



# ALWAYS THERE

The Remarkable Life of Ruth Lillian Kirschstein, M.D.

Alison F. Davis, Ph.D.

THERE ARE VERY FEW people who have such a profound impact on their professions that the telling of their life story is also a recounting of the history of their time and place. Ruth L. Kirschstein, M.D., who provided direction and leadership to the National Institutes of Health (NIH) through much of the second half of the 20th century, was one such person. At a moment in time when professional service to the government is often not given the respect it deserves, the story of Ruth's life, and the positive effect she had on public policy, public health, and the training of several generations of biomedical researchers, should inspire those considering public service and give great satisfaction to those currently serving the nation and the world.

Ruth Kirschstein was the daughter of immigrant parents who weathered the disgraceful prejudice and stereotyping of women and Jews, which would have prevented her professional contributions if not for her perseverance and hard work. She went on to become a key player in the development of a safe and effective polio vaccine, the first woman director of a major institute at the NIH, and a champion of the importance of basic biomedical research and training programs that provided opportunity to all talented students, especially underrepresented minority students.

She was both a guiding force and witness to much of the drama that NIH research brought to the public's attention: the polio vaccine, the Women's Health Initiative, recombinant DNA research, congressional budget hearings, and the eventual strong bipartisan support that the NIH now enjoys from both houses of Congress. In an engaging and informal account of Ruth's life, Alison Davis brings out the humanity and the strength of character that enabled the success of this remarkable public servant.

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ALISON F. DAVIS, PH.D.

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The modern world is one of celebrity and notoriety. We live during a time in which recognition seems to be bestowed more generously for bad deeds than for good ones and is more often than not the product of self-interest. Therefore, it is truly gratifying when we have an opportunity to look back and recognize the contributions of those who change the world, quietly, through their keen insight, their instinctive generosity, and their selfless hard work.

Ruth Kirschstein, whom we were fortunate to know as a devoted mother and a loving wife, was one of those rare people who truly made a difference for the good in this challenging world. Over the span of her life she was a classically trained pianist, an accomplished scientist, a highly effective administrator, and a brilliant advocate for science and scientists. She brought to each of these roles an unparalleled dedication, passion, and seemingly limitless ability to achieve.

Ruth was simply “always there.” Her overflowing enthusiasm enriched the lives of everyone around her: at the National Institutes of Health (NIH), in the wider scientific community, and even in low-income communities in Washington, DC, where she inspired schoolchildren by revealing to them the excitement of science. From childhood, Ruth showed strength of character, dedication, enthusiasm, passion for social justice, and an appreciation of beauty in all its forms. She had an uncanny ability to see potential in others, and she knew the power of attention and of words to transform.

Throughout her long career, her various talents directly touched literally tens of thousands of people, from laboratory assistants on the NIH campus, to those scientists and administrators whom she mentored personally, to researchers across the country, to members of Congress. Although only a few know much about Ruth’s scientific contributions in virology and pathology, these efforts were among her proudest achievements. Millions have benefited from the broader reach of Ruth’s work, through the polio vaccine safety test that helped vanquish a horrific paralyzing disease from many corners of the world as well as through the support of young scientists working at the front lines of discovery whose contributions will further future public health in innumerable ways.

This biography provides a window to view Ruth’s extraordinary life and gives us a chance to apply the broad themes and touching details within

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the context of our own lives. There is no question that Ruth would not have wanted the recognition afforded through a book, seeing instead the need to “get on with things.” But we and her NIH family could not let the story of this remarkable woman go untold. We believe that, quietly and humbly, she would have been touched by what this book represents: a celebration of the progress that resulted from her energy and her passion.

For those of you knew Ruth, we hope that this book brings smiles (and possibly some tears) to you, as you read and celebrate her spirit. For those who did not have the opportunity to be personally touched by her, we hope that this work will allow you to share in the good fortune of those of us who were guided, enriched, and blessed by her presence and to take with you a little of her innate enthusiasm, courage, dedication, and goodness—to make in your own way a better world. She would have wanted that. 🍀

Arnold B. Rabson, M.D.

Alan S. Rabson, M.D.

DECEMBER 2011

ne needs to journey back only as far as the 1950s to encounter a world that many people today would have difficulty recognizing. Consider the polio hysteria that held American families captive to a horrific, untreatable disease that preyed mainly on children. At a moment's notice, theaters and public pools would close, and children would be warned to avoid drinking fountains. Many worried parents would simply flee cities entirely. Public panic was at an all-time high then, particularly during the summer months when polio outbreaks were common. This disease was one of the most feared contagions of the day, a fear instigated not so much by the sheer number of deaths—cancer and tuberculosis were deadlier—but rather by images of children crippled for life and of iron lung machines that, so frightening in appearance, actually gave people life, enabling polio victims to breathe when their respiratory muscles had been deadened.

And so the first polio vaccine that emerged from research and testing in the early 1950s met with enormous enthusiasm worldwide. But something went very wrong in 1955, something that would almost undermine public faith in medical research—something that Ruth L. Kirschstein, M.D., an unknown and unlikely hero, would help to set straight and, as a result, reestablish American trust in the burgeoning field of vaccine development.

In that year a batch of tainted polio vaccine threatened the health of the public. This tragedy, which turned out to be one of the biggest public health controversies the nation had ever known, became known as the Cutter Incident of 1955. Ruth's response to the emergency would be the first of her many accomplishments that would have national, if not global, significance.

As with the public health climate, cultural norms in the 1950s might seem foreign to many of us today as well. Women and many minority groups were denied access to much of what we now take for granted: schools, jobs, and many public services and events. And this bias was by no means subtle. Minority applicants to colleges were told coldly to apply elsewhere, if they received a reply at all. Employers routinely denied minority individuals job opportunities without any feelings of shame or fear, essentially because there were no equal-opportunity laws in place.

Ruth lived through this forbidding time. The countless incidences of gender and ethnic bias she faced as a woman and as a Jew—coupled with



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the gross inequality for people of color she witnessed in New Orleans during her medical training—instilled within Ruth a lasting commitment to social justice. She would learn, through experience, to question inequality and the complacency of the medical establishment.

Ruth overcame these early obstacles in her life and became an outstanding scientist, a consummate leader, and a gifted communicator. She rose quickly through the ranks of the NIH, becoming the first female director of an NIH institute, the National Institute of General Medical Sciences (NIGMS); the first female deputy director of the NIH; and the agency's first female acting director. Ruth is widely lauded for transforming the NIGMS into the major institute that it is today for supporting basic research, dramatically increasing its budget, and, more important, convincing members of Congress that seemingly esoteric basic research could lead to breakthrough cures. Indeed, by 2011, NIGMS had funded the work of 74 scientists who went on to win a Nobel Prize.

Along the way, partly due to her life experiences, Ruth was exceptionally supportive of women and minorities in science. While much more progress is needed—a concept certainly not lost on Ruth—she helped to change the demographics of the NIH, recognizing talent and encouraging the hiring and promotion of female and minority researchers into leadership roles. So committed was Ruth to equal opportunity and to research training that Congress, in 2002, renamed the National Research Service Awards in her honor.

So who was this woman, Ruth Lillian Kirschstein? She was the daughter of immigrants, a dedicated student, a direct victim of inequality ... a wife, a mother, an astute researcher, a visionary administrator ... a member of the esteemed U.S. Institute of Medicine, a passionate mentor and wise counselor, and a charmer of Congressional committees. Through it all, Ruth was the very embodiment of the NIH spirit while showing the world what a smart, spunky lady could do.

Ruth was many things to many people. And her story begins on Ellis Island. 🌀

Michael M. Gottesman, M.D.

NIH DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH



# Coming of Age

*“It never occurred to me that I could not do anything I wanted.”* — RUTH L. KIRSCHSTEIN, M.D.

HAVING HIMSELF ARRIVED ONLY WEEKS earlier as a refugee but already manning the immigration desk at Ellis Island, the German attendant worked through a long line of Eastern European immigrants to the *goldene medine*. America had become the “golden land” for Jews escaping the growing wave of ethnic cleansing that had swept through southern Russia.

“Name?” the attendant questioned the next family in line. He heard something that began with a “k” sound, and he believed that he had heard it correctly. Time was short, and many details were lost in the transition to a new home.

Less concerned with the pronunciation of their family names and eager to begin life in America, thousands of early immigrants to the United States were routed through this government-owned gateway in Jersey City, New Jersey, just across from New York City. The goal was to get through, and quickly, and so “Kirschstein,” the German translation of “cherry stone,” seemed to work fine for an 8-year-old boy named Julius, his siblings, and his parents.

Many years later, Julius’ daughter, Ruth Lillian Kirschstein, would note, “I have no idea, nor did my father, what the family name was originally.” They had come from “near the borders of Poland and Russia ... but the border and the village names did not always stay the same.”

Family trees like that of the new Kirschsteins sprouted branches as hard-working pioneers sought to make their way in America. And a hard way it was. The marvels of mid-20th century public health achievements—hygiene, good nutrition, and antibiotics—were far in the future.

At the time, childhood survival was iffy, and the Kirchststein family had been no exception. Julius had made it, but some of his siblings had not. From the age of 8 he would know America—not his birthplace in Russia—as home.

Like many other turn-of-the-century immigrants wanting safety, stability, and harmony, Julius' parents had first settled in the Lower East Side of Manhattan. Then, as with many other newly arrived families, the Kirschsteins moved across the East River to Brooklyn, the most populous of New York City's five boroughs and a collection of ethnic enclaves. Even today, Brooklyn's official motto is "Een Draght Mackt Maght," which also appears on the borough's seal and flag and in original Dutch means, "In Unity There Is Strength."

In time, Julius would meet, and marry, Elizabeth Berm. Ruth, the couple's only child, was born on October 12, 1926. Ruth never knew any of her grandparents but had heard stories about her paternal relatives from her father. Many years later, she recalled the little she knew about her heritage:

"When my grandfather on my father's side settled on the Lower East Side of New York he went in the business of bottling of sodas, seltzer water ... He must have been involved in some sort of glass bottling business in Russia, because I inherited some beautiful cut glass. Some of it is stained ruby red and [that] is similar to what I have seen in Russian exhibits on occasion. ... One of my uncles, my father's brother, actually went on and continued the business, because he used to provide us with seltzer water at the house."



Young Ruth spent much of her childhood in a modest apartment on the Eastern Parkway, the main artery of the Brooklyn workaday bustle. She later recalled spending many contented hours in the Brooklyn Library, the Brooklyn Art Museum, and the Brooklyn Botanical Garden. Her parents were devotees of the arts, collecting and maintaining what must have been for the time a very impressive library of books and 78-rpm classical music records.

As a child of two working parents, Ruth depended on the subway to get to and from the yeshiva day school she attended from grades one through eight, just three stops down from the family apartment and next to one of several

synagogues that served the local Jewish community. A love of learning came early and easily to her. Both Elizabeth and Julius were teachers and were eager to feed their daughter's curiosity and provide a great stream of information about the world and how it worked. Reading was a primary activity, as were frequent, lively dinner discussions with a collection of "very intellectual, free-thinking" people, as Ruth later remembered.

The nurturing, if not sheltered, care she received from her parents notwithstanding, Ruth's childhood was inescapably affected by the Great Depression and the spartan environment and attitudes it brought. In the fall of 1929, just two weeks after her third birthday, Black Tuesday plunged the nation into a period of sustained economic collapse, initiating a hardship for a generation of Americans.

Discriminatory hiring practices presented the family with even more challenges. One of only two Jewish men in his college graduating class of 30 or 40, Ruth's father had earned his chemical engineering degree at Columbia University after a brief period of service in World War I. Julius' commitment, persistence, and diligence no doubt helped form the pioneering spirit Ruth would go on to display throughout her life. Those traits went only so far, though, when it came to her father's actually getting a job. Upon graduation from college, he and his Jewish school chum were told by their professor, "I have no jobs to give you," and then the two friends watched as everyone else in the class found work.

Although unable to work as a professional engineer, Julius had the good fortune to find part-time teaching work. Teaching high school chemistry appeared the best and most interesting use of his talent and time, leaving some of the latter for investigations and tinkering in the family's sixth-floor apartment. While such pursuits nurtured his intellectual needs, they did not bring him much income or fame.

One of Julius' part-time teaching positions was at Peter Stuyvesant High School—then and now a prestigious New York City public high school specializing in mathematics and science. Four Nobel laureates are among the school's alumni.

To Ruth, Julius' role went far beyond being an engineer or teacher, he was now her hero. Because her mother, Elizabeth, suffered months-long bouts of an at-the-time undiagnosed illness that resulted in long hospital stays, Ruth did not see much of her mother in her formative years. At the time, children were not permitted to enter hospitals if they were not themselves patients.

“[The hospital staff] would put [mother] by a window, and I was down on the outside street looking up and waving at her,” Ruth remembered.



Elizabeth had become ill when Ruth was 8 or 9 years old—roughly the same age Julius had been when he arrived in America to start a new life. Perhaps he had a particular empathy for his daughter at this tender age as a result: He spent nearly all his free time with the girl at museums, at the library, and attending concerts of all sorts. This fervent attention to culture likely framed a devotion to the arts that would inspire and enrich Ruth’s entire life.

Ruth’s mother eventually overcame her illness and could return to work. A German refugee doctor at Montefiore Hospital in the Bronx connected the dots of Elizabeth’s symptoms to a relatively little known, but manageable, disease called nontropical sprue (later identified as celiac disease). After the doctor said to Julius that a change in diet might alleviate her symptoms, Elizabeth took control of her health by avoiding wheat gluten, cutting fat, and increasing her consumption of fruit. Her symptoms virtually disappeared, freeing her of the repeated hospitalizations and eventually allowing her to return to work full-time.

Elizabeth Kirschstein taught at various public schools scattered throughout New York City—some were 15 miles away in Harlem, which required more than an hour’s travel each way by subway—but most were in the Red Hook neighborhood of downtown Brooklyn, a mainly Italian enclave that had once been the home to mobster Alphonse Gabriel “Al” Capone.

As was customary for the day, Ruth’s mother covered the entire range of educational subjects in her lessons with elementary-age students, later specializing in English and mathematics with junior high school students. Ruth remembered her mother as a highly regarded and well-loved teacher who practiced her craft long after mandatory retirement (age 70 at that time), volunteering her substantial classroom skills until her death at 89.



That Ruth enjoyed constant exposure to culture was a testament to her parents’—mostly her father’s—enthusiasm for the arts, and for music in particular. Despite the fact that the Kirschsteins did not have a large amount of disposable income, Julius invested in a second-hand piano for 6-year-old

Ruth and started her on piano lessons. That early and routine exposure to music would blossom into a lifelong source of joy for his daughter.

Ruth also adored the enrichment and escape offered through reading. Beginning around the age of 8 or 9, she canvassed the entire literary collection of Willa Seibert Cather, the American author who chronicled frontier life in the early-20th century Great Plains. Cather herself disliked most contemporary women writers, judging them overly sentimental, and she had originally intended to become a doctor before becoming a celebrated writer. Cather's no-nonsense approach to characterizing everyday life, and her challenging of the norms of the day, may have influenced a young girl whose own parents—Elizabeth in particular—were so supportive in encouraging Ruth to pursue her own interests regardless of societal attitudes.

Indeed, Ruth noted later, "... it never occurred to me that I could not do anything I wanted ... nor would my mother have thought that."

Ruth's parents had sent her to a private, Jewish day school in Brooklyn. But after a few years of piano lessons in the neighborhood, it became evident that Ruth's talent would soon exceed the capabilities of her local teacher. Recognizing musical potential in their daughter, as soon as the time came, Julius and Elizabeth enrolled Ruth in a performing-arts high school, the High School of Music and Art, where she enjoyed a multifaceted education rich in the arts, but excellent also in languages—and importantly—in math and in science as well.

Ruth spent an hour each way on the subway commuting to school. She learned to complete her homework assignments en route, both to pass the time and because many other things had to be done at home.

Although she loved the musical environment in high school, Ruth concluded that her own musical talent was not good enough to be an outstanding professional. She was not content to be a "second-[rate] French horn player in a minor orchestra," she said, adding that "if I was not going to be able to be first-rate, I was not interested in [becoming a professional musician]."

Ruth then decided that while music would always be a significant part of her life, she would pursue a career in medicine.



For college, Ruth's parents did not want her to travel away from home. Ruth settled on Long Island University, mainly due to its small size and her sense

that it offered the best chance for a Jewish girl from New York City to have an opportunity to be admitted to medical school.

When Ruth started college amid World War II, in 1943, the population of Long Island University consisted almost exclusively of merchandising students and premed majors, including those men who had been deferred from military service to acquire medical training. Four years later, in 1947, Ruth was the only student in her undergraduate class to make it into medical school.

Years of practice doing homework on the subway paid off for Ruth in college, when she used any spare time to earn spending money that she did not want to ask her parents for—she felt their sacrifice for her education was enough as it was. Tutoring math and giving piano lessons consumed her free hours when she wasn't studying or playing French horn in the college band.

Getting into medical school was an uphill challenge—not for academic reasons, but due to the social constraints of the day. Few women were prepared to persevere through the gender discrimination that kept females from being considered at all for medicine. And to be Jewish, on top of that, made matters much worse: Almost all medical schools had instituted quota systems for Jewish students.

Ruth's strategy was a full-court press. She had written to every medical school in the country, but her reception was almost universally chilly: "We don't take out-of-staters," she remembered. "We don't take women."

Then, her luck changed: Tulane University School of Medicine, which, according to Ruth, had a reputation for not having the same quota system, invited her for an interview. It would be conducted locally by an alumnus living in Brooklyn. It went very well: Ruth knew walking out of the interview that New Orleans would be her home for a while and that she had climbed a key step toward achieving her dream.



Of approximately 4,000 applicants in fall 1947, Ruth and 109 other freshmen were admitted to the Tulane medical school class that would graduate four years later in 1951. Ruth had also been accepted to the medical school at New York University, which she refused to attend for fear her parents would "smother" her. Moreover, she said, "If I had gone to NYU medical school, to this day I would be practicing medicine in the [doctor's suite] of the apartment complex, and living in the apartment where my parents had lived."





ARNOLD ROBSON AND BARBARA BARNETT

Julius Kirschstein was “hero” to young Ruth.

Every school other than New York University and Tulane had turned her down, and some were quite direct in doing so. Ruth recalled one case of what she perceived as outright bigotry: “Have you ever considered changing your name to get accepted into medical school?”

Competition was tough, and medical school was no cakewalk for Ruth. While she had been first in her class in college and nearly first in high school, she remembered being only “something like fortieth” in her medical school class. “It was not easy,” she recalled, and she studied nearly all the time.

Ruth did all she could to live in the world of medicine, reading scholarly publications like the *New England Journal of Medicine* faithfully despite the demands of her curriculum. She was especially enamored of the *New England Journal's* famous case reports—in which doctors describe authentic experiences with patients, often recounting unusual situations and illnesses—and she absorbed the stories as would other people reading fiction.

One day during medical school, Ruth was part of the team conducting patient rounds—a practice in teaching hospitals in which students, residents, and senior physicians go from hospital room to hospital room talking about the current cases. On one such morning, Ruth put to use what she had learned from her independent reading of medical journals. The team of doctors happened upon a patient with an unusual condition; Ruth remembered raising her hand, speaking up confidently, and then explaining succinctly how to handle the medical challenge for the patient who lay in front of them. She had read about a similar case in the *New England Journal of Medicine*.

At Tulane, a higher-than-expected number of students, compared to national percentages of the time, were Jewish, but Ruth was the only Jewish female in her class. The class was also a good bit older than was typical, and several classmates had come from Puerto Rico or South America. Just after the war, and due largely to the GI Bill that provided college or vocational education for returning World War II veterans, several students in Ruth's class were older than she was, married, and had had their tuition paid by the U.S. government.



Of the 10 women in her class, Ruth was the only one not from the South. Yet, she embraced the beauty of New Orleans. As winter approached during her first year at Tulane, Ruth found herself downright startled, but delighted, at seeing camellias blooming. Conversely, trips back to New York City during school breaks brought a rude, cold-weather shock. During the first two years of medical school, Ruth roomed with two women, one of them divorced and with a daughter, near the undergraduate campus in the Garden District, a leafy, lush area of New Orleans. Although she had her own room, Ruth shared a bath with the women. Because she ate all her meals on campus and had a heavy class load, however, she spent little time at home.

She liked New Orleans, but the conditions in which Ruth lived did not matter much to her. After deciding on medicine as a career, she was fully

dedicated to succeeding and doing all the work required to make that happen. She was at medical school to learn how to become a doctor, and nothing would deter her from that goal. Accordingly, she did not pursue many outside activities—and forewent tutoring, piano lessons, and other interests to stay on course.

As with all medical schools, the two phases of instruction were separated in time. At Tulane, they were also separated in space: the school had two entirely separate campuses across town from one another. Ruth's first two years of medical school were spent mastering the details of basic science. Year one consisted of gross anatomy, histology, embryology, biochemistry, physiology, and pharmacology. In year two, the medical students extended the foundation set down in year one by pursuing various applications of the basic science curriculum, and took pathology, microbiology, and physical diagnosis. These classes were the entrée to the clinical years three and four.

Throughout medical school, Ruth grew increasingly interested in the study of the diseases themselves, an interest that would direct her career to pathology, the branch of medicine that deals with the laboratory examination of samples of body tissue for diagnostic or forensic purposes. Tulane's department of pathology and bacteriology then consisted of five professors and five instructors and was led by Charles E. Dunlap, M.D. Under his tutelage, Ruth became especially fascinated with pathology, planting a seed for a career in medicine and research that would span more than a half-century.

Another seed was about to be planted—one that would shape her personal and professional life in ways unimaginable to her.

## A Perfect Match

*"We loved to talk about school, about medicine, about the world."* — ALAN S. RABSON, M.D.

"I HAVE A FRIEND FROM COLLEGE who I think you would like more than you like me. If I give you his address, will you write to him?"

"No," Ruth replied quite frankly to Donald Feldman, a microbiology student at Tulane, perhaps a bit put off by her friend's suggestion to strike up a relationship with someone she had never met. Later, she would change her mind, and that decision would alter her entire life's course.

In fact, the truth was that "Donny," as only his closest friends called Feldman, thought the world of Ruth and would have preferred to continue a relationship with her. But the timing wasn't right, he recalls, now a half-century later in 2011.

Although Feldman had not gotten into medical school on the first try—and had decided to pursue graduate studies instead—he did share a room with medical students. Both Southerners, Feldman's roommates teased him incessantly about being from New York. He recalls now, "They never realized that 'damn Yankee' was not one word until they started medical school!"

His roommates also talked a lot about a female student from the North who always sat down in the front of the class and rushed around between classes—atypical behavior for the more laid-back attitudes characteristic of New Orleans. Curious to find out more, Feldman began attending the early-

morning medical school classes to see firsthand this student, who, he said, turned out to be motivated, pretty, and hardworking. Ruth Kirschstein was her name, they had said. Feldman introduced himself to Ruth, they became friends, and then dated a bit. Feldman recalls many good times with Ruth, even visiting with her family one school break and having dinner with them in Brooklyn, about an hour from his family home in Islip, New York.

Feldman had a friend, Alan S. “Al” Rabson, whom he knew from the Men’s College on the River Campus of the University of Rochester in upstate New York. Al was a little ahead of Feldman in school, however, having spent time in the U.S. Merchant Marine during World War II, and he also had college credits from classes he took at Queens College in New York City.

Because he intended to complete graduate school and then apply to medical school, Feldman saw many years of training ahead of him—at least 15—until he would have a paying job. He decided that a long-term relationship with Ruth would be impractical for him and unfair to her. Feldman knew that his friend, Al, on the other hand, was older and had already been accepted as a student at Long Island College of Medicine.

Feldman’s matchmaking skills would turn out to be spot on.



Al’s family had settled in Queens, New York City, a reality that had significant implications for him, his sister, and his parents. They struggled to get by after Al’s father, “Abe” Rabinowitz, died relatively young from a heart attack when Al was a teen, leaving his mother Florence to single-handedly raise Al and his sister during the Depression. The family ran a candy store, which doubled as a home, as the Rabsons lived in a back room of the busy store. The business was a huge commitment for the young family; its doors were open seven days a week and every day of the year. Anti-Semitic sentiment ran deep in early-20th century Queens, and Al suffered the brunt of it. He would, as did many Jewish families, later change his name, in this case from Rabinowitz (in Hebrew, “rabbi’s son”) to “Rabson.”

“I got beaten up all the time because I was Jewish,” he says now, noting that nearly all of the store’s customers were not Jewish. The religious discrimination Al encountered throughout his childhood persisted, making it extremely hard for him to pursue higher education. The quota system for admitting Jews to professional training studies such as medical school was rigid, and it suffocated many dreams. Almost ready to give up and try another

career, Al got into what he jokingly called a “second-rate” medical school, the Long Island College of Medicine, thinking that it would be his only chance to become a doctor. In reality, the medical school was a trailblazer in medical education, integrating the teaching of medicine with patient care. Today, it is part of the State University of New York Downstate Medical Center.

Al grew up fast and learned quickly about the necessity of working hard for his very livelihood. Although the candy store pulled in enough profit for the family to survive, and Al had free access to the cash register, after covering necessities there wasn’t much left for any discretionary spending. Ruth, on the other hand, was well-off in his eyes since her parents had job security—a godsend in Depression-era America.

Even though Ruth had been hesitant at first to write letters to Feldman’s friend, Al, she eventually complied. That did not matter much, though, since Al hadn’t exactly taken “no” for an answer and had been writing numerous letters to Ruth. She finally wrote back. Over the next few months, they got to know each other, beginning a decades-long romance and partnership rivaled by few.

“Even before we met in person, I felt like I knew who she was. We traded pictures. She was very attractive, and we loved to talk about school, about medicine, about the world,” said Al Rabson of Ruth Kirschstein.

They were a perfect match.



However well suited Al and Ruth were to each other, there was still Julius Kirschstein to reckon with.

In 1949, after Ruth’s second year at Tulane, she returned to Brooklyn for the summer. And Al was standing there at Penn Station waiting for her. Unfortunately, so was Julius, who upon learning of his only child’s new romantic interest was decidedly displeased and offered Al an unfriendly glare. The three quickly parted ways in the station, and Ruth’s father proceeded to warn his daughter about how becoming distracted would get her flunked out of medical school. And yet Al was undeterred, and only a few hours passed before he called Ruth at home in her apartment that night. They saw each other the next day and every day that summer, even as Ruth recuperated from a bout of mononucleosis. The two sat and talked medicine as she rested. On better days during that first summer together, Al and Ruth went to outdoor concerts at Lewisohn Stadium, on the grounds of the City College of

New York. At the time, it was one of the town's public landmarks and hosted regular performances by a range of artistic talents. Of course, it goes without saying that as children of the Depression, Al and Ruth found the activity was very accessible. It was "the cheapest thing we could do," according to Al, who recalls spending only 35 cents a ticket to see the New York Philharmonic perform on a regular basis.

"She was smart and concerned about the world around her," Al remembers of those engaging discussions their first summer together.

One year ahead of Ruth in medical school, Al finished up his last year in Brooklyn, set to graduate in 1950. Meanwhile, Ruth went back to New Orleans and the two continued to write to each other. They reunited over the winter holiday break in Miami, where Al's sister, also named Ruth, lived with her husband and child. Al and Ruth stayed in separate rooms in Miami—being together away from home and still unmarried was a bit daring for the times.

In the summer of 1950, preceding her final year at Tulane, Ruth got a job conducting research in New York City at the Sloan-Kettering Institute (today, the Memorial Sloan-Kettering Cancer Center). This enabled her to try clinical research. At that point, neither she nor Al knew where Al would be serving his internship. When Ruth and Al learned that it would be in Boston, marriage was the logical solution to being able to see one another on weekends while staying within the boundaries of the good will of Ruth's parents. They became engaged.



Al and Ruth's wedding took place on June 11, 1950, only five days after they decided to get married. The ceremony was performed in the apartment where Ruth and her parents had lived, by the rabbi from the Jewish center at the day school she had attended.

The wedding ceremony was a traditional Jewish one, and it was private and simple. Ruth chose to wear a dress she had stored in the closet, and she and her mother prepared all the food themselves. The Kirschstein household was not kosher, however, and "the poor rabbi did not get to eat anything," Ruth recalled later. Most family members, including Ruth Powell, Al's sister, came on very short notice to celebrate the marriage.



Al Rabson and Ruth Kirschstein were a perfect match.



After the wedding, Ruth decided to keep her name, for two reasons: First, she and Al had already talked about how confusing life might be with more than one “Dr. Rabson.” Perhaps more significant, though, was her desire to perpetuate her own family’s name. Here was a chance to have a Dr. Kirschstein in the family.

Ruth’s love of living fueled the countless professions, interests, and relationships of what would become a very rich life. Not surprisingly, then, in medical school, although Ruth had professed her strong interest in pathology—ultimately the medical specialty she chose for a career—she was quick to admit that “I fell in love with everything I did.” Talented and entertaining professors in pediatrics ... psychiatry ... and many other subjects led her to thinking that the lesson of the day might be her professional calling.

Nonetheless, to accommodate the wide array of interests that lay potentially ahead in her career, Ruth decided, smartly, to pursue broad experience in her postgraduate training. First, she did a one-year internship at the tremendously busy Kings County Hospital in Brooklyn, her time split evenly between medicine and surgery. She was able to experience a bit of all of the options available to her.

Ruth was attracted to Kings County for a reason beyond its location in New York City, where Al would be doing his residency in pathology at New York University’s University Hospital. She was impressed with its humanitarian mission. Built in 1831 as a one-room infirmary for publicly supported care of the sick, Kings County then and now provides care to everyone regardless of ability to pay. This environment of commitment and the hospital’s concern for social justice came at a formative time in Ruth’s training and seemed to have influenced her entire career.



Interns like Ruth were expected to jump into action, performing sometimes for the first time, without help, procedures that ranged from delivering babies in the middle of the night to responding to trauma and a wide variety of other medical emergencies. Interns are professionally and personally “tested” for their ability to make quick decisions that have heavy consequences. For example, Ruth was left to perform appendectomies without supervision on occasion due to a lack of staff and too many patients to serve.

Thus, interns—lowest on the totem pole of physicians in the hospital—spend a lot of time on the job. Like the other approximately 100 interns at

Kings County, Ruth spent five, sometimes six nights a week on duty. Sleep was a precious commodity that took second place to the needs of whoever came through the door.

At Kings County, the needs were huge. As a public hospital that provided free care, the wards were packed, and patients lined the hallways. Inescapably, Ruth's on-the-job training was fast, furious, and comprehensive.

"The hospital was enormously overcrowded. ... We had patients who would not go home. We had patients who were very sick. We had patients who were pretending they were sick. We had all sorts of things," Ruth said.

Meanwhile Al, who was on his own schedule as a resident in pathology, was much more emergency free, and his time was more predictable. And so Al would go visit Ruth when she was on duty in the hospital. Ruth repaid the favor by playing Beethoven sonatas and Mozart pieces for him on the piano in the hospital recreation room.

"Our time together then was absolutely terrific," Al remembers with a wide smile.



The more than 1,000 miles that separated Kings County in Brooklyn and Charity Hospital in New Orleans didn't make too much difference in the types of maladies Ruth encountered every day. Infections, tumors of all types, liver disease, heart disease, and strokes were common. Tuberculosis, in particular, was rampant. Nearly 10 percent of the interns got it, including Ruth. However, she would not know for decades that she had contracted tuberculosis during her internship at Kings County. The disease would lie dormant in her body until it was detected many years later when she was living in Bethesda, Maryland.

Many tuberculosis infections in humans work like they did in Ruth's case—lying dormant for years. In fact, a fairly low percentage of tuberculosis infections cause the condition's classic symptoms: chronic cough with bloody spit, fever, night sweats, and "consumption," the gradual but steady weight loss that seems to rob a person of his or her body over time. Tuberculosis, which is caused by a bacterium, is spread through direct contact with the microorganism via coughing, sneezing, or exposure of unwashed skin.

While today a tuberculosis skin test takes only 48 hours to deliver a response, and if positive, a DNA-based test can confirm infection quickly, for Ruth and the rest of the doctors at Kings County and the other hospitals

and clinics across the country, managing tuberculosis was incredibly difficult. The disease was hard to diagnose, hard to treat, and it killed a lot of people. Diagnosis was a long waiting game in which the hospital laboratory placed a small sample of a patient's saliva on a culture plate and waited to see if it grew.

During her time at Kings County, Ruth saw many sides of medicine, learned a lot, and became adept at lightning-quick decision making. She had made a measured choice to do an all-purpose, intensive internship, and she was accomplishing her goals.



As did many of the relatively few women doctors of the time, Ruth felt a good deal of pressure from others to pursue medical specialties common to women—pediatrics and obstetrics/gynecology in particular. However, for whatever reason, she did not feel any need to take that suggested course.

It also helped that Al was supportive of the decisions Ruth made. The couple had a partnership they both treasured. Their mutual attraction and dedication to each other had as much to do with intellect as it did with romance: Al was proud of having a working spouse, and Ruth cherished the freedom and professional accomplishment this understanding between the two of them offered her.

Together, they decided that pathology would suit both of their careers—satisfying the intellectual need to solve medical mysteries and providing a fairly regular schedule for raising a family.

By now, there were new pressures in postwar America. Peacetime drafts had started with the Selective Training and Service Act of 1940; the second peacetime draft, begun after World War II, contained a new provision aimed at bolstering the ranks of health care workers in the military. In addition to requiring all men between the ages 18 to 26 to register, this second peacetime draft established the “doctor draft,” which meant that, barring special exemptions, male physicians could be called for up to 21 months of active duty and five years of reserve-duty service.

The Public Health Service Act gave academically oriented male physicians like Al another option: to join the Service's Commissioned Corps. Rejecting an initial offer to serve in the remote Pribilof Islands off the Alaskan coast—“What would my wife do there?”—Al pursued an opportunity to join the second class of the Epidemic Intelligence Service, the forerunner of today's

Centers for Disease Control and Prevention. The two made plans that would help to shape their future careers.

Her year-long internship complete, Ruth had put her own residency on hold until Al's assignment was sorted out. During the summer of 1952, the two lived in military barracks in Chamblee, Georgia. Al traveled daily to downtown Atlanta to take courses at Grady Hospital, home to the city's Veteran's Administration's pathology department.

Renowned epidemiologist Alexander D. Langmuir, M.D., M.P.H., had founded the Epidemic Intelligence Service and guided the fates of the newly installed members of the Commissioned Corps. Respecting Al's intellect and political dexterity, Langmuir appointed him to a special, short-term assignment in Detroit, Michigan. The sensitive nature of this assignment—to address the concerns of Canadian government officials that Detroit automakers were polluting the air and creating public health risks for their citizens—called for equal doses of knowledge, skill, and tact. Al had them all.

Meanwhile, Ruth started looking for a pathology residency program in Detroit. For the newly trained medical couple, the place and its people were a perfect introduction to their later lives of blending research, medicine, and diplomacy.

It turned out that Detroit was a haven for academic pathologists. Ruth thrived in the environment, and when Al got word that his temporary assignment had run its course and he had chosen as his next career move pursuing virology in Ann Arbor, Michigan, Ruth considered carefully whether a move would be in her best professional interests.

The decision was made for her when she learned that the University of Michigan pathology department did not intend to hire a woman. In what seems to have been a harbinger of her future pragmatism, Ruth decided to continue her training at Providence Hospital in Detroit, a little over 40 miles from Ann Arbor. They decided to, for the time being, work in different cities during the day, with Al meeting Ruth at the Ann Arbor train station each night. This would allow them to be together every evening after work.

Both Ruth and Al found living in Ann Arbor a good experience, but it didn't last long. As much as they liked the vibrancy of living in the Big 10 college town of Ann Arbor, Al and Ruth recognized that the next place they would call home would be dictated by their career path, because now it truly was a shared path. In a twist of fate that Ruth welcomed gladly, Al was accepted into a pathology residency program in New Orleans. Tulane's

pathology department invited Ruth to continue her training there, and the two physicians got into their brand-new Chevy and drove to The Big Easy.



Meanwhile, other changes were happening throughout the country. America was thriving in the postwar economic boom. Federal investments in science had taken root more fully. Vannevar Bush, Ph.D., an American engineer and administrator known for his contributions to analog computing and as the primary organizer of the Manhattan Project, was beginning to play a significant role in the scientific direction of the country. Bush worried that basic research exploration and targeted military spending were not compatible.

At Bush's urging, President Franklin D. Roosevelt saw that basic research acquired federal backing, taking form in agencies such as the young and growing National Institutes of Health (NIH) and the then-new National Science Foundation (NSF). By that time, the NIH had moved to Bethesda, Maryland, and on October 31, 1940, President Roosevelt had dedicated the agency's buildings and grounds.

Throughout the 1940s, the NIH grew rapidly, and several institutes were established by Congress. In November 1949, work started on the NIH Clinical Center. The NIH would become the source of a continuous series of amazing discoveries, new medical knowledge, and life-saving treatments, and, in just a few years, it would become Ruth and Al's place of lifelong employment.

## The Life Worth Living

*"I remember so fondly the expression on her face upon hearing great music. She was transported to another place."*

—ARNOLD B. RABSON, M.D.

IN 1955, FEELING FULL OF PROMISE, the Kirschstein-Rabson duo came to the NIH and instantly knew they had made a good choice. As Al describes it, "We stood on the steps of Building 1, looked at each other, and said 'This place is for us.'"

The two had decided to pursue research careers, and the NIH was the place to do it. Al joined the National Cancer Institute (NCI) as a pathologist. Ruth had completed a year of pathology residency in New Orleans but had been accepted by the NIH into its program (and intended to spend a second year of residency there). Although Ruth was pregnant, she had intended to begin the NIH program right away but was encouraged to wait.

"No. There is no reason why I can't do this," Ruth said to that suggestion, but she relented and delayed her start date nonetheless. Afterward, she would be relieved that she had done so, because a son, Arnold, came two months sooner than expected. He was born on August 19, 1955, and with a great deal of fanfare. Ruth had gone into labor during a rare Washington, DC hurricane ("Diane"), which had come on the heels of Hurricane Connie. That Arnold was premature made it all the more frightening.

“It scared the hell out of them,” says Arnold now of his parents, who as physicians, were acutely aware of the potential peril he faced. Premature births in 1955 carried significant risk.

Arnold spent the first month of his life in the maternity/newborn ward of the George Washington Hospital in Washington, DC. Finally, Arnold was cleared to go home. More fond of sleeping than of eating, but requiring constant sustenance to survive, tiny Arnold needed an every-couple-of-hours feeding from his mother. This went on for a few months, and he soon gained weight and began to thrive.

When Arnold was born, his parents’ friend Donny Feldman had become the boy’s unofficial godfather. Donny and Arnold remain close to this day. In addition to introducing Al and Ruth to each other, Feldman got the credit for being Arnold’s “first friend,” as so proclaimed the boy at age 7.



Ruth planned to return to work as soon as possible after Arnold was strong enough to be in the care of a nanny. In January 1956, they were fortunate to find and employ a wonderful woman to look after young Arnold.

Mrs. Peters had a music degree from the University of Michigan, but she had also earned a degree in practical nursing. After her husband passed away, it was the degree in nursing that helped her make a living. Throughout Arnold’s infant and toddler years, Mrs. Peters came to the Rabson house every weekday morning at eight o’clock and stayed until six o’clock in the evening. Her sole responsibility was to care for Arnold, and by Al and Ruth’s accounts, she was a marvelous success at doing so.

What a boon this proved to be for Ruth.

“Ruth loved motherhood, but she had absolutely no conflict with also being a doctor,” said Al. “She was so smart, but she was also very concerned about the world around her, and I loved that.”

Ruth did not feel guilty that she was not cooking every day and doing all the things that made you a “good housewife” in those times. She loved Al, she loved Arnold, and she loved her work. And she always seemed to find the bright side.

“Everything was ‘wonderful’ and ‘marvelous,’” her son Arnold said years later. “And if it wasn’t, she made it that way. She had a tremendous enthusiasm I have seen in very few people anywhere.”

After Ruth's father, Julius, died from emphysema, Ruth's mother moved near the couple and offered to help out with Arnold. From the time Arnold started first grade—around age 6—Ruth's mother Elizabeth would stay with him when he was home sick from school, and she helped Al and Ruth with cooking and household chores. The family was grateful for Elizabeth's help.

From the earliest days, Ruth kept her only child close. After having spent long hours in the laboratory, Ruth spent every evening with her young son. On weekends, the family ventured out together. Arnold grew very close to both his mother and father. Even when Ruth had to study for the medical boards, young Arnold leafed through the pathology text like another child would read a children's book. This was an image Ruth remembered fondly and would carry close to her heart for the rest of her life.

"It was work, Al, and Arnold," Ruth said, "and that was it."



The Rabson family lived first on Battery Lane in downtown Bethesda. The Rabsons' neighborhood was home to scientists and physicians who worked at the NIH, at the institution that is now known as Walter Reed National Military Medical Center, or at many prestigious academic centers in the DC metropolitan area.

When Arnold was 5 years old, in 1960, he and his parents moved into a two-bedroom apartment on the campus of the NIH, where Ruth and Al would remain residents for more than a half-century. A few years later, the family moved into a house, also on the NIH campus.

Arnold grew up with the leafy NIH campus as his backyard, where he and Al would play softball behind what is now the Children's Inn. His peers and his babysitters were the kin of some of the NIH's most well-known researchers in the 1950s and 1960s.

This closeness to science, medicine, and his parents' phenomenal marriage and careers made a deep impression on young Arnold.

"I tried hard to talk him into other [careers], but to no avail," remembers Al. "He was committed to becoming a doctor and a scientist."

Ruth said much the same: "From the time he was [very small], my son had no doubt what he wanted to do."

And Arnold confirms these observations from his parents today, "My parents were incredible role models; they were so happy in everything they did." In addition to the everyday dinnertime science chats, Arnold remembers



fondly living the life that scientists' children get to enjoy: traveling all over, seeing new places, discovering new foods, and, always, meeting lots of new people.

Indeed, Arnold did follow closely in his parents' footsteps, earning his undergraduate and medical degrees from Brown University and then doing a residency in anatomic pathology at the Brigham and Women's Hospital in Boston, a teaching hospital of Harvard Medical School. As Al and Ruth had done many years before, Arnold first accepted a position at the NIH, and then he worked for nine years at the National Institute of Allergy and Infectious Diseases (NIAID) on the molecular biology of human retroviruses. He then pursued an academic career at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. Now 56, Arnold B. Rabson, M.D., runs the Child Health Institute of New Jersey there and continues his research on the role of viruses in cancer and how the immune system affects various childhood diseases.



ARNOLD RABSON AND BARBARA BARNETT

Arnold was born in 1955, the year Al and Ruth arrived at the NIH.

Ruth would, many years later, be awarded an honorary degree from Arnold's alma mater, Brown, as well as from Tulane and several other schools. These included many predominantly minority institutions that had worked to increase diversity in the biomedical workforce, something that would become one of Ruth's career passions.

"Receiving these honorary degrees were among her proudest moments," Arnold said, who attended the Brown and Tulane ceremonies with his wife Barbara Barnett, also a Brooklynite and who had lived half a mile from Ruth's girlhood home. The two were married in 1989, when Ruth made her first trip back to her old neighborhood since her father Julius' death in 1962.

Today, Arnold feels ever grateful to have spent so much time with his parents and to have absorbed some of their "committed joy," as he calls it. Looking back, Arnold said he also felt lucky to be witness to Ruth's astonishing verbal skills.

"She was, and still is to me, the most articulate person I've ever met," he says. "There was a total elegance to her thought process: Every word just seemed to come out right."

Those skills would be tested later as Ruth testified before Congress about the NIH, the value of basic research, and her own steadfast commitment to ideas and individuals she believed needed to be championed.



Ruth's third love—in addition to her family and science—was music. Throughout Ruth's girlhood, music had been paramount, and in fact her parents had pretty much assumed, if not decided, that she would be a professional musician. Her early success with piano fueled those aspirations. She gained her first experiences with music teachers associated with the Lower East Side settlement house community, with which Julius and Elizabeth had been substantially involved.

After young Ruth had outperformed the capacity of the neighborhood piano teacher, her father enrolled her in the Third Street Music School Settlement, the oldest community school of the arts in the United States and a renowned place of musical study.

Julius Kirschstein's own convictions undoubtedly harmonized with Third Street's founder, Emilie Wagner, who saw the power of music to nourish and sharpen the mind as well as to create a common language among the varied immigrant subgroups.

Later, while still just in high school, Ruth taught music theory and composition—hardly “throwaway” classes—and maintained a cadre of private piano students on the side. While these pursuits most certainly provided Ruth with living and spending money, they also shaped her ability to work effectively with a range of people.

Ruth’s school, the High School of Music and Art, was founded in 1936 by the popular New York politician Fiorello H. LaGuardia, who had been elected mayor of New York City in 1933. He had noted that the “most hopeful accomplishment” of his period serving as mayor was the creation of the high school later named for him, the Fiorello H. LaGuardia High School of Music & Art and Performing Arts.

Above all, LaGuardia’s premise was that children of some musical inclination deserved to have their talents developed even if they did not plan to become professional artists.

When Ruth applied, a child didn’t even need to play an instrument to be accepted to the school. Aspiring students took what is commonly referred to as the Seashore Test of Musical Aptitude and then were helped to choose an instrument to study. The test looked for signs of innate musical ability, as Ruth recalled: “Can the child tell which note is higher and by how much? Could the child distinguish between a trumpet and a French horn?”

Pianists like Ruth were assigned an additional instrument so that they could play in school ensembles like the orchestra. For reasons “not apparent to me,” Ruth noted, “they chose the French horn for me.” This member of the brass family is one of the more difficult starter instruments. Someone must have seen promise in Ruth’s musical ability and perseverance. She persisted with the French horn until she started medical school.

The experimental nature of the school was inviting to special musical guests—an exciting environment for Ruth and the other students. Trips included concerts in Carnegie Hall, where the students got to perform with renowned conductors like Leopold Stokowski and Sergei Koussevitsky and guest artists like the legendary violinist Isaac Stern. The experiences during these years imprinted an indelible mark on Ruth. Throughout her life, playing music would give Ruth intense joy.



Science, music, and family—Al Rabson and Ruth Kirschstein truly were “joined at the hip,” as reported by so many people who knew the couple well.

They did everything together and rarely traveled apart: maybe four times total, says Arnold.

While Ruth was devoted to classical music—Beethoven and Mozart in particular—she enjoyed many different composers and genres and played at home on their Steinway upright piano in the evenings until Arnold was about 5 years old. Al dabbled outside the classical realm, listening to jazz, swing, and big band music and playing jazz trumpet himself. Growing up, Arnold tried piano. Attempting that instrument was pretty “traumatic,” he remembers now, but he ultimately pursued jazz saxophone as a hobby later in life—more in line with his father’s musical tastes.

But of his mother he said, “I remember so fondly the expression on her face upon hearing great music. She was transported to another place. It was a very important part of her.”

Part of the family’s travels when Arnold was a boy included several summer trips to Aspen, Colorado, as part of the Given Institute Advances in Molecular Biology Conference series sponsored by the University of Colorado School of Medicine.

In keeping with what was known as the “Aspen idea,” the research conference at the Given Institute created a space for thinkers, leaders, artists, and musicians from all over the world to join each other in a setting to feed the “mind, body, and spirit.” Al and Ruth were familiar with the series from their pathology connections. Donald West King, M.D., then chairman of the department of pathology at Colorado, was the original organizer of the conference. Long days were packed with talks about cutting-edge science, with breaks for hiking in the Rockies, followed by high-caliber classical music at night.

During those Aspen summers, Ruth was enthralled with the confluence of the things she held dear: her science, her music, and her family. She would return from the experience with a renewed sense of commitment: one that would require a lot of courage and a lot of work. She would work hard to implement change where change was needed, and Ruth never forgot her own struggles. Advocating for others was deeply personal for her: why should the road to success be paved twice?

Ruth’s parents had set the stage for her to get a good education and had instilled the value that one needs to work hard at something you love. That said, Ruth recognized fully that not everyone got a fair shake in the work world, and she set about to try to make that situation change.

## Seeds of Social Justice

*“The first thing that caught my eye was the two water fountains with the signs. ... Those two water fountains gave me the shock of my life.” —RUTH L. KIRSCHSTEIN, M.D.*

EVEN AS A CHILD, RUTH LEARNED the significant importance of social reform. Julius and Elizabeth were politically progressive in their thinking: Both had grown up in liberal, free-thinking households. Both had also gotten quite involved in championing human rights, and at the time they found a way to demonstrate their concern by helping new immigrants find their footing in America through their work at settlement houses in New York City.

The settlement house concept had arisen in the late 1800s, a time when European immigrants were pouring into crowded tenements on Manhattan’s Lower East Side. Most of these immigrants had fled their homelands in the Old World, escaping oppression, poverty, and ethnic scorn. Toward the middle of this period, relatively young Eastern European idealists founded the Madison House of the Downtown Ethical Society to confront the social ills that were unduly affecting poor immigrants.

Since poverty’s frequent companion is disease, the need for help was readily apparent to many observers. The overcrowded slums of the Lower East Side served as incubators for the scourges of the day: tuberculosis, pneumonia, typhoid, and diphtheria. In the pre-antibiotic era, disease spread rapidly

and unabated among the Italians, Jews, and Irish who had recently come to America.

According to Ruth, her parents—Julius in particular—had “flirted” with a movement known as Ethical Culture. A mix of ethical, educational, and religious notions framed its thinking and actions: its mantra was “deed, not creed,” emphasizing morality over religious belief. Its principal leader, Felix Adler, promoted the Ethical Culture Society’s basic tenet that helping people who could not help themselves was paramount. Essentially, Adler believed that basic human rights do not have to be earned.

The Ethical Culture movement ultimately became one of the founding member organizations of the International Humanist and Ethical Union. Today, this global umbrella organization addresses humanitarian matters across religions and cultures.

Julius and Elizabeth Kirschstein, and Ruth from early on in her childhood, were supporters of President Franklin Delano Roosevelt and most of his principles. Although he himself had not come from the working or lower classes, President Roosevelt did look out for the interests of the “forgotten man.”

Ruth herself remembered, at age 10 in late October 1936, standing with her parents and hundreds of other Brooklynites as they watched President Roosevelt’s entourage travel down Eastern Parkway as he campaigned for reelection. The next month, President Roosevelt went on to win a second term in office in a landslide victory that took 46 of 48 states.

Young Ruth had listened on the radio to President Roosevelt’s now-legendary series of radio talks, his famous fireside chats, in which the President delivered his ideas directly to the American public. In particular, she remembered vividly President Roosevelt’s memorable “one-third” speech that professed the need to address that third of the nation that was “ill-clothed, ill-housed, and ill-fed.” In his second term, President Roosevelt established the Works Progress Administration and signed into law the Social Security Act to help meet the needs of the working class.



Beyond her childhood experiences, a truly defining moment for Ruth’s views on society and equality occurred in adulthood during her medical school years at Tulane.

Because her 40-year-old cousin had been killed in a plane crash, Ruth’s parents would not let her fly. And so Ruth always traveled from New York to

New Orleans, and back, by train. On her first trip home from medical school in August 1947 she saw something that would affect her outlook on the world as it was and would shape her desire to try to change it.

Her overnight train stopped at the station in Hattiesburg, Mississippi. Ruth raised the window shade as the first morning light crept in.

“The first thing that caught my eye [was] the two water fountains with the signs,” she said. “Those two water fountains gave me the shock of my life.”

That blacks and whites could not drink from the same public water fountain, which was the widespread practice throughout the South, enraged Ruth. She also deplored the segregated trolleys and buses in New Orleans, which were equipped with devices designed to separate passenger seats. Wooden structures fitted with pegs could be inserted into holes that had been drilled into the back of each seat in the vehicle. The intent was for white people to move the divider as needed to assure that “colored” people always sat in the back—or if there were not enough seats, did not sit down at all.

Ruth spent the next four years standing up on all the trolley cars and buses she rode about town. She refused to sit down.

The hospital wards were also segregated into white and black sections, an uncomfortable reality Ruth could do nothing to change. She could, however, be sure she delivered the same care to all her patients.

Facing such bigotry in the South was all the more alarming to Ruth because New York City was far more integrated. One example of combating discrimination in New York came in the late 1930s, when Governor Herbert H. Lehman (D-NY) signed a bill into law that colleges could not require photographs on their applications. The rationale was that the images could not be used to discriminate in the admission of new students.

The need to alter the inequity of a segregated world had become firmly implanted in Ruth during this pivotal period of her life.



Many years later, Ruth had the opportunity to do something about such discrimination, at least within the worlds of science and research.

Since the first days she spent at the NIH, she was a strong advocate for women and for underrepresented minorities. She was the first woman appointed to run an NIH institute, the National Institute of General Medical Sciences, or NIGMS, which supports basic research that contributes to

improving human health. She worked tirelessly to expand the ranks of women and minority individuals in science everywhere.

Ruth did so in spite of—or maybe in response to—the unfairness she experienced. For example, during the late 1960s, while working as a laboratory chief in the Division of Biologics Standards (DBS) at the NIH, Ruth was turned down twice for a promotion to earn a GS-15 salary (about \$20,000 then). Ruth recalled being told that since she and her husband Al made plenty of money, she didn't need the raise. Wondering whether the same persistence would have been required of a man in the same position, Ruth did not give up and got the promotion on her third try.

When Ruth started her job at the DBS in 1957, minority employees were almost nonexistent at the division, which had been set up to monitor the safety of new vaccines that were being developed by pharmaceutical companies. And yet Ruth recognized the contributions of those employees who were minorities, and she took great pains to advance these individuals. For example, Ruth knew very well that a group of highly dedicated animal caretakers and underpaid technicians were vital to the success of the entire DBS operation. These employees earned mostly GS-2-level salaries, which at the time amounted to about \$4,000 per year. All of them were minority individuals, and most were black.

Animal husbandry was an essential task within the DBS; one of the animal husbandry workers, a black man named George Rusten, performed all of the procedures in which virus samples were injected into test animals. This was the only documented method at the time to determine whether certain batches, or “lots,” of particular viruses were safe to use in vaccines for humans. Rusten had started working at the NIH as an animal caretaker in the early 1940s, when Ruth had been a teenager in Brooklyn.

Ruth's view was that all people deserved a chance to succeed. Although many administrators in the 1960s and 70s wouldn't have bothered training their technicians, Ruth spent many hours at this training and then rewarded successes with regular promotions for individuals.

Ruth noted that Rusten had performed his studies with such remarkable precision that she had learned most of what she knew about the results of the studies from him. Through a series of hard-earned promotions from Ruth, he rose to the level of a GS-11 employee and thus was able to secure a very good wage for that time.





ARNOLD FABSON AND BARBARA BARNETT

Ruth earned many honorary degrees for her tireless efforts to increase diversity in science and medicine.

Ruth knew of the overt inequality in the hiring of women scientists from her own experiences and from the experiences of others. Dating back to the 1930s, only a few women had achieved prominence within the NIH research community. Among them was bacteriologist Margaret Pittman, Ph.D., whose commonsense nature and unrelenting toughness—she had been raised hunting animals, including alligators—would inspire Ruth for many years to come.

“[Maggie] was one of the most remarkable women I have ever known,” Ruth said.

Pittman was a quarter century older than Ruth, but her background had striking similarity to Ruth’s childhood in a key way. She had been born in rural Prairie Grove, Arkansas, a Confederate battleground during the Civil War and had served as an unofficial apprentice to her physician father James Pittman, M.D. So, like Ruth, young Margaret had spent a lot of time with a male authority figure who respected her. This experience no doubt inspired Pittman’s own career: Although she started her professional life as a high school teacher, in 1929, she earned a Ph.D. in bacteriology from the University of Chicago. Pittman had already been on staff for some two decades at the NIH when Ruth arrived in the late 1950s, and before that, she had earned an international scientific reputation from her tenure at the Rockefeller Institute in New York, a premier research facility.

In 1952, Pittman was named the first female chief of a NIH laboratory, and in various ways, her career modeled a path for Ruth. Pittman had been involved in the production, testing, and standardization of vaccines to prevent typhoid, cholera, whooping cough, and other diseases. She was instrumental in promoting the idea of a standard potency, or “strength,” test for vaccines, which she believed absolutely had to be assessed through laboratory tests to set official potency limits. Later, Ruth would borrow from this strategy and take the lead in developing a safety test for polio as well as other vaccines.

Some would have called Margaret Pittman Ruth’s mentor, as she encouraged promising women during her career. Ruth was never comfortable with the label “mentor,” however. The word, to her, seemed to imply something much more formal than the act of lending a hand, providing moral support, or paving a way—something Ruth herself continued to do for others throughout her long career.

When asked about her own mentors, Ruth said, “I guess I had lots of people who, in the technical sense, gave me advice, but I never had one

person that I would go to for mentoring, per se. I also was not hesitant to go and ask people for advice, but I would ask Dr. X for advice on Y subject, and Dr. A for advice on B subject. I did not tend to do it with one person for everything.”

Another of Pittman’s protégés was M. Carolyn Hardegree, M.D., a pediatrician who had come to the NIH with her physician husband; he had been part of the doctor draft that attracted many physicians to the NIH to do research. Ruth and Hardegree worked together on various research projects and became very close friends. Later, Hardegree would hold senior positions at the NIH and the Food and Drug Administration (FDA).

In Ruth’s early days at the NIH, there were other women working in various institutes, most of whom were in biochemistry or a related field. One was Maxine F. Singer, Ph.D., a molecular biologist who became known for her contributions to solving the genetic code and, later, her leadership of the Carnegie Institution of Washington. Singer also played a significant role in the ethical and regulatory debates on recombinant DNA techniques in the mid-1970s, and she co-organized the Asilomar Conference on Recombinant DNA. This conference would prove to be a watershed moment for the scientific community in establishing a set of voluntary guidelines for the use of DNA-based technologies to manufacture biologics products.

Ruth would say decades after her early times at the NIH that she had observed a real shift in the representation of women in the scientific workforce, and at the NIH, in part due to these powerful female role models.

But although the relatively few women in leadership positions had helped their colleagues achieve the same levels of accomplishment, women could also discriminate against their peers. And as for men, Ruth said, it was a mixed bag. A good part of that, she reasoned, had to do with the fabric of a man: how he was brought up, his parents and family, and the woman he chose to marry. Ruth constantly gave credit to her supportive husband.

## Chasing Down Disease

*“Well tell him no female pathologist will work for him, and I will go somewhere else!” — RUTH L. KIRSCHSTEIN, M.D.*

AT THE HIGH SCHOOL OF MUSIC AND ART on the Lower East Side of Manhattan Ruth had received daily lessons in harmony, music theory, and instrumental and vocal instruction. But as an eager and involved student, Ruth did a whole lot more: “I took as much science as I could, and also French, German, English, English literature, and history,” she said. Ruth especially enjoyed her “wonderful” teachers who set up hands-on experiments in chemistry and biology class. She had good memories of those high school days, but they had been marred by a tragic event.

As juniors, Ruth and a small group of girls ate lunch together every day in the school cafeteria. One day, one of the regular girls wasn’t there. The group soon found out that this 16-year-old had died of an aggressive bacterial infection.

“The whole school went to her funeral,” Ruth remembered, sadly. “It was a huge blow to all of us.”

Before the widespread use of antibiotics, many children—like this otherwise healthy girl—died from infections that would be easily cured today with a few doses of penicillin or one of a whole range of other routinely used antibiotics.

Most people who had endured the misery of the Great Depression and soon thereafter the Second World War were completely unaware that

the dawn of an amazing era of medicine was on its way. Over the next decades, major advances in public health—vast improvements in sanitation and hygiene, antimicrobial treatments, and preventive vaccines, to name a few—would change the health of America and the world for the better.



Although many ancient cultures—including the Egyptians and Greeks—had employed various concoctions of mold, dirt, and plant mixtures to treat infections, it wasn't until 1928 when the specific idea for penicillin first came about from the near-accidental discovery by Scottish bacteriologist Sir Alexander Fleming, M.D., that a bluish lump of mold growing on a culture plate could kill bacteria. It would take another two decades of research and hard work to turn this discovery into a stable and reproducible form of the antibiotic penicillin. At the turn of the 20th century, German scientist Paul Ehrlich, M.D., who first came up with the idea of screening for synthetic chemicals that could kill bacteria, had already discovered the first antibacterial chemical, but that arsenic-based substance had serious side effects. Because penicillin had few side effects, its discovery and large-scale manufacture became the true breakthrough.

At the time penicillin came into wide use, Ruth was a medical student at Tulane. Not unlike most medical students then and now, Ruth wanted exposure to the “real thing”—patients to heal and illnesses to defeat. Mid-20th century New Orleans was a ready source of patients who suffered from a wide array of diseases. As a port town, it was an international city and home to one of the nation's Marine Hospitals that cared for sick sailors.

During an epidemic of yellow fever, on July 16, 1798, President John Adams had created the Marine Hospital system by signing the first federal public health law, “An act for the relief of sick and disabled seamen,” to help care for disabled sailors in the U.S. Merchant Marine and U.S. Coast Guard. Revenue for the Marine Hospital Fund came from the merchant seamen themselves, and it was deposited into the U.S. Treasury. The seamen paid 20 cents per month (a little under \$5 today), but there was a limit to the amount of time they could spend in the hospital, and some sailors were rejected if they had chronic diseases.

In August 1887, the Laboratory of Hygiene at the Marine Hospital on Staten Island, New York, had been established under bacteriologist Joseph J. Kinyoun, M.D., as the first public health research center. At the turn of the

20th century, the laboratory focused its studies on basic and applied biomedical research. In May 1930, it officially changed its name to the National Institute of Health (NIH), and NIH, the research program, began in 1931. Among the first major discoveries from the NIH was that fluoride could prevent tooth decay.

And so the Marine Hospital had evolved over a century to give rise to the NIH: Today, the NIH (which now uses the plural “Institutes”) is the largest biomedical research institution and the largest public source of funding for medical research in the world.



The 1940s introduction of penicillin, and later, other antibiotics, into medical care was incredibly important: So common were syphilis and gonorrhea among the seamen that Ruth and the other medical students were told to ask patients whether they had “bad blood,” or syphilis, acquired by sailors and soldiers during contact with people infected with sexually transmitted disease. It was at about this time, just after the Second World War, that penicillin had been shown to cure syphilis, and the drug was beginning to be used commonly for this purpose.

In addition to seeing patients at the Marine Hospital in New Orleans, Ruth and the other medical students visited the Carville National Leprosarium, one of two leprosy hospitals in the United States. Originally an abandoned sugar plantation, this facility was taken over in 1921 by the U.S. Public Health Service. Before an effective treatment for the highly contagious and disfiguring disease had been developed, many people came to the leprosaria and never left, put under mandatory quarantine.

By the time Ruth and her fellow Tulane medical students visited the leprosarium and its grounds, the facility was run by the nuns of the Catholic nursing order of the Daughters of Charity, who displayed extraordinary caring for this lonely and neglected population. In an extremely generous act, the leprosarium’s residents offered themselves for research that eventually led to a cure for leprosy: antibiotics. Some of the patients began to benefit from the discoveries.

“Carville has had excellent results with three sulfa drugs: Promin, Diasone and Promizole (streptomycin, now under test, also looks promising). Last year the leprosarium discharged 37 patients, this year it will discharge 40 or more,”

said its medical chief, Dr. Guy H. Faget. “The sulfones have stopped even the most hopeless cases in their tracks.”



In 1954, three years after Ruth graduated from medical school at Tulane, and after her training in Detroit, she talked with the Tulane’s pathology department chair, Charles Dunlap, about continuing her pathology training. This was in part because Al had been offered a Public Health Service pathology residency there. Dunlap agreed, and he made arrangements for Ruth to work with George E. Burch, M.D., a leading cardiologist and chairman of medicine at Tulane. Her payment was courtesy of a fellowship from the then-National Heart Institute (today, the National Heart, Lung, and Blood Institute, or NHLBI).

In addition to doing heart disease-related research with Burch, Ruth refined her clinical skills as an assistant visiting pathologist at Charity Hospital downtown, where she was responsible for performing autopsies and teaching pathology to residents. Her duties at Charity included teaching residents how to do the autopsies themselves. Not unlike Kings County Hospital in Brooklyn, Charity Hospital was a busy public hospital that served a sizable population of destitute and very sick people.

Given her more specialized position as a pathologist, Ruth’s schedule was considerably less hectic, and she had time to pursue research through her NIH-sponsored fellowship. Burch’s research interests, and thus Ruth’s fellowship focus, were in studying heart valves that had been damaged by disease.

In all, Ruth’s collection of duties was a good mix for a budding pathology researcher. In fact, she would confirm this notion more than two decades later: “My experience ... as a recipient in 1954 of a NIH postdoctoral research fellowship at Tulane University Medical School led me to a career in research.”

Among Ruth’s students at Tulane was Herschel Sidransky, M.D., a pathology resident, whom she taught to do autopsies. Sidransky, who had spent time doing research before coming to Tulane to earn his medical degree in 1953, a few years after Ruth, was about Ruth’s age and they got along well. As a research fellow with Burch, Ruth approached autopsies with an especially careful eye, looking for clues that might shed light on the cause of heart disease.

Sidransky's first autopsy case turned out to be rather unusual, and the two of them set about to figure out what had happened to this unfortunate patient. Upon opening up the body, Ruth and Sidransky saw an enormous growth clinging to the lining of the man's heart. They dissected the tissue, took samples, and grew cultures to learn more. What they found was a massive overgrowth of fungus, which Ruth and Sidransky reasoned had come about probably not from a *lack* of antibiotics but from *too many* antibiotics and other medications. An overabundance of such substances likely threw the man's body into a fatal immune imbalance by allowing droves of fungi to thrive and overtake his body, the two reasoned.

It was the first-ever report of this rare type of fungal infection. The discovery also became the basis of Ruth's first scientific publication, "Mycotic endocarditis of the tricuspid valve due to *Aspergillus flavus*," and her official entrance into the world of biomedical research. It was a crucial stepping stone for Sidransky as well. He went on to a successful pathology career that culminated with his being named department chairman at George Washington University in Washington, DC. He and Al and Ruth remained good friends for many years.



Diseases caused by microorganisms touched nearly everyone in the mid-20th century, and Ruth was no exception. She had learned about a microscopic bacterium that killed a teenaged friend virtually overnight, and she had witnessed the effects of microbial over-treatment kill a man. As a girl, Ruth had been frightened by the recurrent epidemics of disease caused by the poliovirus. As a medical student, she saw people suffer in quarantine at the Carville National Leprosarium; they had fallen prey to a microbial menace called mycobacterium leprae. And she had seen the revolving door of tuberculosis infection as an intern at Kings County Hospital—also the handiwork of mycobacteria, a class of bacteria that can be very difficult to treat.

To be sure, tiny microorganisms were a huge challenge, and public health officials did all they could to prevent the spread of infection. For example, all of the students in Ruth's medical school class had been tested for tuberculosis. Everyone who did not have the disease received the Bacillus Calmette-Guérin (BCG) tuberculosis vaccine. First used in humans in 1921, the vaccine offered only hit-or-miss protection, however, ranging from 14 percent to 80 percent



effectiveness in preventing tuberculosis. Yet, the risk of getting tuberculosis was so significant, especially among health care workers, that the imperfect vaccine was frequently used in that setting. Other than in health care settings, it has never been used widely in the United States.

Despite this attempt at protection—and although Ruth had not experienced any symptoms of tuberculosis in medical school, during the year she and Al spent in Ann Arbor/Detroit, or as a pathologist at Tulane—she had contracted silent tuberculosis. She would learn this a few years later when she and Al arrived at the NIH in 1955 to begin their research careers. Shortly after returning from the hospital after giving birth to Arnold, Ruth received a physical exam in preparation for starting her new job at the NIH: a medical screening every new employee took as a matter of course and that included getting a state-of-the-art X-ray. To her surprise, she tested positive for the disease.

“Here [I was], this mother of a baby, which [by then] weighed maybe 6 pounds and who seemed fine,” Ruth remembered.

The X-ray had been taken by the NIH Clinical Center radiology department, which at the time offered the best radiography in the world. Upon reading the film and reexamining Ruth’s scans dating back to Detroit, NIH physicians determined she had actually been infected with tuberculosis for several years. Most likely, overwhelming exposure to the infection during her internship at Kings County Hospital had been the culprit.

Ruth’s infection was what was termed “quiet,” though, as determined by an expert on tuberculosis, who advised Ruth to be sure to have a chest X-ray twice a year. Ruth carefully complied. Sure enough, after a few years the “quiet” tuberculosis roared to life. There was a telltale hole in her lung, shown on the X-ray. Ruth underwent surgery and took medicine for a year to treat it. It never came back, and Arnold never contracted the disease.



Ruth’s clinical pathology residency at the NIH, which began in January 1956, coincided with an impressive time of scientific discovery in which she and her husband could participate. Al had taken and passed the Board examinations in pathology, and as a pathologist at the NCI he performed research along with his other pathology duties. Al and Ruth would sometimes do studies together. They even had a double microscope with two eyepieces for analyzing slide samples at the same time.



NIH HISTORY OFFICE

Ruth loved the challenge and mystery of medical research.

Ruth and her colleagues got the chance to test out a brand-new instrument invented at the NIH, the Coulter counter. The device had been invented by an electronics engineer to count and determine the size of a variety of different types of particles, ranging from floating debris in molten metal, to cells in a drop of blood, to particulates in air. Today, the device is a staple in hospital laboratories, used mainly to accurately and quickly count and distinguish white and red blood cells in a patient's blood sample.

NIH scientists like Ruth were grateful for inventions like the Coulter counter. Before it was available, analyzing a sample of blood for the distribution of cells involved preparing a blood cell stain and manually counting each type of cell under a microscope. The process took about 30 minutes per sample. That was time that could be used in so many other more valuable ways.

In addition to witnessing various technological innovations, Ruth was delighted to be working on the same campus as many of the research greats of the day. The richness of the scientific environment was quite different from

that she had encountered during her Tulane years: The NIH was a world-renowned research laboratory facility and research hospital where everyone was chasing down one disease or another and making history toward improving health through biomedical research.

Ruth saw all sorts of cancers and many rare diseases. After James D. Watson, Ph.D., and Francis H.C. Crick, Ph.D., had published their landmark structure of DNA in 1953, researchers across the NIH were making significant progress in understanding fundamental concepts in biology with this new information.

The NIH was the place where Marshall W. Nirenberg, Ph.D., while working with the National Heart Institute, cracked the genetic code, determining how DNA is interpreted by cells to make proteins. Ruth, Al, and the Nirenbergs lived in the same apartment building on the NIH campus. This was a rare kind of collegiality, living and sharing science at the NIH: a truly electric atmosphere to experience.

Also during the mid-1950s at the NIH, Ruth saw a paradigm shift in the treatment of cancer. Until this time, surgery and radiation had been the mainstays of cancer therapy. Ruth watched, at the NIH Clinical Center, the first injections of the anticancer drug methotrexate into women with choriocarcinoma. The treatment became a cure for this deadly cancer of the placenta. Other NIH scientists were experimenting with innovative combinations of chemotherapy drugs for leukemia and other tumors, showing that the drug mixtures, or “cocktails,” could be far more effective than individual medicines had been alone.

Ruth’s NIH residency year was one of discovery and also a year of preparation for her first “real” job as a pathologist. After she took and passed her Pathology Board exams, she applied for three pathologist positions. One interview, with the U.S. Army at Fort Detrick, Maryland, resulted in a job offer, but it was a 40-mile drive each way, a commute she found less appealing with a child at home.

Ruth also applied for two pathology jobs at the NIH, each earning a GS-13 salary, only to be told, “No female pathologist is going to get a GS-13 for her first job.”

To which Ruth calmly replied, “Well, you tell him no female pathologist will work *for* him, and I will go somewhere else.”

That somewhere else was the NIH’s Division of Biologics Standards (DBS).

The DBS housed one of three NIH pathology “camps” and was established in June 1955 by then-NIH Director William H. Sebrell, Jr., M.D. Ruth served as a “free-floating” pathologist, paid by the DBS but working with all three entities: the others were in the NCI (where her husband Al worked) and in the then-National Institute of Arthritis and Metabolic Diseases (NIAMD).

Among Ruth’s varied duties were autopsies commissioned by the Indian Health Service, whose own hospitals did not have sufficient resources for autopsies. Ruth called it “mail-order” pathology, but she loved it since it kept her routine pathology skills well honed. She enjoyed working on a variety of projects.

While Al was one of Ruth’s scientific collaborators, there were many others. From these early days in her research career, Ruth sought true collaboration—colleagues working with each other, not simply doing jobs for each other. For example, instead of reading a slide at the end of a series of experiments, she promoted working together from the start. “We talked from the beginning and planned the studies accordingly,” she said.

In working with others, Ruth had an uncanny ability to see the positive and to work every situation toward a good outcome. For example, of her former collaborator on virology studies, Lawrence Kilham, M.D., she said, “He was a cantankerous person, but he was wonderful.” Years later, Kilham would go on to a storied career in virology whose impact is still felt today in areas such as gene therapy research.

Investigating a potential link between viruses and cancers was a topic of mutual interest to Ruth, Al, and several of their NIH colleagues. Two women, in particular, Sarah Stewart, M.D., Ph.D., and Bernice E. Eddy, Ph.D., were among the first to observe that tumors could be “spread” between laboratory mice. At the time, despite Ruth’s own fascination with the hypothesis, she did not have a lot of confidence in her peers’ methodology.

“[Sarah and Bernice] were creative and bright,” Ruth noted, but she remained concerned that in their excitement, the women may have moved too quickly. “[To me], it was absolutely crucial to have meticulous data,” Ruth said.

Proving a virus causes a tumor, Ruth would explain to them, requires that the preparation injected into a test animal is 100 percent free of cells, which would indicate an infectious cause independent of the tumor cells’ own ability to multiply out of control.

Eddy and Stewart continued to work on the problem, however, and ultimately they were resoundingly correct. They published the first evidence that a monkey virus, SV-40, caused tumors in animals. Several other researchers made the same discovery independently and also identified traces of SV-40 and other viral contaminants in monkey cells that were used to prepare vaccines for use in people.

As for Ruth, she refused to include her name on that now-classic paper connecting SV-40 with animal tumors. She viewed the imprecise nature of data gathering that yielded questionable evidence as a line not to be crossed. "If it had been an error, my career might have been finished," she said.

Ruth never regretted this absolute reliance on accuracy. Later, working on polio, that attention to detail brought huge success for science and public health in certifying the ultimate safety and worldwide use of the polio vaccine.

## A Crippling Disease

*“They would come around and collect dimes... and then more dimes.”* —RUTH L. KIRSCHSTEIN, M.D.

LOOKING BACK AT HER CHILDHOOD, Ruth recalled lazy summer days sitting on a park bench at the Brooklyn Botanic Garden. There, she could bury herself in books she picked up during her frequent trips to the Brooklyn Public Library. Ruth’s father would tell his daughter to stay on the bench and read to herself.

By committing Ruth to hours and hours of “free” time at the park, Julius Kirschstein was actually doing something else. He was keeping her away from other kids. He and Elizabeth sequestered the young girl during a good part of her childhood, when poliomyelitis, or polio, was a terrifying reality in America—ultimately taking the lives of thousands of people in the United States and paralyzing hundreds of thousands more. Worldwide, millions were affected.

The Kirschsteins were not unique in their caution for their child: Some American towns had even passed city ordinances to bar people from entry, hoping to stall polio’s spread. Most people believed that mingling with other children in public places of recreation, pools in particular, provided access to lethal incubation chambers for the terrible virus. People were scared and rightly so. Although many who contracted the illness developed no symptoms,

or at most only mild, flu-like symptoms, the disease could cause permanent paralysis or disabling deformities.

Most people who were infected with polio didn't know it. They had few to no symptoms, were never diagnosed with polio, and recovered completely. However, they could still infect others unknowingly. About 1 in 10 of those infected, though, had serious symptoms affecting the nervous system: severe headaches, meningitis, and, in the worst cases, paralysis. In these people, their symptoms occurred when the virus snuck its way into the spinal cord and destroyed the long, spindly nerve cells that transmit electrical signals down the legs and arms.

Such spinal polio is the most common form of the disease. It causes complete and permanent paralysis, which occurs very quickly—within days after the virus enters the spinal cord—and sets off an overwhelming immune system overreaction and inflammation. Depending on which region of the cord is affected, any limb or combination of limbs receives no electrical signal to its muscle cells, causing the limbs to go limp and immobile. This could be a leg, an arm, both, or any combination of these extremities.



Although polio had existed, mostly quietly, for thousands of years, it began to become prevalent, even epidemic, in the late 1800s—first in Europe and then in the United States. That these epidemics began paradoxically just as public hygiene was improving reflected the loss of natural immunity that occurs in populations not exposed to viruses early in childhood. The face of polio in the mid-20th century was widespread and diverse, having touched even the future president of the United States, Franklin Delano Roosevelt, causing him to use a wheelchair.

After he became president, Roosevelt continued to work toward a cure for polio by helping to found the National Foundation for Infantile Paralysis. Now known as the March of Dimes, the organization's original purpose was to raise money for polio research and to support the care of those who had the disease. National, nonpartisan, and public, the March of Dimes effort began with an appeal on the radio that everyone in the nation contribute 10 cents to fight polio. The organization soon ramped up its efforts, collecting dimes at various public events: teas, luncheons, and parades. President Roosevelt's efforts in this regard were commemorated by placing his portrait on the dime after his death.

Recently, it has been suggested that President Roosevelt may not have even had polio. Today, there are researchers who believe that he suffered instead from Guillain-Barré syndrome, a disorder affecting the peripheral nervous system and one that also causes paralysis. Regardless, the president's condition did have an important impact on public awareness of polio.

The fear of polio and the messages from President Roosevelt were strong memories for children growing up during these difficult years. In the summers, during the height of the polio epidemic, Ruth remembered, “[The March of Dimes] would come around and collect dimes ... and then more dimes.”



Although public health officials originally believed that polio was transmitted directly through contact with water, such as in pools, that wasn't the whole story.

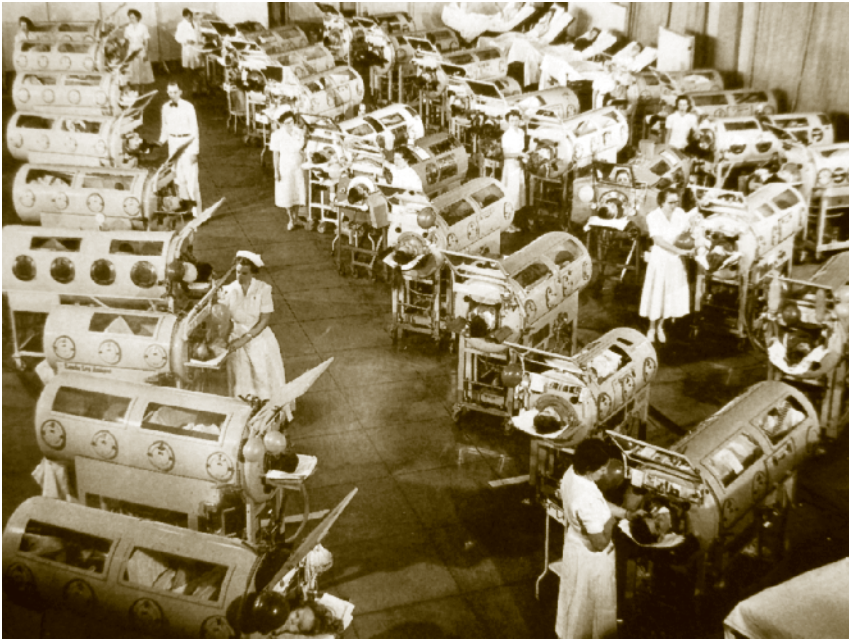
Many microorganisms that make people sick through infection, such as polio, spread mainly through what is called the “fecal-oral” route. In the case of polio, the virus remains infectious in human feces and sewage. A person can become infected by drinking untreated water containing raw sewage from rivers, lakes, or streams. Or, a drink from tap water that had been incompletely purified could infect someone. A child inadvertently gulping contaminated swimming pool water could be exposed as well.

After entering the body, the poliovirus starts its cycle anew, winding its way through the digestive tract and making copies of itself all along the way until it ends up in stool. Children, who are usually not as aware of or as careful about hygiene as are adults, are especially susceptible to these germs and even better at passing them to other kids through hand-to-hand contact.

Polio is especially virulent, meaning that it spreads easily and quickly, and is highly seasonal in those climates that have a genuine summer and fall. The disease's incubation period, the time between first exposure and the appearance of symptoms, is about one to three weeks.

In the first half of the 20th century, people diagnosed with polio had their legs placed in splints and on frames, which kept the body “at rest,” which doctors reasoned would keep muscle pain under control. Pictures of people in these braces are now emblematic of these sad times. Treatments that were built around this kind of logic were primitive and are now known to be incorrect.





This 1953 hospital ward housed dozens of people with polio who required iron lung machines to breathe.

The iron lung was another treatment for polio, and the machine became an iconic image of the disease. Doctors used this device, an artificial breathing machine, to treat people whose polio infection had deadened the function of critical muscles in their lungs. The iron lung was used during an acute polio infection until a person could breathe independently, usually in a few weeks. The iron lung provided temporary and, in some cases, permanent breathing support for a polio sufferer, but it also confined him or her to a life of extreme immobility and discomfort because the electrically powered tube-like structure enveloped the person's chest as she/he lay flat on a table for weeks, months, or even longer. Today, many polio survivors with permanent respiratory paralysis wear a special ventilator jacket that helps them breathe and enables them to move around.

Epidemics of polio were historic in their effects on society and culture. President Roosevelt had founded an organization to combat the disease, others launched efforts to raise money for research, and still others lobbied for improved care—ultimately spawning what is today a very active field of rehabilitation therapy.

Intensive care medicine also got its start in the fight against polio, when special units were created to house iron lungs needed by polio patients who could not breathe on their own. Polio survivors—according to the World Health Organization (WHO), there are now about 10 to 20 million worldwide—also set in motion the disability rights movement through strong advocacy for and by people with disabilities.



Because polio was such an immediate and extreme threat to public health, people were desperate for advances. Scientists got to work trying to get the disease under control.

Ironically, and before vaccines, poor sanitation was actually helpful in stemming infections such as polio. That is because moderately unclean water provided people with a constant low-level exposure to the virus, which created a natural immunity to it. People's immune systems reacted to the foreign virus as an enemy, launching an immune attack that generated antibodies to first recognize, then kill, the virus like the intruder it was.

The vast improvements in public sanitation and hygiene that occurred in the 1800s and early 1900s thus increased the number of adults at risk for polio by reducing childhood exposure and consequent natural immunity to the disease. Furthermore, since the virus was widespread, most people were infected as children, who tended to contract milder forms of the disease. Paralytic polio, by contrast, tended to occur in those who had escaped childhood infection but were subsequently afflicted as adults, although some infants were paralyzed as well.

Ultimately, vaccines would change all of that, but only after scientists first clarified how natural immunity worked. Physician researcher and former medical missionary William M. Hammon, M.D., Dr. PH., then at the University of Pittsburgh, reasoned that antibody-enriched fluid extracted from the blood of polio survivors might be used to treat or prevent infections like polio in other people that were either uninfected or had a mild form of the disease. Hammon's clinical study results were very promising, showing that the immune "power" of antibodies could indeed prevent infection.

And yet, drawing blood from individuals and separating their cells from the fluid in blood called plasma was not a practical approach for a widespread treatment strategy. Thus, in the 1950s researchers began working in earnest on creating a polio vaccine.



To make a vaccine against poliovirus or any microorganism, scientists need a representative part of the organism—enough to make it noticeable and appealing enough to engage the immune system to fight it. They also need to see whether the potential vaccine actually works in people as well as in animals. Although that task may seem simple, it is not. While people and animals share a lot of biology and have the same general structure and body organs, immune systems are hugely variable among species. Dogs, for example, do not suffer the sniffles and head-clogging congestion of the common cold caused by the rhinovirus, a microorganism that prefers human cells and not those of most animals.

Vaccines basically trick the body into thinking it is under attack. They prompt a swift, retaliatory action that includes creating a “memory” of the intruder (impersonated by the vaccine) that permits the immune system to respond rapidly to a future infection.

Vaccines can be constructed in the laboratory from dead or inactivated organisms or from purified products derived from the organisms (proteins or other molecular “pieces” of a virus, bacterium, or parasite). To develop a vaccine, scientists can kill a microorganism in a range of ways: with chemicals, heat, or other methods. Another way to make a vaccine is by attenuating, or dulling the activity of, a microorganism such as a virus. When scientists inactivate a virus in this way it is not actually dead, but it is too weak to cause disease. Importantly, though, an attenuated virus can still be recognized by the immune system, which then produces antibodies that protect the person who receives the vaccine.



Creating the first polio vaccine, an attenuated version, were virologist Hilary Koprowski, M.D., and bacteriologist Herald R. Cox, Sc.D., at the pharmaceutical company Lederle Laboratories in New York in the late 1940s. They made the vaccine from a sample of polio that had been obtained from an infected person and then weakened by several “passages” through the brains of mice, rats, and monkeys. Passaging, in this sense, means infecting an animal or its cells growing in culture, extracting the infectious agent, and then repeating the process many times. Through this passaging, the virus gradually loses its

ability to cause disease. Creating a vaccine from a virus in this way requires finding that “sweet spot” in which the virus can no longer cause disease but can still trick the immune system to trigger the needed response—the production of protective antibodies.

Koprowski first tested his vaccine in 1950 on an 8-year-old New York boy. Seeing no side effects, he tested the vaccine on 19 other children. Later still, a group of 60 children received the vaccine.

Among others working to conquer polio was virologist Jonas E. Salk, M.D., at the University of Pittsburgh School of Medicine, who had obtained a research grant from President Roosevelt’s National Foundation for Infantile Paralysis. The grant was given to study the poliovirus but Salk, trained as a physician, saw the chance to do more than just learn about polio. He wanted to create a vaccine that would control it. His work took seven years, and this second polio vaccine was quite different from the one Koprowski had been testing.

Salk produced his vaccine by infecting cells growing in culture. He then inactivated the virus-infected cells with the chemical formaldehyde. Formaldehyde is commonly used as an industrial-strength disinfectant, and as a preservative in mortuaries and medical laboratories. Salk’s clinical studies showed that three doses, in the form of “shots,” of his inactivated vaccine provided immunity to polio in 99 percent of people tested.

Salk was thrilled with the public health implications of his polio vaccine, as was the American public. Word began to spread quickly about a possible end to one of the scariest disease epidemics America had ever seen. In March 1953, Salk’s enthusiasm, and his desire to offer hope, drove him to appear on CBS radio to report the findings of his successful test on a small group of adults and children. Two days later, those results were published in the *Journal of the American Medical Association*. Amazingly, more Americans were aware of Salk’s vaccine trial than knew the full name of the president, Dwight David Eisenhower, according to a May 1954 Gallup poll.

As a result of a large study of 1.8 million children who received either the vaccine (made commercially by either the Eli Lilly or Parke-Davis pharmaceutical companies), a blank injection, or no injection at all, on April 12, 1955, Salk’s inactivated polio vaccine was declared safe and effective. Later that same day, an advisory committee to the Laboratory of Biologics Control at the NIH, which had the authority to license biologic (nonchemical) products in the United States, gave the vaccine a “green light.” The NIH gave licenses

to five separate companies to produce the Salk vaccine. In addition to Eli Lilly and Parke-Davis, the companies included Wyeth, Pitman-Moore, and Cutter Laboratories. The licensing process took only two and a half hours.

## From Dream to Nightmare



*"Let's see how you do the test."* —RUTH L. KIRSCHSTEIN, M.D.

ON APRIL 26, 1955, JUST TWO WEEKS after public release of the new Salk polio vaccine, things took an abrupt turn for the worse. William G. Workman, M.D., sitting in his Bethesda, Maryland office as director of the NIH Laboratory of Biologics Control, answered one frantic telephone call after another.

The people on the other end of the line signaled the beginning of a health nightmare unfolding in California: Five children there had become paralyzed after receiving doses of the injected Salk polio vaccine. Each child had paralysis in the arm in which she or he had received the shot. Equally worrisome, every affected child had received a vaccine made by the same company, Cutter Laboratories, located in Berkeley, California.

Workman was in charge of the NIH group that had certified the safety of the Salk polio vaccine, and he feared something had gone horribly wrong. Ordered by the federal government, health officials from the Epidemic Intelligence Service of the Communicable Diseases Center swung into action. They quickly determined that two lots—about 120,000 doses—of Cutter-produced polio vaccine were the cause of the problem. These doses had actually contained infectious poliovirus, they learned.

A huge number of children, about 40,000, who had received vaccine from this particular production batch had gotten achy and feverish, had flu-like symptoms, and experienced muscle weakness. About 50 of them became paralyzed, and five died. They all had polio. Even worse, some children and adults who had not even gotten the vaccine came down with the disease, and five of those also died: they had caught the highly infectious disease from contact with children who had already been vaccinated.

Health officials immediately recalled the Cutter-produced polio vaccine batches. However, it was too late for the many thousands of children and adults who had already received a tainted dose. Tragically, most were healthy 7- or 8-year-old schoolchildren.

Two years later, the parents of Anne Gottsdanker, one of the paralyzed children, filed a lawsuit against Cutter Laboratories. Ultimately, Cutter was acquitted of outright negligence, but it was found guilty of “breaching an implied warranty.” As for the other children affected, many never returned to normal health, as the unfortunate effects of the tainted vaccine had left a terrible imprint indeed. In addition to the personal tragedies of affected families and the legal troubles for Cutter Laboratories, the catastrophe had the effect of prompting an uproar within the federal government that had been responsible for assuring the polio vaccine’s safety.

Then-NIH Director William H. Sebrell, Jr., left the government, as did Oveta Culp Hobby, the first secretary—and first female secretary—of what was then the Department of Health, Education, and Welfare (HEW). The Laboratory of Biologics Control that had been headed by Workman was detached from its parent National Microbiological Institute (which later became the National Institute of Allergy and Infectious Diseases, or NIAID) and expanded into a more independent, division-level status within the NIH.



It did not take long for the Epidemic Intelligence Service scientists who had been put on the case that April to determine why vaccinated children were getting sick: cell debris within Cutter’s vaccine preparation had prevented adequate exposure of the poliovirus to virus-killing formaldehyde. In short, not all the virus particles were killed because live polio had been hiding in chemically impenetrable clumps of virus.

Nationally, the production of all polio vaccines came to a screeching halt. DBS scientists jumped into action, trying to figure out how to get rid of the

clumps of virus that were obviously to blame for harboring infectious virus particles in the vaccines produced by Cutter. Part if not all of the problem was due to the fact that Salk's experiments showing that formaldehyde could inactivate poliovirus had been modeled after the use of this chemical to inactivate influenza virus and the making of flu vaccine. However, the flu virus is very different from the poliovirus, and as scientists reconstructed the events later, it became clear how different they were. This difference was a serious problem.

To make his vaccine, Salk had started with a very high titer, or concentration, of poliovirus, adding formaldehyde and letting the mixture sit for a long time. He took samples, measuring virus activity at several time points afterwards, until he could no longer detect live virus.

Those experiments told him that the chemically treated virus became less and less able to infect after three to four days of formaldehyde treatment. Seeing the level dropping precipitously, Salk predicted that the decay in activity would continue until there was none at all and the virus could be declared completely inactivated. Even so, he performed experiments to be sure the virus, although "dead," was still effective in stimulating the production of protective antibodies.

But the virus's ability to infect never went away completely, as Salk had originally predicted it would. It gradually decreased, but it never went all the way to zero, apparently because the formaldehyde had an unintended effect, causing tiny virus particles to clump together. Salk had known of this problem, but he likely did not recognize the significance of the virus clumps.

In time, and in a panic, Salk did see it though, as did the DBS team. They recommended that manufacturers add a second filtration step designed to remove the clumps.

Unfortunately, as became clear when so many vaccinated children got infected with polio, the extra filtration step was not enough.



When the Cutter tragedy occurred, it was clear that the federal oversight process for approving manufacturing standards for vaccines needed an overhaul. The Laboratory of Viral Products within the newly created DBS that had been tasked with cleaning up the Salk vaccine testing process was in charge, but with all the other work that had to be done it needed extra help.

Just before Sebrell left and a new NIH director, James A. Shannon, M.D., Ph.D., came on board in August 1955, Roderick Murray, M.D., was picked



to lead the DBS. Murray agreed to take the post reluctantly: He had been in the Army during World War II and had built a reputable research career studying hepatitis. He was neither well suited to, nor interested in, leading a crisis operation.

Ruth described Murray as an excellent scientist but a reluctant leader.

“[Roderick Murray] really did not want that job,” she said. “He was a very shy, introverted South African and realized, I think, in his own mind, that having that enormous responsibility was not something that he would either enjoy or wish for.”

Yet, as a member of the Commissioned Corps of the Public Health Service, his job situation was inherently subject to a superior’s wishes, and thus he did not really have a choice. Still, Murray put the best people he could find on the job. He recruited Samuel Baron, M.D., one of the leading virologists of the time and a polio expert, to work at the NIH to help sort through the complicated challenge. Baron had trained with renowned University of Michigan virologist Thomas Francis, Jr., M.D.

After Baron arrived at the NIH in 1955, one of his first priorities was to help refine the formaldehyde treatment step in the production of the Salk vaccine to ensure that the poliovirus would be truly inactivated, allowing it to be used safely to prevent disease. Baron and others figured out a way to adjust the manufacturing process and, as a result, the Salk vaccine would become slightly less potent while still appearing to be reasonably effective. Importantly, it was free of virus clumps.

Meanwhile, the NIAMD, which housed one of the three pathology research groups on the NIH campus, also stepped in and agreed to hire a dedicated scientist to work within its Laboratory of Pathology to do the polio safety testing. Already on the NIH payroll working as an up-and-coming pathologist, Ruth appeared to be the ideal scientist for the job, and she joined the DBS in 1957.

She would go on to do important work related to vaccine development. Ruth played a prominent role in firmly leading the effort to ensure the polio vaccine’s safety by creating a lifesaving test.



Before 1955, the nationwide demand for a public health response to the polio crisis—and, thanks to Salk’s enthusiasm, rumors of a promising vaccine in the works—had created intense pressure for the government to act quickly.

According to Ruth and many others who were involved at the time, the response was too rapid, to the extent that formal written regulations for the licensing and manufacture of polio vaccine had not been sufficiently reviewed and finalized.

Finding a vaccine for polio had been especially difficult because it is a disease of humans. Nonhuman primates like monkeys can get it too, but not from every exposure, and it is not contagious between monkeys as it is between people. In “virology-speak,” there are no known animal “reservoirs” of polio, meaning that it requires human-to-human contact to spread.

Humans become exposed to polio “naturally,” either from fecal contamination of ingested water or from putting dirty hands in their mouths. But the most serious effects of so-called neurotropic viruses like polio occur when the virus finds its way, after initial infection, from the intestines to the brain and spinal cord.

Thus, testing the safety of a neurotropic vaccine like the polio vaccine requires experiments that show what happens when such a virus comes into direct contact with nerves. Accordingly, nonhuman primates were used to test the safety of the polio vaccine. The only way to be absolutely sure that such contact occurred was to inject it directly into nerves.

That task would turn out to be difficult and frustrating, and the DBS staff tried all sorts of conditions in order to understand cause and effect. They tried injecting virus into one area of the brain, then another, then into the spinal cord. Injecting virus into muscle caused infection sometimes, but not always, as did dampening the immune system with steroids. The whole process was a tangled mess.

When Ruth arrived in 1957, she approached the situation with a fresh set of eyes. As a pathologist, she was asked to “read,” with a microscope, the polio vaccine laboratory slides—a task she professed “very boring” since there were so very many slides to read.

Curious about how the polio safety test had been performed, she said to Baron, “Let’s see how you do the test.” The two determined rather quickly that the test had not been very precise at all, and so they began to work together to figure out what was going on. Their efforts led them to conclude that the most efficient way to cause infection in animals, and thus to screen for safety, was to inject the Salk polio vaccine into the lower region of a monkey’s spinal cord.



ARNOLD RAISON AND BARBARA BARNETT

Ruth Kirschstein and Samuel Baron led the way to a highly accurate polio safety test.

At the same time that the drama with the Salk vaccine was going on, other researchers were working on their own polio vaccines. Virologist Albert B. Sabin, M.D., working at the Children's Hospital Research Foundation in Cincinnati, Ohio, was one of them. He was convinced that a live vaccine that entered the intestinal tract directly could theoretically provide lifelong immunity and could be given by mouth, not requiring an injection and a medical facility.

Sabin's starting material was the attenuated, live vaccine that had been developed by Hilary Koprowski and Herald Cox. It could be taken orally, and it worked to generate immunity because the virus strain he used could reproduce in the gut (the first destination after swallowing), but it could not grow and copy itself in nerve cells like those in the spinal cord (where infection takes place). It seemed a good alternative to the injected Salk vaccine.

Creating a version of live poliovirus with those special properties took a lot of work. The challenge was in attaining just the right virulence, or strength, to be strong enough to interest the immune system in making antibodies against it but keeping it weak enough so as to not cause polio. Accomplishing that balance required Sabin to subject the virus—which itself was a mix of polio samples from several different healthy children with natural immunity to polio—to 70 sequential passages through various animals and cell cultures.

Sabin then worked diligently to test his virus on 9,000 monkeys, 150 chimpanzees, and finally 133 young adults. Between 1955 and 1960, he embarked on a large-scale, international trial that tested the oral vaccine on at least 100 million people in what was then the USSR, parts of Eastern Europe, Singapore, Mexico, and the Netherlands. The results enabled him to perform a large study of the oral vaccine in the United States in April 1960 on 180,000 Cincinnati schoolchildren. The experiment appeared a huge success, basically wiping out polio in Cincinnati.

But not all was going perfectly well.

Some people questioned why an oral vaccine was needed if an effective, injectable version (Salk's vaccine) was already available. By then, all batches of the Salk vaccine had been thoroughly tested and declared safe. Other concerns, expressed by both scientists and public health officials, centered on the fact that Sabin's attenuated, live virus could not be relied upon to stay stable. They worried that the weakened virus might shuffle its genetic material around enough to change it from a helpful vaccine into a disease-causing

menace. The fears were based on real evidence, including the polio-induced death of the unvaccinated father of a German child who had been given an attenuated vaccine and had apparently spread an “awakened” form of the virus to her dad. Similar cases began to crop up.

In 1958, the NIH created a special committee on live polio vaccines and placed it in charge of testing the virus strains that had been OK’d for use in manufacturing the oral vaccine. Researchers around the world began intense studies of their effectiveness and safety of Sabin’s polio vaccine. Sam Baron and Ruth Kirschstein led the charge.



Having learned that testing, and assuring, the safety of the inactivated Salk vaccine required injecting it into the spinal cords of monkeys, Ruth envisioned that the same might be true for testing the oral Sabin polio vaccine. To her dismay, it wasn’t.

In fact, used against the Sabin oral vaccine, that test produced paralysis in test animals from every single injection of the same doses that had appeared perfectly safe in studies with people. In contrast, no monkeys given the Sabin vaccine by mouth developed polio, and injecting it into muscle was hit-or-miss. Ruth began to wonder whether, in the absence of a reliable safety test for the Sabin vaccine, it could ever be useful at all.

Ruth and other DBS scientists turned their attention to injecting the Sabin poliovirus preparation into the brain, seemingly the last remaining option for safety testing. Injecting anything accurately into the brain is no simple task, however. The only way to hit specific targets is through a technique called stereotactic surgery, in which surgeons use skull markings—lines where bones fuse during development—and make a reproducible pattern to navigate the soft tissue of the brain regions enveloped underneath.

Ruth consulted with specialists in this type of work, and she brought them to the NIH to teach her how to inject virus accurately and consistently into the thalamus, a walnut-sized region of the brain that is most often damaged in people who become paralyzed by the poliovirus. One of the main functions of the thalamus is to act as a relay center from the brain to the body, sending messages that control sensation, spatial sense, and motor activity.

Trial and error led the team to develop a technique using a very fine needle and a special guide bar that very precisely delivered a small amount of virus, with almost no bleeding or any other tissue damage, straight into the

thalamus. The handmade device cost about \$40 to make originally, and \$15 later when the DBS scientists made several at a time. After injection, DBS scientists would carefully track the animals for any signs of disease, and they also took tissue samples and analyzed them under the microscope. Only if everything came up clean was a vaccine sample declared safe.

Ruth and her colleagues validated their results by going backwards to see if the polio safety test could identify known cases of vaccine-induced polio. They learned that the stereotactic injection test was remarkably accurate.

The Sabin vaccine appeared to have the best safety profile and became standard. Ruth taught manufacturers from all over the world how to do the test—just as other NIH researchers like Margaret Pittman, M.D., Carolyn Hardegree, M.D., Paul D. Parkman, M.D., and Harry M. Meyer, Jr., M.D., had done in years past for other vaccines such as those that protected against whooping cough, cholera, measles, or mumps. The NIH provided the special \$15 surgical devices to everyone who came to the agency to learn how to do the polio vaccine safety test—with the stipulation that they had to do the test precisely as they had been taught.

On several occasions, Ruth traveled to Geneva, Switzerland, to participate in WHO-led meetings on polio. According to Ruth, a good dose of diplomacy was needed, since no one wanted to see the United States be inordinately powerful in matters of health and, by uncertain inference, in matters of state. The work was grueling—the WHO would never send meeting materials in advance—and so on arrival in the morning by Geneva time (and the middle of the night, Maryland time), Ruth found a gigantic stack of papers to plow through in preparation for the discussions. Even for a highly dedicated, interested scientist, reading them was a chore that brought on many impromptu naps, Ruth would joke later.

Based on her expertise and involvement, Ruth became the NIH's face of research on the safety of polio vaccines and advised researchers far and wide about their use. For American companies, every single lot of polio vaccine had to be tested for safety using her test before it could be cleared for public use. Even one case of paralysis in several animals tested caused the whole lot to be tossed out.

Ruth had decided that there would never be another Cutter incident with this level of precision testing.



Today, both the Salk and the Sabin vaccines are used to control polio, based on their unique advantages in different settings.

An oral vaccine like the Sabin vaccine was considered the only practical option in the developing world, where access to clean needles, medical facilities, and health personnel is not reliably available. It was, and is, the preferred and cost-efficient tool for mass vaccination campaigns that involve millions of people.

However, there is still an infinitesimal risk—one case of vaccine-associated paralytic polio for every 300,000 to 500,000 doses given—of contracting polio from an oral vaccine, because although it has been weakened, it is still “live” and potentially infectious. Because of the variability in how long it takes vaccinated people to shed the virus in their feces, and the tendency of this vaccine to change its infectious nature along the way, the attenuated polio vaccine can in unusual cases cause polio, particularly in people with a relatively rare condition called B-cell immunodeficiency.

Since 1987, an enhanced version of the Salk vaccine—which is both safe and very protective—is used almost exclusively in the United States and in the developed world, where polio has been eliminated. People who receive three doses (through periodic booster shots) have near-100 percent immunity to polio. Another key advantage to an injectable vaccine is that several vaccines can be combined in a single shot. Currently, for example, the combination vaccine Pediarix, which was approved for use in the United States in 2002, contains five vaccines: inactivated polio, diphtheria, tetanus, whooping cough, and hepatitis B (a pediatric dose).

Sadly, however, eradicating an infectious disease like polio completely is almost impossible. To date, only two such diseases have been effectively erased from the planet: smallpox in the 1970s, and in 2011, rinderpest, a plague that destroys herds of cattle.

Efforts to get rid of polio completely, worldwide, began with Ruth’s efforts to certify the safety of the Sabin polio vaccine in the 1950s and 1960s, but they have accelerated since 1988 due to focused attention from the WHO, UNICEF, and the Rotary Foundation. The number of poliovirus infections worldwide dropped from 350,000 in 1988 to a few hundred cases in 2011.

Today, several regions of the world have been certified polio free, including the Americas in 1994; however, a small number of cases stubbornly persist in certain corners of the globe, including Nigeria, India, Pakistan, and Afghanistan.

## A Leader Is Born

*“Albert Sabin did not believe us, Herald Cox did not believe us, and Hilary Koprowski did not believe us.”*

— RUTH L. KIRSCHSTEIN, M.D.

RUTH, ALTHOUGH SHE WAS ONLY 5 feet, 2 inches tall, had no trouble standing up to big figures in science, and during the time she was developing the polio safety test she consulted regularly with the researchers making the vaccines. Yet, the researchers didn't always want to listen to government-issued advice.

“Albert Sabin did not believe us, Herald Cox did not believe us, and Hilary Koprowski did not believe us,” Ruth said, referring to those researchers' refusal to admit that their own versions of the polio safety test were not stringent enough.

But the firmest proof came from the field: Ruth's test successfully corroborated cases of polio in children in South America where the Cox vaccine was being used in clinical trials. Collectively, all of the evidence that the DBS had gathered in testing the polio vaccines had led the NIH to recommend Sabin's vaccine for both national and worldwide use.

Likely as a result of her outstanding work in the midst of a national crisis, Ruth was named Chief of the DBS Laboratory of Pathology in 1965, eight years after joining the Division. Her high-energy, no-nonsense approach to solving problems had everything to do with her success. Lewellys F. Barker,



M.D., M.P.H., who was a medical officer in the DBS Laboratory of Virology and Rickettsiology and Ruth's colleague, summed it up this way:

"She had the moxie, she was enthusiastic, and she was anything but casual. Ruth was intense, and she jumped right in and dealt with the polio vaccine and any problem very scientifically."



According to Barker, criticisms did not dissuade Ruth easily. In fact, he added, "She found disagreement healthy."

Beginning in the late 1950s, however, there was plenty of disagreement on another topic. In this case the controversy concerned the emergence of mounting evidence that viral contaminants in human vaccines could cause cancer.

The problem stemmed from the way vaccines were manufactured in large quantities. After selecting the original, "seed" virus sample, pharmaceutical companies that made vaccines grew large batches using cell culture. Here, cells infected with the vaccine virus are grown under controlled conditions in the laboratory. Scientists had determined that the best cells to use for mass-producing the polio vaccine were monkey kidney cells.

Jonas Salk's inactivated polio vaccine had been one of the first biological products to be made in bulk using this method. In fact, three scientists (John F. Enders, Ph.D., Thomas H. Weller, M.D., and Frederick C. Robbins, M.D.) had won the 1954 Nobel Prize in Physiology or Medicine for figuring out how to propagate poliovirus in monkey kidney cell cultures. These scientists had been supported by the NIAID and the NIGMS.

The problem, however, was that monkeys are simians and harbor viruses unique to their species that remain in the cultured cells throughout the several rounds of growth called "passages" that are required to generate sufficient amounts of virus vaccine. One of these simian viruses, in particular, SV-40—the 40th simian virus found in monkey kidney cells—was a potential cause for alarm.

The DBS's Bernice Eddy had published a report showing that SV-40 caused tumors in animals; this was the same paper on which Ruth had refused to be listed as a coauthor.

And yet more data trickled in showing the same results, including a report in 1962 from Maurice R. Hilleman, Ph.D., a leading vaccinologist at Merck, the pharmaceutical company that had discovered independently that SV-40

was present in the Salk polio vaccine that had been mass-produced commercially and given to humans. Ruth and Al had also been studying the problem, publishing accounts in 1962 (and also in 1965) of SV-40 infection causing tumors in hamsters.

The question was, did the presence of the SV-40 virus cause problems for humans? Was there a need for recall of the currently used vaccines, or were some other regulatory actions needed to ensure safety in these products?

The companies were ready, the government was convinced, the public was eager, and there was little patience for any delay. Like everyone, Ruth felt the pressure of being ready to release and distribute a safe and effective oral polio vaccine, but the DBS team had identified previously approved lots of Sabin oral polio vaccine that contained SV-40.

So, they had to go back and fix the problem: “We had meeting after meeting after meeting of how were we going to do something about this,” Ruth remembered.

After months, the job got done, and before 1962 was over the Sabin vaccine was declared completely SV-40 free and safe for widespread use.

As for the contaminated Salk vaccine that had already been administered, nothing could be done. Millions of people received the potentially contaminated batches of vaccine, but there is no way to know whether they were exposed to the virus and, if so, whether it was in a quantity or by a route that caused later infection.

SV-40 is still hypothesized to be a culprit in human cancer, but to this day the certainty of that connection remains unclear. Most of the available data refutes such a link.



Retrospective studies look backwards in time, as did the several studies that investigated the possible SV-40 cancer connection. Prospective studies, by contrast, track research participants over time, looking ahead.

In 1967 the NIH hosted a conference to look at prospective approaches to studying cell cultures for the production of virus vaccines. They were seeking ways to assess progress and figure out how to go about future studies to assure vaccine safety. In light of the ambiguity surrounding viral contaminants in vaccines, and as a result of this conference, the DBS was charged with issuing contracts to develop cell lines (cells grown in laboratory culture) that could

be studied extensively over time. If determined to be safe, the cell lines could then be used for vaccine production.

A top priority were nonhuman primate “diploid” cells—monkey cells that contain two sets of chromosomes just like those in humans. The prevailing view at the time was that human cell lines might harbor some unknown risk, such as a disease-causing virus, and that monkey cells were preferable. In addition to making those cell lines available to researchers, the DBS set up prospective studies, as defined by the federal regulations mandating them to do so:

The field studies shall be so conducted that at least 5,000 of the susceptible individuals must reside when inoculated in areas where health related statistics are regularly compiled in accordance with procedures such as those used by the National Center for Health Statistics. Data in such form as will identify each inoculated person shall be furnished to the Director, Division of Biologics Standards.

Creating cell lines was not one of Ruth’s areas of expertise. In addition, she had many responsibilities at the DBS, including the SV-40 work and the ongoing studies with polio and other vaccines such as the one for rubella. And yet she recognized the seriousness of protecting the public’s health, and creating nonhuman primate cell lines seemed the way to go about assuring vaccine safety. And so she found help from one of her newest hires, John Petricciani, M.D. A pediatrician who had just completed his internship and who had arrived in 1968 at the NIH via the Public Health Service, Petricciani was neither a virologist nor a cell culture expert. Ruth, however, reasoned that his personality and skills qualified him for the cell culture project.

Petricciani quickly became committed to the task, motivated by Ruth’s apt leadership. “That support in my early, formative years as a scientist was so important,” he said, adding that the early experiences were truly instrumental to his career. Petricciani never returned to pediatrics, but he went on to serve as director of the FDA Office of Biologics and later at the WHO and the U.S. Department of Health and Human Services (HHS).

Of Ruth’s managerial style, Petricciani noted that she was incredibly nurturing. She recognized talent, but like a good parent she let her charges shine on their own and learn how to fix their own problems. He described Ruth’s evenhanded management of all people within her organization, ranging from administrative help to animal caretakers to technicians to top scientists:

“She treated all of us with the same level of respect and truly cared for us as people,” he said with fondness.



One of Ruth’s many protégés, Yvonne T. Maddox, Ph.D., whom Ruth hired many years later in 1985 and who subsequently became a close friend of Ruth’s, agrees that people always came first with Ruth.

“Ruth was my mentor, my rabbi—everyone needs one—a mother figure, and one of, if not, my closest friends,” Maddox said. She recalled that when Ruth first hired her—as a program administrator at the NIGMS, where Ruth would become the first woman director—she had specific things in mind for Maddox, based on her unique skills and talent.

“When I came in for my interview,” Maddox explained, “I was required to give a seminar, which I did. I understand from all of the attendees who I later spoke with, that Ruth thought it was a wonderful seminar. [Apparently] one of the attendees said, ‘She is so good, let’s have her fill the vacancy for the scientific review administrator for the minority program.’ [But] Ruth remarked, ‘No, [we] are going to put her in the position we are recruiting for and that is the program director of the new trauma and burn injury grants portfolio. She is a physiologist and we are going to take advantage of that expertise.’”

“She saw me as more than a minority who could fill a position that was slated to administer a set-aside program,” recalls Maddox, who is African American. “That was good of her and quite typical.”

Later on the same day of the interview, Maddox, who now serves as deputy director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), says she learned her first important lesson about both Ruth’s priorities and her personality.

“We were walking down the hallway from my seminar/lecture,” Maddox remembers, “and quite frankly, I was feeling pretty good about my performance. Ruth happened to comment on my purse. She said it was lovely.”

Maddox explained that she had carried that particular purse that particular day for another reason, to show off. She continued, “This was my way of telling Ruth that my husband was director of security for HHS and had accompanied Secretary Margaret Heckler on a trip to Italy, where she assisted him in selecting the purse, was the regional inspector general for HHS, and had been a former Secret Service agent at the White House. ... To my chagrin, I soon found out—and in no uncertain terms—[that I would not] get any brownie

points for my name-dropping. But Ruth did want to know more about my husband and quickly forgave me for my naïveté.”



Francis V. Chisari, M.D., was another of Ruth’s protégés at the DBS. He served in the Public Health Service but did not arrive until 1970 during the Vietnam War. Chisari had trained in internal medicine. He was interested in infectious diseases, but he was mostly interested in being a local doctor.

“I was planning on a career modeled after Marcus Welby, M.D.,” referring to the title character of the popular 1970s television medical drama portraying a California family practitioner.

But that was not to be: On the day he arrived at the DBS, where he had been assigned, Chisari sat across from Ruth at her desk. They talked for about an hour about what kind of research he would be doing. The main thing, she told him, was to look after the cholera vaccine work that was ongoing in the DBS.

“Oh, and by the way,” she added, “there are two other things I want you to do,” Chisari recalls. “First, I want you to take over the polio vaccine regulatory functions.” Then, he remembers, she pointed to a huge pile of trays behind her desk. “See that stack of slides?” he remembers her asking him. “I’m a little behind in my collaboration with Lew Barker. We’re working on identifying a virus in blood that causes hepatitis.

“Lew [Barker] is after me to get on this,” Chisari recalls her continuing, “So, can you move these to your office and look at one tray [about 25 slides] every night until we get through them?”

As was Petricciani before him, Chisari was drawn immediately to Ruth’s energy and enthusiasm for science. He agreed to everything. As part of a group of about 20 people under Ruth, he quickly got to work as part of the team that took very seriously its job of protecting public health.

“[Ruth] had a mountain of other things to do, and I had nothing to do,” Chisari said. “For some reason, Ruth decided to give that impossible job to me. I had no idea what to do. I was just a medic, but she seemed to have such confidence in me, so I did it.”

As a side project to her other required duties, Ruth had been working with her colleague Barker on the hepatitis research collaboration. They were part of a team that had injected various types of monkeys with serum that had been taken from the blood of people who had hepatitis (at the time, the subtypes

A, B, C, etc. were unknown). Hepatitis is an infection that eventually destroys the liver and can lead to death. After injecting the monkeys with the virus, the scientists then looked to see whether the livers of the animals had become damaged. If the livers were damaged, the scientists made microscope slides of the monkey liver cells.

Ruth's part in the research was to analyze those slides in the hope of tracking backward to see which animals had become infected with the patient serum. The whole idea was to create an animal model of hepatitis, which did not exist at the time but which was an essential first step to developing and testing the safety of a hepatitis vaccine. This was a huge challenge, with no obvious chance of success at the outset.

About six months passed as Chisari chipped away slowly at analyzing the slides. One day, he saw something: one slide sample showed angry-looking liver cells from an injected monkey that looked just like the liver cells from people who had confirmed hepatitis. The sample traced back to one chimpanzee. Other researchers had shown that chimpanzees could get hepatitis, and so Chisari's finding looked very promising.

The next morning, Chisari hurried in to work, planted himself in Ruth's office, and told her what he had seen. "She got really excited at the results," Chisari remembered, and the two of them went to see Barker immediately.



Chisari took on the next steps with zeal, asking for help from Ruth when needed and receiving her special blend of management, encouragement, and advice. There was a lot of work to do to confirm the initial microscope slide finding. First, the original (and additional) samples of serum from people with hepatitis had to be tested in more chimpanzees to be sure the results could be repeated.

But the hard part was going beyond what appeared on the slide to something that could be measured accurately and repeatedly. Today, this is easily done with antibodies that have been prepared using cell culture methods and can be applied to slides. The antibodies attach to viral proteins, and powerful imaging equipment can detect those molecular interactions.

But in the early 1970s there were no laboratory antibodies available to attach to the hepatitis virus and no methods to detect an antibody-bound virus complex. Chisari pored over the research literature and found a paper written by immunologist Thomas S. Edgington, M.D., in San Diego who had

developed a technique that used natural antibodies from people who had recovered from “type B” viral hepatitis to detect signs of hepatitis in tissue samples. Chisari teamed up with Edgington, and the two ultimately succeeded in developing a test to measure hepatitis B on laboratory slides. It would turn out to be a turning point in his career.

Chisari’s work, with Barker’s and Ruth’s capable support and leadership throughout, led to the first animal model of hepatitis B. Other researchers at the NIH, universities, and at Merck (the pharmaceutical company) went on to develop a protective vaccine against the disease. That vaccine is now administered to people all over the world. In the United States, it is one of a standard set of vaccines given to infants within the first year of life.

As for Chisari, Marcus Welby didn’t stand a chance. He has been working on viral hepatitis ever since and credits the roots of his career successes to the work he began with his former mentor’s support and under her watchful eye.

“Ruth turned me into a virologist for good,” he said.



The DBS (the former Laboratory of Biologics Control) acted as a regulatory body, which made it quite different from the rest of the NIH, which was dedicated solely to research. This arrangement had been put in place by the 1902 Public Biologics Control Act, authorized four years before the 1906 Food and Drug Act. Thus, the first act gave the NIH control over biologics. The main reason for a separate level of scientific scrutiny for biologics is that the manufacture and quality control of these products, made from such living organisms as microorganisms or human cells, is often idiosyncratic, variable, and finicky—rather unlike the assembly line-style production of chemical drugs.

Today, regulatory authority for biologics falls solely within the purview of the FDA. This change occurred on July 1, 1972, when the DBS was moved—with considerable controversy and worry—out of the NIH and into the FDA. Many, including Ruth, had considered the balance of research and regulation in the DBS a healthy one and one that led to new research products that could be refined and tested using the most up-to-date research and techniques.

Moreover, the dual role of the DBS in the NIH made it an extremely exciting place to work. Some of the nation’s leading virologists, including George A. Hottle, M.D., Ralph D. Lillie, M.D., and many other well-regarded

scientists, created a strong cadre of researchers. These scientists realized that, unlike chemically produced molecules, biological products based upon living organisms were extremely complex in structure and function. Overseeing the licensing of vaccines needed to be grounded in good science, and there was, for the most part, a comfortable balance between researchers, regulators, and manufacturers.

The companies making vaccines depended on DBS scientists who could “walk the walk and talk the talk,” explained Barker, adding that Ruth was up to the challenge. “Ruth was really tough—she was anything but a wallflower.”



She may have been up to the challenge, and able and willing to talk the talk, but that didn’t mean it was always easy or pleasant.

In addition to managing problems caused by menacing microorganisms, Ruth had to contend with some strong personalities. One of those was Joseph E. Smadel, M.D., deputy director for science under NIH Director James Shannon.

Smadel was a well-known virologist and, in 1962, the first Albert Lasker Award winner in the area of clinical medical research to be brought to the NIH from Walter Reed Army Medical Center. He specialized in rickettsial diseases, so named for microorganisms often carried by ticks, fleas, and lice. He earned the Lasker Award for finding a cure for typhus.

Despite Ruth’s respect for Smadel’s scientific accolades, she found him rather hard to work with. “He was the brashest, rudest, most profane, difficult person I think most of us had ever met,” Ruth recalled.

He was also a close ally of the NIH director. Smadel had a lot of power at the DBS, according to Ruth. Smadel also had a lot of contacts and connections with the Armed Forces Epidemiological Board, where vaccines were of a significant interest and priority.

According to Ruth, and perhaps as a legacy effect from the earlier Cutter incident with contaminated polio vaccines, another reason for putting Smadel in this position was that director Shannon had remained worried about the DBS. Shannon wanted Smadel to keep an eye on it for him. He did this, letting Roderick Murray stay in charge but making it clear that little got done without first checking with Smadel, Ruth recalled.





In time, Smadel's presence at the DBS would exert a longer-lasting effect that was not entirely his own doing. Smadel had brought with him the person who would play a pivotal role in the division's ultimate demise at the NIH; that man was J. Anthony "Tony" Morris, Ph.D. He was concerned about the potential conflicts of interest posed by the DBS as a single organization regulating the products it was also involved in researching and developing.

"Tony Morris was difficult, and he got it into his head that Biologics was not serving its regulatory function very well. He would constantly make innuendoes to the effect that we had missed something, that there were tumor viruses in products, and he was doing little studies and so forth," remembered Ruth.

Mainly, though, Morris had personal grievances with the DBS leadership and had set the wheels in motion to try to dismantle its authority. Morris worked together with consumer lawyer James S. Turner—at this time, in the late 1960s, the consumer movement was gaining momentum—and the two began to make serious allegations about the ability of the DBS to play its dual role in research and regulation. Turner had been the one who attacked the FDA on behalf of Ralph Nader's Center for the Study of Responsive Law.



The NIH's DBS welcomed internationally known researchers such as Albert Sabin (11th from left) to polio meetings held on the campus.

On October 15, 1971, the DBS stepped into an awkward political spotlight when Senator Abraham Ribicoff (D-CT) announced that he had received notification about serious problems at the division.

Senator Ribicoff went on to detail a lengthy list of charges outlining events that had transpired since the DBS had been established in 1955. According to an article by Nicholas Wade (today, a noted *New York Times* science writer, then, a reporter for the journal *Science*), Senator Ribicoff's informants were none other than Tony Morris and James Turner. Morris had clashed with his supervisors on several occasions in his role as the DBS influenza control officer. He had contended that his concerns about the strength and effectiveness of the flu vaccine had been dismissed (and that he believed he had lost his related responsibilities as a result).

The whole encounter prompted senior NIH leadership to investigate the matter. A new NIH director, Robert Q. Marston, M.D., had recently come on board, bringing with him a new deputy director for science, Robert W. Berliner, M.D., whose job was to keep an eye on the quality of all of the agency's science, both on its campus and in the research that the NIH supported at academic and other research institutions across the country and in the world. He was troubled by the possibility that regulatory controversies and political interference could sully the excellent reputation of the NIH.



Moving the DBS out of the NIH would protect the agency, Marston reasoned, and in 1972, the old DBS became the new FDA Bureau of Biologics, which is now the Center for Biologics Evaluation and Research.

Ruth and many others, whose research was based on the very balance that defined the division within the NIH, were deeply concerned about the change, believing that the quality of regulation would suffer in the absence of ongoing scientific research to bolster these important scientific efforts. She could not convince the NIH and HHS leadership, however.

By now, Roderick Murray, whose health was in decline, had begun to rely more and more heavily on Ruth not only to take care of administrative duties but also to play a lead role in decision making for many products under scrutiny by the division. Murray retired in 1973.

Charles C. Edwards, M.D., commissioner of the FDA at that time, considered who he thought would be the best person to lead the new Bureau

of Biologics. Edwards interviewed Ruth, and he interviewed Harry Meyer, a protégé of Smadel's, who was also an Army officer at Walter Reed.

Edwards chose Meyer, telling Ruth that she would be Meyer's deputy because her background was broad enough that there might be other things for her to help Edwards with at the FDA. Ruth noted that she respected Meyer.

True to his word, about four months later, Edwards asked Ruth to be deputy associate commissioner for science for the FDA. In that position, Ruth would work for the associate commissioner, chemist Lloyd B. Tepper, M.D., described by Ruth as a "wonderful man who was a good scientist but was biding his time at the FDA waiting for an appropriate industrial job."

As Edwards had planned, he had put Ruth's good leadership skills, political tact, and problem-solving skills to good use. While Tepper traveled frequently, Ruth was working hard in her leadership position in the Office of the Associate Commissioner. She immersed herself in the position, even taking the FDA's course on food and drug law at night. She told Al that if she were 10 years younger, she might even have gone to law school.

Ruth learned about problems with foods, problems with pesticides, and problems with drugs. She also learned about bureaucracy and how not to become ensnared in it. She learned how to run meetings in a way she had never known before. It was a rewarding time and a time for learning crucial skills that would serve Ruth very well later in her career.

But she discovered after about a year and a half that she really missed the NIH. Ruth began looking around, and when an advertisement for a director of the NIGMS came along, she was intrigued.

She visited John F. Sherman, Ph.D., deputy director under then-NIH Director Robert S. Stone, M.D. She said, "John, I miss NIH. I would like to come back. Are there any positions open?"

He said, "No, Ruth, I don't think so," to which she replied, "You have an advertisement for the directorship of the National Institute of General Medical Sciences." Sherman then said, "Oh, I hadn't thought of you for that," Ruth recalled.

Very matter-of-factly, she looked at him and said, "Well, think about it. Here's my CV."

## No One Ever Died of General Medical Sciences

*“Whether conservative Republicans or liberal Democrats – they were convinced by Ruth that the best way to serve the needs of everyone was to resist the temptation to [appropriate] funds according to the disease of the month.”*

— CONGRESSMAN DAVID R. OBEY (D-WI)

SOON AFTER RUTH HAD GIVEN NIH Deputy Director John Sherman her curriculum vitae outlining her credentials, she was called in for an important interview.

Ruth knew she needed to study the NIGMS carefully and be fully prepared. Her friend Leo von Euler, M.D., whom she had known for many years, was currently serving as acting director of the institute. The previous director, DeWitt “Hans” Stetten, Jr., M.D., Ph.D., had been recruited to take another NIH post, to work with the NIH director as a scientific advisor. Ruth asked von Euler if he could point her to information that fully described the NIGMS and its accomplishments. He sent her to Building 31 (now the Claude Pepper Building, named in 1988 for Congressman Claude Denson Pepper (D-FL)) on the NIH campus and the place where many institute directors and a good number of their staff members had offices.

The next afternoon, Ruth drove down Rockville Pike, a roadway connecting the towns of Rockville, Bethesda, and other Washington, DC suburbs and a main route between the FDA and the NIH. She arrived in the afternoon,

around four o'clock, and was surprised to see that the NIGMS offices were all empty, prompting the thought, "Gee, these people go home early," and making her wonder what she might be getting into. She poked around a bit, found what she needed, and went home to read more.

The next week, sitting in an FDA meeting held at the NIH, Ruth noticed that NIH Director Stone's secretary was motioning to her. Stone wanted her to come see him. At a break, she got up and met him in his office two floors below in the same building.

"I would like you to take the job," Stone told Ruth. She said yes, and in September 1974 became the first woman director of an NIH institute.



Ruth was adding to a long history at the NIGMS, including differing styles of leadership. Ruth's predecessor at NIGMS, Stetten, had worked in and out of government. He had left his position as scientific director of the National Institute of Arthritis and Metabolic Diseases in 1962 to pursue his personal dream of starting a medical school at Rutgers University in New Jersey. That had not worked out in the way he expected, however. In 1970, he had been recruited to come back to the NIH, this time to lead the NIGMS. At the time, the NIGMS was the major source of research support to such medical school departments as biochemistry, physiology, anatomy, and pharmacology, with which Stetten was very familiar. It was a great fit for him.

The NIGMS was unlike any of the other NIH institutes in one major way: It did not have an intramural program supporting research scientists working on the Bethesda campus. This difference is still true today with the exception that the NIGMS does support a small intramural training program for pharmacologists. For that reason, the NIGMS budget, then and now, goes almost entirely to research grants for scientists working at universities throughout the country. NIGMS is also known for its support of a number of separate research training programs for graduate students and postdoctoral fellows.

Before Stetten's tenure, the director of the NIGMS was Frederick L. Stone, Ph.D. Most of Stone's scientific emphases had been on applied, not basic, research, and he had established specific programs in clinically related areas such as anesthesiology, trauma and burn research, and bioengineering. When Stetten arrived at the NIGMS in 1970, Congress had begun to pay more attention to this institute that was not identified with any disease or body part. Some members of Congress would say, "no one ever died of general medical

sciences,” which he and others felt belied the importance of basic science in establishing key knowledge applicable to advancing human health.

Joshua Lederberg, Ph.D., one of the nation’s leading scientists and a pioneer in the science of genetics, delivered testimony before the appropriations committees of the House and Senate on Capitol Hill in which he argued effectively for support that would blend basic and clinical studies in genetics through a series of centers at medical schools. Stetten could not have been more pleased that Congress had agreed to appropriate funds to set up such programs across the country. He broadened the utility of the investment by establishing (through a government contract) a working collection of human cell lines that each contained a genetic mutation, enabling researchers to more easily study inherited diseases in the laboratory. The NIGMS still actively supports this resource, the Coriell Institute for Medical Research in Camden, New Jersey, and it has led to important advances in the diagnosis, treatment, and prevention of a number of inherited conditions.

Stetten’s decision to support basic research through the genetics program, and a similarly fashioned program to probe cell biology, had been a different tack from Frederick Stone’s, but a direction Ruth was keen to continue.

A few years later, in the mid-1970s, the investment in basic genetics research would begin to blossom into a full-scale revolution: one that Ruth would help support in dramatic ways—and one that would help launch today’s multibillion-dollar biotechnology industry.



It wasn’t until after Ruth was on the job as director of the NIGMS that she finally solved the Building 31 missing-persons mystery.

Because the institute did not have an intramural research program on the NIH’s campus and did not require specialized laboratory space, most of the staff of the NIGMS worked off campus in a rental property a few miles away at the Westwood Building in Bethesda. It was not particularly pleasant or glamorous, and it was quite isolated from the rest of the NIH’s scientists and staff.

Because all NIH institute directors had an office on the campus, Stetten worked in Building 31, he was the only person from NIGMS who was on campus, and he kept a stash of informational materials there. Having this office became a necessity for Stetten, whose health was in decline. He had long battled with vision problems and, at this point in his career, could

hardly see at all. Having a “home base” where he could interact regularly with other scientists and managers and could physically find his way around was important.

And so Ruth realized the reason why no one was at work at 4 o’clock in the afternoon. It was not because the staff were lazy people; it was because they were at work somewhere else—just not on the NIH campus. They were in the middle of Bethesda.

Ruth saw Stetten as a man with “enormous vision” and a propensity to be a big-picture thinker. Losing his eyesight “broke his heart,” Ruth remembered of Stetten, but it did not keep him from thinking, talking, and strategizing about science with “whoever would listen,” she added.

Because of Stetten’s poor eyesight and physical distance from the NIGMS staff—and by then, a substantial leaning toward studying the philosophy, not pursuing the management, of science—he had left most of the running of the organization to a few proficient deputies. Among them was then-NIGMS Executive Officer Gordon Klovdahl, “whose greatest joy in life,” Stetten said, “was to receive a difficult assignment from me or from others of the scientific staff and to find some way—perhaps, occasionally, an unorthodox way—of accomplishing the desired purpose.”

Stetten also relied heavily on his scientific staff: Leo von Euler, Vincent Price, M.D., and Charles A. “Charlie” Miller, Ph.D., who became invaluable to Ruth as well. Upon her arrival, Ruth found this NIGMS scientific triumvirate to be extremely capable, talented, and dedicated.

In particular, Ruth trusted von Euler to help her with a range of duties and challenges. The son and grandson of Nobel laureates, he had science in his blood, she remembered. He also had an incredibly calm demeanor well suited to problem solving, and like her he had trained as a pathologist. Moreover, as a member of the Public Health Service Commissioned Corps, von Euler had a skill set that was inherently flexible. Ruth could apply his skills and savvy in various ways.

Ruth worked very hard to hire the best people to work at the NIGMS, realizing that the strength of an organization hinges on its staff. On occasion, though, there were problems, issues that were thorny or staff in whom Ruth did not have complete confidence. In those kinds of situations, she would ask von Euler to solve a variety of problems on an as-needed basis.

“Each time this happened, [Leo] would come home and tell me he had a new hat,” his wife Mary von Euler, J.D., recalled, referring to his many assignments.

NATIONAL INSTITUTES OF HEALTH

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# **Dr. R. Kirschstein Returning to NIH As GMS Director**



THE NIH RECORD

In September 1974, Ruth became the first woman to direct an NIH institute.



Within two months of her arrival at the NIGMS, Ruth had hired, in her words, nine “terrific young scientists” to fill nine staff vacancies. The whole tenor of the institute began to change. She was adamant about finding quality people and would not bring anyone on board without interviewing him or her personally. She felt that setting a high bar wasn’t foolproof but still the best approach to establishing a climate of excellence.

“Yes, you make mistakes, but you make fewer that way,” she said to describe her approach. Her staff quickly came to agree.

The first person Ruth hired at the NIGMS was W. Sue Shafer, Ph.D., who began work as a program director in the institute’s cellular and molecular basis of disease program. Shafer would quickly rise up the ranks, ultimately becoming director of the Division of Extramural Activities in 1989. Almost a quarter-century later, when Shafer retired, Ruth remembered her fondly and with pride: “Sue Shafer was a very creative scientific administrator, and was highly esteemed by scientists in the academic community and by all of us at NIH. I will miss her deeply as a colleague, a dear friend, and as one of the nicest people I know.”

Ruth built a cadre of people who, like Shafer, von Euler and others, could effectively balance smart decision making, team play, and hard work: Morale at the institute got even better. In turn, it became easier for Ruth to attract more good people. The institute was growing stronger. And she had demonstrated a clear style.

“Ruth had very high expectations—she was incredibly careful in hiring people, and when they came, they stayed,” said physicist John Norvell, Ph.D., who retired from the NIGMS after more than 30 years at the institute. “She set standards that persisted long after she left.”

Ruth was heavily involved in all the activities of the institute, from personnel decisions to those about the science and programs it supported. Some viewed her as a micromanager, but the same people would also say that her absolute dedication to doing a good job drove that incredible intensity. Ruth’s sharp focus on detail—everything from insisting on correct grammar in every bit of institute correspondence, to reading every single grant application submitted, to spending months preparing congressional testimony—was her vaccination against being caught off guard.

With her institute in good shape, Ruth launched her next important campaign—helping Congress understand the importance of basic research and its contribution to all research findings.



Basic research can be hard to explain. By nature, it involves untargeted exploration of the unknown and the long-term support of scientists making incremental, often unpredictable progress. Tangible deliverables are not always obvious, and measuring scientific inspiration that is the engine of creativity and innovation is difficult, if not impossible. Narrating this story in ways nonscientists—such as most members of Congress—can understand and appreciate is tough.

Many successes have come from basic research: new medicines for cancer, pain, heart disease, and infections; new products like artificial skin; chemical manufacturing techniques; and new tools and tests that help doctors look inside the body or diagnose illness from a sample of blood or cells. The most important product of basic research, however, isn't a specific outcome at all. It is growth in the foundation of knowledge about biology, the common currency for all biomedical scientists seeking to understand the mysteries of the human body and mind. Ruth knew that.

She had already been living in the research world, and her own studies of polio and viruses had made it clear that fundamental research was essential for progress. Among other proponents of this philosophy was Vannevar Bush, who ran the Office of Scientific Research and Development, a federal agency that coordinated scientific research for military purposes during World War II. Bush, who was in effect the first presidential science advisor, noted in his 1945 report to President Roosevelt that “new products and new processes do not appear full-grown. They are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science!” His recommendations led ultimately to the creation of the National Science Foundation (NSF) and to general support of basic research in other agencies, including the NIH but also the U.S. Department of Energy and other federal agencies.

But basic research remained a hard sell. Despite growing acceptance from Congress, President Richard M. Nixon, during his first term in office, had not been supportive of research in general (although he did sign into law the National Cancer Act on December 23, 1971, declaring a “war” on

cancer). In 1973 President Nixon impounded all NIH research training funds (an action taken in which the president proposes not to spend all or part of a sum of money already appropriated by Congress), effectively discontinuing support for research training until 1975, when Congress passed the National Research Service Award Act, which restored the funding and included pay-back provisions. President Nixon also boosted the role and influence of the Office of Management and Budget, which oversees federal spending practices and policies.

Stetten had acknowledged the relevance and importance of research training programs (which educate and mentor the next generation of researchers) but had separated them: Under Stetten's leadership, the NIGMS was essentially two separate entities, one dedicated to research grants and the other to research training. In Ruth's mind, the two should have been more integrated.

But whatever Ruth thought or believed about the philosophical importance of melding research and training mattered only so much. The Nixon administration's general view of the matter was the most serious obstacle: Scientists should pay for their own training, since they would be gaining skills that would provide the income for recouping the costs of the learning investment.

And so for Ruth at the NIGMS, combining research and research training had another less obvious, but critical, rationale. Combining training programs with research programs could help assure the long-term support of both.

It was an adroit move, noted von Euler, and the first of many times Ruth would figure out a way to get things done. She would have plenty of practice over the next decades in managing science policy through her extensive interactions with members of Congress and their staff.



Serving as NIGMS director initiated Ruth in the procedures and importance of interacting effectively with Congress, which appropriates funds for federal agencies like the NIH. For example, each year during the appropriations cycle, in addition to providing a prepared, written statement for the record and an opening statement that was spoken before the committee, she would respond to questions and more questions. The process, according to Ruth, was either a "free-for-all that could be either good, clean fun, or a miserable experience, depending upon the attitude of the committee and its chairman."

Procedures have changed somewhat since the mid-1970s, when she began testifying before Congress, but Ruth recalled the event as highly

choreographed and involving many people. She would begin months in advance, reading extensively, talking to her scientific staff and grantees, and creating a giant folder full of yellow index cards stocked with facts, figures, and testimonials.

“It was like the ultimate exam prep,” remembered Norvell, who not only accompanied Ruth to the hearings but also helped her prepare in a seemingly endless number of advance meetings. Von Euler, who also always accompanied Ruth at congressional hearings, made a wry observation about her, “She had this red testifying dress, and she knew just how to use a woman’s touch, but only when a woman’s touch was needed.”



Testifying before Congress—especially at a time when the process was dominated by men—wasn’t always easy, considering some of the personalities involved. The first two years Ruth was called to testify for the NIGMS she faced Congressman Daniel J. Flood (D-PA).

Congressman Flood had been a vaudevillian earlier in his life, and he had a handlebar mustache as a reminder of that time. He became famous for his various shenanigans, which included casting “spells” and wearing an opera cape. He had a fondness for Shakespeare that no witness dared try to match, remembered Ruth.

“I was scared to death,” Ruth said, but somehow she managed to stay cool. Over time, she came to respect Congressman Flood’s many abilities running the Subcommittee on Labor, Health and Human Services, Education, and Related Agencies. Ruth persevered in working with the Congressman and his staff, continuing to emphasize to them that “you cannot make something happen if you do not have good [scientists].” They were receptive, as were other members of the subcommittee. In time, Ruth developed a following of sorts among legislators.

Leading the appropriations subcommittee on the Senate side was another whirlwind of a personality, Senator Warren G. Magnuson (D-WA). Senator Magnuson’s hearings were mostly uneventful. However, one year’s appropriations hearing, Ruth recalled, was quite memorable, for a very nonscientific reason. That year’s Senate hearing had been scheduled in a tiny room in the basement of the Capitol. Ruth and her staff were characteristically prepared and on time for the meeting, sitting at a small table that clearly did not

have enough seats for everyone in the room. Ruth sat down in a seat near Magnuson, readying herself to deliver her prepared testimony.

One of Senator Magnuson's staffers entered the room and announced that there wasn't enough room for everybody. Ruth recalled, "[The staffer] looked at me and said, 'Well, maybe you can sit on the senator's lap,'" to which she replied, "Maybe he'll sit on mine," and that was the end of that.

Overall, though, Ruth's two main strategies with lawmakers were persistence and honesty.

"Ruth's ability to develop relationships with people on [Capitol] Hill was unmatched," said Donna E. Shalala, Ph.D., former secretary of the HHS, who knew Ruth well as both a colleague and a friend. "Fundamentally," Shalala continued, "Ruth was a great teacher, and she reminded the congressmen of the favorite teachers they had had in school."

In her testimony, Ruth would talk about exciting research results that had come from federal support—adding or including information, as needed, about topics with ready public appeal: such as burn and trauma research, or progress in specific disease areas that affected various congressmen. She was extremely articulate—her absolute command of the English language and uncanny ability to explain difficult concepts won her many friends on the Hill.

"She always spoke in perfect sentences, even when answering questions on the fly," remembered von Euler.

Federal procedures state that an NIH institute director testifying as a witness before Congress cannot ask for funds beyond what has already been suggested by the President in the budget, an activity known pejoratively as "budget busting." In rare instances, however, NIH directors could request additional support, but only in the context of specific questions offered by members of the appropriations subcommittees.

Ruth's ability to deftly seize this opportunity was apparent in the area of genetic diseases, which appeared to be a curiosity for many of the members of the House Appropriations Subcommittee. Ruth had hired an excellent scientist, Fred H. Bergmann, Ph.D., to run the NIGMS-funded genetics centers, and Ruth depended on his expertise to keep her up-to-date on developments in the field: stunning advances in amniocentesis and prenatal diagnosis, genetic counseling, and the tracking of genetically transmitted diseases. She would talk up those programs and their discoveries.

Even though she was good at it, testifying before Congress remained a challenge for Ruth, especially given a growing membership in the "disease-of-the-month" club among members of Congress in the late 1970s and early

1980s. Advocacy organizations strove to affect funding decisions by highlighting specific diseases rather than basic research.

Congressman David R. Obey (D-WI), who was a member and later chairman of the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, was well aware of this pattern. He had become unpopular with voters for refusing to join other lawmakers in identifying funds for research on specific diseases in response to the demands from advocacy groups.

Congressman Obey saw Ruth dedicate herself to delivering the message that basic, untargeted research was a fruitful strategy for advancing understanding about health as well as treatments for all diseases. To a great extent, she succeeded in these lessons, according to Congressman Obey: “Whether conservative Republicans or liberal Democrats—they were convinced by Ruth that the best way to serve the needs of everyone was to resist the temptation to [appropriate] funds according to the disease of the month,” Congressman Obey said.

It seemed that whatever Ruth said, Congress listened, and its members understood what she was talking about. During her tenure as director, the NIGMS budget quadrupled.

## Power to the People

*“Ruth was the NIH face of training.”* — FORMER NIGMS DIRECTOR  
MARVIN CASSMAN, PH.D.

THE JOB OF AN NIH INSTITUTE DIRECTOR is a complex one that requires extraordinary savvy. In addition to keeping close tabs on the needs of the American public, which funds federally sponsored research through its taxes, institute directors must follow what is happening on Capitol Hill and what the institute’s staff are saying. Further, the director must keep up with research grantees and with advocacy organizations that have a stake in the outcomes of biomedical research. Without question, an institute director has many masters to please.

Another obligation for an NIH institute director—or opportunity, depending on one’s outlook—is addressing the requests of the NIH, the HHS secretary, and the White House. Ruth considered the blend of duties and responsibilities that came with her job an intriguing challenge and one she never underestimated. Just a few months after being named NIGMS director, Ruth got the chance to prove her multitasking ability.

One Friday afternoon in spring 1975 around five o’clock p.m., her phone rang as she was alone and sorting through work in her Building 31 office. As a matter of routine, each day she would stop at the main campus before and after spending the day with her staff at the Westwood Building in Bethesda.

“Ruth,” said then-NIH Deputy Director Ronald Lamont-Havers, M.D., “we have a new project. It is the study of the system of peer review for grants. We would like you to be a member of the committee; in fact, we would like you to *chair* the committee.”

Ruth considered it an odd request and didn’t feel particularly qualified. “You know,” she replied to him, “I have just spent 20 years of my life in the [NIH] intramural program. Then I went to FDA ... I have spent only six months learning about the NIH grants program, and I do not think I have a real grasp on it yet. Why are you asking me?”

The answer was that Lamont-Havers saw Ruth’s intelligence, political acumen, and remarkable management skills as being perfect for the difficult task. But what was especially appealing about her was what she didn’t have: a chip on her shoulder about how she thought the system was supposed to work.

He wanted fresh eyes on the problem. Ruth agreed to serve, and she was relieved that Lamont-Havers had already secured the help of a very knowledgeable scientist who had managed grants at various NIH institutes.

“She was the most wonderful person I have ever dealt with,” Ruth said of Mathilde Salowey, Ph.D., a microbiologist who was much older than Ruth and had retired from federal service at the NIH. Salowey had found herself rather bored by retirement and eager to work on the project as executive secretary of the Peer Review Study team.



Peer review is a form of objective review. It is an assessment of the scientific or technical merit of research grant applications by other scientists with knowledge and expertise equivalent, or “peer,” to that of the researchers whose applications for support they are reviewing. At the NIH, this initial peer review is followed by a second-level assessment by groups called Advisory Councils, which consider policy and other related issues at all the NIH institutes.

Quickly, Ruth and Salowey got to work picking members of the Peer Review Study committee. The committee decided to host a series of meetings on the NIH campus as well as around the country to learn what seemed to be good and not so good about the current system.

The committee was thorough in soliciting input, arranging public hearings in Chicago, San Francisco, and Washington, DC. The group also gathered



extensive input from people applying for grants, from people reviewing grants, and from NIH staff managing the grants. Ruth divided the team into subcommittees, each with a particular issue to visit, and told them to report back within a month or two.

The Peer Review Study had been launched because NIH senior leadership had decided to assess its own peer review practices. Reports had come in questioning whether scientists could really qualify as peers to judge the scientific merit of a project and recommend it for federal funding. Even though she was new to the topic, Ruth saw the value in taking stock of such an important activity. Ruth recognized that the entire NIH structure hinged on the strength of its peer review system. In fact, she once testified before Congress that “just like liberty, the price of good peer review is eternal vigilance.”

Perhaps most important, Ruth also recognized that any activity that requires human judgment is prone to human error and that precautionary measures should be put in place to help account for potential bias. For example, many of the criticisms came from the scientists themselves, calling NIH peer review an old boys’ network. Ruth agreed that there was a problem in the way grant reviewers recommended their successors when it was time for them to rotate off the review panels.

Some of the complaints she heard, though, were rather outlandish. Noting that scientific success and modesty do not always, or even often, go hand in hand, Ruth recounted one experience talking to a microbiologist who was griping about not receiving an NIH grant, despite the fact that he had received many awards from scientific societies.

“I said something [to him] about the decision being a peer review procedure,” Ruth recalled, prompting his startling reply to her explanation, “‘I have no peers,’ and there was not a trace of irony in his voice.”

But on the whole, Ruth discovered, there did seem to be an “incestuous” tendency to the process of selecting reviewers. More troubling, though, to her and some others, were the apparent gender and ethnic biases, which were not helped at all by the fact that few women or minorities were themselves reviewers. And so one of the recommendations that Ruth’s committee put forth after the year-and-a-half study was complete was that as review slots opened, other scientists should be allowed to self-nominate. The committee had also urged more diverse representation of women and minorities.

Another key recommendation that resulted from the work of the Peer Review Study was allowing applicants to be able to see the critiques of their

grant reviews. While this is routine practice now, revealing what was behind that curtain was absolutely revolutionary at the time.

The committee also suggested the need for second chances, to allow applicants to argue their case if they felt the scoring was inaccurate or not fair for some reason. It took many years for that particular recommendation to fall on receptive ears at the NIH.

“Usually, the things I want get done eventually,” Ruth would joke later.



With the Peer Review Study behind her, Ruth was glad to be focusing fully on directing the NIGMS. The 10th director of the NIH, Robert Stone, who had hired Ruth to lead the institute, left a year later, in 1975, with less than two years of service in that position. Short as it was, however, Stone’s tenure at the NIH had left an impression that was well timed for Ruth’s arrival.

In the late 1960s and early 1970s, before coming to Bethesda, Stone had lived in New Mexico, a far more ethnically diverse environment than suburban Washington, DC. Stone lamented the lack of diversity at the NIH and is said to have commented that he “didn’t see anyone who wasn’t a WASP,” using the term for white Anglo-Saxon Protestants, a group that dominated the power structures of American society up until the mid-20th century. Stone saw immediately the need to bring some people of color to the NIH. As a start, he hired a Hispanic secretary, Belle Ceja, and would continue to support changes in hiring practices at the NIH that Ruth also felt were badly needed.

Ruth got to work assessing the state of affairs. What programs existed at the NIH? What programs were working? Could more be done to diversify the research workforce? These were questions fresh on Ruth’s mind, and she intended to use her leadership position to address them directly.

When she became NIGMS director, Ruth inherited some NIGMS programs that aimed to help introduce women and men from underrepresented populations into the world of science. Although Stetten had been supportive of such a notion, most of the push for putting those programs into place arose from another individual who originally came from outside of the NIH.

Several years earlier, in 1964, a black microbiologist with a Ph.D. from the prestigious, women-only Radcliffe College had been appointed to the council that advises NIGMS. She had visited NIH Director James Shannon on a mission to increase diversity in the scientific workplace, wanting help from the

NIH. Shannon sent her to NIGMS, as the institute was the lead on all things training and this request involved human capital.

Geraldine P. Woods, Ph.D., was herself a pioneer and was committed to getting more women and minorities into science. Woods was an activist, she knew Martin Luther King, Jr., well, and she had strong connections in the minority community. And she was connected to the NIH, indirectly, as a member of the NIGMS Advisory Council. After her four-year council term was complete, the NIGMS director at the time, Frederick Stone, asked Woods to serve as a special consultant to the institute to work out a plan for developing research and training programs targeted to historically black colleges and universities. Woods, Stone, and a few NIGMS staff traveled around the country, mostly the Southeast, to visit some of those schools. They assessed faculty, institutional, and student needs, and they also got a firsthand sense of the needs of the community.

Noting an early approach to educating some staff about disparities, Ruth said, “Some of my own staff who [had been] there at the time were non-African Americans who later moved into the ghettos in Atlanta to live for a while to see what things were like.”

In 1970, Woods presented her findings to the NIH senior leadership, reporting that minority institutions were eager to improve their ability to train new scientists as well as to enhance their facilities and science curricula. She also got in touch with black lawmakers, notably Senator Edward William Brooke III (R-MA), Congressman Louis Stokes (D-OH), and Congressman Augustus F. “Gus” Hawkins (D-CA).

By the 1970s, the social climate in the United States had benefited from the civil rights movement that had intensified a decade before—presenting ripe opportunity for action—and Ruth’s own moral leanings were echoed at work. According to Ruth’s NIGMS colleague, Leo von Euler, “NIGMS staff across the board were strongly supportive of social justice.”

In 1972, and with the backing of Senator Brooke, the NIH established and funded the Minority Schools Biomedical Support program and funded, within the Division of Research Resources (which later became the National Center for Research Resources), grants to about three dozen minority institutions. Woods also helped set up the Minority Access to Research Careers (MARC) Visiting Scientist and Faculty Fellowship program at NIGMS. Meanwhile, Woods was also working with NIGMS staff to put together an individual fellowship program for minority doctoral students to attract them to research careers. By necessity, the effort had a narrow focus: at that time only three

historically black institutions in the country offered a Ph.D. or M.D. degree: Meharry Medical College in Nashville, Tennessee; Morehouse School of Medicine in Atlanta, Georgia; and Howard University College of Medicine in Washington, DC.

Despite Ruth's drive to face the challenge of enhancing the representation of minorities in science and research through NIGMS programs, she did not see that the current route would lead to a timely solution, and she lamented: "... it seemed like a terrible, snail's-pace way to go—with only a hundred fellows a year, maybe less, we would never make any progress."



Ruth reasoned that while the MARC idea was a good one, it seemed to be basically too little and too late. Sending what amounted to a relatively small number of minority students and faculty to big-name institutions—and the converse, sending research faculty at top-tier institutions to minority schools—wasn't going to work on a large enough scale to really make a difference, she thought, and various advisors had told her the same thing.

"The only way we might be able to do anything," Ruth said she thought, "was if we became quite radical and if we moved into the undergraduate level and [convinced] young men and women at [minority schools] into being interested in science so they would go on to graduate-level training."

But the HEW, the predecessor to today's HHS, did not agree with Ruth's suggestions.

"College education is none of the NIH's business," she said they told her. "We do education." But, Ruth was not talking about teaching students; she was thinking of something more creative.

Ruth and her staff prepared a series of documents that explained to the HEW that their intent was to foster a "continuum of research training" to prepare students for graduate degrees in science. The basic idea was to squeeze into the students' normal schooling experience extra science honors courses, summer research, and enrichment programs designed to pique their interest in research as early as possible.

After a year of pushing, Ruth succeeded, receiving approval for the Honors Undergraduate Research Training program, which would be a component of the MARC program already in place. In 1977, the first honors program grants were awarded to 93 students at 13 minority-serving institutions.

“Most of [these institutions] had started as small, one-room schoolhouses to teach freed slaves to read and do numbers,” Ruth explained.

The program soon became a victim of its own success, though, growing quickly to about 90 schools. Another unintended consequence—though not a bad one, in Ruth’s mind—was that the effort increased the number of American physicians of color but not necessarily the number of researchers of color. That outcome hadn’t been too much of a surprise to Ruth, who knew that most of the students supported under the honors MARC program had been the first in their families to go to college. Research was an unfamiliar goal.

“You are going to have to make a decent living, and I do not know whether you will be able to do that with a Ph.D. in embryology,” Ruth imagined parents telling their children.

Later, some officials questioned the value and success of a program designed to foster research that turned out doctors instead. Although she acknowledged that the program had its flaws, Ruth was unfazed by most of the criticisms.

“We changed the face of those schools. The curricula and faculty improved. The students who wanted to do science increased massively in numbers. Most of them went to medical school—and why [shouldn’t they] if it assures [them] of earning a living ... I would argue that many of those people [would become] scientifically literate, think about science, or will [go on to] do some sort of science.”

Ruth had also built strong relationships with the schools and with the minority research community in general. That legacy lives on today.

In the late 1970s, remembered Clifton Poodry, Ph.D., who went on to lead minority programs at the NIGMS for many years, beginning in 1994, “[Ruth] just exuded commitment,” even routinely attending meetings of the MARC program. “Here was the director of an institute, attending every review meeting. The community was astounded,” Poodry concluded.



Nonetheless, Ruth did worry quite a bit about the rapid expansion of the MARC program, since she had reached out personally to staff in the minority education community and learned that only a few dozen minority schools, at most, really had the capability to house such programs successfully. Luther S. Williams, Ph.D., then a prominent African American molecular biologist on the NIGMS Council and later an advisor to the institute, told Ruth as much.



JENNIFER HALEY

Inspiring people of all ages, like these students at Ketcham Elementary School in the southeast section of Washington, DC, was one of Ruth's favorite activities.

“You want to increase the numbers of those who are really good; you do not just want to increase the numbers,” she recalls him saying. And so the NIGMS broadened the honors program, extending it to include schools that had a blend of minority and majority students, aiming to recruit a broader swath of minority students.

In less than 10 years, the MARC program had begun to have a robust effect: a 1985 report stated that 76 percent of the program's former trainees had enrolled in graduate or professional school.

As for Woods, she would never be totally satisfied. She was not pleased with the changes to widen distribution of the funds beyond traditional minority-serving schools and moved to the Division of Research Resources, where another program, the Minority Schools Biomedical Research Support program, was being administered.

Woods and Ruth had disagreed, and for a number of years the various NIH programs targeted to improving the diversity of the research workforce remained separate. Finally, in 1989, the NIGMS acquired the Minority Schools Biomedical Research Support program, and other changes were put in place to enable any NIH institute to award grant supplements to support minority scientists working with NIH grantees.

Ruth continued to push for the integration of programs that she thought would serve the minority research community the best. In 1991, she got her wish when the Minority Opportunities for Research Programs branch at the NIGMS was established. The programs' nickname, "MORE," had not been an accident. Ruth thought the acronym was particularly apt.

"It was a nice [way to say it]: You need *more*," she explained.

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Providing NIH money to increase diversity in the scientific workforce was not, however, an easy sell to everyone in the scientific community, the NIGMS Council, and various others of the institute's stakeholders.

Competition for NIH money has always been fierce, as there are many more good ideas than funds to pursue them in the research world. Even in the best of times, when budgets for science are robust, applicants for NIH research funding face a 1-in-4 or 1-in-5 chance of receiving the grant money to do their research.

What's more, in addition to the individual scientists competing against each other for grant funding, larger projects and programs supported by the NIH need support. The research programs targeted to minority-serving institutions that Ruth was so passionate about were only one item on a menu of many choices. Her job as an NIH institute director, then, was none other than a giant balancing act that, in the end and if "successful," left everyone a little unhappy.

"... while there were people that felt that there was so much exciting science to do that even this measly amount of money that we were giving to [minority] programs could be better used elsewhere, I had a deep commitment [to doing it] then, and I still have a deep commitment now," Ruth would say many years later.

Research training was another area where Ruth had to defend the use of precious funds that could otherwise have gone to established individual scientists known to have great ideas for their research projects. Her logic was precisely the same: People needed opportunities and the best environment possible to grow and thrive. The research training investment, Ruth reasoned, was priceless.

When she arrived at the NIGMS in 1974, the stage had been already set to help her achieve this goal to create opportunities for the next generation of scientists. Although the NIH had supported research training since 1930—and

fellowships to individuals had been the primary training mechanism throughout the 1950s—things changed in 1975 with the establishment of the National Research Service Award program. A change in emphasis was clear: Research training funds were to be targeted to scientists, not health professionals. Moreover, the allocation of funds was to be much more strategic than before, “channeled explicitly to those fields in which there was an identified need for biomedical and behavioral research personnel.”

At the NIGMS, Ruth endorsed the need to spread the wealth to as many individuals as could benefit, focusing most of the institute’s training resources on institutions (through institutional training grants), not individuals (through fellowships).

Ruth was such a strong proponent of high-quality training that many years later, on May 22, 2002, Senator Thomas R. “Tom” Harkin (D-IA) announced that Ruth’s name would be added to the NIH’s main training grant program, the Ruth L. Kirschstein National Research Service Awards.



One signature program at the NIGMS in Ruth’s time, and still today, was the Medical Scientist Training Program (MSTP) established in 1964. It had been then-NIH Director James Shannon’s vision, but Ruth was also a proponent of the program, which aims to help build a cadre of highly able physician scientists who can better bridge the gap between basic science and clinical research. The program started small, with three schools, but grew over time to its current size of 44 programs in which, through NIH funding, awardees get substantial support toward earning both an M.D. and Ph.D. degrees.

The hope was that those graduates—not saddled with debt, still fresh from research training, and with an eye toward patient care—would go on to pursue research that directly probes human health and disease. That has to a large extent been the case, although the number of trainees has been relatively small. According to an NIGMS report, most of the M.D./Ph.D. graduates trained by the program have eventually chosen to enter academia, government, or industry, with medical research a centerpiece of what they do.

Certainly, from her earliest days at the NIGMS, Ruth was committed to establishing, and protecting, high-quality research training programs like the MSTP, but there were many others deserving support that she continued to fight for, including the institutional training grants that went to genetics,



cell biology, bioengineering, pharmacology, and other science departments at schools.

Over the years, NIGMS-supported training programs at institutions throughout the United States went on to develop a reputation for providing stellar experiences for individual students. These programs created a “halo” effect at the schools, as other students and faculty benefited from the “spillover” effects of good curricula, state-of-the-art facilities, and a dedication to developing talent. This is different from the model in which one simply chooses the best students and lets them succeed.

“[Ruth] was the NIH face of training,” said Marvin Cassman, Ph.D., a biochemist who was Ruth’s successor as NIGMS director and, before that, her deputy. “She truly believed that the quality of a postdoctoral training experience depended on research. She saw it as a symbiosis.”

## Time for a Revolution

*“That little lady back there taught me everything I know about genomes.”* — SENATOR PIETRO V. “PETE” DOMENICI (R-NM)

IN MAY 1973, ROBERT S. STONE, M.D., was appointed by the Nixon Administration to head the NIH. Stone was named after his predecessor, Robert Q. Marston, M.D., was forced to resign after a dispute with the Nixon administration about the funding distribution between basic and targeted research in the NIH budget. At the same time, Stetten left the NIGMS to become NIH deputy director for science under NIH director Stone.

Interestingly enough, Stone and Al Rabson had been classmates in medical school, and so Ruth and Al knew him. Not many on the campus knew Stone, however, and so skepticism ran high about the new Nixon appointee. Stone’s selection of Stetten to advise him on matters of science won some favor with the NIH community, as did the fact that Stone had studied management at the Massachusetts Institute of Technology.

Neither Stone nor Marston, however, had ever really been able to step out of the shadow of former NIH Director James Shannon, who had led the agency during a period of exceptional growth. Although Stone was very supportive of the NIH, and reasonably well liked, he clashed with his superiors at the parent HEW: in particular, with Theodore “Ted” Cooper, M.D., the assistant secretary for health, who had been recruited from the National Heart Institute (NHI).

When President Nixon resigned from office on August 9, 1974, and President Gerald R. Ford was sworn in as the 38th U.S. president, Cooper seized the opportunity to encourage the NIH director to appoint his friend and colleague Donald S. Fredrickson, M.D., who had been scientific director of the NHI and had just spent a year at the Institute of Medicine of the National Academy of Sciences. Fredrickson became NIH director in July 1975.

The change was not entirely a surprise to Ruth.

Like Ruth and Al, Ted Cooper lived on the NIH grounds. He had been given a place on the campus to accommodate the many meetings he had to attend with NIH staff. One spring day, Ruth remembered, she and Al were taking a stroll around the NIH when they saw Cooper walking alongside Fredrickson, who was riding his bicycle.

She remembered, "I looked at Al, and he looked at me, and we said together, 'There's the next director of the NIH.'"

People were happy about Fredrickson's arrival, and as noted by Ruth, "Don brought back to the NIH a civility, an understanding, a deep conviction about science, but also something else: the need to realize that we were giving to the American people ways of handling disease. ... he did understand that there were people out there who could and must benefit [from] the research."



To Ruth, Fredrickson was inclusive. She felt Fredrickson had a good sense of history and the recognition that engaging people in decision making was important and fruitful. Fredrickson held frequent meetings with the NIH institute directors, discussed issues with them, and solicited their advice on topics of both policy and science. He used the directors' connections to the academic community to keep his finger on the pulse of the needs of working scientists. One of Fredrickson's legacies was prioritizing long-term funding stability for researchers.

He was also a gifted communicator—a talent that did not go unnoticed by Ruth, in particular, and earned him respect with Congress. All of these qualities became vital when, soon after taking the NIH director position, Fredrickson faced a controversy brewing over the rights and responsibilities of scientists working on a new technology called genetic engineering, a direct outgrowth of the genetics research sponsored by the NIGMS under Ruth's watch.

In the early to mid-1970s, the burgeoning field of genetic engineering had begun to cause a big stir in both science and policy circles. Scientists had figured out a way to create recombinant DNA by intentionally mixing and matching sequences of DNA (often from different species) using chemical “scissors” and “glue” to custom-make DNA scripts. Those genetic scripts could then be used to manufacture sizable quantities of either natural (such as insulin) or novel proteins. The proteins, in turn, could be used for a range of purposes, such as treating diseases like diabetes or making vaccines to fight infections.

Research progress in the area was proceeding extremely fast—perhaps too fast, some people thought. They reasoned that recombinant DNA research might not be entirely benevolent, and in fact it might be outright dangerous. Discussions about some of the scientists’ even going so far as to fund a company to commercialize the potential of the new work fueled more concern about the need for regulating the new science. As the debate intensified, Congress became aware of the public’s concern and proposed laws to keep everything under control.

Fredrickson believed, essentially, that “less was more” when it came to controlling science and scientists. His advisors on the topic of genetic engineering, in particular, agreed that establishing laws would be too restrictive and inflexible, especially given the fast-moving nature of the science. But convincing everyone was another story.

“Don had to fight off the Congress,” said Ruth, explaining that it was Fredrickson who set the wheels in motion for the scientific community to take the lead on controlling its own behavior. Ruth observed the situation with great interest and became involved as needed. The reputation of the NIGMS—and the science that was making daily headlines—was at stake. Ruth knew the power of this research could change lives, and she was eager to see it continue, as well as to acquire kitchen-table familiarity, along with her institute’s name.

“Within months, maybe a year, because the science was so exciting, we were able to get that science in the newspapers every day,” Ruth remembered. Research from the NIGMS was helping to incite a revolution.



Readers of the July 26, 1974 issue of the journal *Science* learned indirectly of the NIH's efforts to protect the important research in a letter from a group of well-respected American scientists working in the area:

... Several groups of scientists are now planning to use this technology to create recombinant DNAs from a variety of other viral, animal, and bacterial sources. Although such experiments are likely to facilitate the solution of important theoretical and practical biological problems, they would also result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance. There is serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous.

Lead signer of this letter—Fredrickson himself did not sign it, nor did any federal officials—was molecular biologist and NIGMS grantee Paul Berg, Ph.D., a molecular biologist at Stanford University. At the same time, Fredrickson and his NIH colleagues, including molecular biologist Maxine F. Singer, Ph.D., had been busy assembling an able group of researchers to take the lead in putting together voluntary guidelines to police their own behavior in working with recombinant DNA.

The letter went on to describe which types of experiments should be avoided until more information was available about potential effects on animals, people, and the environment. It spelled out specific concerns about the need for biological and physical containment—the ability to control completely the growth and spread of genetically altered microorganisms. The letter also recommended two specific action items that brought the NIH to the table and invited participation from the larger community:

... Third, the Director of the NIH is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules, (ii) developing procedures which will minimize the spread of such molecules within human and other populations, and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules. Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming

year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

Fredrickson entrusted Berg with organizing the now-famous gathering down the California coast near Monterey, the Asilomar Conference on Recombinant DNA. More than 100 participants, including not only biologists but also lawyers, physicians, and others, convened to discuss the potential benefits and harms of the new DNA-based technology. Singer had been another major player in putting together the meeting; she was Fredrickson's close "in-house" advisor. He called her "an indispensable member of the kitchen RAC," his inner circle of advisers on recombinant DNA, using the nickname of the Recombinant DNA Advisory Committee that continues to this day.

A main goal of the meeting was to hash out a set of voluntary guidelines to promote the safe use of the powerful new technology that enabled DNA to be employed essentially as a manufacturing tool for biologics products. The Asilomar meeting achieved its goals and was groundbreaking in its impact: The voluntary guidelines developed there not only helped assure scientific consistency and ethical rigor among scientists using genetic engineering methods but also raised the profile of biomedical research across the United States and the world.

Within a decade, the genetic revolution was just that. Recombinant DNA risk assessment experiments recommended by the Asilomar conference were performed in large part by two of Ruth's early virology colleagues at the NIH, Wallace P. Rowe, M.D., and Malcolm A. Martin, M.D. Interestingly, Ruth's son Arnold Rabson would work on related projects in the 1980s with this team. The rigid restrictions on much of recombinant DNA research were dramatically relaxed, and experiments using the new technologies became commonplace.

This in turn sparked a cascade of discoveries that earned several Nobel Prizes and led to the development of precise diagnostics and drugs that have saved countless lives, largely through launching the biotechnology industry. Perhaps a less obvious, but much more pervasive, impact was that DNA-based tools and methods became routine in just about every biomedical research laboratory throughout the world.

Another outcome of the Asilomar meeting was that the oversight committee, the Recombinant DNA Advisory Committee (the "RAC"), was assigned

to the NIGMS. Researchers proposing work in the area of genetic engineering submitted their plans to the institute's Office of Recombinant DNA Activity, which was run by then-staff scientist William J. Gartland, Jr., Ph.D., who promptly issued the guidelines to scientists in the United States and elsewhere in the world.

Ruth recognized that while the publicity from advances in genetic engineering was healthy, asking the NIH institute that was funding the research to also review and police the actual studies might not be so healthy.

"... it became clear to me that it was to some extent a conflict of interest to have the very grantees that NIGMS was supporting also to have to deal with [the RAC]," Ruth said.

Perhaps her experiences with the Division of Biologics Standards (DBS) were all too fresh. The RAC was moved out of the NIGMS and today resides separate from any NIH institute, within the NIH Office of Biotechnology Activities.



Paul Berg (center) co-organized the 1975 Asilomar conference on recombinant DNA, with the blessing of NIH Director Donald Frederickson (right).

With its regulatory responsibility for recombinant DNA gone, the NIGMS had plenty to do to keep up with the new science that was growing and maturing at breakneck speed. One area of interest that had been incubating in the minds of researchers involved collecting and comparing DNA sequences within and between species. Were there similarities, and if so, what did that mean? Could the information be useful?

At the leading edge of this inquiry was a man who was not even a biologist. Walter Goad, Ph.D., was a theoretical physicist working at Los Alamos National Laboratory in New Mexico. That organization began as a secret Manhattan Project laboratory during the Second World War, and it later evolved into a research hub for physicists, mathematicians, and computer scientists. It was mostly funded by the U.S. Department of Energy. Goad had developed an interest in biology, and in particular, how physics and computer science might be useful adjuncts to studying the patterns of nature.

In 1970, Goad traveled to England to spend a year working with Francis Crick, who with James Watson had discovered the structure of DNA two decades earlier. When Goad returned to New Mexico, he spent all his time working on biological problems, intrigued by the recent availability of methods to “read” the DNA sequences of genes with methods that broke the DNA into pieces and traced its “alphabet.”

At the end of the decade, in 1979, Goad attended a meeting of like-minded researchers who shared his vision. The meeting was held at the then-Rockefeller Institute for Medical Research. Soon thereafter, Goad took the lead in putting together a national data bank for DNA sequences that had been analyzed by computers. The data bank was the earliest iteration of what would become GenBank, which today is an essential tool for millions of researchers all over the world.

But that might never have happened if someone hadn’t seen the need for a team approach to get the thing off the ground. Although senior leadership at the NIH had sent scientists to the Rockefeller meeting, according to Ruth no one knew that apparently those delegates had agreed to take the next steps. She, for instance, had learned only several months later that the meeting had happened at all, from NIGMS-funded geneticists at the Cold Spring Harbor Laboratory in New York who had plenty of questions.



She remembered them asking her, “Whatever happened to this plan to do DNA sequencing and have the federal government pay for it? We know that so-and-so went to a meeting.”

Ruth investigated, learned more, and helped assemble a group of people at the NIH, the NSF, and other agencies that were also interested in the potential of DNA information to advance biological research. In 1982, GenBank was approved for funding: the NIGMS took the lead, with relatively small contributions from the other agencies.



Geneticist Elke Jordan, Ph.D., was then the deputy director of the genetics program at NIGMS, and in that role she managed the GenBank project, which began as a contract and grew in size and scope very quickly. GenBank’s growth was both good and bad, since agency budgets were not growing at the same pace.

“Everybody else began to back out, and we found ourselves with more and more of the [GenBank] budget,” Ruth said, fully aware how important the project was to advancing the science of genetics and to fundamental biology in general. “It was quickly eating NIGMS out of house and home, but our grantees were delighted to have it. We were providing them the information for free. But nobody else was keeping up with it.”

Something had to give.

Ruth knew that very promising work was going on in the NIH’s intramural research program on the Bethesda campus. One of the young stars, David J. Lipman, M.D., was keenly interested in keeping GenBank alive. Lipman, although he had trained as a physician, had become intensely interested in computational biology and was working with the Mathematical Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) as a research fellow.

“David and I used to have long talks [about GenBank], and he wanted to do more,” remembered Ruth. Together, they strategized, and Lipman convinced Donald A.B. Lindberg, M.D., director of the National Library of Medicine, that GenBank’s rightful home was there, in the world’s largest biomedical library. In a few years, Lipman helped to launch the National Center for Biotechnology Information (NCBI), where GenBank has resided since 1989. He has been the face of the wildly successful project ever since,

but without an initial boost from NIGMS, through Ruth, history might have been different.

“GenBank wouldn’t have been possible without the contributions and support from many [people]. NIH had the vision, under Ruth Kirschstein’s work at NIGMS, to start GenBank,” Lipman noted in 2008, at a celebration of the 25th anniversary of GenBank.

Looking back, Ruth recalled that GenBank was one of various projects that had gotten off the ground at her institute. “NIGMS always had the tendency to start something, and then other people took it over,” Ruth said, and in fact, a similar story had already begun to play out.



The fact that the NIH had offered to help pay for DNA sequencing and analysis captured the interest of leading biomedical scientists who wanted this information badly. Perhaps the most vocal and insistent among them was DNA co-discoverer James Watson of the Cold Spring Harbor Laboratory. But Watson himself was having a tough job convincing others that sequencing all the DNA contained in human chromosomes—the human genome—was worth doing. Money for research was tight, and the long-range relevance wasn’t clear to everyone. That included NIH Director James B. Wyngaarden, M.D., who was convinced that reading DNA sequences was more of a technique, albeit a very valuable one, than a distinct field of inquiry. He felt that, as a method, DNA sequencing should be best applied through the lens of specific diseases. That is, have diabetes researchers learn about insulin genes, have heart researchers learn about heart genes, and so on, to match the research to disease. Additionally, the high cost and risk of the endeavor led many others in the scientific community to have this same perspective.

The Department of Energy (DOE), on the other hand, was already convinced about the merit of funding the DNA-sequencing project. The agency was interested in the effects of radiation and energy-related chemical exposures on human health. New Mexico, home to the DOE-funded Los Alamos National Laboratory, was also home to the influential Senator Pietro V. “Pete” Domenici (R-NM). Senator Domenici saw great potential benefits for his state from funding the massive science project at Los Alamos with DOE funds, and he was hosting a meeting there to discuss the project. Hearing this, Wyngaarden acknowledged that he ought to at least hear about possibilities, Ruth remembered.

“We had better have representation,” Ruth remembered him saying. Wyngaarden considered all those institutes that were interested in diseases and decided, “I had better keep this out of the disease arena, so, Ruth, you go.”

Accordingly, as leader of the NIGMS, Ruth traveled to Senator Domenici’s hearing in Santa Fe to represent the NIH. Ruth knew that her boss had not yet signed off on any financial commitments, and so she remained mostly noncommittal on behalf of the NIH. She herself was not convinced that the work would not sap precious funds. Nonetheless, she quickly seized on the opportunity to talk up the science, and in the presence of mostly physicists and nonscientists, she was the perfect person to do so.

Ruth explained—in a way it seemed that only she could do—why this basic research was important and how sequence information on human DNA could advance science and health. A few months later, back in the nation’s capital, she knew she had succeeded, in one way. Observing from the back of a congressional hearing room in which NIH Director Wyngaarden was testifying about a related matter, Ruth grinned when she saw Senator Domenici seek clarification on a statement:

“That little lady back there taught me everything I know about genomes, she’s here,” Senator Domenici said, looking straight at Ruth.



Although the Department of Energy had jumped aboard and begun its own work to fund human DNA sequencing projects, the NIH had still not committed fully to the idea. James Watson was persistent and kept urging Wyngaarden to fund the project. Eventually, Wyngaarden agreed, but only to a small program.

“Okay,” Ruth remembered Wyngaarden told her. “We will start it as a small little unit of that genetics program here at NIGMS.” Then he asked her to get other NIH institute directors interested in chipping in their support. She could not. Although the NIH leadership seemed interested, Ruth remembered, no one was willing to put up the money. Wyngaarden finally agreed to provide some agency funds to NIGMS to continue the work, albeit still on a relatively modest scale.

James Watson continued to be active in discussions with the NIH and in meetings at the Office of Technology Assessment in downtown Washington, DC. That office was a federal entity whose stated task was to provide Congress with objective and authoritative analyses of emerging science and

technology. Watson continued to push for more support, and he was named director of the new NIH Office of Genome Research within the Office of the NIH Director, for which Wyngaarden had secured a budget.

In 1990, the Human Genome Project was officially launched as a dual project of the Department of Energy and the NIH as documented in a jointly prepared plan for the first five years. Watson held the director post for a few years, until he resigned in 1992 after a dispute with the then-new NIH Director Bernadine P. Healy, M.D. After Watson resigned, Healy recruited Francis S. Collins, M.D., Ph.D., to the post in 1993.

Collins was a physician-geneticist noted for his landmark discoveries of disease genes. He was a recognized star in the research world. Under his leadership, the Center became the National Human Genome Research Institute (NHGRI) in 1997. Collins went on to lead the government's Human Genome Project, which culminated in the first draft sequence of the human genome in 2003, almost 50 years to the day since the structure of DNA had come to light.

Collins' leadership of the Human Genome Project would earn him substantial acclaim: In 2007, President George W. Bush awarded him the Presidential Medal of Freedom, the nation's highest civilian award. And in 2008 he was awarded the National Medal of Science. Collins served as NHGRI director for 11 years, left for a brief period, then returned on August 17, 2009, to become the 16th director of the NIH.

## Research Saves Lives



*“Ruth loved to harness other people’s passion.”* — MARTHA PINE

WHEN SHE FIRST CAME TO THE NIH to begin the second phase of her pathology residency, Ruth could not have known that within a few years she would be working across an NIH parking lot from some of the pioneers of cancer chemotherapy—and that she would one day owe her own life to this research.

Research on various types of chemotherapy was going on at a new national drug development program at the NIH, the Cancer Chemotherapy National Service Center. The idea for the Center had been prompted by promising research showing that toxic chemicals (nerve gases like nitrogen mustard) could kill cancer cells. Other studies had shown that molecules that disrupt normal cell metabolism could be repurposed as tumor-killing agents. Working as a scientist at the NIH, Ruth would see those results up close when one of these molecules, methotrexate, was used for the first time at the NIH Clinical Center to cure a rare cancer that appeared during pregnancy.

In the early 1960s, NIH scientists, including Emil J. Freireich, M.D., and Emil Frei, M.D., had proposed a new approach: using combinations of chemotherapy drugs to treat children with leukemia, then a routinely fatal diagnosis. Even though these children faced a grim outlook, many people were horrified

at the notion of treating pediatric patients with a mix of the “poisons of the month,” as many researchers then referred pejoratively to chemotherapy drugs.

Concerns about chemotherapy, even one drug at a time, were understandable and justifiable. Although the drugs killed cancer cells, they produced significant side effects, and they could make people with cancer extraordinarily sick. Healthy cells and cancer cells use essentially the same molecular pathways to grow and survive, and so chemotherapy does collateral damage to healthy cells—particularly to immune cells, cells that make hair, and cells lining the gastrointestinal tract. This leads to a common but miserable trio of chemotherapy side effects: infections, hair loss, and vomiting.

In those early days, even though many researchers and physicians thought that giving half a dozen chemotherapy drugs at once was ill-advised and dangerous to patients, the logic behind mixing treatments was compelling. The combination therapy was designed to attack various aspects of cancer cell growth, all at once, aiming to leave the aberrant cells defenseless to fight back.

Frei, Freireich, and others proceeded cautiously. Before long, they had gathered enough evidence to convince themselves and others that their approach was safe to try in children with cancer. Their results would turn out to be game changing for people with cancer in general, and later Ruth would be one of those people who would benefit.



“Without Al, I could not have gotten through it,” Ruth said, 16 years after her diagnosis with a severe form of breast cancer that at the time promised only one year’s survival, at best.

In her many years working as a pathologist, Ruth had stared disease in the face time and again, and she had developed an ability to disconnect from it as any doctor must learn to do. But this time, she was truly scared. “I did not think that I was going to make it. Nobody else had [made it] with this [type of breast cancer],” she said. Ruth channeled her fear and worry into an intense desire to beat the cancer. Throughout, her husband remained supportive and positive.

“Al was convinced I was going to survive,” she remembered.

Ruth and Al consulted with an NIH friend, cancer specialist Marc E. Lippman, M.D. As part of a research team that included surgeons and other physicians, Lippman was recruiting patients for a study at the NIH Clinical

Center. The study was testing combination, or multimodal, chemotherapy against breast cancer. This was a variation on the method first discovered by Frei and Freireich to be successful in treating children with leukemia. No one was sure at the time if treating aggressive breast cancer would work the same way, but that possibility had to be tested.

Al and Ruth knew that the tumor was inoperable, meaning that it was too late for surgery since her cancer had begun to spread. They also knew that the NIH clinical trial provided hope. Ruth agreed to join the study in which she would receive a mix of six chemotherapy drugs, then surgery, then radiation, then more chemotherapy to target any remaining cancer cells that lingered.

The ordeal would take about a year and a half, and it would be incredibly tough on both of them.



Ruth knew all this but she also believed in the power of research. From the beginning, she and Al had accepted the need to allow the aggressive molecular weaponry to take on the enemy inside her. Despite everything Al knew about the cancer that was assaulting his wife's body, together they plunged forward in the belief that Ruth might somehow make it. Staying busy and working hard became their therapy for moving on.

"[Al and I] structured our lives around being able to work, not doing anything else, and getting better, and we did it," Ruth said later.

Ruth followed Lippman's instructions and received all her treatments. When they made her violently ill, she soldiered on with the help of anti-vomiting medicines and frequent small meals. Ruth also got support from the other women she'd see in the clinic when she went in to get chemotherapy injections. Ruth recalled thinking that she was the lucky one, since some of the other women had husbands who had left them, some were traveling long distances to the NIH, and many "were having a harder time than [I was]," Ruth said.

As is common with people who have received chemotherapy, Ruth's hair never grew back completely and looked "scruffy," as described by Al. And so for the next 26 years, Ruth wore one of the half dozen wigs she owned.

After her diagnosis and treatment, Ruth lived for more than a quarter of a century, defying unimaginable odds. In a 2004 report, Lippman detailed the 20-year follow-up of the early 1980s clinical trial in which Ruth had participated. Not everyone had done so well: Many of the women who like Ruth had inflammatory breast cancer lived only a few years.

In medicine—and with cancer in particular—survival is a matter of statistics. No one really knows who is going to succumb to an illness or who will beat the odds. But attitude can sometimes really make a difference, according to Lippman. “Ruth had what I call ‘healthy denial,’” he explained, adding that she did not let it get her down nor get in the way of her living.



Ruth learned she had breast cancer in her tenth year as director of the NIGMS, but she told only a few staff. Being a very private and humble person, she might well have disapproved of the adjectives those people used many years later to describe Ruth during those uncertain times, words like “amazing,” “indefatigable,” “incredible,” “upfront,” and “positive.”

Martha Pine, who worked with Ruth for many years and later served as executive officer of the NIGMS, described a secret escapade in which she and her NIGMS colleague Sue Shafer, also a close friend of Ruth’s, planned a surprise “victory celebration” to acknowledge Ruth’s conquering cancer after the treatments were complete. It was a special kind of celebration, though, more of a quiet tribute to a friend who had braved a difficult period.

Pine had known that in addition to classical music, Ruth and Al loved modern art, spending many weekend afternoons strolling within the National Gallery of Art and other museums in Washington, DC. And so to celebrate Ruth’s recovery, Pine and Shafer purchased a few of Ruth’s favorite Matisse prints and had them specially framed. They hung the prints in a conference room of the Westwood Building in Bethesda, where the NIGMS staff worked. On seeing the prints during a meeting, Ruth was touched by the unspoken kindness of her friends. Few others knew about the meaning of the prints, as Pine and Shafer understood that Ruth would prefer it that way.



In the mid-1980s, halfway through what would be nearly two decades of being the NIGMS director, Ruth had developed a highly effective management style: “leadership by walking around,” as Pine and others called it.

Unlike some managers at NIH, Ruth was well-known for the amount of face time she spent with her staff. Ruth held regular brown-bag lunches several times a week: sometimes to discuss science and policy issues and sometimes to trade gossip.



Whatever the occasion, Ruth's lunch was exactly the same every day: half a roast beef sandwich, a piece of fruit, and a Diet Coke. Every once in a while, she might bring cookies or chocolate to share.

(According to Al, Ruth's lunch-packing routine, modeled after that of her own mother, involved buying the meat on weekends, then preparing and freezing several sandwiches for the week ahead. "She never got tired of it," Al said, admitting to his own occasional trips to the cafeteria despite possession of the identical packed lunch he carried daily.)

Ruth's predictable lunches were an indication of her frugality and general concern about keeping a healthy weight, and she was conscious about dressing for success. Yet, she was no zealot when it came to fitness. She often joked that when the urge to exercise came along, she would simply wait a few minutes for it to pass. At yearly institute picnics that featured an occasional softball- or tennis-related injury, Ruth would feel vindicated in her position.

"See, that proves that *no* exercise is best," Pine remembers Ruth joking.



Beneath the high-energy intensity of her walking the halls in her trademark sling-back heels that could be heard "a mile away," as some staff noted, Ruth was full of compassion for the people she worked with. Exactly as had been the case with her staff many years before, in the DBS, Ruth treated everyone with respect, simply because she thought it was the right thing to do.

Ruth was also always on the prowl for unnoticed talent that she could unleash among her staff. As with young scientists Frank Chisari and John Petricciani years before, Ruth had a genuine interest in seeking opportunities for others to grow and learn.

"She loved to harness other people's passion," Pine said.

When Ruth wasn't roaming the halls, she consulted with people in her office. "I had an open door, and everybody came in," she recalled.

Spending so much one-on-one time with staff meant that much of the work that didn't get done during the day came home with Ruth every night over the course of her NIH career. Several satchels stored dozens of documents that had to be dealt with in one way or another.

"Ruth would tell me," said her friend and colleague Yvonne Maddox, "that if she touched a piece of paper, it would never go back to the same place." And sure enough, Maddox said, when Ruth returned the next day to work, every paper in the satchels had found a destination, either to a person or a file folder.



When Ruth was not in her Westwood building office, she was roaming the halls talking to staff.

Ruth's high ethical standards led her to create a "squeaky clean" institute: one that for many years would lead the NIH in its adherence to strict policies and which left a legacy that sometimes brought disdain from staff about being too careful. Ruth remained unfazed, believing as with the polio vaccine safety research that one could never be too careful when public health or stewardship of public resources was at stake.

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In addition to keeping close tabs on her staff and listening to their advice, Ruth worked hard to gather information from a wide group of consultants. They included friends, scientific advisory committees, members of Congress and their staffers, NIH colleagues, and many others.

One of them was James "Jim" Dixon, M.D., a U.S. Army thoracic surgeon who had served as a medic in the Korean War and upon whom the television show *M\*A\*S\*H* had modeled a character. Dixon had abandoned practicing surgery after developing a disability that impaired his fine motor skills. He then acquired training in bioengineering. For a time at the NIGMS, he ran the bioengineering program and had been in place before Ruth arrived. The two got along famously, and she relied on him for crucial advice.

Leo von Euler, Ruth's right-hand man at the NIGMS in her early days there, remembered her close alliance with Dixon. According to von Euler, Dixon was extremely alert to Washington politics, which led Ruth to consult him on a wide range of issues related to the institute.

Another person in the category of close friend and advisor was Nancy Wexler, Ph.D., a psychologist and geneticist whose investigative work led to a presymptomatic genetic test for Huntington's disease. Wexler's father, a psychologist, had established the Hereditary Disease Foundation when his wife was diagnosed with Huntington's disease. The diagnosis gave both Nancy and her sister a 50 percent chance of inheriting the errant gene known to cause this disease.

Ruth knew that Wexler lived every day with a genetic risk, and she wanted to understand what that felt like. She looked to Wexler for a dose of reality about people living with inherited diseases: the ultimate stakeholders of the NIGMS genetics research program. Their relationship went beyond consulting, though, and the two became longtime friends. Wexler is now a professor at Columbia University as well as president of the Hereditary Disease Foundation.

Ruth's frequent interactions and never-ending phone calls with all sorts of people kept her in the know. "She always knew who the players were downtown," said Ruth's friend and NIH colleague, Wendy Wertheimer, referring mostly to Ruth's awareness of Capitol Hill science and health policy goings-on. As Yvonne Maddox described it, Ruth's circle of advisors was not for show but rather "the real deal."

"Ruth really wanted support from the common man and woman," Maddox said. "She wanted to hear the voice of the community, 'What are people *really* saying?'"



As time progressed, well after the James Shannon years at the NIH, institute directors became more interactive and collaborative, an idea Ruth endorsed heartily. She had always been a strong proponent of collaboration in general, and "playing with the team" was her particular strength.

In the 1970s and 1980s, when Ruth led the NIGMS, "the [NIH] institutes were fiefdoms," she recalled. "They had enormous power unto themselves and enormous autonomy." Donald B. Tower, M.D., director of the then-National Institute for Neurologic Diseases and Blindness, shared Ruth's view

that the leaders ought to work together more, and the two conspired to arrange monthly brown-bag lunches with the NIH leadership.

“The first time we had one, nobody came,” Ruth said, which only prompted her to try harder. She sweetened the deal by offering to bring cookies, which helped a little. “I used to be known as the cookie lady. They did come for a while. Then they stopped coming. They really wanted to work by themselves.”

Over the years, science changed, leadership changed, and personalities rotated through the NIH.

NIH institute directors had begun gathering on a routine basis to discuss issues of common interest and to foster collaborations across institutes. When those meetings first began, though, not a whole lot got done. “They would be mostly show-and-tell,” Ruth said, noting that most people (staff also attended these meetings) “were frightened to death to say anything.”

But Ruth did not hesitate to speak her mind about issues that mattered to her, the NIGMS, and the NIH. Ruth recalled Belle Ceja, an NIH employee who helped organize the meetings, saying to her, “Ruth, you’re the only one with spunk,” to which Ruth replied, “I figured if they wanted to fire me, I would go out and practice pathology.”

The formal meeting of the NIH institute directors was held twice a month on Thursday mornings at 8:30. Everyone had a particular seat they used each week. During the time Ruth endured treatment for her exhausting cancer she did not miss a day of work. However, her chemotherapy treatments were always scheduled for Wednesday afternoons, and the next morning, Thursday, she would feel the effects and come in a little late, forcing her to miss the NIH institute director meetings for a long period.

“No one sat in [my] chair the whole time I was gone,” Ruth said, clearly touched by the respect of her colleagues.

## Pay It Forward

*“Ruth was a world-class nudger.”* — FORMER HHS SECRETARY  
DONNA E. SHALALA, PH.D.

RUTH DID NOT NEED TO BE TOLD that women and men often got treated differently.

She fought hard for gender equality, frequently behind the scenes, trying to convince a university dean or a department chair to hire this woman or that woman. She worked endlessly with high-level government colleagues, urging them to formulate and then enforce policies that upheld equal representation for all those who weren't getting equal treatment. She was on the phone constantly, making demands and pleas, and she would not hang up until she got “yes” for an answer.

“Ruth was a world-class nudger,” said Donna Shalala, president of the University of Miami since 2001. “She was all over everybody to hire more women and minorities,” said Shalala, herself a fervent advocate for the same cause. Over time, Shalala noted, Ruth's constant pushing caused the rules at universities to be changed, and more women were hired at the NIH, throughout government, and in policy circles.

But in the early- to mid-1980s it became clear that women were not getting a fair shake in another important way: in research. Despite the fact that it was well known that the bodies, life experiences, and disease symptoms of men and women were often quite different, most research studies had been

conducted in men only. Only afterwards would the findings be “generalized” to women, and there was no guarantee that the guesswork would be accurate.

As a key architect of what would become the Office of Research on Women’s Health, Ruth helped to change the way people thought about women from a scientific perspective. As had become a common refrain in Ruth’s professional life, her involvement in getting this organization off the ground started with a request from a friend—Edward N. Brandt, Jr., M.D., then the HHS assistant secretary.

Ruth knew of Brandt from his past work, including that in the early 1980s, when Brandt declared the acquired immunodeficiency syndrome, or AIDS, a top health priority for the nation despite the fact that it was still in the early stages of spreading and that the governing Reagan administration was intent on cutting spending. As physicians, Brandt and Ruth’s NIH colleague, Anthony S. “Tony” Fauci, M.D., (who at the time was a senior investigator with the National Institute of Allergy and Infectious Diseases and in 1984 became its director) had quickly recognized the gravity of the health problem and worked behind the scenes to obtain adequate research funding for the NIH during this critical time.

Brandt had also recognized the need to move forward on women’s health issues, in part as a result of a government report outlining health objectives for the nation. One of the problems outlined in that report was that women were not allowed to participate in clinical trials if they were within childbearing age, which had been defined by the FDA as any age from 13 to 55. The policy essentially barred most women from participating. Part of the rationale of excluding women (and their children) from research studies was to protect them—but many saw that logic as flawed, since doctors actually had little scientific evidence on which to base their treatment decisions for women.

Getting the effort under way required putting together a public health task force, with two representatives assigned from each federal agency that had a stake in the issue. Brandt approached NIH Director James Wyngaarden, asking for one additional NIH representative, since he already knew that Ruth would be the first. But she did not know until after the group was in place how significant her role would be.

Brandt’s assistant approached Ruth and asked her to write the charter for the group. “Didn’t Ed Brandt tell you?” Ruth recalled her saying, “You are going to be the chair of this task force.”



And so Ruth, who was working through cancer treatment and leading an NIH institute at the same time, became even busier. She enlisted help from a young NIH presidential management intern, Valerie Williams, whom Ruth described as “magnificent” and who worked hard to help Ruth gather data and produce a report over the course of a year or so. Ruth remained vigilant about finding new talent and assigning those individuals substantive work.

The first order of business was to think carefully about how to approach the topic, given the political winds that were blowing: Ruth had learned that a previous report had never seen the light of day since it focused mainly on the need for access to abortion and contraception, issues that were unpopular with the Reagan administration. And so she strategized that the most scientific approach for addressing the topic was to craft the plan around health issues that occur universally in the stages of a woman’s life: childhood, adolescence, young adulthood, menopause, and old age. Ruth and the task force collected input from women by hosting public meetings in Washington, DC, and across the country.

Each federal agency was told to also organize an internal working group: Ruth was disappointed—actually annoyed—when she received only women’s names in response to requests for suggested members. Ruth declared, “We are not going to have this. Women’s health is as important to men as it is to women.”

And so she handpicked some male scientists at the NIH to ask to join, and they did. The task force worked hard and made several recommendations that addressed multiple facets of women’s health, ranging from treatment and prevention to workforce recruitment to policy guidance for lawmakers.



Meanwhile, beginning in the late 1980s, several women members of Congress also had become active in pushing for the inclusion of women in clinical research studies. Ruth stayed engaged with them, a bipartisan mix of representatives and senators that included Patricia S. Schroeder, J.D., (D-CO), Olympia J. Snowe (R-ME), Barbara A. Mikulski (D-MD), and Constance “Connie” Morella (R-MD)—Ruth continued meeting with them, listening to their concerns, and relaying information on a routine basis.

Although one key recommendation of the task force that Ruth led was a requirement that all NIH-funded studies should not exclude women, the recommendation at first had “no teeth,” and the congresswomen knew it.

An audit of the NIH by the General Accounting Office had revealed that the NIH was not adhering to the recommendation—a finding that Ruth had found particularly embarrassing for the agency and was eager to make right—and the lawmakers continued to push for action.

In September 1990 the congresswomen held a press conference on the NIH campus to express their concerns about the lack of inclusion of women in clinical research. In response, then-Acting NIH Director William F. Raub, Ph.D., used the occasion to announce the establishment of the Office of Research on Women’s Health, with Ruth as its head. Within a few years, including women in clinical research became federal law, as part of the NIH Reauthorization Act of 1993.

Ruth went about the process strategically, rejecting many people’s suggestions to name the new entity the “Office of Women’s Health Research.” Ruth argued that research should remain central to the mission of the office, which would also focus on increasing the number of women in biomedical careers.

“I was very afraid that they were going to drop the last word and it would be called the Office of Women’s Health, so I insisted that it be *research* on women’s health,” she explained. Ruth wanted the word *research* central to the office’s acronym so the word would not be dropped. The Office of Research on Women’s Health (ORWH) is today among the offices in the Office of the Director of the NIH.

With an even fuller plate, Ruth knew she needed some good help to get things under way, and she assembled NIH staff she knew were qualified, interested, and willing to work on the problem.

One key initial hire was Wendy Wertheimer, who had met Ruth years earlier when Wertheimer, as a legislative assistant to Congressman Jacob Javits (R-NY), had worked with Ruth on a number of issues related to NIH policy. Several years later, in 1990, Wertheimer had been working on AIDS-related issues, on assignment with the WHO in Geneva, Switzerland. Through a news article, she had learned that Ruth would be heading up the new ORWH at the NIH.

Wertheimer called NIAID Director Tony Fauci, whom she knew from her AIDS work, and asked him about it. In turn, Fauci asked Wertheimer whether she knew Ruth, and Wertheimer replied yes, but that many years had passed and she wasn’t sure Ruth would remember her. Wertheimer got her answer within 10 minutes, when she received a phone call from Ruth. Wertheimer learned that Ruth and Al were scheduled to come to nearby Basel, Switzerland, and would Wertheimer join her for breakfast at 9 o’clock?





NIH HISTORY OFFICE

NIAID Director Tony Fauci, who came to the NIH in the early 1970s, knew Ruth for many years and the two shared a mutual admiration.

She agreed. The two ate, talked through the morning, then the afternoon, and then, joined by Al, who had returned from a business meeting, through the evening. Wertheimer was so taken by Ruth, her energy, and her new plans, that she barely made the last train back to Geneva that night.

A few months later, Wertheimer found herself back in the United States, having agreed to help Ruth set up the ORWH. She promised to stay a year at the most but ended up staying at the NIH much longer, and now, 20 years later, she is a senior advisor in the NIH Office of AIDS Research. Ruth mentored Wertheimer throughout the years, sometimes delivering tough lessons.

Wertheimer remembers, for instance, arriving at the NIH to find her new office on the NIH campus, with a window overlooking a garbage dumpster. She had been spoiled at the Geneva locale, housed in a glass building with spectacular views. But when Wertheimer complained one day about her current setting, Ruth swiftly put the matter to rest.

“You don’t have to look out the window to do this job,” Ruth told her curtly, as someone completely uninterested in the “trappings” of top positions, according to Wertheimer, who laughs when she recalls the encounter. The two remained close friends over the years, and Wertheimer was ever grateful for Ruth’s guidance on so many issues.

“I loved her with all my heart, but she was tough,” Wertheimer said. “Ruth was like the hardest teacher you ever had.”

Another of Ruth’s colleagues, Hilda Dixon, former director of the Equal Employment Opportunity Office (EEO) within the Office of the NIH Director (OD), also recalls the many lessons she learned from Ruth. As NIH deputy director, several years later, Ruth met with senior OD staff and oversaw the work plans of the EEO.

“I will always remember Ruth as a teacher,” Dixon says. “She could teach you in such a way that you didn’t even realize you were being taught. I really learned so many things about leadership, and being a leader from her. ... She never sat on the sidelines of issues. She was fearless. ... She never backed down from saying what she felt was right.”



As the NIH was preparing a new ORWH in 1990, NIH leadership was about to change again with a recent change in the national administration. President George H.W. Bush nominated noted cardiologist Bernadine Healy from the Cleveland Clinic in Ohio to lead the NIH. She was the agency’s first woman director and a strong advocate for women’s health.

Ruth knew Healy, and she knew that Healy shared her interest. Before Healy arrived at the NIH in April 1991, she had consulted Ruth about women’s health. Soon after Healy’s arrival, the two were sitting in a meeting of the NIH Advisory Committee to the Director. Ruth attended the meetings from time to time when issues of interest to women’s health or the NIGMS were topics of discussion. At this particular meeting, Healy was announcing the new office (the ORWH) and that Ruth would be serving as its acting director until a permanent leader could be found.

One of the invited scientists in attendance was Vivian W. Pinn, Ph.D., a pathologist at Howard University in Washington, DC. Healy had known of Pinn from her medical school days at Harvard, where Pinn had teaching responsibilities as part of her faculty position at the Massachusetts General Hospital in Boston. Pinn had been the only woman and the only African American in her class at the University of Virginia School of Medicine.

Pinn’s passion for the importance and relevance of the new women’s health research effort—in particular, the need to include women in clinical trials—stood out to both Ruth and Healy, who agreed that Pinn would be a perfect choice to lead the new office. Since Ruth was eager to get back to

being NIGMS director full-time, Healy recruited Pinn to the ORWH position, which she held until she retired in August 2011.

Although Pinn had an intense interest in both women's health and in the representation of women in science and medicine, it was a sideline to her main job at Howard. Pinn was intrigued by the opportunity to join government, but she was unsure of giving up a tenured, full professorship and work that she loved. Ruth recognized this, but she could also foresee that Pinn would succeed at the NIH post. And so she set up a temporary position in which Pinn could take a "leave" from her faculty job while leading the ORWH. As Ruth predicted, Pinn decided to stay at the NIH.

As details for bringing in Pinn were being worked out, Ruth organized a three-day meeting at a nearby conference facility in Hunt Valley, Maryland, about 15 miles west of Baltimore, to kick off the efforts of the new office. She invited a wide range of people, including advocates and scientists, and gave them a chance to share ideas in working group sessions. Healy gave a keynote address, and Shirley M. Tilghman, Ph.D., a molecular biologist at Princeton University who in 2001 became president of that institution, also spoke to the group. Tilghman had at first hesitated to accept the offer to speak. "Why? I am not interested in that topic," Ruth remembers her saying. But Ruth continued to coax Tilghman, sending her data on women in the scientific workforce and other issues. Tilghman came.

Over the years, Pinn continued to rely heavily on Ruth for advice and ideas. "We [at the ORWH] always consulted Ruth," Pinn said. "I liked to get her ideas and her blessing."

But there was more than just advice about the women-in-science topic that the two women cared so much about. As a fellow pathologist, Pinn saw Ruth as a role model—and as someone who had "survived all kinds of bias," yet still made it to the top.

Above all, Pinn learned from Ruth how crucial it was to be objective. "As a leader, Ruth knew that the focus had to be on science, and that is how she built this office—around science."



Bernadine Healy remained deeply interested in making a difference in research on women's health at the NIH. In addition to her staunch support of the process that led the NIH to require the inclusion of women in clinical trials, she made progress on numerous fronts. Shortly after her arrival, Healy

was in discussions with the NHLBI about a long-term research project focused on prevention of the major causes of conditions that affected postmenopausal women, especially the role of menopausal hormone therapy in women’s heart health. Healy succeeded in broadening the effort beyond heart disease to include bone health, cancer, and other health issues.

In short order, Healy had convinced Congress of the need for a budget “carve-out,” and the Women’s Health Initiative (WHI) was born in 1991 as a 15-year research program that would address the most common causes of death, disability, and poor quality of life in postmenopausal women.

Again, with a change in the presidency, Healy left the NIH in 1993 to return to research and administration. She served in top leadership roles in medicine and health until her death in August 2011 after a long struggle with brain cancer.

Without the WHI’s founder Healy, and under a new president, William J. “Bill” Clinton, J.D., Ruth helped transition the WHI to the NHLBI, despite the fact that the research would also address issues that were not heart related. She helped convince the other institutes that had a stake in the research and its outcomes to work together. Led by the NHLBI, those other institutes (the National Institute of Arthritis and Musculoskeletal and Skin Diseases, or NIAMS, the NCI, and the National Institute on Aging) joined in, with the ORWH providing an advisory role.

To date, the WHI has involved more than 150,000 women participants—nearly half of them Hispanics and African Americans—and over the years has made a number of landmark findings that have helped millions more. For example, WHI researchers learned that the long-term use of menopausal hormone therapy put women at greater risk for heart disease, breast cancer, stroke, and pulmonary embolisms. As a result, the use of menopausal hormone therapy declined in the United States and around the world, followed by a decline in breast cancer.



Throughout her career, Ruth often played the role of getting things started and then trusting others to follow through. Yet, she would never leave people stranded: Ruth mentored men and women, old and young, senior leaders and junior scientists. But she did not seek praise or affirmation for good deeds.

“Unlike a lot of ‘queen bees,’ [Ruth] just kept working,” said former HHS Secretary Donna Shalala.



Ruth, Ed Brandt, and Vivian Pinn were key players in forming the NIH Office of Research on Women's Health.

People were always the main focus for Ruth, and she cherished the role of teaching. Like her mother before her, Ruth volunteered in local public schools in Washington, DC. She visited several to talk about science. In the summer of 2000, the NIH had adopted Alice Deal Junior High School in northwest Washington, DC, to help foster the children's interest in research at an early age. At the time, the school had the most diverse student population in the city, and Ruth was thrilled to help out. Along with Yvonne Maddox, who by then was working as Ruth's deputy while Ruth was NIH acting director, and several other NIH staff, Ruth visited the school on many occasions.

Later, in 2002, Ruth visited fourth graders at Ketcham Elementary School in a low-income section of southeast Washington, DC, as part of "Project Out-of-the-Box." The outreach project aimed to help children take responsibility for their own health as well as to learn about science, health professions, and the work of the NIH. It had been launched by the EEO after Maddox had begun sending surprise packages to a Honolulu elementary school she had visited on a work-related visit to that state. The packages were wildly popular, prompting the NIH to expand the program to Ketcham and to two other schools.

Visiting the DC students, Ruth helped the boys and girls set pedometers, explaining the importance of exercise to their health. Even though she was known to disparage exercise for herself, she knew it was important for the

children. She talked to the girls and boys about how to reduce their chance of getting colds and the flu. When one student agreed with her and proceeded, proudly, to share his own good health habits with the group, Ruth beamed.

“My, that’s excellent!” she said. “Think about becoming a doctor.”

As Ruth’s visit drew to a close, she turned to one student who looked as if he had mustered the courage to speak up:

“Dr. Kirschstein, do you like your job of talking with children?” To which she replied enthusiastically, “Yes I do. It is the best!”



It was this, Ruth’s attitude, which made all the difference in the Out-of-the-Box outreach effort, according to former EEO Director Hilda Dixon.

“There was an obvious age difference and obvious racial and status differences between Ruth and the children. But real caring transcends age and race and status. You could tell that she was really getting through to them. ... The [EEO] staff wrote the scripts for these events, but she always went off the script. ... You would think that race, poverty, position—any of those, or all of those—would have been a barrier to making this program work ... but she really cared and they connected with her.”

Ruth’s enthusiasm was infectious. Jennifer Haley, an EEO assistant who prepared background material for the project and accompanied Ruth on the visits, remembers that Ruth’s participation in Out-of-the-Box went a long way toward getting leaders in other NIH institutes and centers to sign on to the program.

“Word caught on around NIH,” Haley said, “and several other [institute officials] started showing an interest in visiting schools. “By looking at what we were doing and seeing it as important and valuable to the next generation, she made this the best kind of outreach. I look back at that time as the best time in my career,” Haley added.

Dixon, who retired from the NIH in July 2011, adds, “Over the years, I accompanied a lot of officials on visits to schools. ... There was always a certain level of trepidation or anxiety. Ruth was undaunted, though. She was not anxious or nervous about the atmosphere at Ketcham, which was ... in need of serious repair at the time.

“She might as well have been at the White House for all her surroundings mattered.”

## Winds of Change

*"We're a team, a family that is quite remarkable."*

—RUTH L. KIRSCHSTEIN, M.D.

RUTH WAS APPROACHING HER 20th year leading the NIGMS when she ran into acclaimed molecular biologist and Nobel laureate Harold E. Varmus, M.D., at a scientific meeting in late spring of 1993. Ruth knew Varmus well, since for a number of years he had been an advisor on various aspects of science, genetics in particular, within the NIGMS research portfolio.

More relevant at the time, though, was a rumor floating around that Varmus might succeed Bernadine Healy to become the 14th director of the NIH.

On this day, Varmus approached Ruth during a meeting break and said, "I want to talk to you." Ruth arranged to meet him, and they sat down and talked over lunch. In response to his questions, Ruth shared what she knew about the NIH director's position, which she had seen about a half-dozen people hold since her arrival at the agency in the 1950s.

Varmus continued talking, Ruth recalled, asking her who she thought he ought to hire as his deputy. She replied, "Well, I have some great ideas for you," suggesting her own deputy, Marvin Cassman, as well as a few other people she thought would fit the bill.

They talked for a while until Varmus interrupted her and said, "No, no. Stop beating around the bush," Ruth remembered him saying. "I want you."

But within a few days, it became clear that her new job as deputy director for the NIH would have to wait. Ruth got a call first from HHS Assistant Secretary for Health Philip R. Lee, M.D., and then from Lee's boss Donna Shalala, secretary of the HHS.

Would Ruth agree to lead the NIH in an acting capacity?

That would mean keeping a big secret, revealing to no one that the rumors about Varmus were true until he received an official nomination to be the NIH director from President Clinton. That could be a month or six months.

Yes, she replied to Shalala. Certainly, Ruth was up to the task.



On July 1, 1993, Ruth became acting director of the NIH. She left her position at the NIGMS and moved to Room 126 in Building 1—home of the Office of the NIH Director—to be acting until the new director arrived. Simultaneously, Shalala had named Ruth NIH deputy director.

Again, Ruth saw her plate fill quickly. She knew she would be running the place for just a few months, waiting for Varmus to be appointed and confirmed by the Senate. She had lots to do, including making arrangements to help move a half dozen members of his laboratory from the University of California, San Francisco, to Bethesda. And she had to keep the whole undertaking under wraps.

Ruth quickly sent a note of reassurance to the NIH community she considered her family. "I want everyone at NIH to know that there will be no long interim period when there's no one in charge who cares about all the people at NIH," she said.

"I know many, many people here at all levels of activity, from scientists, to technical people, to support staff, to animal care workers. I want them all to know that a sense of continuity will be maintained. I share a feeling of the importance of everyone's task. We're a team, a family that is quite remarkable."

And then she got on with directing the agency.

One of her first challenges was to respond to a congressional request that there be a review of the "role, size, and cost" of the NIH intramural research program. The inquiry focused on the research conducted in the NIH's own laboratories and in its research hospital in Bethesda. Although the NIH intramural program had a very distinguished history of scientific discovery (including, at the time, four Nobel laureates who had done their award-



winning work at the NIH) and translation of basic science into new treatments for disease (such as Ruth's own vaccine work), Congress wanted a new look to be sure the program was as efficient and effective as possible.

"Ruth did an amazing job of assembling a team of highly respected experts, chaired by Dr. Gail Cassell and Dr. Paul Marks, to thoroughly review the intramural program," noted Michael M. Gottesman, M.D., who was asked by Ruth to help implement these plans at the NIH, initially as chair of the intramural executive working group and subsequently as deputy director for intramural research a few years later under NIH Director Harold Varmus. "The group made recommendations in 1993 that, to this day, are a blueprint for the successful oversight of research in the intramural program," Gottesman added.

A little over four months after taking the reins, as planned, Ruth handed control over to Varmus, just before Thanksgiving of 1993. All leaders have their own styles, and Ruth had seen the full range in the 38 years she had been at the NIH. She could see immediately that Varmus was going to be even more different than most, and it was clear to Ruth and others that he would leave a lasting mark at the agency.



"I am just in awe of how good he is," Ruth said, "... all of us [here at the NIH] had no doubt whatsoever that [Harold] would be visionary in moving the basic science, and particularly the genetics." He also recognized clinical needs, had great political instincts, and could spot an error on a budget spreadsheet after studying a sea of numbers for only a minute or two, Ruth recalled.

Varmus brought new energy to the NIH, and he was intent on giving the agency a novel look and feel. His NIH would be more like an academic campus than a government agency. His NIH would work more holistically and as a team, with "big science" projects spanning (and benefiting) several institutes and the entire scientific community. His NIH would be more open—with widespread sharing of data and results.

Varmus' NIH tenure was dramatic. Ruth respected Varmus a great deal, even if her own views and philosophy of science and the NIH did not always match his. Although Ruth had never been a fan of big science, she became convinced by Varmus that as scientific boundaries were beginning to blur, those sorts of trans-NIH projects would be important and necessary.

Ruth also recognized and appreciated Varmus' ability to connect with Congress. An English literature major in college with a master's degree in

English from Harvard University, Varmus was a gifted communicator. Ruth especially respected the high bar that Varmus set for excellent writing. She spent many nights rewriting memos and other correspondence covering a wide range of material destined for the eyes of the NIH director.

Ruth later remembered, “It is time-consuming, but I do not think that [Varmus] should have to do it, and besides which, I am almost ashamed to show him how badly some people write.”



During the time Varmus led the NIH, the agency enjoyed support from both Democratic and Republican members of Congress. Varmus was well respected on Capitol Hill, and he shone during testimony either defending the budget or speaking about the wide variety of issues that affected the NIH.

“Dr. Varmus receives such respect from everybody in the Congress, even when they are tough on him,” Ruth said, “And [he] testifies beautifully. There is absolutely no question about it.”

Ruth recalled one instance when Varmus had been called to provide testimony at an appropriations hearing on Dolly (the cloned sheep). A reporter had attended the hearing and contacted Ruth about it afterwards, clearly in awe of Varmus’ talent. “In the hushed room with television cameras blazing,” Ruth recalled the reporter’s story text, “the world’s greatest scientist gave the world’s greatest science lesson to the Congress.”

Beyond dealing with Congress, Varmus’ job as the NIH director involved countless other tasks: interactions with government staff, stakeholders, the public, and the media. There were also committees to chair, meetings to run, and crises to manage. As Varmus’ “right-hand woman,” Ruth helped out as needed, and her vast experience with the NIH made her a valuable resource.

“[Ruth] knew everything, everybody, every rule, and was an incredible resource,” Varmus would say of his colleague, years later.

“I tried to keep issues that I consider not of the highest importance and soluble away from [Harold] simply to save his time,” Ruth explained. “I am in some ways the individual who runs the day-to-day activities of the Office of the Director.”

Beyond interacting with Congress, the scientific community, the public, and hundreds of other stakeholders, a key job of the NIH director is to hire institute directors. Finding good people and convincing them to come is no small task. But Varmus excelled at this, too.

He recruited several outstanding researchers from outside the agency at universities and medical centers. Soon, several prominent scientists accepted senior leadership positions at the NIH. Zach W. Hall, Ph.D., and later, Gerald Fischbach, M.D., came to lead the National Institute of Neurological Disorders and Stroke (NINDS). Richard Klausner, M.D., took the helm at the NCI; Alan I. Leshner, Ph.D., at the National Institute on Drug Abuse (NIDA); James F. Battey, M.D., Ph.D., at the National Institute on Deafness and Other Communication Disorders (NIDCD); Allen M. Spiegel, M.D., at the NIDDK; and Steven E. Hyman, M.D., at the National Institute of Mental Health.



As Varmus' deputy, Ruth would often accompany him to Capitol Hill when he testified before Congress on a range of issues. From past experience, Ruth was accustomed to interacting with lawmakers, and she had forged several close alliances with several senators and representatives over the years. During her time at the NIGMS, Ruth had worked closely with Congressman William H. Natcher (D-KY), and in her first year working with Varmus, Congressman Natcher was the chairman of the powerful U.S. House Committee on Appropriations.

"Mr. Natcher was one of the most charming gentlemen from Kentucky that one would ever meet," Ruth described. "He had all the charm of a Southerner and was very deferential, not just to women, which he was, but to scientists as a whole, and he was totally dedicated to making sure that NIH's budget would be as good as possible."

Congressman Natcher had been in Congress a very long time, having been first elected in 1953, and Ruth had testified before him many times in the 1970s and 1980s. The two had become friends and colleagues: Congressman Natcher saw Ruth's input and guidance as critical in doing his own job. Congressman Louis Stokes (D-OH) noted later, "Bill Natcher was one of [Ruth's] greatest admirers."

Congressman Natcher's death in 1994 was mourned by many people in Washington and at the NIH. President Clinton attended the funeral in Bowling Green, Kentucky, as did Harold Varmus. Ruth was also invited, and the two traveled together as part of a large assemblage of planes that took off from Andrews Air Force Base, southeast of Washington, DC. Ruth remembered the event as very fitting for the man she knew to have a great heart and a special respect for her NIH home.

Ruth had worked with Congressman Natcher many years before on a project unrelated to science but directly related to the NIGMS. She and her staff had come to a tipping point working at the Westwood Building in downtown Bethesda. "It had become almost uninhabitable," Ruth remembered, not so fondly. "I cannot tell you how many times the alarm would go off and there would be bomb threats and so forth, and nobody ever found anything."

With an overwhelming desire to obtain support for a new building, Ruth had then looked for options. She approached then-NIH Director James Wyngaarden, who told her that a special, rent-to-own contract could be arranged. The NIH would pay a contractor to build the building, pay rent for a number of years, and then own the building. Congressman Natcher was supportive of the idea, and he helped to encourage a Congressional appropriation. In turn, the building acquired his name.

The NIH broke ground for the William H. Natcher Building ("Building 45") on September 14, 1992. During the time that it was being built, Congressman Natcher became very ill and was hospitalized for several months across the street from the NIH at the Bethesda Naval Hospital. Ruth remembered that Congressman Natcher would watch the construction from his hospital bed, where he could see it firsthand.



Working with NIH Director Varmus from 1993 to 1999, Ruth would witness the steady march of progress: in science, in health, and in the government policies that affect both in one way or another. Over the six years, research advances continued to spring from NIH-funded research on and off the campus: the identification of genes that cause some cases of breast cancer and Parkinson's disease, proof that changes in diet and lifestyle can markedly decrease high blood pressure, and research toward the development of the first drug useful for preventing breast cancer in some susceptible women.

During this time, the Internet had become increasingly a part of people's everyday lives and a key conduit for researchers in many areas of science. The Human Genome Project was well under way, as were DNA-sequencing projects for a zoo-full of different model organisms that are a mainstay of biomedical research. Across the Atlantic Ocean, researchers had produced an identical copy, or "cloned," a mammal, Dolly the sheep. That scientific

achievement set off a cascade of concerns about the ethics of biology and medicine.

Science was moving fast, and some people were concerned that progress was outpacing society's ability to understand and deal with it. Struggles emerged, as science and society occasionally collided in unexpected ways. Managing these issues became a frequent focus for Varmus, and for Ruth, and together they worked hard to explain the science and its relevance to Congress, the media, and just about everyone who asked.



Ruth was close to many lawmakers, including Congressman Mark Hatfield (R-OR).

Another passion Ruth and Varmus shared was a deep concern for the value of basic research.

Beginning in the 1970s, as NIGMS director, Ruth worked very hard to convince several members of Congress that funding for science should not be “earmarked” for specific diseases. She had laid important groundwork, explaining time and again that peer review — not politics, advocacy groups, or even burden of disease — was the best decider of excellent science that ultimately benefits health. In part, she would explain, the choice of which science to support should depend on which methods are available and applicable to the biomedical problems of the day, and thus which ones are most amenable to solutions.

In the early 1990s, the pendulum had begun to swing again, toward pressuring the NIH to fund certain areas of research according to need determined by advocacy groups and forces outside the peer review system. Several members of Congress and a group of scientists had convinced the Institute of Medicine of the National Academy of Sciences to commission a study on how the NIH sets its priorities and receives funding sufficient to address them.

In a December 17, 1990 interview published in *Time* magazine, Leon E. Rosenberg, M.D., then a researcher at Princeton University, put it this way:

We need a group of people brave enough to be willing to set down a point of view for the next five to ten years and then to develop a consensus that will replace the one-year-at-a-time haggling. ... I would call upon the President to appoint a commission to develop policy guidelines for science in general and for biomedical research in particular. We haven't had a major policy statement in 50 years. Everything suggests not only that the time is right, but that the time demands such broad thinking.

“Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at NIH” was the 1998 report issued by this committee, which was chaired by Rosenberg, Varmus, and members of Congress, also offered suggestions to the committee, which then issued a final report. It recommended mechanisms to help NIH increase public input into the setting of research priorities, and the NIH quickly responded to each of these recommendations. Specifically, the report recommended that the NIH add additional public members to its Director’s Advisory Council. It also urged the NIH to create

new Offices of Public Liaison within the Office of the Director, as well as in each of its component institutes, so that interested members of the public could find opportunities to remain engaged with the NIH.

As part of the implementation of the report's recommendations, Ruth became involved in establishing the NIH Council of Public Representatives (COPR), and Varmus selected the first 20 members of the inaugural COPR "class." Its first meeting was held April 21, 1999, less than 10 months after Varmus had launched the nomination process.

At this meeting, Varmus delivered the group's charge:

"This council should have two functions that operate in differing directions," Varmus said. "On the one hand, the group should have a role in bringing NIH to the public. It should be a vehicle for transmitting NIH's views, activities and aspirations to the general public and to specialized constituencies."

"Also," he continued, "you should be bringing public views to NIH to help improve our accountability by looking at the way we do things, and advising us of the appropriateness of the actions we take."

The COPR members represented a range of professions, ethnicities, communities, and geographic locations. The group, modeled after the Advisory Committee to the Director (a scientific advisory group), would meet twice per year to communicate directly with NIH leadership and would present perspectives not of special interests, but "leave their hats at the door," to offer more global perspectives for and to the NIH.

Ruth could not have been more pleased with the outcome of the group's first meeting and of the general prospect of inviting public input on a broader scale.

"[The Council members] are enthusiastic and fresh and ask wonderful questions and make wonderful statements ... absolutely wonderful," she said.



During his years leading the NIH, Varmus convinced Congress to double the agency's budget: a process that began in 1998 and one that would have far-reaching consequences at the NIH campus and all over the nation, where most NIH funds are spent. Varmus also worked hard to obtain funding for a stunning new NIH Clinical Center, where Ruth had first worked at the NIH when she arrived in the mid-1950s.

On November 4, 1997, Vice President Albert Arnold “Al” Gore, Jr., and Senator Mark O. Hatfield (R-OR)—who had served as chairman of the Senate Appropriations Committee from 1981 to 1987 and again from 1995 to 1997—attended the groundbreaking ceremonies for what would become the Mark O. Hatfield Clinical Research Center. The next year, Building 20, NIH’s apartment building—which had been Ruth and Al’s first home on the grounds of the NIH—was demolished to make way for the expanded, state-of-the-art Clinical Center, the largest hospital in the world devoted to clinical research.

The NIH leadership changed soon thereafter as well. After leading the NIH for six years, on December 31, 1999, Varmus left to become the president and chief executive officer of Memorial Sloan-Kettering Cancer Center in New York City.

On January 1, 2000, Ruth became the acting director of the NIH for the second time in her life. The agency would once again be in her steady hands.



## At the Helm

*“Ruth did more than just connect existing circuits. She surveyed the culture of biomedicine and found the shadows where no wires yet reached. She laid those wires personally.”* — NIH DIRECTOR FRANCIS S. COLLINS, M.D., PH.D.

JANUARY 1, 2000, RUTH’S FIRST DAY of work in her second shift leading the NIH, was a landmark day: the beginning of a new millennium. Many people were worried that catastrophe might soon unfold with the appearance of the “millennium bug,” a curiosity of computer programming resulting from the practice of abbreviating a four-digit year to two digits.

People throughout the United States and the world worried about possible massive computer malfunctions when the New Year rolled in at midnight. The media published thousands of stories, and people stocked up on food, water, and living supplies.

Then, nothing happened: No nuclear power plants melted down, no planes crashed, and utility, transportation, and financial systems around the world continued to work just fine. The NIH, highly dependent upon computers for communication, scientific resources, data storage, and building functions, had made detailed contingency preparations, but Ruth was thankful this was one crisis NIH had averted. The emergency planning, however, would turn out to be a useful drill for other unexpected disasters.

Ruth was ready for anything. Taking charge meant just that, and Ruth interpreted the title “acting director” somewhat differently than some of her predecessors had. As she had said in 1993, when taking over for a few months before Harold Varmus arrived, Ruth saw no reason to keep the NIH in a holding pattern: She was prepared to take the helm right away.

“She was not *acting* while she was acting [director],” said Michael Gottesman, deputy director for intramural research at the NIH, and a cancer biologist. “[Ruth] was used to being in charge, and she was an outstanding leader.”

Ruth chose her colleague Yvonne Maddox to be acting deputy director. She had known Maddox since hiring her at the NIGMS in the mid-1980s, and in 2000, Maddox was serving as deputy director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). She was thrilled to be asked by Ruth to help.



As 2000 progressed, plenty was going on at the NIH. Varmus had worked hard with Congress and many agency stakeholders to boost support for the agency. His efforts succeeded, and the NIH was enjoying incredible financial support during a period that was called, informally, “the doubling.” Ruth knew that the generosity would require even greater responsibility: The NIH would need to be able to demonstrate what was accomplished with this significant investment. She worked tirelessly to stay apprised of progress—and to deliver that information back to Congress, and to the public.

As had been her routine at the NIGMS, Ruth worked extremely hard to prepare for congressional hearings. She and Maddox would consult with NIH institute directors to learn about research success stories, hot-button issues, and new scientific opportunities. She would later submit herself to what Maddox referred to as “murder board” sessions, at which top NIH staff drilled Ruth on potential questions that might arise from senators, representatives, and congressional staff.

Testifying before the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies in defense of the fiscal year 2001 president’s budget request for the NIH, on March 30, 2000, Ruth thanked the lawmakers for their support and assured them that she was taking care of business.

“Although this is the first time I have appeared before Congress to testify about the overall NIH budget, it has been my privilege to appear before this subcommittee annually for 19 years as director of the National Institute of General Medical Sciences and for six as deputy director,” Ruth said, directing her comments to Congressman John E. Porter, J.D., (R-IL). He had been a main architect of the budget doubling and was retiring from Congress and thus leaving his post as head of the subcommittee. She continued,

“Mr. Chairman, all of us, we at NIH, members of Congress and the citizens we serve, have similar expectations for medical research. ... In the last century, the scientific community, both public and private, worked in collaboration to cure or prevent once deadly infections that are now given no more thought than the common cold. I was fortunate enough to be at the forefront of the final development of the polio vaccine, one of the truly monumental achievements of the last century. ... As we begin a new century, medical science stands on the threshold of research advances that were once inconceivable. ...”

Ruth took very seriously the NIH’s need to stay sharply focused on its mission, continuing,

“By any measure, the amounts we received in FY 1999 and 2000—both nearly 15 percent increases—were dramatic and unprecedented. ... We feel confident of public support for our research enterprise, but are aware of our need to deliver to the public two things it wants most from the NIH: research advances, year after year, that improve the health of all members of society, and assurance that we spend the public’s money wisely.”



Ruth would have the opportunity to showcase many scientific and public health achievements during her tenure as NIH acting director from 2000 to 2002.

Ruth saw scientific investments that she had helped support many years before, at the NIGMS, grow and mature. One was the announcement on June 26, 2000, that the Human Genome Project public consortium led by Francis Collins, then-director of the NHGRI, had achieved a “working draft” of the DNA sequence of the human genome. The effort, under Collins’ leadership, came in ahead of time and under budget, both extraordinary achievements for a program of this size. The news was made public in a historic White House event announced by NHGRI Director Collins, along with J. Craig Venter,

Ph.D., of Celera, a company that had worked in parallel with the government effort, President Clinton, and, via videolink, British Prime Minister Anthony C.L. “Tony” Blair (because the project involved researchers working in the United Kingdom as well).

The human DNA sequence information was being housed in GenBank—a project helped along by Ruth many years before. This terrific resource would be freely available to scientists anywhere for their biomedical research experiments.

These investments were helping basic research thrive, and Ruth could not have been prouder.

Earlier, in March 2000, the NIH had launched the first phase of a consumer-friendly database, ClinicalTrials.gov, a portal for people to search for information on thousands of federally (and, later, privately funded) medical studies involving volunteers from all over the country. In announcing the resource, Ruth was sure to acknowledge the citizenry’s vital role:

“Most of the trials in the [ClinicalTrials.gov] database are funded by NIH institutes and centers, and result from a long, fruitful partnership between NIH and the American people, who support and participate in our work.”

Also in 2000, the Office of Research on Minority Health—established in 1990 and modeled after the Office of Research on Women’s Health—hosted a conference at which Ruth took the opportunity to renew her call for the value and necessity of diversity in science. She reported to the group that active recruitment efforts had helped increase the number of minority individuals participating in NIH-supported clinical trials, but she recognized the progress could not be equated with victory.

“... success in this area has been painfully slow, a fact we must sadly acknowledge,” Ruth said, noting that she was working on plans to raise the stature of the office to a center, which would give it the authority to award grants. Ruth made that happen later in the year, when the National Center on Minority Health and Health Disparities (NCMHD) was established and signed into law by President Clinton on November 22, 2000.



On the last business day of 2000, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established as the 27th independent component of the NIH. Ruth promptly appointed Donna J. Dean, Ph.D., its acting director. Ruth had mentored Dean and knew her leadership strengths: Dean

had served as a senior advisor to Ruth when she was NIH acting director, and she had held a senior position in NIBIB's precursor, the NIH Office of Biomedical Imaging Bioengineering. Dean eased into the role, working from a template that Ruth had helped to mold. During her first year of leadership at the NIBIB, Dean reiterated good advice she had gotten earlier from Ruth.

"I have found myself quoting something [Ruth] has often said, 'We do not think that we can differentiate between science that is relevant to health and science that is not.' We need all the disciplines to help us move toward better health for everyone."

As Ruth had noted years before, her view of the NIH was never as a power structure, but as a family—where care and respect were paramount. She saw the need for a healthy balance between the NIH director and the institute directors.

"I really believe this is a partnership, and I think that's what Congress had in mind when—in what I consider a stroke of genius—it set up the budgets separately," she said in an interview with the journal *Science* in 1993. However, Ruth did not interpret the relationship as "anything goes," either. "As far as I'm concerned, the institute directors are the board of directors, if you want to use corporate terms, for the NIH director."

As the months passed, Ruth enjoyed what she herself called "enormous support" from the NIH institute directors, with many of whom she had been a long-time colleague. That teamwork would pay off for years to come.

"Ruth had tremendous command of the facts and nuances of past decisions and current issues," said Jeremy M. Berg, Ph.D., who knew Ruth well and served as NIGMS director from 2003 to 2011. In fact, his decision to come to the NIH had been cemented by a personal phone call from Ruth.

"She had a clarity of mind and the ability to appreciate many dimensions of an issue—scientific, human, political, and other—that made her contributions to discussions particularly compelling," he said.

Berg noted that Ruth's strength wasn't so much in letting a consensus view develop on its own but rather in her ability to enter a discussion having already considered in advance its many perspectives. That ability, Berg said, left a lasting mark on her fellow leaders at the NIH.

"[Ruth's] rigorous and sensitive approach led many in the NIH leadership to ask themselves, 'What would *Ruth* do in this situation?'"



In keeping with Ruth's action-oriented style, she made several hires to top leadership positions while serving as NIH acting director. One of them would be Lawrence A. "Larry" Tabak, D.D.S., Ph.D., to lead the National Institute of Dental and Craniofacial Research. Ruth saw Tabak, a fellow Brooklyn native and accomplished dentist-scientist who focused on basic research questions, as a comrade whose principles meshed with her own.

"As NIH focuses on racial and ethnic health disparities, we are fortunate to have someone who has designed and managed a successful training program aimed at recruiting and developing minority investigators," she stated in an announcement to NIH staff of Tabak's pending arrival.

When he joined the NIH, Tabak would become part of a "club" of scientists and administrators known as the FoRKs. The "Friends of Ruth Kirschstein (FoRKs)," an informal designation known to the group only, was a very special guild.

Stephen I. Katz, M.D., Ph.D., acquired this recognition as well. Katz had been hired by NIH Director Harold Varmus to be director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases in August 1995. Katz was a research dermatologist, working in the NCI's intramural program, and a highly regarded researcher who studied the immunology of skin. Ruth was very impressed with him.

"I was overwhelmed by the interview with Steve, and Steve has become one of our really outstanding directors," Ruth said after she had watched him on the job for a few years.

But, like anyone else, Katz had encountered challenges in his leadership position early on, and he had turned to Ruth for help. He had known Ruth personally, since Ruth's husband Al had been Katz' boss for 20 years, and the three of them gathered socially, at concerts, for dinner, or at other activities. One year, Katz remembered, Ruth and Al accompanied him and his wife to the Wolf Trap Foundation for the Performing Arts to watch Katz' daughter, a stage actress, perform in *Fiddler on the Roof*.

"Ruth was genuinely interested in people's lives," said Katz. "She wasn't just 'all business' — Ruth really wanted to know the substance of people. She cared a lot, and did whatever she could to make sure they landed in the right place."

"Ruth was a major mentor to me," Katz continued. He recalled a specific experience where she guided him soon after he had assumed the director post. "I was facing a very difficult personnel-related challenge that went way

beyond my level of experience,” Katz recalled. “Ruth really helped focus my thinking and presented a practical solution to the problem.”

Michael Gottesman was close to Ruth as a friend and a colleague, and as such he was a part of the Ruth’s “guild.” He explained that the FoRK group was about getting and giving advice, friendship, as well as a platform for mentoring. Gottesman explained that to “qualify,” Ruth required several things: You had to respect science, have a sharp intellect, and have leadership potential.

Gottesman summed it up more practically, “You had to be smart and have common sense,” he said, joking that the two traits don’t necessarily coexist all that often.

Developmental biologist Judith H. Greenberg, Ph.D., whom Ruth hired to be a program director at the NIGMS in 1981, benefited from Ruth’s guidance for decades and enjoyed interactions over the many years the two crossed paths at the NIH. When Ruth hired her, Greenberg had been a senior staff fellow at the then-National Institute of Dental Research and was early in her career.

“I think [Ruth] saw herself in me,” Greenberg said, “She followed what I was doing, and she put me forward for [positions]. She mentored me, and she watched me ‘grow up.’”

NIAID Director Tony Fauci was another ally, and he often traded advice with Ruth. “We were mutual friends and fans [of each other],” he said. The two worked together on countless issues in science and in science policy.

Fauci, who had come to the NIH in the early 1970s, said that even then, Ruth was already somewhat of an institution. Over the years, she watched over many careers, including his own, he said, always expecting the best.

“When you think of integrity, you think of Ruth,” Fauci said.



The second year of Ruth’s NIH acting directorship would prove to be an interesting one. It began mostly uneventfully, although the recent change of power in the nation’s capital with the election of President George W. Bush had introduced a new tone in Washington, DC. The second half of 2001, however, would really put Ruth’s leadership skills to the test. One issue that arose in late 2001 was a policy announcement that threw the NIH and scientific community into a state of confusion.

On August 9, President George W. Bush announced that federal funds could be used to support stem cell research using only those existing lines of human embryonic stem cells that met certain criteria. Considerable debate had arisen in social and political circles about the ethics of using human cells obtained from very early embryos for research purposes. At the time, the cells in question had not been supported by NIH funds.

President Bush attempted to satisfy the concerns by allowing the research to continue, but only on very specific terms. Although on their face the restrictions he defined appeared to be straightforward, implementing them on a nationwide scale required a careful inventory of embryonic stem cells that had been created by U.S. companies or by researchers in other countries. The job required a lot of work and a good deal of tact in talking about both progress and problems.

To get things under way, Ruth called in Judith Greenberg, who was by then a division director at the NIGMS. Greenberg acquired all the relevant data about existing cell lines that would be necessary to make decisions. Because the lines came from such different sources and had variable amounts of descriptive information, the task was very challenging and time-consuming. In part, Greenberg reasoned, Ruth had chosen her for the task because Ruth knew Greenberg would work hard and stay neutral and calm while sifting through all the information.

Lana R. Skirboll, Ph.D., director of the NIH Office of Science Policy and the agency's lead on policy issues related to fetal tissue, cloning, and stem cell research, then used the data to guide a group of NIH staff to draft the 2000 (and later, a 2009 version) of the NIH Guidelines for Research Using Human Embryonic Stem Cells. The process was long, complicated, and politically charged.

The NIH also developed a registry of the known human embryonic stem cell lines so that researchers could identify in their funding applications which sources of stem cells they planned to use. The number of eligible cell lines, originally predicted to be over 100, was actually far less, only about two dozen, that qualified as satisfactory for NIH-funded research.

Carrying forward the task of communicating this news to the scientific community fell to Ruth as NIH acting director. She depended upon NIDCD Director James Battey, who had been appointed by Varmus as the chair of the stem cell task force, or science policy director Lana Skirboll to respond to questions, depending upon the nature of the question.



The second major event of 2001, about one month later, would eclipse the stem cell issue for a while.

On September 11, 2001, NIH employees learned that the United States was under attack: terrorists had brought down the Twin Towers of the World Trade Center in New York City and the Pentagon building in Washington, DC, by hijacking and crashing airplanes into the buildings. The terrorists had also targeted either the Capitol building or the White House, but that plane had crashed in rural Pennsylvania, near the town of Shanksville, after passengers on board attempted to acquire control of the aircraft. No one aboard any of the planes survived. In all, nearly 3,000 people—including occupants of the buildings, bystanders, and rescue personnel on the ground—perished.

As with the rest of the nation, the news transformed the peaceful Bethesda campus into a tumult of disbelief, worry, tension, and, soon thereafter, a deep sense of grief.

In less than a half-hour, the federal government had shut down, with only essential workers to remain. Ruth and Yvonne Maddox got busy organizing and implementing plans as well as staying apprised of instructions and guidance from the HHS and the White House.

Ruth and Maddox both had early meetings the morning of September 11, and they were in their offices when the first plane hit in New York City. Ruth called a meeting of all of her senior staff to discuss an official NIH response and to set the stage for enhanced security measures.

That would be the first of dozens of meetings to follow. A key issue to work out was determining an exit plan for NIH employees to leave the sprawling campus in the event of another potential attack, and as a key government official, Ruth was assigned security protection on her person whenever she traveled by foot or by car.

“The period of about two weeks following the attack was the most intense of any that I have experienced at NIH,” Maddox remembered.

NIH staff were alerted to breaking news and given instructions about what to do, and—in an act of extraordinary generosity—the NIH family stepped forward to donate blood in unprecedented numbers, overwhelming the Clinical Center’s capacity to store it. Ruth issued emails of concern and support, as did HHS Secretary Thomas George “Tommy” Thompson. Grief counselors had been made available, and the Clinical Center’s spiritual ministry department organized and offered an ecumenical service, providing

an opportunity for prayer and remembrance. Other NIH employees, as volunteers of the PHS-1 Disaster Medical Assistance Team, quickly mobilized to what was called “ground zero” at the World Trade Center in the weeks following the attacks. Members of the NIH’s genome research community and David Lipman’s group at the National Library of Medicine developed new genomic techniques to allow identification of human remains from ground zero in New York.

Ruth and Maddox could never have imagined being in the middle of such an awful unfolding tragedy, and yet they pressed on. Also a vital helper to getting through the disaster was Charlette Bronson, Ruth’s assistant for many years, first during the time Ruth served as NIH deputy director from 1993 to 1999 and then later when Ruth served as NIH acting director from 2000 to 2002.

On shepherding the NIH family through the 2001 terrorist attacks, Bronson remembers, “The [Maddox-Kirschstein] team certainly was put to the test during the trials and tribulations of 9/11.”

“And if I do say so myself, my girls took care of business and held it down.”



The 9/11 tragedy had a lasting impact on the nation, and effects on the NIH would be no exception. The grassy, tree-lined campus that resembled a college much more than a government agency would never be the same. At the December 6, 2001 meeting of the Advisory Committee to the NIH Director, Ruth provided an update on just how different things would be.

Explaining that in the past, the NIH’s attempts to require employees to wear identification badges had fallen short, Ruth said, “Scientists are a very independent group, and some resisted. But Sept. 11 changed absolutely everything. ... a perimeter fence will have to be built around this beautiful, open campus.”

In truth, plans for the fence had already been in place after the April 19, 1995 terrorist bombing of the Alfred P. Murrah Federal Building in downtown Oklahoma City. That tragedy had claimed 168 lives and injured hundreds more. As a federal facility, the NIH was also at risk, its senior leadership had already decided after the Oklahoma City tragedy, but the 9/11 events created a new sense of urgency to move even more quickly.

“We’ll try to make [the fence] attractive and not too difficult to manage. It will take some time to do. But there is no question we’re an attractive target—we’re the world’s premier biomedical research institution,” Ruth said.



YVONNE MADDOX

While leading the NIH, Ruth and her deputy, Yvonne Maddox, consulted frequently with government officials, including then-HHS Secretary Tommy Thompson (left).

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As NIH acting director, Ruth was multitasking every day. The job required handling difficult situations and dealing with unexpected problems as well as the routine aspects of running a huge organization smoothly.

Ruth also used the leadership position to rally for important causes that affected biomedical research and the American people. She continued to push for wider representation of women and minorities in research as well as in scientific jobs.

“She truly was one of the pioneering women in science,” said NIAID Director Tony Fauci, adding that her concern was definitely genuine. “She made [diversity] a real part of her career, not just something she had to do.”

Ruth continued to stand her ground on issues she considered important, discounting attempts to prove that health disparities were a problem too difficult to solve. At the December 2000 meeting of the NIH Advisory Committee to the Director, John Ruffin, Ph.D., who at the time directed the Office of Minority Health at the NIH, was describing recent legislation that, the month before, had authorized creation of the NIH National Center on Minority

Health and Health Disparities. Ruffin walked the group through the details of how the NIH would construct the center. When some of the committee members expressed skepticism that “throwing money at the problem” would have any impact on dissolving health disparities, Ruth chimed in and offered a humorous antidote to the criticism.

“The only thing I don’t know how to do is print money,” Ruth said, affirming her deep-seated commitment to getting the job done, one way or another. On January 9, 2001, Ruffin was formally sworn in as the Center’s first director by then-Deputy Secretary of the HHS Kevin L. Thurm, J.D. The ceremony was held in Ruth’s office and attended by Congressman Jesse Jackson Jr. (D-IL) and former Congressman Louis Stokes (D-OH).

“Spreading the wealth” was another of Ruth’s specialties, dating back to her NIGMS days in establishing training programs at universities and at minority institutions that might not get NIH funding without a push.

As NIH acting director, for example, she supported the creation of a pilot program, the Biomedical Research Infrastructure Network, as a subcomponent of a larger program aimed at broadening the geographic distribution of NIH research funding. A key goal was to increase the competitiveness of scientists at colleges and universities in states with little or no NIH funding, and in 2001, that was nearly half the number of states in the nation. The pilot proposed planning and feasibility grants to encourage schools to collaborate toward fuller national participation in biomedical research.

Here again, Ruth confronted resistance from her advisors, who warned her that “throwing funds on infertile ground” may not be a responsible use of NIH money. To which Ruth replied that without giving the idea a chance, it would be impossible to know whether the ground was fertile or not.

Ruth’s capacity for, and dedication to, connecting people, institutions, and opportunities did not go unnoticed. As observed years later by Francis Collins, who had left the NHGRI in 2008 but returned to the NIH in 2009 to serve as NIH director: “Ruth did more than just connect existing circuits. She surveyed the culture of biomedicine and found the shadows where no wires yet reached. She laid those wires personally,” Collins said.



After 9/11, the remainder of Ruth’s tenure as NIH acting director witnessed more science advances and continuing budget increases for the agency, including a surge in funding for counterterrorism. Fauci, director of the

NIAID, formulated and released that institute's Counter-Bioterrorism Research Agenda, which described an accelerated research plan for the most threatening agents of bioterrorism: smallpox, anthrax, and plague. While Fauci led the post-9/11 bioterrorism research planning, he acknowledged that Ruth played an active and crucial role as a sounding board and advisor during that time.

By spring of 2002, Ruth and the rest of the NIH learned that she would be stepping down, as well as who the next NIH director would be. On May 2, 2000, Elias A. Zerhouni, M.D., executive vice-dean and professor of radiology and of biomedical engineering at the Johns Hopkins University School of Medicine, was confirmed by unanimous voice vote of the full U.S. Senate to lead the NIH, and his first day was a few weeks later, on May 20, 2002. In announcing his vision for the NIH under his leadership, Zerhouni spoke of his desire to embrace "team science" in new ways. Zerhouni's NIH tenure would ultimately be best known for his design and implementation of the NIH Roadmap for Medical Research, a plan that encouraged groundbreaking cooperation among NIH institutes along with shared funding for projects that overlapped their scientific territories.

At the June 6, 2002 Advisory Committee to the NIH Director meeting, Ruth handed over the gavel to Zerhouni. Several of the committee members offered appreciation and gratitude for her service leading the NIH in the interim between Varmus and Zerhouni.

One of the members, Donald E. Wilson, M.D., then vice president for medical affairs and dean of the School of Medicine at the University of Maryland, knew Zerhouni well since the two were at neighboring institutions. After welcoming the new leader, Wilson turned his attention to Ruth.

"For at least the last 30 years, I've been an employee of the NIH for several days a year, and over this time it's been my privilege to work with our Ruth Kirschstein, and I just want to thank her for all she's done over the years."

Wilson's comments let loose a barrage of salutes to this woman who had done so much for the NIH in the nearly half-century she had been in Bethesda. Ever modest, Ruth tried to quell the tributes until Zerhouni himself recognized her obvious success.

"On my last day, I wish there would be as much unanimous sentiment," he said.

Several years later, at a symposium honoring Ruth's many contributions, Wilson summed up his views.

"As I look back, it seems like she was always there."

## Always There, Always Prepared

*“Ruth came to work every day with fiery-like enthusiasm and a laser-like focus.”* — FORMER NIH DIRECTOR ELIAS A. ZERHOUNI, M.D.

AFTER STEPPING DOWN FROM HER position as NIH acting director in June 2002, Ruth remained active and involved in the agency. From 2002 to 2009, Ruth served as senior advisor to the NIH director, an umbrella role that would see her perform a range of duties that called upon and drew from her extensive leadership experience and the deepest institutional knowledge anyone knew of at the NIH. She also filled in as Zerhouni’s deputy director from the time he arrived until February 2003, when Zerhouni appointed Raynard S. Kington, M.D., Ph.D., MBA, to take that post.

“Ruth came to work every day with fiery-like enthusiasm and a laser-like focus,” said Zerhouni, who appointed her as his senior advisor.

Although she would not work day-to-day with Zerhouni, with that title, Ruth would be called on for all sorts of tasks that hinged on her deep knowledge of the NIH and her amazingly broad reach across its thousands of staff. She never forgot a name and would always be ready to recommend a person for a top position.

“You need another woman on that committee,” she would often say.

Among the tasks she was given was preparing and delivering follow-up reports on issues she cared about and had worked on for years—such as research training and the preparation of young scientists. She maintained

ongoing interactions with NIH leadership about issues related to diversity and about various matters pertaining to establishing and maintaining ethical standards at the NIH. From her days at the NIGMS, Ruth had very high expectations of NIH staff and was ever concerned with upholding the agency as one of the crown jewels of the U.S. government.

Former NIGMS Director Marvin Cassman put it this way, “[Ruth] could have a very low boiling point, which usually showed up when she found behavior that in any way compromised the ability of the institute or the NIH to carry out its mission.”



During the period in which Ruth served as senior advisor to the NIH director she was also called upon, again, to serve in an acting leadership role. This time, beginning in November 2006, it would be to provide interim leadership to the National Center for Complementary and Alternative Medicine (NCCAM). The Center’s director, Stephen E. Straus, M.D., who had worked hard to strengthen the scientific base in an area that was weak, had become suddenly ill with a brain tumor that would prove fatal within two years.

Ruth would have taken on the challenge regardless, but she had helped to recruit Straus, an immunologist, to the position. She felt she could keep her colleague’s momentum alive until a permanent replacement could be found. Moreover, she found it important to facilitate that process as well.

The replacement would be one of the group of female NIH scientists Ruth associated with, mentored, and continually supported for years as their careers grew—Josephine P. “Josie” Briggs, M.D., a kidney specialist who had worked in the NIDDK for many years. Briggs had recently left the NIH to work at the Howard Hughes Medical Institute. When she saw the job announcement for NCCAM director, she was enticed to come back, and Ruth put forward her name. Zerhouni hired Briggs in 2008.

Briggs recognized, as did Ruth, that a lot of work would need to be done to advance the evidence base in the fledgling area of the science of complementary and alternative medicine. Of Ruth’s time at the NCCAM, Briggs said a key feature was filling the vacuum that had emerged when Straus died and other staff left. Ruth made some key decisions and “exercised superb judgment,” Briggs noted, enabling Briggs to walk into the job and get going quickly. Ruth had taken care of some problems and had already begun to attract a new cadre of well-trained scientists to work in the field.



NIH HISTORY OFFICE

Former NIH Directors Bernadine Healy, James Wyngaarden, Elias Zerhouni, and Harold Varmus (left to right) and Ruth (center) at the 2004 Mark O. Hatfield Clinical Research building dedication.

But aside from Ruth’s help with the NCCAM, what Briggs appreciated most about Ruth was her wise counsel of women leaders at the NIH like herself. “She knew all of us and mentored us continually,” Briggs said. Briggs especially admired Ruth’s ability to hold her own as a woman leader.

“What an incredible stalwart she was among all the alpha males [at the NIH],” Briggs joked.

Briggs noted that among the many people Ruth mentored and maintained within her inner circle—which also included men—it was common knowledge that Ruth was a tough critic. She did not like everybody, Briggs explained, and she was not an “automatic cheerleader” by any means. For “her” women, especially, Ruth set extraordinarily high standards, and she would hold people to them.

“She expected really great things from all of us,” Briggs said. “She was a critic of all things sloppy.”

Beyond the ability to achieve goals and succeed in leadership, Ruth believed that, aside from dressing appropriately and strategically, as any man would also do, women should distance themselves from “feminine activities.” Briggs recalled an experience in which Ruth was a speaker at a scientific lecture and became “infuriated” when two women attending the meeting were knitting in the front row.

Ruth’s many women envoys continued to carry her torch. Sue Shafer, Ruth’s first hire at the NIGMS in 1974, worked tirelessly for many years to



increase the number of minority and female scientists in biomedical research. She, too, acquired Ruth's gift for mentoring others.

"Watching other people grow and succeed has been the most rewarding part of each of my jobs," Shafer said when she retired from the NIH in 1999.

Judith Greenberg, another of Ruth's protégés who in 2011 was acting director of the NIGMS, said that Ruth was willing to do whatever it took to help the NIH. "She was the ultimate good soldier."

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During the middle 2000s, the usual mix of ups and downs affected the NIH. In 2003, the budget-doubling period came to an end, requiring then-NIH Director Zerhouni to orchestrate as "soft a landing" as he could. Zerhouni's vision for much more extensive collaboration among the components of the NIH would culminate in his September 30, 2003 announcement of the NIH Roadmap for Medical Research.

Consistent with his vision of collaboration, Zerhouni encouraged the establishment of the Common Fund, a shared source of funds to support research efforts that involved more than one NIH component. Zerhouni also pushed for a larger slice of funding within the NIH Office of the Director, beefing up the Director's Discretionary Fund, an effort that Ruth supported and helped execute.

The next year, 2004, saw the grand opening of the Mark O. Hatfield Clinical Research Center. The rebuilding and modernization of the largest medical research hospital in the world was a seven-year project initially launched by then-NIH Director Harold Varmus. The grand opening lauded the facility as the "House of Hope." Fittingly, in September 2011, the NIH Clinical Center won the Lasker-Bloomberg Public Service Award, honoring its contributions to research and health over many years.

From 2003 to 2005, the mood at the NIH became clouded by allegations from some members of Congress that the agency's conflict-of-interest regulations were too loose. The HHS would ultimately issue a "sweeping" ban on consulting and other activities that employees could perform outside of their NIH positions. Staff on the campus were both confused and angry over the rules, which they felt targeted all NIH employees with complex reporting requirements and stock-holding limitations, when only a few scientists had exercised poor judgment in their outside activities.

Ruth had an office in NIH's Building 1 during the years she served as senior advisor to the NIH director. It was next door to the end-of-the-hall corner suite of NIH Deputy Director for Intramural Research Michael Gottesman. "Ruth was a wonderful advisor ... she was wonderfully capable of keeping people out of trouble." Gottesman also considered Ruth's diligence and energy extraordinary, "Ruth worked at least 24 hours a day," he joked.

Ruth and Al shared a work ethic that involved little break time. The two were so dedicated to their careers, and to the NIH, that the lines between work and play were blurry. However, for the most part, Saturdays were days off, and Al and Ruth immersed themselves in culture.

They always had season tickets (the best seats in the house) to performances of the National Symphony Orchestra at the Kennedy Center in northwest Washington, DC. They would first attend a matinee performance, walk to neighboring Georgetown to eat, then walk back to the Kennedy Center and work upstairs in the building for a few hours before attending another, evening performance of the symphony.



Ruth shares the stage with friend and colleague Michael Gottesman (center) as he receives an NIH Director's Award in 2002 from then-NIH Director Elias Zerhouni.

Many NIH scientists who also frequented the symphony concerts were dumbfounded to see Ruth reading "pink sheets," or summary statements (the reviewer-comment pages of NIH grant applications), during concert intermissions. Ruth did not think twice about it. To her, it was free time (as was the same period during theater performances and before the lights went out at

the movies), and the task had to get done. Given the widespread availability of portable electronic communications devices, we are now used to these stolen moments of work embedded in periods of leisure, but Ruth was one of the original multitaskers who combined work with relaxation.

Other weekend days, Al and Ruth would visit the multitude of free museums in the nation's capital; however, both were New Yorkers at heart, and they also loved to stroll the streets of that city to visit all sorts of galleries and museums. Lining the walls of the staircase in Al and Ruth's NIH campus home were original prints from New York artists—purchased with the small honoraria each received from various scientific speaking engagements. During most of their careers at the NIH, Ruth and Al never took any vacation time away from work; this was part of their dedication to their jobs and to their stewardship of the public funds that paid their salaries.



Absolute diligence and fastidious preparation explained Ruth's success at the many things she tried. Reading all the pink sheets kept her in the know: with her grantees, with her staff, with Congress. Walking the halls of the NIGMS and talking all day to people kept her informed of brewing crises or upcoming opportunities. Working for months on congressional testimony assured that she was always prepared for any question and would never be caught off guard.

That Ruth worked so hard on documents for Congress, in particular, paid off enormously. She was legendary on Capitol Hill for her ability to spout information about not only her own interests but also those of sister institutes or other organizations with which she had some professional alliance.

"She never glossed over anything, and she never lied to [Congress]," said former HHS Secretary Donna Shalala.

Another guiding light was a strong moral compass. Ruth's life experiences, beginning from her earliest childhood days in Brooklyn, had etched a sense of justice that helped her persist throughout many challenges.

"I think my moral and ethical underpinnings came way before I ever came to the NIH. I have not wavered in them," she said. "I honestly believe that, whereas many people I know have become more careful, conservative [after being here a while]—I do not mean that necessarily purely politically, but in their outlook on things—if anything, I have become less so. Not that I have not been careful, but less conservative."

## Ruth's World

*"I have felt, and still feel, that there is no more worthy endeavor than to serve the country, its people, and the science which has given me so much joy." —RUTH L. KIRSCHSTEIN, M.D.*

RUTH WAS 83 WHEN SHE DIED peacefully on October 6, 2009. Al, Arnold, and Arnold's wife Barbara were by her bedside at the NIH Clinical Center: She had always said she wanted to die at work, at her beloved NIH.

About two years earlier, during a routine medical checkup, Ruth learned, through abnormal blood counts, that she had cancer again. But this time it was in her blood, a relatively rare type of cancer called multiple myeloma. She and Al had fought a battle with cancer before, and so they readied themselves. Al found the best myeloma specialist he could find for his wife, and the three discussed the situation.

Ruth began treatment, responding well at first, Al said, until the cancer reappeared. Ruth went through a series of experimental treatments, one after another, but she and Al remained hopeful about the power of cutting-edge medical research to heal. It had, before, and they were steadfast and patient about trying all the options.

"They'll find a new [drug]," Al remembers telling Ruth, "Don't worry, we'll just try another one."

Ultimately, there weren't any new ones, and Ruth lost the battle being fought inside her own body.

Until the week before her death, Ruth was still working.

She had continued to phone in to the biweekly meetings of the NIH institute directors, and she had kept up her frequent calls with colleagues, confidants, and anyone who needed something from her. And she talked to Al from her hospital bed, by phone, at least ten times a day. The couple was separated by only a few hundred feet, but neither could get around easily, and the phone kept them connected.

After learning of Ruth's passing, NIH Director Francis Collins sent a broadcast email message to the NIH community, "The world has lost one of its dearest, most dedicated public servants—one with a huge heart and brilliant mind."

It was clear by their tributes that many felt the world Ruth left behind was most definitely better because of her. A memorial symposium held in Ruth's honor in May 2010 was held in a lower-level auditorium in NIH's Natcher Building. Dr. Collins announced to the audience that the auditorium had been renamed in her honor to reflect her substantial and sustained impact on the NIH. To enthusiastic applause, he unveiled a beautiful plaque bearing her picture and an inscription. Considered by many at the NIH to be one of the nicest, if not the nicest, meeting spaces on the campus, the Ruth L. Kirschstein Auditorium is booked daily for important scientific conferences hosting researchers from all over the nation and the world.

At that memorial symposium, a long list of fans offered memories and anecdotes about Ruth.

Among them was Senator Tom Harkin (D-IA), who spoke to her profound influence, "Ruth's greatest accomplishment—her living legacy—are the people she inspired and continues to inspire. NIH: You all stand not in Ruth's shadow, but in her light," Senator Harkin said.



During Ruth's 83 years, there were huge changes in society, in politics, and in science. Throughout her life, Ruth witnessed extraordinary advances in public health and an explosion of knowledge resulting from investments in basic biomedical research. People were living nearly twice as long in 2009 as they did at the turn of the 20th century.

When Ruth was born in 1926, major scientists of the day were Albert Einstein and Sigmund Freud. By far, most of the noted scientists were male and white. People died routinely of infections, and polio epidemics

were commonplace. The NIH was little more than a few-men show, “the Laboratory of Hygiene,” which had started in New York and then moved to Washington, DC.

When Ruth entered college, in the early 1940s, the United States was at war, and the economy was bleak. DNA had been isolated in the laboratory, but its structure and function were still a mystery. The antibiotic properties of penicillin and other molecules had been discovered and were beginning to be applied. Women in science were still rare: geneticist Barbara McClintock, Ph.D., and biophysicist Rosalind E. Franklin, Ph.D., were notable exceptions. The year Ruth finished college, scientists isolated the poliovirus, but it still wreaked havoc among children.

After Ruth completed her medical training and arrived at the NIH in the mid-1950s, the double-helix structure of DNA had been solved, and a polio vaccine had been developed. Biomedical research at the NIH was a hotbed of activity, with many of the country’s best scientists working on treatments and cures for a range of diseases. Cancer chemotherapy was born.



Ruth’s personal and professional triumphs were many. She played a significant role in assuring the safety of the polio vaccine, and millions of people were spared this disabling disease as a result of the pioneering work she and others did. She shepherded the NIH through many achievements and as many crises. And she nurtured the lives and careers of so many.

“[Ruth] will be fondly remembered in many ways through the unique lens of each of the many individuals whose careers gained direction and success through her guidance and direction,” said former Office of Research on Women’s Health Director Vivian Pinn.

However, Ruth’s strongest passion—increasing diversity in science—had mixed results. While minority representation has increased, it still has a long way to go. Of all the achievements Ruth sought, this was one area where her work was not done when she died.

“If you had told me in 1974 that we were going to have as little effect on the number of minority investigators as we have had, I would not have believed it. I would have thought we would have done better,” Ruth said in 1999. “It is one of the great disappointments of my life.”

Yet, she remained ever hopeful for improvement, and at the same time continued on her efforts and encouraged others to carry the baton further.

And there were high points: She liked to tell a story about one young man who she believed had overcome unimaginable odds and could be seen as a clear success.

“His name is Jose Vargas, and he just won the Rhodes Scholarship,” Ruth explained. “He came from [the Dominican Republic] ... He is going off to Oxford to work in a prestigious laboratory in genetics with a wonderful geneticist. ... He has been admitted to Harvard Medical School, and they will defer him for the three years that it will take him to get the equivalent of a Ph.D. in England.”

“Vargas got his start in a special program at the NIH for gifted high school students, and then he was partially supported through college as an NIH Undergraduate Scholar,” recalled Michael Gottesman later. For his Rhodes Scholarship, Vargas earned a D. Phil. in genetics from Oxford, and he met his future wife there. They returned to the United States, and he earned his M.D. from Harvard Medical School. After doing a residency at Johns Hopkins, he is currently a postdoctoral fellow at the NIH studying the genetic basis of coronary heart disease.

“He came to the United States at the age of 13 ... Talking to him was one of the most exciting experiences of my life,” Ruth said.



Ruth and Al called the NIH their home for more than 50 years, walking its paths and holding hands all the while. Even though she traveled very little, Ruth’s impact was vast.

“You could go anywhere in the world and find a Ruth connection,” said Congressman David Obey (D-WI), former lawmaker who saw Ruth testify so many times before Congress and had worked closely with Ruth on a range of science policy-related issues.

Congressman Obey considered Ruth and her husband to be humanitarians of the highest regard.

“Ruth and Al cared so much about people,” he said. “When they learned that someone they knew had an illness, they didn’t react as scientists, but as human beings.”

Throughout their time at the NIH, NIH’s “power couple” considered it both a duty and a pleasure to help anyone who asked to find medical advice on a vast number of health-related issues. Their concern and diligence in meeting this need left innumerable marks.



Wendy Wertheimer and Ruth enjoy a light moment.

“We could fill a stadium with the number of people that said, ‘Ruth and Al saved my life,’ or, ‘my secretary’s life,’ or ‘my mother’s life,’” said friend Wendy Wertheimer. “Together, they were the world’s greatest counseling and referral center.”

Charlette Bronson, Ruth’s longtime assistant and friend, was in awe of Ruth’s many talents. Bronson had met Ruth in the 1980s when the two worked in the Westwood Building in Bethesda, but the two women had not crossed paths professionally. Nonetheless, Bronson would go on to work for Ruth during her several years spent in Building 1.



“Who knew that a decade later, [Ruth] and I would begin a working relationship that blossomed into a special one which was dear to both of us and would last until her death?” Bronson said at Ruth’s 2010 memorial symposium, next speaking to her friend’s ability to work together and to maintain a magnificent marriage:

“When reminiscing about [Ruth], one major characteristic which comes to the forefront is teamwork. Any woman married to one man for 59 years definitely knows a lot about teamwork,” she joked, but only half jokingly, and winning a hearty round of applause and laughter from audience members who clearly seemed to agree.



The many accolades and awards Ruth received over the years didn’t mean too much to her, and the awards often ended up in a closet. Yet, a few honors could trigger the release of her customary humility.

For example, in 1985, Ruth was given the Presidential Rank Award for Distinguished Executives, the highest rank a civil servant can earn. She was to receive the award from President Reagan and planned to bring Al along to attend the ceremony at the White House. They traveled downtown to the Old Executive Office Building, where official clearance was required to be admitted. Ruth had been cleared through, but the officials could not find the papers for Al, although she knew he had sent them.

Ruth was angry.

“They kept telling me to move, and I said, ‘I am not going without him.’ I made them do the whole thing and get [the clearance], and finally he got cleared to go in with me,” Ruth remembered with a chuckle.

Among the awards of which she was most proud was the Federation of American Societies for Experimental Biology’s (FASEB’s) Public Service Award. When she got a call from FASEB president Shu Chien, M.D., Ph.D., in 1993, telling her she had won it, Ruth was shocked and overwhelmed with the honor. Upon accepting the prestigious award at the formal ceremony, she summed her feelings:

“I have felt, and still feel, that there is no more worthy endeavor than to serve the country, its people, and the science which has given me so much joy.”

On learning of Ruth's death, scientists, government officials, members of Congress, and many friends offered their remembrances of this woman who changed so many lives. Said Harvard developmental biologist and NIGMS grantee Marc W. Kirschner, Ph.D.:

"She kept the values and spirit of that greatest generation of American scientists active and passed that on to all of us ... When I hear a voice calling me to devote my time to service, it is her distinctive tone that echoes in my ears. I will miss that insistent tone."

Perhaps the biggest impact Ruth had is one that can never be measured. Today, about 70,000 trainees have received support from NIH grants that provide money to universities to set up high-quality research training programs. The majority of them are proudly designated Ruth L. Kirschstein National Research Service Awardees.

Kirschner continued, "I am sorry the young scientists of today will not have the opportunity to know Ruth, someone so sure she was right [that] she never flinched to work night and day to provide the opportunities for scientists young and old to make their best contribution."

At Ruth's memorial symposium, Wendy Wertheimer offered her own depiction of this remarkable woman:

"Ruth loathed pretentiousness, materialism, hypocrisy, injustice, lazy thinking, bad writing, comma errors, prima donnas, and drama queens," said Wertheimer.

"She loved politics, classical music, modern art, movies, New York City, *McNeil-Lehrer*, silk scarves, tote bags, good chocolate, and good gossip." ॐ



of public health in the 19th century.

In the year 1854 a Federal Hospital was established in the Marine Hospital, New York City. Four years later the location was transferred to Washington and quarters with accommodations of 100 at New Jersey Avenue and a street, founded by the Congress appropriated by one floor building for the Hygiene Laboratory which they erected in Building 5th and 6th Street, Northwest on land acquired by the War Department. The total building cost at that time was enlarged by one building purchased by Congress in 1916 and by two buildings constructed in 1920. In the later year by act of Congress the name was changed to THE NATIONAL INSTITUTE OF HEALTH.

In the year 1891, 1892 and 1893 \$100,000,000 of Federal Money was used a tract of land in the United States for the purpose of The National Institute of Health. During year funds were allocated for the purpose of the building of the War Department of the government.

KIM CHENSHI

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—Alison Davis

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**Alison F. Davis, Ph.D.**, is a freelance science and science policy writer living near Washington, DC. Alison earned a B.S. in biochemistry from Virginia Polytechnic Institute and State University and a Ph.D. in pharmacology from Georgetown University. While finishing postdoctoral research at Stanford University in the mid-1990s she discovered that she could feed her dual passion for science and words by communicating science to nonscientists. She completed the Science Communication program at the University of California, Santa Cruz, and began her writing career at *The Stanford Daily*, *The Palo Alto Weekly*, and NASA's Ames Research Center, where she worked with the Lunar Prospector moon mission.

Since 1998, Alison has written for several components of the NIH, including the Office of the Director and several institutes and centers, and as a speech-writer for senior scientists in and out of the NIH. She had the opportunity to watch Ruth Kirschstein in action on several occasions, learning firsthand about this woman's deep love of science and the NIH and hearing many personal accounts of her special relationships with so many people.

Alison has also written for the Lymphoma Research Foundation, the *Darwin Awards* series of books, and the Presidential Commission on Bioethical Issues. In addition to being a fanatic about science and words, she is a music lover and an outdoor enthusiast and lives in Clarksville, MD, with her husband, two sons, and several pets.

