-old who received the drug could be found “sitting up in bed entirely well” a day after treatment with sulfapyridine. An eighteen-month-old girl who had the added complication of an ear infection showed “rapid improvement” when she received the drug. Another child, a nineteen-month-old boy who was febrile and short of breath on admission, showed a “prompt and striking recovery in less than twenty-four hours after sulfapyridine.”
Whereas no children with post-measles pneumonia survived at Sydenham before the mid-1930s, after the introduction of sulfapyridine almost half did, an “astonishing recovery rate,” trumpeted the Baltimore Sun.57 Such was sulfapyridine’s success for Sydenham’s pediatric patients with pneumococcal infections that Hodes and his colleagues subsequently declared that, although research was underway to develop a pneumonia vaccine, “infants and children respond so readily to treatment with sulfonamides that it does not seem advisable to attempt mass immunization of children against these organisms.”58 But like sulfanilamide, sulfapyridine provided clues that dosing metrics were not always proportionally based. Cincinnati Children’s Hospital pediatricians Glenn E. Cullen and Armine T. Wilson noted with frustration, the variables relevant to dosing the pediatric patient were “not fully understood.”59 In other words, a child 10 percent the size of an adult did not necessarily need 10 percent of the dose relative to a full-grown person. Sometimes it was more, other times less. Cullen and Wilson observed that Perrin Long’s recommended dosing rubric, tracking serum levels, was risky for the pediatric patient because of the drug’s narrow safety margin: “[W]e realize that it is necessary to have some program for determining the preliminary dosage for patients of various ages and sizes.”60

Sulfapyridine received national attention as its use became more widespread in the United States, raising hopes that bacterial pneumonia was headed for extinction. The Los Angeles Times, for example, ran a story in 1939 proclaiming “Pneumonia, America’s No. 1 Killer, Declared Conquered,” and quoting Harvard pediatrician Charles F. McKhann: “The medical profession has whipped pneumonia.”61 The media celebrated this vital breakthrough in the treatment of infectious diseases in the popular science literature, news journals, and newspapers. An article in the New York Times in 1941 announced “Sulfa Drug Saves Baby,” concluding with a quote from the attending physician that it was “the first time in his knowledge that the ‘miracle’ drug had been used on a newborn child.”62

The paucity of surviving evidence makes it difficult to get a sense of how sulfonamides may have changed the experience of sick children or their parents at Sydenham or elsewhere. It is reasonable to assume that parents rejoiced at improving survival rates, and youngsters appreciated receiving the drug orally, unlike serum’s intraspinal or intravenous route. But unintended consequences followed both sulfanilamide’s and sulfapyridine’s introduction at Sydenham. The institution needed to scramble to quickly build a modern laboratory on site, because doctors needed ready access to one so that patients’ bacteria could be identified and urine and blood samples could be monitored for drug side effects. Additionally, the drugs heightened Sydenham’s already acute nurse staffing problem. While some children improved immediately after receiving a sulfa drug, others remained ill for long periods of time or
developed complications from the infection or medication-related side effects. Often these problems required oxygen, intravenous fluid, or mechanical ventilation and intensive medical and nursing monitoring. Within a few years, Hodes lamented that these factors were driving up Sydenham’s costs exponentially. They also played a major role in completing the transformation of the children’s ward or hospital from a homelike environment to a medicalized, technologically driven space.\(^63\)

Despite the 1938 law, it soon became clear that children remained especially vulnerable to drug-related problems. For example, in March 1941 the Massachusetts Department of Public Health contacted the Boston FDA office with ominous news. A three-year-old girl had slipped into a coma after receiving the newest sulfonamide, sulfathiazole. An investigation revealed that the machine that compressed sulfathiazole powder into pill form sat next to one for a potent sedative, luminal, and the medications had become mixed.\(^64\) Despite this tragedy, however, the sulfonamides dramatically changed the therapeutic landscape for both children and adults. Over the course of the next few years, drug companies made capital investments, building laboratories and hiring chemists and researchers to develop and test new sulfa drugs. As a result, dozens of new sulfonamides poured into the market. One after another they were tested in Sydenham’s youngsters in the early 1940s.\(^65\)

**Penicillin**

Penicillin’s discovery is one of the most widely known medical history narratives of the past century. Scottish biologist Alexander Fleming’s 1928 observation that no bacteria could grow in the vicinity of *Penicillium notatum* mold in culture intrigued scientists. But the substance did not yield therapeutic results until 1940, when Oxford scientists Howard Florey and Ernst Chain described its chemical structure, prepared an extract, and successfully treated mice they had infected with streptococci.\(^66\) Just after America entered World War II, the congressionally chartered scientific advisory group, the National Research Council, established the Committee on Chemotherapeutic and Other Agents (COC) to allocate the small amount of penicillin available for civilian use. The equipment, commercial techniques, and other infrastructure necessary to generate penicillin in large amounts did not yet exist.\(^67\) Perrin Long served as COC chair for a short time before accepting a commission in the U.S. Army Medical Corps; the role then went to a former Johns Hopkins Hospital trainee, Massachusetts Memorial Hospital’s Chester S. Keefer, who became known as the nation’s penicillin “czar.”\(^68\)

The first pediatric patient to receive penicillin in the United States was a child at the University of Minnesota Medical Center. By July 1, 1942, Merck and Squibb had produced enough penicillin for human trial. A few days later,
University of Minnesota infectious disease physician Wesley W. Spink admitted a seven-year-old girl suffering from an overwhelming staphylococcal infection of the blood, lungs, and bone. When she did not respond to sulfonamide therapy, Spink wired Merck and, with Keefer’s permission, soon received a small supply of penicillin via airmail. Spink’s access likely came quickly because he was one of Keefer’s former students, but the child in question benefited because the COC was especially interested in staphylococcal infection, which was responsible for a high percentage of soldiers’ wound infections.69

By the time the penicillin arrived, the little girl’s condition was grave. She was convulsing, cyanotic, and disoriented with a fever of almost 106 degrees Fahrenheit. Although Perrin Long had recommended, based on his animal research, that children receive 5,000 units of penicillin every four hours intravenously, Spink instinctively doubled the dosage because the child was so ill. Within a few hours, he was amazed to report that the child seemed to feel and look better and was even asking for food. The next day an astonished Spink reported that his patient sat up in bed and played with paper dolls. But in the days that followed, Spink struggled to understand whether the child’s subsequent course of jaundice, nosebleeds, swollen liver, and other symptoms was related to the penicillin dosage he administered or her infection. When he sent his report to Keefer a few weeks later, Spink emphasized that administering penicillin intravenously to a child was significantly more complicated than for an adult. In his response, Keefer readily agreed that it represented a “very great” problem.70 Two weeks after Spink’s patient began therapy in Minneapolis, a second child, this one a four-year-old white male at the Johns Hopkins Hospital’s Harriett Lane Home, received penicillin. Doctors had diagnosed this little boy with a sulfonamide-resistant pneumococcal infection and an empyema, a collection of pus in his pleural cavity. Perrin Long himself sat at the child’s bedside and oversaw the case. After several days of empirically titrating the child’s dose according to his clinical response, trying different routes of administration, he reported that the child was “convalescing nicely” and was discharged a few weeks later, his doctors marveling that he was “much improved.”71

The success of penicillin treatment for these and other patients spurred a race to generate as much penicillin as quickly as possible. But the shortage continued until drug companies could fully industrialize production and increase manufacturing capacity—and the war ended, removing the urgent need to treat soldiers’ wounds. One Harvard pediatrician, Thomas Cone, later recalled that when his infant daughter developed a severe ear infection, he used his connections to acquire experimental penicillin through the military distribution channels. But the substance was so precious that he resorted to reusing what he gave her by collecting her urine. “Whatever
was not absorbed would come out in the urine and we would use that again, it was so rare.”72 In 1943 Keefer distributed the drug to twenty-two of the best-known infectious disease researchers in the United States.73 Civilians infected with a bacterial type often seen in soldiers remained the highest priority. Children received a disproportionate share of the civilian stock of penicillin, but not necessarily due to their privileged status as vulnerable, innocent, and deserving candidates. Researchers quickly realized the advantages of testing on children—more subjects could be enrolled in trials since lower doses were required. In this case, it was the drug that was especially precious, rather than its young recipients.74

Although penicillin was more effective than the sulfonamides for some bacteria, much less was known about how it was metabolized and its toxicity. In 1943 alone in the United States, almost six hundred scientific papers about sulfonamides’ physiological action were published in the medical literature. Clinicians possessed a more robust knowledge base for the sulfonamides upon which to base pediatric dosing and understand adverse reactions and toxicity, benchmarks that had yet to be identified for penicillin.75 One confusing difference between the two drugs was that penicillin was metabolized and excreted quickly, making it difficult to maintain constant concentrations in the blood, a therapeutic goal with sulfonamides. It would take years of research to ascertain that the consistent blood levels necessary to see a response from the sulfonamides (which were bacteriostatic compounds that inhibited the growth of new bacteria) were less important when treating with penicillin, a bactericidal drug (agent that destroyed bacteria). For penicillin, relatively infrequent peak blood levels sufficed, meaning that the drug needed to be administered only several times in a twenty-four-hour period.76

Penicillin’s early formulations could also not be administered orally, a major setback to those who had been excited about this benefit of sulfonamide over serum therapy.77 Thus children who received it required more intensive nursing care, as leading pediatric nurse Stella Goostray noted in her 1945 administrative report for the Boston Children’s Hospital’s nursing service. “The use of penicillin with its frequent administration by hypodermic is a striking example of a time-consuming treatment which is required in the Hospital today,” she wrote. “To give the amount and quality of nursing care necessary will mean a material increase in staff nurses.”78

Finally, abandoning sulfonamide therapy to try this new agent on critically ill children seemed risky to some. By 1943, for example, sulfonamides had reduced mortality from meningococcal meningitis at Sydenham to less than 8 percent.79 Replacing a useful drug with one that might be more efficacious but about which less was known was a high-stakes problem. Physicians needed to consider whether to use established therapy or to test unproven but
potentially more beneficial treatments in ill children, and nurses needed to adapt technology to figure out how to get the drugs into youngsters. This challenge notwithstanding, it was clear that the sulfonamides and penicillin had changed American childhood and parenting within a few short years. As World War II ended, American children stood a better chance of surviving once-fatal infections than they ever had before.