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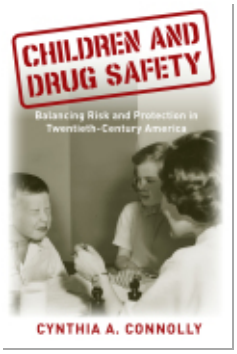
Chapter 3: The Child as Drug Development Problem and Business Opportunity in a New Era, 1945–1961



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The Child as Drug Development Problem and Business Opportunity in a New Era, 1945–1961

As servicemen returned home from World War II, they married and started families in unprecedentedly large numbers, beginning what became known as the baby boom. The benefits of two generations of improved nutrition such as milk pasteurization and public health measures as well as antibacterial and antibiotic drugs redefined maternal and infant mortality as an unusual tragedy for most families, especially those in the growing middle class, rather than as a lamentable but commonplace occurrence.[1] As a result, the influential architect of early postwar science policy in the United States, Vannevar Bush, observed that science (and funding) was moving on to new problems: "This reduction in the death rate in childhood has shifted the emphasis in medicine to the middle- and old-age groups, and particularly to the malignant diseases and the degenerative processes which are prominent in the later decades of life."[2]

But the American Academy of Pediatrics (AAP) leaders believed that children needed much more from their doctors and nurses than infectious disease prevention. While well child care for poor children remained spotty or even nonexistent, by the end of World War II, pediatricians had convinced middle-class Americans that even healthy children needed regular medical check-ups to monitor their growth, administer immunizations, and identify and manage problems early. When ill, their treatment could be subsidized by the growing

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number of employer-based insurance programs. A major infusion of federal dollars for hospital construction through the Hill-Burton Act also meant that pediatric illness care would be more hospital-based than ever before.[3]

Only in hospitals, pediatricians argued, could children receive round-the-clock access to the sophisticated medical and nursing care they often required. Because of antibiotics and better pediatric fluid and electrolyte management, many youngsters who contracted acute bacterial infections such as pneumonia could now be cured. Those with chronic conditions such as cystic fibrosis or sickle cell anemia could survive the infections that often accompanied the disease. Corrective surgery for congenital anomalies was less risky with antibiotics to treat postoperative infections. As a result, drug therapy was increasingly central to the therapeutic management of the sick child. Katharine F. Lenroot, head of the Children's Bureau, acknowledged these advancements in 1950, when she extolled the "valuable tools" in the pediatrician's armament including the sulfonamides and penicillin. Furthermore, diagnostic technologies and drugs could work in synergy with one another: Lenroot argued that the electroencephalograph, a diagnostic tool that helped diagnose epilepsy, should be celebrated primarily because it facilitated the development of "new drugs for its control."[4]

But for the increasingly complex, more corporatized drug companies, funding pediatric research was not nearly as profitable as identifying new drugs targeted for use in the adult population, such as antihypertensives. Even though the number of children in the United States was growing as a result of the baby boom, the percentage who might be prescribed drugs was small relative to adults. This mattered because drug development had grown more expensive as a result of the 1938 Federal Food, Drug, and Cosmetic Act, which required companies to present safety data demonstrating the drug's safety in order to receive approval.[5]

The AMA Council on Pharmacy and Chemistry published the FDA's requirements for new drug applications in its journal, the *Journal of the American Medical Association* (*JAMA*), so that industry and academic investigators had a sense of the evidentiary criteria the FDA sought. The guidelines emphasized the collection of animal and other laboratory data about mechanisms of action, toxicity, and other variables as preliminary steps. They also noted the importance of "establish[ing] the effective dosage range for different age groups," but said nothing about how investigators might accomplish that outcome. Should pediatric data, for example, accompany the new drug application or should pediatric dosing and pharmacodynamics data be based on clinical observations and reported to the FDA after the drug's approval? Congress had been silent about this point in the law.[6]

No recorded discussions about amending the 1938 law to address the specific issue of pediatric drug safety exist in the public record. Why is unclear, but

it may have been because Americans remained deeply ambivalent about what many saw as too much governmental intrusion into private life, and children's issues and health care were no exceptions. While the 1930 Children's Charter outlined a manifesto of rights for American children, it was vague on whether its ambitious goals would be met with public funds, private dollars, or a combination of the two. The class-based approach to children's health meant that some very poor or disabled children qualified for certain health care programs under the Social Security Act, and middle-class youngsters were increasingly covered through their parents' employer-based programs. But access to health care for all youngsters remained spotty, especially for poor children, who were disproportionately African American, Native American, or Hispanic. Two ambitious pieces of legislation during the Truman administration—the National Child Research Act, which would have funded developmental research, and the Children's Act of 1949, a health insurance bill that would have covered all children—failed to pass in Congress in part because reformers believed their needs could better be met by broader laws that benefited all Americans.[7]

Although neither law would have funded pediatric drug development or related research, both bills were a step toward a national policy for child well-being. Both recognized children's unique health and medical needs, and they might have provided a future model for such a policy. Instead, systematic considerations for how to obtain the general information regarding dosing, metabolism, excretion, and other measures for the pediatric patient remained unaddressed. While the federal government in the early postwar era was heavily involved in funding for more hospital beds for children, financing for pediatric medical education, and targeted investments into specific pediatric diseases, it did not take a primary role in drug-related research for either children or adults. This responsibility lay within the purview of the private sector, which responded to any suggestion that government become more directly involved in the development of therapeutics with claims that such control augured the beginning of socialized medicine, a contentious charge in an increasingly heated Cold War context.[8]

Attempts to Develop Systematized Pediatric Drug Knowledge

Consequently, physicians who treated children faced the enduring challenge of how best to approximate pediatric doses, even as the postwar explosion of research continued to document the many physiologic differences between children and adults, and, increasingly, between children of different ages. As new drugs poured onto the market over the the next decade, millions of children began to receive them. But the FDA had no explicit statutory authority to regulate dosage standards, formulation issues, or administration practices as part of the approval process in order to make sure drugs were safe for children.

With the pediatric patient in mind, FDA officials Robert Stormont, chief of the FDA drug division, and medical officer Irvin Kerlan approached the AAP in 1947. The agency had already contacted the organization once before, in 1944, when representatives asked AAP president-elect Joseph A. Wall for assistance with proper pediatric dosing recommendations for several drugs. That effort had not progressed beyond a discussion. This time Stormont and Kerlan flew to AAP headquarters in the Chicago suburb of Elk Grove Village, Illinois, to speak to the executive board.

They asked the AAP to help the agency in two ways: to provide expert advice on Federal Trade Commission (FTC)-related prosecutorial matters and to "undertake studies" on drugs being used in children.[9] Companies that misbranded their products by recommending a drug for children's use without providing warnings and directions violated the law, and the agency needed pediatric experts to provide testimony in court. It also needed pediatricians to provide scientific evidence to help evaluate pediatric labeling provisions for new drug applications because manufacturers were not required to submit pediatric safety data. In their attempt to convince the board that this assistance should be a priority for the AAP, Stormont and Kerlan lamented the fact that the FDA did not have enough scientific information to recommend a dosage range for penicillin in children, despite the fact that the medication was already widely prescribed for millions of them throughout the United States.[10]

Acknowledging that the FDA lacked "scientific people in the field of pediatrics on our staff," Kerlan outlined the problem for the executive board: "[I]f we obtain a new drug for which recommendations are made for use in children and for which an actual dose schedule has been provided, we want to know whether that is safe for children. . . . Manufacturers . . . should provide actual directions for use and warnings against misuse. . . . Warnings must be provided for use in children."[11] Stormont and Kerlan also suggested that it might be in the AAP's interest to partner with the FDA, pointedly remarking that several drugs and devices in which FDA laboratories had found safety-related problems had been openly advertised in booths at the 1945 AAP convention as well as the organization's *Journal of Pediatrics*.

With the mention of drug advertising, Kerlan and Stormont had, intentionally or unintentionally, exposed an issue about which the board and the journal editors were clearly not in full agreement. George F. Munns, board member and professor of pediatrics at the Mayo Clinic, detailed his worries about pharmaceutical advertising in the *Journal of Pediatrics*: "Many of [the drugs being advertised] are still in the experimental stage. There will be a paper about the use of a certain remedy with a favorable report, and the next thing we know the company that is sponsoring the piece of work is advertising in the advertising section of the *Journal*."[12] The ensuing discussion exposed the tensions within the group regarding the way in which advertising decisions

should be made in the *Journal*. It also highlighted the fact that medical journals had interests beyond science: the revenue generated by advertising played an important role in the journals' financial viability.

Having made his point, Kerlan now steered the discussion to the concrete assistance the FDA sought. The FDA wanted advice and, if necessary, expert testimony on specific instances. In the past, the FDA had been hard-pressed to find pediatricians who would consult for the agency because, for physicians in private practice, time not spent with a patient was lost income. Citing a specific case, Kerlan pleaded with the board:

> [I]n that particular instance we had four or five men lined up, and each man in testimony would not contribute more than a half hour. The products must be scientifically sound to be approved by the Food and Drug Administration. We feel that the only people who can give us information in the field of pediatrics are the pediatricians. . . . We want some cooperative organization, like the Academy, to come and say what the feeling of the Academy is and to go on record for or against products.[13]

The board, disappointed that Stormont and Kerlan offered no financing to help the organization develop a meaningful consultative role, deliberated the financial implications of partnering with the FDA. Just as they had when the AAP first approached the AMA about pediatric representation at the USP in the 1930s, scientific issues collided with organizational politics. In the postwar era, the AAP goals were very ambitious, focused heavily on enhancing the pediatric curriculum across all medical schools and increasing the number of pediatricians in the United States. In 1949 more than 80 percent of American children still received their medical care from general practitioners, half of whom had never received training in the care of hospitalized children. Only 2,600 board-certified pediatricians practiced in the United States, and two-thirds of them were located in Massachusetts, New York, or Pennsylvania. Although the AAP convinced policymakers of the need for public investment in pediatric medical education, children did not receive a larger share of federal dollars. Rather, funds were largely redirected from the Children's Bureau.[14]

Although the board expressed ambivalence regarding Stormont and Kerlan's request, members did agree to help and immediately created the Committee to Cooperate with the FDA, placing eminent pediatrician Waldo E. Nelson in charge.[15] Unfortunately, the partnership was unsuccessful: the records indicate the group convened only a few times. Another effort to improve drug dosage knowledge began in 1950, when influential pediatrician Harold K. Faber, in a letter to the AAP executive board, explained that the lack of meaningful data concerning dosage, particularly in infants, was

no longer tenable. The resulting Committee on Drug Dosage spent much of its time surveying pediatricians about how they used specific drugs in their practices. After publishing a few features in pediatric journals, the committee either disbanded or stopped keeping any formal records.[16]

The Growing Pediatric Antibiotic Market

In 1949, drug companies began introducing a new class of drugs known as broad spectrum antibiotics, so named because they attacked a number of bacteria. A number of broad spectrum antibiotics came onto the market in rapid succession: Parke-Davis introduced the first one, Chloramphenicol (chloromycetin), in 1949, followed quickly by Lederle's Aureomycin (chlortetracycline). A few months later, in 1950, Pfizer made Terramycin (oxytetracycline) available, and in 1953 Lederle started advertising Achromycin (tetracycline). These drugs represented a major therapeutic advance because, first of all, they attacked a wider range of microorganisms than did penicillin and the sulfonamides alone. The broad spectrum antibiotics saved time, money, and lives by increasing the likelihood that the drug would kill the bacteria making the person ill.[17]

Additionally, the broad spectrum antibiotics generated profits for drug companies. Previously, any company could create its own formulation of the active compound that served as the basis for both the sulfonamides and penicillin because they had not been patent protected. But because the broad spectrum antibiotics were proprietary—owned by the companies that had funded their creation, either in their own labs or in those of academic scientists whom they had supported—they produced profits on a scale not seen in the past. The introduction of broad spectrum antibiotics ignited an explosion in competition and advertising to doctors. And in order to make sure a busy physician heard about the latest one and its advantages, companies hired more "detail men" (sales representatives) to educate doctors about their drug and provide free samples to them. Given the increasingly crowded antibiotic marketplace and the growing number of children in the United States, companies set out to compete with one another to develop liquid formulations that tasted good to children and were easier to swallow than pills.[18]

The broad spectrum antibiotics arrived at a propitious moment in the history of American childhood, when children's emotional and developmental needs received unprecedented scientific and political attention. The tremendous reductions in infant and child mortality, accompanied by a growing number of immunizations and antibiotics to prevent and treat infectious diseases, had given Americans the luxury of focusing on other dimensions of child well-being. A discussion of child cognition and related issues became the central topic of the 1950 White House Conference on Children. The 60,000

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individuals in attendance debated the variables needed for America to provide "For Every Child a Healthy Personality." This theme of the conference—the importance of developing the American child's unique personality and maximizing the potential to create his or her own destiny—and a focus on nurturing emotional and social development, stood in stark contrast during the early Cold War period to characterizations of Soviet youngsters growing up in an oppressive nation in which they had little opportunity for individual growth.[19]

The Common Sense Book of Baby and Child Care by pediatrician Benjamin Spock added to this rhetoric, as he urged parents to move away from the rigidity and harsh discipline recommended in earlier eras and replace them with a more nurturing approach. Nurses and physicians, too, drew on the work of developmental theorists such as Erik Erikson and Jean Piaget in the planning and delivery of their care.[20] No longer was it enough for clinicians merely to treat a child's physical condition; by the 1950s creating a nursing or medical plan of care that took into account, for example, the security needs of an infant and the fear of pain in a preschooler was important. Since a foul-tasting medication might cause unnecessary distress to a very young child, the company that created one children favored stood to be amply rewarded financially. Flavored medication captured both the cultural and economic moment perfectly. One humorous example of how seriously companies took the issue of palatability in children can be seen in Eli Lilly and Company's 1953 marketing program, in which its "Juvenile Board of Judges" weighs in on medication flavoring.[21]

Originated by the company's product development team, the initiative's purpose was to "Let the kids decide for themselves what flavor they like" by "giving them a taste of their own medicine." For example, when formulating the combination penicillin and sulfonamide drug Sulfa-Neolin (benzethiacil with sulfonamide) the company wanted to know whether children preferred "chocolate-mint, butterscotch, or custard" flavored medicine. Employees' children as well as those drawn from a local school and hospital were solicited for the jury and the company was careful to obtain parental consent before beginning the testing. A registered nurse administered the various samples and the Eli Lilly product development team assessed children's responses carefully. While the youngsters liked the taste of custard, chocolate-mint concealed the medication's aftertaste. As a result, the product came to market with the two flavors combined. Youngsters also had strong opinions about color, texture, and odor, all of which the company measured.[22]

Drugs joined a growing number of products marketed for children as the baby boom continued and as family income rose in the postwar economic expansion in the United States. Trade magazines such as *Advertising Age* and *Business Week* now regularly reminded their corporate readers that "Babies Mean Business," and that those rapidly expanding ranks could bring

FIGURE 2 Eli Lilly & Company Juvenile Board of Flavor Judges, 1953. (*Credit*: © Copyright Eli Lilly and Company. All Rights Reserved. Courtesy of Eli Lilly & Company Archives.)

companies "Two Million New Customers a Year."[23] In addition to enhancing profits, a focus on children's needs also served another purpose for the drug industry. A pediatric formulation could be used as evidence of a company's beneficence toward children. During a Capitol Hill hearing on pharmaceutical industry practices, for example, Philip I. Bowman, president of Bristol Laboratories (a division of Bristol Myers), defended the company's intensive research in developing its own version of a drug already available, marketing it heavily, and setting the price to garner a profit by arguing that the company's actions "benefit[ed] the public." In his testimony, Bowman recounted Bristol's motivations in the early 1950s as child-focused: "Take, for instance, a good-tasting pediatric suspension. Now, probably all of you at one time or another have had the problem of getting medication into children. . . . We were able to make an oral suspension that was relatively good-tasting, and I know that with our children, and with the children of many of our friends, we found that the problems of getting the medication down were solved with this product."[24] Although adults did not enjoy bitter-tasting medication, the issue of palatability was much more important for young children. The research and marketing efforts of drug companies to address flavor illustrate the indirect power of

children as well as the kind of financial investment they were willing to make when they believed doing so would pay off financially.

In 1950, Pfizer microbiologist Gladys Hobby partnered with famed Harvard Medical School and Boston City Hospital antibiotic researcher Maxwell Finland. Their goal was to develop a pleasant tasting pediatric formulation for the broad spectrum antibiotic Terramycin. Explaining that "We are anxious to move these pediatric dosage forms in the near future in view of the fact that we are obtaining many requests for them," Hobby sent Finland ten vials of cherry mint-flavored diluent along with the antibiotic for use in Finland's pediatric patients.[25]

Although Hobby sought data regarding the drug's ability to kill bacteria, she stressed that she also wanted to know whether children thought the product tasted good. When Finland reported that, not only was it easier to get young children to swallow the syrupy liquid than a capsule, but they also liked it, Hobby wrote back within twenty-four hours, letting him know she would send a large shipment to him for further testing. The competitive nature of the broad spectrum antibiotic market is clear in the letter: Hobby reminded Finland—for the second time in several weeks—that the company desired a pediatric formulation "as promptly as possible."[26] And she wanted enough information to satisfy the FDA, which was clearly trying to track pediatric data. "The FDA has asked us to give them data concerning its tolerability for children and some information concerning its therapeutic efficacy," she explained.[27] But this pressure from the FDA came after the drugs had been approved; they were not premarket mandates, so companies were not required to submit such data along with their new drug application.

Within a few days, Finland wrote that four children with pertussis had received the flavored Terramycin in doses his laboratory had calculated would be enough to kill bacilli. He reported that the dosage range he used had produced no side effects and that "clinically children showed gradual improvement as they had with other types of Terramycin."[28] But generating a sound pediatric dosing metric remained a challenge even for one of the nation's leading antibiotic researchers. A few months after Finland sent Hobby his recommendations for pediatric dosing, Ray A. Patelski, coordinator of clinical investigation for Pfizer, informed Finland that the company had doubts about the accuracy of his dosing instructions: "Judged by the rash of letters that we have received from practicing physicians in various parts of the country, our recommended dosage schedules for Terramycin for infants and children under 20 kg in weight appear to be higher than necessary."[29]

Companies quickly realized the pediatric broad spectrum antibiotic market was financially significant enough to warrant a close watch on FDA activities that might influence sales. For example, when the FDA asked the AMA and

the AAP in 1954 whether the labels on drugs should include specific directions for use by children under six years, the influential drug industry newsletter *F-D-C Reports* characterized the request as "bearish" and noted it on page 1, under the anxious title "Children's Medication Products Face Imminent Danger."[30]

By the middle of the 1950s, antibiotic makers considered pediatric formulation essential in order to offer a full product line to doctors, pharmacies, and hospitals. For example, in March 1955 Pfizer sales representative Robert Bittner summarized for his supervisor, H. R. Stewart, the data he had gathered and scrutinized from two pharmacies in Knoxville, Tennessee. It is "very obvious the physician prefers ready-mix pediatric broad spectrum antibiotics" because they are the "favorite" with pediatricians. "I sincerely hope that Pfizer will have a ready-mix oral suspension for us in the very near future," he concluded.[31] Another memorandum, this one from the Pittsburgh sales representative, Howard J. Taylor, argued that it was hard for Pfizer to increase market share for specific antibiotics without a pediatric formulation. As a result of its cherry-flavored suspension, Taylor warned, Lederle was "taking over the broad spectrum market" with the "hottest prescription" drug in the United States, Achromycin. He recommended strongly that "our number-one job" should be to develop a "comparable product to compete" with Achromycin.[32] And Lederle representatives followed Pfizer's efforts just as closely. Internal Lederle correspondence in 1951 referenced a popular comic strip that had run in at least one newspaper in the South. The cartoon featured a nineteenth-century medicine show traveling west on horseback, stopping to receive an inquiry from a stereotypically depicted Native American mother seeking help for her infant's cough. The "medicine man" is shown recommending Terramycin over Lederle's product. Lederle representatives were clearly concerned by the way Terramycin had penetrated popular culture and the free marketing benefiting Pfizer.[33]

The impact of pediatric formulations on sales appeared at times to astound even companies' own salesmen. According to one Lederle field report, a sore throat and fever "epidemic" in Detroit, Michigan, resulted in "remarkable sales" in Achromycin syrup in the region, a particular feat since the city's most influential pediatricians often received drugs free of charge.[34] In addition to its concerns about Pfizer, Lederle also worried about competition from Squibb, which soon had its own pediatric broad spectrum antibiotic available. The 1956 "Dear Doctor" marketing letter that accompanied Squibb's tetracycline formulation stressed its use in children, spotlighting that the medication was "liquid and so palatable, it is readily suited to your young patients."[35]

Although drug companies were prohibited from advertising their prescription products directly to the public, they were allowed to promote their

company's contributions to postwar American society in a general way. As a result, by the 1950s, almost every issue of family-oriented magazines such as the *Saturday Evening Post*, *Life*, and *Parents* carried messages from major pharmaceutical companies such as Parke Davis, Ciba, Lederle, and Eli Lilly, attesting to the ways in which the pharmaceutical revolution in general, and their particular company specifically, had benefited Americans. The advertisements frequently included children, who made good advertising copy. For example, many issues of *Parents* magazine in the years between 1945 and 1960 carried promotions by major pharmaceutical houses featuring a healthy child. A list of the drugs made by a particular company and the ways in which the agents had improved Americans' health adjoined the photograph. Although the ads did not suggest that parents request the products for themselves or their children, the message that drug companies' efforts saved children's lives was clear.[36] They also celebrated white middle-class suburban life and the nuclear family, tapping into cultural anxieties about the growing complexity of raising a healthy child in the postwar era. While subtly reminding parents of the dangers that had befallen American children before the pharmaceutical industry had brought them vaccines and antibiotics, they celebrated American capitalism and the ways it kept children safe.[37]

A *Life* magazine advertisement in March 1956, for example, featured relaxed mothers at a children's birthday party. When one mother complained about her child's health care costs, the other admonished, "Oh, but actually, sickness costs *less* today—and many more children get well," followed by text that highlighted the the example of a child suffering a chronic ear infection that could inflame the nearby mastoid bone in the skull. The advertisement noted that before antibiotics, surgeons could sometimes drain the infection and save the child's life, often at the cost of the youngster's hearing. But "nowadays" the child could be cured with "potent new medicines" as an outpatient, "represent[ing] one of the really extraordinary bargains of your life."[38] Annual reports and other materials companies sent to shareholders also heavily emphasized drugs' pediatric benefits.[39]

Some concerned pediatricians did seek to monitor manufacturers' promotional statements to parents. Allan M. Butler, professor of pediatrics at Harvard's medical school and senior doctor at Boston Children's Hospital, helped found the National Council on Infant and Child Care in 1956. Ostensibly, the council's purpose was to approve any advertising to parents in lay periodicals, virtually offering a stamp of approval from the leading pediatricians who constituted the group. But its goals were also protectionist for the medical profession, reminding advertisers that specific suggestions with regard to child-rearing, nutrition, or health "should remain the responsibility of the physician. Promotion influencing the parent to assume these responsibilities or creating concern regarding the physician's recommendations is not acceptable."[40]

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An Increasingly Vocal Actor in Therapeutic Decision Making: Middle-Class Parents

Almost as soon as the public could obtain antibiotics, physicians began to worry about how they might change medical practice. In 1945, for example, physician Leslie A. Falk expressed concern that the availability of an inexpensive and widely available "magic" therapy like penicillin might result in sloppy medical care, less careful history taking on the part of physicians, or overprescription of the new drug.[41] And what if bacteria developed a way to fight off the medicine? The latter fear, at least, was not unfounded, since the first reports of drug resistance came directly on the heels of the sulfonamides' and penicillin's success.[42] By far the most prevalent fear of many pediatricians was the potential for overuse. The popularity and palatability of broad spectrum antibiotics made parents demand them, sometimes aggressively. Former AAP president Isaac Abt had issued one of the first warnings that the balance of power between mother and physician was shifting, observing in 1944: "[T]he mother of long ago was, in general, easier to work with than the mother of today. Although she was often garrulous, she was quick to observe deviations from the normal and report them exactly, permitting the doctor to interpret the facts. She said 'baby sniffles every night and has a rattle in his throat.' The modern mother, on the contrary, is inclined to make her own diagnosis."[43] At the 1948 Annual Meeting of the Medical Society of the State of New York, physician John Craig also complained about this new type of mother to his colleagues, "Any number of times a mother has told me that after a moderate fever her child has been cured by two doses of sulfa. This, of course, is not true."[44]

Physicians were right to be worried about the potential overuse of antibiotics. So commonly did doctors prescribe penicillin by 1950 that, as one physician reported, American children created a playful chant:

> Mother, Mother I am ill!
> Call the doctor from over the hill!
> In came the doctor, in came the nurse,
> In came the lady with the alligator purse.
> Penicillin, said the doctor,
> Penicillin, said the nurse,
> Penicillin, said the lady with the alligator purse![45]

Managing parents who "demanded" antibiotics and were "responsible to a large degree for the indiscriminate use of antibiotics," as one pediatric researcher, Hattie Alexander, characterized it, became a challenge.[46] Startled by the growing assertiveness of parents during the health care encounter, one doctor sent

his own annoyance through the media. Professor of pediatrics at Yale School of Medicine Milton J. E. Senn, writing in *Woman's Home Companion* in 1953, devoted an entire monthly column to educating parents about their place. His title, "It's the Doctor's Job: Let Him Do It," admonished parents not to overstep their bounds. In great detail Senn scolded that "too often parents label a doctor old-fashioned if he doesn't administer the drugs for even mild illness" and "pressure him" to do so.[47]

One emboldened, more knowledgeable mother reportedly even helped shape the use of the laboratory in her city. Pediatrician Milton Markowitz recollected one home visit he made in Baltimore in 1951 or 1952 when he diagnosed strep throat in a youngster. As he prepared a penicillin injection, the mother startled him by asking, "Wait, aren't you going to do a throat culture?"[48] Markowitz explained to the mother that this would delay treatment since it required sending a swab from the child's throat to a hospital laboratory. The mother was unimpressed with this information, having "just moved from Rochester, New York, where her pediatrician . . . did his own throat cultures."[49] Markowitz called the upstate New York pediatrician, who gave instructions on how to build his own incubator, and he did so. Thus, according to Markowitz, plating and growing samples in a private practice outpatient setting "spread through the city and beyond."[50]

The USP Tries to Bring Order to Pediatric Drugs

As steroids and antihistamines joined broad spectrum antibiotics in the late 1940s and early 1950s, the standard-setting body for drug strength and purity in the United States, the United States Pharmacopeia (USP), turned its attention to children. In an undated memo from this era, Lloyd C. Miller, director of the USP committee overseeing revisions to the standards manual, scrawled a handwritten reminder to himself that the group needed a better roadmap for the "problem of children's doses."[51] The FDA associate commissioner, John L. Harvey, equivocated, however, on whether the USP should take on the issue of children's doses. Absent a uniform system for pediatric dosage calculation, he argued that it might be "impracticable" to seek consensus among leading pediatricians on this topic.[52] Without more knowledge, specific dosing recommendations were difficult to establish, and without established dosing recommendations, clinicians were frequently forced to make determinations based on suggestions from colleagues, their own experience, or the detail man's often heavy-handed sales tactics.

The USP and the FDA ultimately decided to collaborate on a pediatric effort. After a careful search, in November 1950 the USP board asked University of Iowa School of Medicine professor of pediatrics Philip Charles Jeans to oversee the project. Jeans's charge was to convene a panel of experts that

would, first, identify children's "special requirements" with regard to drug therapy and, second, generate a list of the drugs used in pediatrics, including the drug name, dosage, dosage range, and mechanism of action.[53] Jeans was an ideal choice for this assignment because his undergraduate degree was in chemistry, his medical education had been at the top-ranked Johns Hopkins University medical school, and he had completed clinical training at Boston Children's Hospital. His service on the Food and Nutrition Board of the National Research Council had brought him to the attention of the FDA, where staffers respected him for his efforts to fortify milk with vitamins.[54]

Jeans invited four pediatricians with an interest in pharmacology to join him on the committee.[55] The challenge inherent in pediatric drug issues became clear immediately. As the panel debated the dosage range for calcium chloride, a potentially dangerous drug used in infants with metabolic problems, their frustration centered on the lack of data needed to recommend a safe dosing regimen.[56] Just as the committee's work was getting underway, Jeans died abruptly. After a number of eminent pediatricians declined the chairmanship, the USP's Miller turned to Harry C. Shirkey, the most junior member of the panel, who immediately and enthusiastically accepted the appointment.[57] His new USP role drew on all Shirkey's prior professional experiences and interests. A 1939 graduate of the University of Cincinnati's School of Pharmacy, he practiced as a pharmacist at the city's children's hospital while he worked his way through medical school. After graduation, he served a stint in the military and undertook a pediatric residency before joining a private practice in Cincinnati in 1950. Just thirty-eight years old when he received Miller's letter, Shirkey was eager to make his mark at the national level of pediatric medicine.[58]

Miller admitted to Shirkey that "in the past, we have not paid much attention to children's doses, assuming they could be approximated satisfactorily from the Usual [adult] Dose" on the basis of some general factor involving the "weight of the child."[59] He framed Shirkey's potential role optimistically, suggesting that as a pediatrician and a pharmacist he had the opportunity to "break new ground," although he was vague as to how he might do that.[60] But politics were already complicating Shirkey's job, although he did not yet know it. This time, the issues were not between which medical organization, the AAP or the AMA, had the right to set drug standards for children, but whether the USP's actions with regard to children might be perceived by the AMA as overstepping its bounds. In his personal notes surrounding the Shirkey appointment, Miller scrawled a note to himself acknowledging that USP president Windsor Cutting felt that, with regard to bringing order to children and drugs, "the difficulty is too great to work out right now."[61]

Aside from the scientific problems associated with drug safety and dosing in children, pediatric concerns also raised potentially contentious issues—and

FIGURE 3 Undated photograph of Harry C. Shirkey.
(*Credit*: Courtesy of Cincinnati Children's Hospital Medical Center.)

territorial boundaries—between the AMA's and the USP's respective roles, which the USP probably wanted to avoid. Did the USP, for example, have the authority to create a dosing manual for doctors? Even though it maintained a working group on posology (dosing), Miller was not sure, as his personal notes from a meeting with Cutting show. Dosing determinations, he mused, are the "MD's concern and the USP is not a manual of therapeutics"; as such, it did not need to delve substantively into dosing-related issues for any group. Pharmacists, he determined, "were responsible only for knowing the adult

dose."[62] The two men decided the best course of action was a politically expedient one, allowing the organization to avoid any immediate controversy with the AMA or any other group. The USP would "continue to study the pediatric issue" in preparation for the 1960 USP revision, almost seven years away. This approach allowed the USP to neither reject nor embrace a leadership role in this endeavor.[63]

Because Miller's and Cutting's discussions had not included Shirkey, he had little knowledge of their decision to move slowly and he clearly had an agenda for an activist committee. His vision included a publication from the USP with pediatric information for both pharmacists and physicians, and he promptly informed Cutting that the USP manual should be more therapeutically oriented to effect this initiative.[64] Miller acknowledged cautiously that some FDA staffers had suggested that the USP "could render the greatest service" by providing some guidance in pediatric pharmacology, especially since the new drugs coming to market were often used for reasons that differed from adults.[65] Antihistamines, for example, might be used to treat allergies in children, just as they were in adults; yet their antispasmodic properties also showed promise in treating colic, a common infant problem that distressed parents and vexed many pediatricians. But neither he nor any USP official responded to any of Shirkey's specific ideas or proposals.[66]

In 1957, disappointed that the USP had taken no further action on his ambitious ideas, Shirkey decided to do so himself. He wrote to Miller that "the problem of drug dosage in children is one which is becoming ever more increasing and important" to the pediatric USP panel.[67] He and a colleague at Temple University medical school, William P. Barba, had decided to take concrete action. They aggregated as much information as they could find on drugs widely used in children. Published as a section in Waldo Nelson's 1959 *Textbook of Pediatrics*, it became, in effect, the most comprehensive postwar manual of pediatric therapeutics to date. For the first time, a readily available synthesis of drugs, dosing, metabolism, and other useful metrics for clinicians was placed in the same text as the diseases they were used to treat.[68]

As Shirkey grew more confident in his USP role, he became more assertive in advocating his positions. For example, Merck and Company leaders had written to the USP to influence the way the data for the company's cough suppressant Nectadon (noscapine) would be presented in the USP manual (Merck had submitted new data to the USP that the company believed demonstrated an improvement over the earlier formulation).[69] Shirkey noted for the official record that members of his panel had not had adequate time to study the data or its implications for children, yet in his personal comments to Miller about Nectadon, he dryly commented that pediatricians had found the drug "rather useless" in the past and suspected that any new formulation

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would not move it into the category of "absolutely necessary drug or one for which we have been awaiting with outstretched arms."[70]

The USP also asked its pediatric workgroup for recommendations regarding the new tranquilizer Compazine (prochlorperazine), Shirkey took the opportunity to suggest that the USP recommend to its manufacturer, Smith, Kline, and French Laboratories, that the company create a pediatric formulation. He thought, on balance, that Compazine was safe, although he did express concern to Miller about the side effects he had observed in some youngsters at Cincinnati Children's Hospital. Without indicating the number of cases or age of children who received the drug, Shirkey noted that eight youngsters had experienced "moderately adverse reactions" such as "catotonic" [*sic*] and "Parkinsonian" symptoms such as muscle tremors and spasticity.[71]

He also mentioned that these reactions were well known to Smith, Kline, and French through his exchange of letters and telephone calls with the company's representatives. Both he and the company "hope[d]" that the reactions were a "problem of dosage," but he reminded the USP that the issue of working out that dosage fell to individual doctors.[72] Shirkey commented that whether a pediatric warning should accompany the Compazine's listing in the USP was "open to question" but that the decision "primarily should be the responsibility of the company."[73] It is unclear what Shirkey meant by this statement. He certainly believed that more clarity regarding pediatric dosing was critically important. Perhaps his comment reflected an acknowledgment that, no matter what the intent of laws and the wording of FDA regulations were, the balance of power in terms of marketing decisions remained weighted in favor of industry, not the FDA and certainly not his panel.

The extent to which his comments mattered to anyone is unclear. The AMA Council on Drugs reported on Compazine in *JAMA* in 1958, before Shirkey's panel had debated its pediatric safety and utility. Smith, Kline, and French had already developed a pediatric formulation, and the article included a pediatric dosing schedule. The *JAMA* summary noted that side effects were "dose-related," but presented no supporting pediatric data.[74,75] It is easy to understand why Smith, Kline, and French had decided to find as many uses for Compazine for both children and adults as rapidly as possible. Introduced in 1956, the drug showed promise treating nausea and vomiting, and as a result it was an overnight success, boosting company profits almost immediately. Partly as a result of Compazine, the company's consolidated net sales reached over one hundred million dollars for the first time in 1956. Clearly, the lack of supporting pediatric data had not hurt sales. Pediatricians and other physicians using the drug in children were growing used to modifying the adult dose for children through trial and error.

Pediatric Drug Research and Testing in the Early Postwar Era

The growing enthusiasm for biostatistics and randomized controlled trials strengthened the relationships between drug companies and pediatricians.[76] Partnerships between companies and influential private practice physicians—such as Smith, Kline, and French's with Shirkey—or university researchers—such as Pfizer's with Finland—were, of course, not new. They had evolved during research into antitoxins, vitamins, and commercialized serum therapies that accelerated in the 1920s and 1930s. For example, Edwards A. Park, chair of pediatrics at the Johns Hopkins University School of Medicine and its Harriet Lane Home, had worked closely with Pfizer and other companies on pediatric serum research for meningitis and pneumonia during the interwar period.[77] In the postwar era, pediatric departments in medical schools were even more invested in relationships with drug companies because of a growing need for external funding to support their research mission. Although the federal government, through its National Institutes of Health, dramatically ramped up its support for disease-related research and medical and scientific training in the early postwar era, pharmacological research remained largely the province of industry.

As the numbers of drugs used in children increased and the body of knowledge differentiating pediatric subgroups expanded, these pediatrician and drug company partnerships deepened and intensified. In addition to bringing revenue from drug companies to the physician's institution, the relationships conferred professional authority to physicians who undertook the research. When researchers published their findings in the clinical literature, thought leaders like Shirkey used the information in their overviews of pediatric drugs and as the basis for their recommendations to the USP and FDA. Partnerships with the right pediatricians not only gave companies access to large numbers of children, it also substantially affected sales.[78]

In the early 1950s Horace Hodes, the young pediatrician who had played a foundational role in pediatric sulfonamide research at Baltimore's Sydenham Hospital, developed a model of industry and academic pediatrician partnership. Hodes's pediatric research at Sydenham on the sulfonamides, penicillin, infant diarrhea, and other topics had made him one of the nation's most highly regarded pediatric researchers by the late 1940s. When Sydenham Hospital closed in 1949, Mount Sinai Hospital in New York City recruited Hodes to become director of pediatrics. The informal personal exchanges between Hodes and drug company representatives trace the easy familiarity between pediatric researchers who controlled access to the children recruited for the drug trials and the companies that often provided their products free of charge for research purposes.[79]

Wyeth Laboratories funded Hodes in 1952 to test the antibiotic Bicillin (penicillin G benzathine) at a rheumatic fever and chronic disease hospital called Irvington House in Irvington, New York. Hodes gathered pediatric data about the drug's dosing, side effects, and other information requested by Edward F. Roberts, Wyeth's director of clinical investigation. And because children received Bicillin by injection, he also measured another parameter, pain, important given the growing focus on children's emotional well-being. Hodes's work was yet another instance of the way clinicians increasingly drew on developmental psychology to consider children's differential fears and responses to injection, as well as how their anxiety could be reduced through age-specific interventions. Soon, Roberts asked Hodes to gather pediatric dosing and efficacy data that the FDA had asked the company to provide for another new antibiotic, dipenicillin G.[80]

Children who suffered from chronic conditions such as rheumatic fever or who required a prolonged convalescence sometimes resided at congregate institutions such as Irvington House. Others were there because they had neurological conditions such as cerebral palsy or developmental disabilities that left them cognitively impaired, and the facility was considered better equipped to care for them than their homes. Children at Irvington House were a captive population with a nursing staff to gather research data twenty-four hours a day, and their parents were rarely on hand to oversee what was happening or to intervene. Even if their families visited regularly, they were often easily intimidated because many were poor or felt stigmatized for having what they had often been told was a defective child. In many instances, parents may no longer have had the legal authority to provide consent for participation in research because, in order to receive care at state-sponsored institutions, their child had to become a ward of the state.[81]

Permission to experiment on children in institutions often came from state or local health departments. For instance, one of Hodes's early 1950s experiments measured the benefits of penicillin G administered intramuscularly at birth, a treatment to replace the standard practice of silver nitrate drops to the eyes. Silver nitrate treatment was a long-standing practice used in newborns to prevent blindness from gonorrhea, which could be unwittingly transmitted from their mothers during labor. Hodes had written permission for this experiment, but it came from New York State and from the New York City Department of Health. Although he may also have secured parental consent, no mention is made of him having done so. Unlike today, this fact was not regularly noted in research reports or publications.[82]

Formal parental approval for children's research participation was not a standard practice in this era. Questions regarding whether consent for children's participation in research should be sought—and if so, from whom—were not

new. They had been raised early in the twentieth century in the context of institutionalized children's participation in nontherapeutic research involving the testing of vaccines, as well as other experiments such as, for example, pediatrician Alfred F. Hess's 1914 induction of scurvy in healthy infants in order to better understand the disease. In the 1950s, decisions about research ethics were usually grounded, as they had been in the past, in a researcher's mandate to follow his or her own conscience regarding the subject's risks and benefits of participating in a research project, and physicians policed one another for violations As Susan E. Lederer and Sydney Halpern have shown, the norms governing research participation grew out of a paternalistic tradition of physicians serving as primary decision makers for ill patients, especially in life or death situations. Moreover, the boundaries between treatment and research were often indistinct, and no clear standard for informed consent, for either children or adults, existed.[83]

New guidelines for informed consent and research protections had been codified into what became known as the Nuremburg Code, developed shortly after World War II, when the world learned about the Nazi atrocities involving vulnerable populations that were undertaken in the name of research. But the Nuremburg Code had little effect on the subsequent research practice of American pediatric clinicians, who framed their decisions about how and when to use new drugs in terms of their potential to save the lives of sick children and not in any way subject to the Nuremberg-derived ethical principles.[84]

The infant who first received the new steroid adrenocorticotropic hormone (ACTH) in 1950 at Columbia-Presbyterian Babies Hospital in New York City is a particularly well-documented example of the vague boundaries between research and treatment in this era.[85] Born prematurely and weighing less than three pounds, the baby was the child of a senior biochemistry professor whose wife had experienced six miscarriages before delivering a live infant. Experience at the bedside suggested that supplemental oxygen helped newborns with immature lungs stay alive, yet the baby's doctor, one of the founders of modern neonatology, William A. Silverman, knew that oxygen could be a double-edged sword because the high doses required could also hurt premature infants' retinas.

Nevertheless, he treated the professor's baby with the extra oxygen, and, as expected, the infant's lungs improved and he began eating and gaining weight. But soon an ophthalmologist documented the ominous irregularities in the baby's retinal vessels that signaled inflammation. Would the treatment that had saved his life now cause blindness? Preliminary evidence had suggested that steroids had the potential to reduce retinal damage and save babies' vision while they received the oxygen they needed until their lungs matured. Although no infant had ever received ACTH, Silverman wanted to try it. He recalled:

> I couldn't imagine what the dose should be. We quickly looked at some animal work to extrapolate a dose. Unbelievably, within days after beginning ACTH, wild retinal vessel proliferation subsided! . . . We promptly reduced the dose because the side-effects were horrendous. The infant became ravenously hungry, extremely irritable, and weight gain ceased. But, when the dose was reduced, the retinal changes flared up. We increased the dose, and the vascular changes again subsided. The infant was now in pathetic condition; crying constantly and looking horrible with all the signs of adrenocortical hyperactivity. We tried again to reduce the dose of ACTH, and this time there was no retinal flare-up. We stopped the ACTH and the eye changes returned to virtually normal. . . . The whole medical center applauded our daring exploit.[86]

But Silverman and his colleagues quickly realized they had a "difficult dilemma."[87] Although ACTH seemed to be a "miraculous treatment" for the problem of potential eye damage from oxygen, one case did not provide definitive evidence of its benefit.[88] Silverman and his colleagues had recently "got religion" and were now "devotees" of the randomized controlled trial, rather than the observational or case study, for determining whether a drug or treatment worked.[89] Because of ACTH's "horrendous side effects," they wanted to know whether it was worth the risks to babies.[90] As he recalled,

> This was the end of 1950. We went to see the chairman of the pediatric department, Rusty McIntosh. We laid out this dilemma in front of him. We told him we were frightened about the side-effects of ACTH, and we had no concurrent controls. What we would like to do, we told him, is to carry out a randomized clinical trial, a method that had never before been used in studies of human infants. It grew extremely emotional, the idea of withholding a cure for infants simply to test it. All of the issues that we now understand are obvious, but this was the very first experience. . . . Remember, this was years before ethical review committees . . . [when] the chairman of the department decided everything that was done or not done in his department.[91]

After securing McIntosh's approval, Silverman consulted a textbook to develop a randomization strategy, which suggested he first fill a bowl with two different colors of marbles. The protocol stipulated that the nurse caring for a baby in the study close her eyes, reach into the bowl, and choose either a white or a blue marble. Depending on the color she selected, the child was enrolled in either the experimental group that received supplemental oxygen or the control group that did not. Unbeknown, at first, to Silverman and his colleagues, the head nurse kept pulling out marbles until she found the color that suited her assessment of what a particular baby needed, and this unanticipated human factor foiled the randomization technique. The power of randomized

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clinical trials, in which experimenters did not know which patients received a treatment or a placebo, became clear to him when the study showed no statistical difference in retinal change between the treated and untreated groups. In fact, the ACTH group had a higher death rate from infection, a finding that ran counter to Silverman's clinical observations. He later recalled his epiphany when he realized that researchers were not neutral observers; they sometimes drew conclusions based not on data, but on what they hoped to find.[92]

These kinds of experiments that aimed to identify dosing regimens using both healthy and ill children were common as new drugs poured onto the market in the United States in this era. For example, at approximately the same time that Silverman undertook his ACTH research, a young physician named Julius B. Richmond published the results of his drug investigation. Richmond and his colleagues administered sulfonamide therapy orally and subcutaneously to fifty-seven healthy infants at the University of Illinois Hospital to determine the appropriate treatment regimen. They studied dosage in terms of body weight, rate of excretion of the drug, and other measures that would be useful in caring for sick infants. The experiment, published in the *Journal of Pediatrics* in 1950, entailed the babies receive frequent blood drawing and medication injections and, in keeping with the era's norms, the report did not mention parental consent.[93]

In another drug experiment a few years later in 1956, Samuel O. Sapin, Ephraim Donoso, and Sidney Blumenthal of the Mount Sinai Department of Pediatrics in New York City studied fourteen healthy infants under the age of six months to ascertain how much of the powerful cardiac stimulant drug digoxin (administered intramuscularly) was necessary to produce side effects and changes to heart rhythm.[94] Doctors desperately needed this information because babies born with congenital heart disease often needed the drug's heart-strengthening qualities. But the pediatric dosing metric for digoxin had long been, as Cornell medical school faculty member Harry Gold noted in 1947, an "unsettled" problem.[95] Many of the babies in the Sapin, Donoso, and Blumenthal study experienced one of digoxin's most common side effects, vomiting. In a number of the infants, electrocardiograms documented potentially dangerous changes to their heart rhythm from the drug. One even developed a more severe, potentially dangerous disturbance of the heart's electrical functioning known as heart block. Sapin, Donoso, and Blumenthal did not explain the rationale for conducting the experiment on healthy babies, and, in fact, they noted that their findings could not be "directly transferred to babies with diseased hearts."[96] Nonetheless, *Pediatrics* published the study, which, too, lacked any mention of parental consent.

In this trial, as well as Richmond's sulfonamide research a few years earlier, the investigators probably felt they could defend their research because they were confident in their ability to manage any drug-related complications.

Perhaps because they assumed they could reverse any negative effects of the drugs in healthy infants, the physicians believed they were ethically justified in subjecting healthy infants to the research because they were generating knowledge that might save the lives of ill, much more fragile babies. Moreover, no one had proffered a better way of deriving pediatric drug-related information. The publication of their research in leading journals implies that most of their colleagues probably agreed. These drug studies were clearly welcomed by the institutions and academic settings in which they took place and helped advance the careers of the physicians who oversaw them.[97]

It was in this era that New York University pediatrician Saul Krugman began research at Staten Island's Willowbrook State School that later became infamous. Krugman investigated whether injections of antibodies protected uninfected children from the hepatitis virus. He and his investigators had observed that young children housed at Willowbrook, almost all of whom had profound cognitive impairment, often contracted hepatitis early in their stay. These children, they observed, suffered a less severe form of the condition than did older ones or adults. In another study, the investigators deliberately infected newly admitted youngsters who had received antibodies with the virus. A control group received the antibodies but were not infected with the virus. Children whose parents consented to have their child infected with hepatitis received expedited admission to a unit that had a higher nurse-to-patient ratio.[98]

Ethical standards were even less clear when the research took place outside the United States. At the 1957 Fifth Antibiotic Symposium, held in Washington, DC, one of many conferences held throughout the decade to synthesize the rapidly growing body of antibiotic research into therapeutically manageable guidelines, Elmer H. Loughlin, Louverture Alcindor, and Aurele A. Joseph, faculty at New York Medical College, informed colleagues of their research on children in rural Haiti, undertaken to ascertain the pediatric effects of long-term use of Pfizer's antibiotic Terramycin. They wanted to know whether the drug influenced children's growth. Beginning in October 1956 and continuing through 1957, the doctors administered varying doses of Terramycin to at least 240 schoolchildren and reported at the conference that the same kind of "growth-stimulating effects" that had been noticed in farm animals who received antibiotics could be observed in Haitian children.[99] Finding "no toxic or untoward effects," Loughlin, Alcindor, and Joseph proposed a potentially novel use for Terramycin. They hypothesized that the drug might be useful in treating "undernutrition" in "tropical children," especially since "correcting the undernutrition by supplying diets rich in high quality proteins, including milk, has not been economically practicable because foodstuffs are unavailable or too expensive."[100]

When drugs saved lives, the payoff in terms of scientific advancement and children's lives could be profound—as they had been with the sulfonamides in the 1930s and penicillin in the 1940s. One of the most significant postwar pediatric success stories came in the area of cancer. With the founding of the National Institutes of Health (NIH) in the 1940s, the federal government made a major investment in cancer-related research and treatment. The collaboration between the government, industry, scientists, and clinicians became one of the primary justifications for a public-private partnership in the U.S. approach to funding science and medicine. Lederle, for example, sponsored research by Boston Children's Hospital pediatric pathologist Sidney Farber, who was convinced that he could find a more successful way to treat pediatric leukemia than the traditional modalities of surgery or radiation, tools that did little for a blood cancer. Based on his laboratory research suggesting that folic acid played a role in nourishing cancer cells, he and his colleague Louis Diamond had tried a new agent, Aminopterin, on children very ill with leukemia. Their May 1948 report in *New England Journal of Medicine*, which outlined their ability to achieve temporary remission, created a sensation.[101]

Subsequent pediatric clinical trials in the 1950s and early 1960s yielded data that increased remission periods for youngsters, especially those with acute lymphocytic leukemia (ALL). There was little debate about whether or not to experiment using these new therapies because children with ALL died in such large numbers. As researcher Emil J. Freireich argued to his superiors at the National Cancer Institute when he sought permission to use what became known as chemotherapy on his young patients, "I've got children on the ward right now that are dying, who have no hope for living. What harm is there in doing it?"[102] By the next decade the industry, academic, and government partnership paid off as combination chemotherapy—a timed cocktail of multiple drugs, each with a different mechanism of action—began to reduce mortality in children with ALL substantively.

Chloramphenicol and Children in the 1950s: High Stakes Problems

Although the popular press reported the Elixer Sulfanilamide and sulfathiazole disasters, most stories in the media about drugs and their development in the early postwar era celebrated the advances emerging from pharmaceutical companies. When safety issues did arise, the power of drug companies could hamper the investigation as it did in the example of chloramphenicol. Chloramphenicol had quickly proved itself to be extremely profitable for its manufacturer, Parke-Davis and Company, which sold it under the trade name Chloromycetin. Within a year of its 1949 release, the firm sold more than

twenty-seven tons of the drug, and it had earned the company a quarter of its more than 100 million dollars in sales by the end of 1950. By 1951 the company was well on its way to achieving its goal of number-one position in the American market, sales having risen by 30 percent in the previous year, in large part as a result of chloramphenicol's success.[103]

Many physicians favored chloramphenicol for pediatric use because, first, it appeared to have fewer side effects than the sulfa drugs, penicillin, or streptomycin and, second, Parke-Davis had figured out how to formulate the drug in a vanilla-custard-flavored liquid popular with children.[104] All seemed to be going well until 1951, when the FDA and Parke-Davis received reports that chloramphenicol could cause a potentially life-threatening condition in both children and adults. The condition, known as aplastic anemia, resulted in the bone marrow producing an insufficient number of oxygen-carrying red blood cells.[105]

In 1952, Albe Watkins, a California physician, and his wife Geraldine, a nurse, watched in dismay as their nine-year-old son James, who had received the drug for a urinary tract infection, developed aplastic anemia and subsequently experienced a gruesome death. Watkins, like most other physicians, learned about the latest drugs on the market from the companies' detail men. As historian Thomas Maeder recounted, the Parke-Davis sales representative had provided Watkins with a wealth of information heralding the therapeutic benefits of chloramphenicol. After James's death, Watkins wrote to Parke-Davis, sure that the company would want to know of his son's aplastic anemia. Their indifferent reply suggested to him that they had little interest in what had happened to James. The company's response made Watkins so angry that he loaded his family in the car and headed to Washington, DC, to talk to the FDA directly about the drug and his son's death.[106]

During their cross-country odyssey, the family stopped briefly in Chicago, where Watkins sought out AMA president Austin Smith. Watkins believed that Smith, too, showed little concern for the absence of any warnings about aplastic anemia in Parke-Davis's marketing literature. The frustrated father began his own informal epidemiological investigation as the family continued its trip east. Each evening when they stopped to rest in a particular town, he called colleagues with whom he had trained to discuss chloramphenicol. In areas where he knew no one, he looked up physicians' names in the phone book and cold-called them to inquire about their experience with the drug. He identified new cases of aplastic anemia in both children and adults all along the way. Watkins was so anxious to present his findings to Henry Welch, director of the FDA Division of Antibiotics, that the family did not even check in to their hotel when they finally reached Washington. His wife and surviving children waited outside in the car while Watkins showed his data

to an amazed Welch, who could not believe that Watkins's informal epidemiological investigation closely approximated what his agents were beginning to find.[107]

Partly as a result of Watkins's tenacity, the resulting investigation became one of the FDA's largest up until that point. It exemplified what many saw as a glaring problem with drug regulation in the United States, that the companies that stood to profit from the drugs were also expected to play a major role in tracking any side effects, adverse reactions, and negative outcomes that might threaten their bottom line. Watkins and others whose family members had become sick or died from chloramphenicol-related aplastic anemia would later bitterly note that physicians had begun informing the company of the side effect within a few months of the drug's release. Indeed, the AMA's own *Journal of the American Medical Association*, noted the side effect. The 1952 *JAMA* article even cited a case, published just a few months after chloramphenicol's release, from an Australian journal that mentioned that the drug had caused aplastic anemia in a child.[108] Chloramphenicol's relationship to aplastic anemia had particular cultural resonance in Cold War America, where nuclear tests were rapidly increasing. It seemed incredible, a *Los Angeles Times* article noted about the Watkins family's saga, that one of the new infectious disease-fighting "wonder drugs" could cause a condition "that depletes the blood structure and attacks bone marrow in the manner of atomic radiation."[109] Although Watkins, as a physician, possessed enough political and economic clout to bring his findings directly to Welch and the FDA leadership, he was only one of many parents who contacted the FDA about chloramphenicol. For years after aplastic anemia's link to chloramphenicol came into public consciousness, letters from other family members, especially parents, who felt betrayed by Parke-Davis, the FDA, or the doctor who prescribed the drug to their child arrived at the FDA or Capitol Hill.[110]

Parke-Davis soon faced another chloramphenicol-related disaster, this one affecting very young infants exclusively. Doctors had begun treating a newborn with the drug when a mother developed a fever while in labor or when her water had been broken for an extended time before the baby's birth. Both conditions were considered risk factors for neonatal infection, and doctors were optimistic that administering a broad spectrum antibiotic such as chloramphenicol as a preventive to such infants might avert a life-threatening illness. By the late 1950s, however, doctors in Alabama, Ohio, and California had observed that mortality rates in some nurseries in which babies received antibiotics were going up, not down. A young Los Angeles pediatrician, Joan Hodgman, noticed the same thing and decided to investigate how and why this was happening. She and her team randomly assigned 126 premature newborns into one of four groups: Group One, no antibiotic; Group Two, chloramphenicol; Group Three, procaine penicillin and streptomycin; and Group

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Four, all three antibiotics. Chloramphenicol's toxicity became obvious when the group that received it exhibited a high mortality rate.[111]

Although 41 percent of the infant subjects in the overall trial died, it was the comparative deaths between the groups that was the most shocking. The mortality rates for babies who received no treatment or the procaine penicillin and streptomycin combination were 19 and 18 percent, respectively. But 60 percent of the babies administered chloramphenicol and 68 percent of the procaine penicillin-streptomycin-chloramphenicol group died.[112] Hodgman's study confirmed what was being observed elsewhere empirically. After a few doses of chloramphenicol, some infants developed respiratory distress and turned a dusky gray. The death rate was highest for premature infants because they often lacked the necessary enzymes to metabolize the drug adequately in their liver.

Hodgman later expressed regret about parts of the study to an interviewer regarding what quickly became known as gray baby syndrome:

> We discussed stopping the study early, and the decision was made—I was a junior faculty member at that time, working under the chief of the premature service, and the decision was not altogether mine, though I wasn't against it—that unless you have convincing evidence, nobody's going to believe you. We had to convince more than ourselves. We had to convince the public that the standard practice and the recommended doses were wrong. We weren't Harvard: we were a county hospital. So we continued the study as it had been designed. . . . We would do it better now.[113]

But she also reported somewhat bitterly in a 2004 oral history about the bind in which individual physicians found themselves. Unless a company requested information about the performance or dosage for its products, doctors were largely on their own, with no financial or statistical support, to answer important clinical questions such as Hodgman's. Moreover, Hodgman had gone beyond the ethical practices of many of her colleagues because she had received written informed consent from the parents of the children in the untreated group. She recalled: "[A]t the time, other people were killing half their preemies with chloramphenicol and not appreciating it. But we did it carefully, and we had permission from our research committee. We didn't have permission from all the families because we were giving them standard doses, but we did get permission from the untreated group," considered, in a sad irony, to be more at risk by the investigators than the babies who received an antibiotic.[114]

Hodgman was certainly correct about chloramphenicol's widespread use at other institutions, even the most prestigious hospitals. Surviving records from the Harriett Lane Home at the Johns Hopkins Hospital, for example, reveal

that almost 75 percent of infants under the age of two months who received the drug in the late 1950s died.[115] Chloramphenicol became the first drug to carry a warning label with regard to its serious, potentially life-threatening side effects, what today is referred to as a "black box" warning.[116] The episode also added to the growing body of information about the ways in which untoward reactions from drugs could sicken and even kill people. Physician Robert H. Moser, for example, added chloramphenicol to his new compilation of unforeseen consequences to novel technologies and drugs known as *Diseases of Medical Progress*.[117]

The reaction by at least one Parke-Davis drug metabolism expert, Anthony Glazko, to the infant deaths reflected his interest in the adverse events caused by chloramphenicol. In 1960 Glazko wrote to Maxwell Finland, explaining the way gray baby syndrome had stimulated him to become "interested in the question of proper dosage in children" from a scientific perspective. He ended his letter to Finland emphasizing another reason his preoccupation with "pediatric problems" in drug development had recently taken "a more practical turn." His wife had just given birth to a baby boy.[118] Through Finland, Glazko had connected the previous year with a physician at Boston City Hospital, Rudi Schmid, who was caring for a two-year-old patient with a liver condition that caused him to metabolize drugs similarly to a premature infant. Believing that research on this child's unusual metabolism might provide useful information, he expressed no concern about its potential untoward effects to the child despite its connection to aplastic anemia and gray baby syndrome.[119]

Trying to Find a Way Forward

The FDA's efforts in pediatrics remained at a very basic level. As late as 1957, for example, FDA staffers were still debating at what age infancy ended in the context of developing rubrics for evaluating drugs.[120] This operational definition was not unimportant in terms of drug labeling, but the drug-information needs of pediatricians were acute and clearly went far beyond this issue.[121] As a result, individual physicians stepped up their efforts to investigate drugs in children.

With funding from the AAP, for example, Massachusetts General Hospital's chief of pediatrics, Allan M. Butler, and his colleagues made their own study of children's dosages, which the hospital used in its formulary. Interestingly, doctors at the nearby Boston Children's Hospital were engaged in similar research, and the efforts of the two institutions appear to have operated parallel to one another, even though they were in close geographic proximity and most of the senior doctors at both hospitals served on Harvard's medical school faculty. Despite their common affiliation, they did not cite one another's work, nor were they collaborating; it seems clear that both hospitals were jockeying for preeminence in pediatric therapeutics. Theirs is an instance

of professional competition, one that also showcased the changing role of the hospital pharmacy in pediatrics.[122]

In 1960, according to its chief pharmacist, Arthur Thompson, the role of the pharmacy at Boston Children's Hospital was virtually unrecognizable from what it had been two decades earlier. It had expanded to a new, much larger space for storing and dispensing medications. Thompson noted that, although the drugs decreased the number of days many children needed to stay in the hospital, cost savings from their use were elusive. Unfortunately, the reduction in nursing time afforded by a pharmacy that prepared prepackaged drugs in a pediatric formulation was offset by the larger pharmacy staff required to make that happen. Pharmacists' workload at Boston Children's Hospital was so heavy because, according to Thompson, "most pharmaceuticals are manufactured for adults with little or no attention directed to pediatrics."[123] Unless industry saw potential to make significant profits on pediatric formulations—such as with the broad spectrum antibiotics—it had no financial incentive to do so. As a result, Boston Children's Hospital needed to purchase whatever dosage forms were on the market and then use a hand-operated capsule machine to compound its own pills.

Thompsons's and his colleagues' role at Boston Children's Hospital was now as an outlier in the world of pharmacy, more akin to their predecessors in decades past. At the beginning of World War II, for example, 75 percent of the drugs doctors prescribed needed to be compounded, a process in which the pharmacist mixed chemicals and prepared the drug prescribed by the physician. By the late 1950s more than 95 percent of all prescription drugs came to a pharmacist ready-made. The pharmacist's role in general practice increasingly became that of dispenser, transferring the number of pills ordered by the doctor from a large container to a small bottle. But at premier pediatric institutions such as Boston Children's Hospital, the labor-intensive process of compounding drugs for children because of their many different sizes remained the norm. According to Thompson, the need to prepare drugs on site did have one important benefit. Pharmacists could use the capsule machine to efficiently and quickly compound investigational drugs provided by pharmaceutical companies free of charge to doctors and the hospital.[124] Despite its modernized and larger space, however, Thompson complained that the new pharmacy was already out of date. For example, any volatile solvents needed to prepare drugs had to be stored in the cellar and brought up and down using a "hand-operated, antiquated elevator" before being brought to and from the pharmacy on a "dangerous spiral stairway."[125] Thompson wearily noted how his department was stretched thin: "[T]he staff is hardly adequate to accomplish all that is necessary."[126]

Another variable that reduced any nursing cost-savings brought on by more robust pharmacy support at Boston Children's Hospital was the increasing

complexity involved in administering medications and caring for the children who received them. While the expanded pharmacy saved nurses preparation time when their young patients required an oral medication, more and more children required an intramuscular, subcutaneous, or intravenous injection. Many of these drugs arrived on the ward in a powdered vial into which nurses needed to inject sterile water or saline to reconstitute it, calculate the amount of medication to be drawn into a syringe, and then administer the agent to the child. In addition to managing children's and parents' anxiety and educating them about the drug in a developmentally appropriate manner, late 1950s procedure manuals for the hospital detailed the expansive medication-related nursing protocols.[127]

At the national level, Harry Shirkey continued encouraging the USP to take a leadership role in knowledge dissemination for pediatric drugs. In 1959, the same year he accepted a position as medical director at Birmingham, Alabama, Children's Hospital, Shirkey eagerly sought reappointment as chairman of the USP Panel of Pediatrics.[128] The committee revealed its ongoing frustration in 1959 as members contradicted one another in their debates about dosing and safety, even about potentially dangerous drugs such as the cardiac drug digoxin and the sedative chloral hydrate. The panel's notes to one another included comments such as the one by University of Colorado pediatrician Henry Kempe, who opined that the USP's "doses for digitalis preparations are completely inappropriate for children and particularly infants."[129] An attempt to provide a pediatric dosing regimen for the sedative chloral hydrate was impeded when Boston Children's Hospital pediatrician Robert Haggerty noted the limitations of weight-based criteria: "Here again is the problem of children's doses and use. . . . If this adult [dose] is scaled down, it would be too little."[130] Shirkey himself reversed his own earlier opinion on one of the formulations of Compazine (prochlorperazine edisylate) he had supported a year earlier. Subsequent clinical experience now led him to believe unequivocally that it was "bad for children."[131] It is unclear what, if any, formal action Shirkey or the USP took to communicate the information about Compazine to Smith, Kline, and French. The drug remained on the market with indications and company-recommended pediatric dosing schedule that Shirkey now did not support.

Almost three decades after the Philadelphia Pediatric Society had first proposed the idea to the AAP, there was a growing consensus that the organization should play a central role in advising government and the USP when it came to questions of drugs for children. USP president Windsor Cutting noted as much in 1960 when he proclaimed that the AMA judged the worth of drugs "in all instances except for pediatric patients," where that responsibility fell to the AAP.[132] Shirkey hoped that together the USP and AAP could address the pediatric scientific and policy issues generated by the plethora of new drugs

continuing to flood the market. The AAP executive board agreed, and in October 1960 the organization allocated funds for a new Committee on Drug Dosage, with Harry Shirkey as chair.[133] Sensing that the time was right, Shirkey doubled the size of his USP pediatric committee in 1961, adding a number of interested and activist pediatricians, making the Panel on Pediatrics larger than any other USP specialty group. Moving ahead with his agenda of including pediatric therapeutics and dosing in the USP manual, in 1961 he reminded the organization's leadership with growing force that his panel was of the "very strong opinion that Pediatric dosage is still in a chaotic situation."[134] At the same time, individual physicians increasingly pressed the FDA to take a more visible role with regard to children. As leading pediatrician William L. Nyhan argued, "suppliers of drugs should be required to establish, before marketing, the presence or absence of differential toxicity in the very young."[135]

Shortly afterward, the FDA, which had increased its internal discussions about drug safety in children, hired its first pediatrician in the New Drug Division, Washington, DC, pediatric cardiologist John Nestor. Recognized as the "key man" in the FDA's "intensified pediatric program" by the trade journal *F-D-C Reports*, Nestor was at the center of the agency's "new pediatric emphasis."[136] Warily characterizing him as a "strong-willed, crusading, pediatrician," the *F-D-C Reports* article signaled to the drug industry that Nestor had significant influence.[137] More stringent federal oversight of drugs as they related to children seemed imminent as industry representatives were informed that "All NDAs that may have pediatric implications are now routed to Dr. Nestor for special scrutiny. He is the FDA staffer with whom the pharmaceutical MDs have to discuss pediatric drugs, implications, and dosages."[138] Any company submitting a new drug application was now supposed to submit pediatric data; if it did not do so, the agency might require a disclaimer, "not for pediatric use," on the label.[139] Left unsaid was what the consequences of such a label would mean, since a physician could prescribe any drug off-label, meaning a dosage or purpose outside that approved by the FDA.

Simultaneous to Nestor's hiring, interest on Capitol Hill was growing in this now major sector of the American economy. Senator Estes Kefauver's Antitrust and Monopoly Subcommittee was focused on practices such as questionable pharmaceutical industry advertising, potential price gouging, and companies' outsized profits. Although Kefauver was not uninterested in children's issues—he had chaired 1954 hearings investigating whether comic books could harm children's psyche and even induce them to become juvenile delinquents—his committee's interest in 1961 had little to do with children. Neither pediatricians nor the FDA had reason to believe that would change.[140]