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“Remarkable Improvement”: Sulfa Drugs and Pediatric Meningococcal Meningitis, 1937–1949

Lauded as one of the greatest developments of 20th-century medicine, the “wonder drug” penicillin reshaped the treatment of infectious diseases and altered patterns of mortality. As a result, the breakthrough that preceded penicillin—the development of the sulfonamides—is often overlooked.^{1–3} Using records from Sydenham Hospital, a municipal communicable disease institution in Baltimore, Maryland, in which nearly 75% of patients were children, we show the transformative role that sulfa drugs played in pediatric practice through a case study of meningococcal meningitis.⁴

Through the 19th and early 20th centuries, physicians observed patients ravaged by what they called “epidemic” or “cerebrospinal” meningitis. No matter how much mercury, opium, or arsenic they prescribed and no matter how many times they injected sterilizing agents into the dural space or drained infected cerebrospinal fluid via lumbar puncture, the disease proved fatal in nearly all cases.^{5–8} The first significant therapeutic breakthrough arrived when the Rockefeller Institute’s Simon Flexner developed an intrathecally administered serum treatment. By the early 1920s, eminent Johns Hopkins pediatrician Kenneth Blackfan ex-

ulted that the serum lowered the mortality rate at the hospital’s Harriett Lane Home from nearly 100% to 52%.⁹ Sydenham physicians used serum therapy with positive results. Their protocol, in which patients received meningococcus serum both intravenously and intrathecally, lowered the mortality rate to ~30%.¹⁰ Although serum therapy saved Baltimore children’s lives, it proved challenging to administer, because it required numerous intravenous injections and lumbar punctures. It also required physicians to identify the specific strain of bacteria causing the illness and then inject the antibodies into patients in hopes of boosting their natural immunologic response. Treatment continued until the spinal fluid was free of bacteria. The infants and children who endured the painful treatments undoubtedly found it highly traumatic.¹¹ Many children treated at Sydenham Hospital also experienced serious, even fatal, allergic reactions to the serum.

In 1935, Francis F. Schwentker began his service as medical director at Sydenham Hospital following his work at the Rockefeller Institute and as a resident pediatrician at the Harriett Lane Home under eminent pediatrician

Edwards Park.¹² Aware of the limitations of serum therapy, Schwentker investigated the much-heralded new class of drugs soon to be known as sulfonamides—synthetic organic dyes with antimicrobial properties, particularly against Gram-negative organisms. Sydenham Hospital soon became the epicenter of international sulfonamide research.

Schwentker and his Sydenham colleagues revolutionized meningococcal meningitis treatment in 1937 by administering sulfanilamide subcutaneously and intrathecally to 10 patients, 5 of whom were younger than 10 years. Only 1 of these 10 patients died (a black male adult). Schwentker and colleagues quickly published their findings in the widely read *Journal of the American Medical Association*.^{13,14} Although he hesitated to overstate his results given the small sample, he reported at the annual research meeting of the American Pediatric Society that year that the new chemotherapeutic agent held “great promise” as an adjunct to or even a substitute for serum treatment. In addition to its possible greater efficacy, it offered a major advantage over serum in that it could be administered orally. However, even as Schwentker documented sulfanil-

amide's curative potential, he acknowledged its troubling adverse effects such as rash, fever, hemolytic anemia, and renal complications.^{15,16}

Schwentker arranged for construction of a modern laboratory at the hospital to improve diagnosis and investigate patients' responses to serum therapy, and he quickly realized its value in monitoring sulfonamide toxicity and for determining the best dose for infants and children as new sulfonamides became available.¹⁷ Using techniques developed by Johns Hopkins pharmacologist Eli K. Marshall, Sydenham clinicians compared children's responses with the concentration of the drug found in their body and collected other laboratory data and refined their protocol accordingly.¹⁸

When Schwentker returned to the Rockefeller Institute in 1937, pediatrician Horace Hodes became medical director at Sydenham Hospital. Like Schwentker, he previously worked at the Rockefeller Institute and trained at Johns Hopkins. Under his leadership, investigation of the sulfonamides continued with a focus on their use in meningococcal meningitis. In 1942 he reported that of the 110 patients admitted between 1938 and 1942, only 2 of the children younger than 15 years had died.¹⁹

A sample of Sydenham Hospital patient records (every tenth case) now held by the National Library of Medicine reveals how the adoption of sulfonamides proceeded as physicians witnessed once commonly fatal diseases become treatable.²⁰ In the sample, there are 34 records of children with meningococcal meningitis treated at the hospital between 1941 and 1949. Nineteen of the cases come from children younger than 5 years; 9 are for youngsters between the ages of 6 and 12 years. Eight children younger than 5 died, as did 2 children between the ages of 6 and 12.

A fairly typical patient—a previously healthy 6-year-old black girl with a

4-day history of symptoms including a stiff neck entered the hospital on June 7, 1941. Her white blood cell count was 17 500, and her cerebrospinal fluid cultures grew meningococci. Her record states: "Before blood therapy could be begun, the patient's temperature rose to 105. . . . Sulfathiazole was immediately begun with the temperature returning to normal within 12 hours." The physician's exuberance at the child's recovery appeared in the next note: "Within two days the patient began to show remarkable improvement."²¹ For physicians accustomed to delivering challenging serum treatments and nonetheless seeing many youngsters die of meningococcal meningitis, the successful and relatively easy application of new drugs must have seemed almost miraculous.

Not all patients recovered as rapidly. Also, when a child had an ambiguous response to sulfa therapy, physicians needed to ascertain whether a symptom came from the infection or its treatment. In some cases they initiated and then temporarily halted chemotherapy. In 1944, a 3-month-old white male infant was admitted gravely ill with a fever of 104, white blood cell count of 13 500, and the worrisome petechial rash. After a positive meningococcal culture, doctors initiated the standard sulfonamide protocol. They were encouraged when the infant's temperature dropped rapidly, but when it again escalated on day 4, they discontinued sulfa treatment for fear of a drug reaction. Because the fever continued to rise, however, they reinstated chemotherapy. Thereafter, the course was uneventful, and the child was soon discharged.²²

The sulfa drugs won great acclaim locally and nationally, foreshadowing the plaudits that would come with the widespread introduction of penicillin several years later. The *Baltimore Sun* quoted city Health Commissioner Hun-

tington Williams in 1943, proudly announcing that "there has never been anything to equal this [the development of the sulfonamides] in past medical history," reflecting public opinion as well as that of physicians.²³ That same year, *Time* magazine described the sulfa drugs as "lifesaving."²⁴

The sulfa drugs changed medical treatment for infectious diseases from antisera or supportive care such as sponge baths to reduce fever to attacking the organisms responsible for infection. Thanks to the investigations of physicians at Sydenham Hospital and elsewhere, pediatricians treating meningococcal meningitis and other infections had a template for formulating and testing medications to determine rational dosages for their young patients. When the next breakthrough drug—penicillin—arrived, the intellectual groundwork and laboratory infrastructure required for its successful use were already in place.

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