Hope and Suffering

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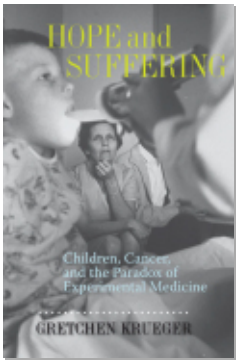

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"Against All Odds"

CHEMOTHERAPY AND THE MEDICAL MANAGEMENT OF ACUTE LEUKEMIA IN THE 1950S

Only a few weeks after her six-year-old daughter, Mary Sheila, died of acute leukemia, Angela Burns and her husband read *Death Be Not Proud.* Moved by the Gunthers' story, the grieving mother sent John Gunther a seventeen-page letter in which she recounted her daughter's diagnosis, her nine months of treatment at the Jimmy Fund Clinic in Boston, and her death in January 1949.[1] Like the Gunthers, Burns lamented that, although they had tried "against all odds to save our child," the diagnosis of acute leukemia was a death sentence for Mary Sheila and for all children diagnosed like her in the 1940s and 1950s.[2]

Cancer remained a frustrating medical enigma at a time when science and medicine were publicly lauded for producing "magic bullets" to cure a comprehensive list of acute, infectious diseases, including tuberculosis and diphtheria.[3] The development of polio vaccines reduced parental anxiety caused by this highly visible, potentially disabling disease. In addition, the introduction of broad-spectrum antibiotics provided dramatic evidence of medical achievement by reducing the public dangers of sexually transmitted diseases and altering morbidity and mortality rates from childhood killers. During World War II, a collaborative research group composed of members from government agencies, universities, and pharmaceutical companies from the United States and Britain had conducted pioneering research in microbiology, and, as industry recognized the potential profits from this new field of prescription medicine, they broadcast the news of these revolutionary drugs.

Although improved nutrition, housing, and living conditions may have also contributed significantly to the declining rates, sulfa drugs and penicillin helped bring diseases that were once considered "incurable" under control in industrial countries. During this decade and the next, attention shifted from acute disease to chronic conditions.

For decades, however, cancer resisted a chemotherapeutic breakthrough because it was generally perceived as a localized disease treatable through surgery or irradiation, not a systemic illness that would respond to drug therapy. Those involved in this area pursued two lines of research: one group tried to elucidate the mechanisms of basic cell growth, while the other identified and tested possible chemotherapeutic agents against tumors in animals. The first method was viewed as challenging, but more rational and practical than the far-reaching search for effective drugs. With the discovery of the structure of DNA in 1953 by James Watson and Francis Crick and the development of novel theories about cell division and replication, some investigators deemed this path more promising. They believed this knowledge of cell structure and function would enable them to separate the "normal" from the "pathological" and then develop appropriate therapeutics. The second group adopted an approach that was criticized as too random but had the potential to yield major rewards. Despite this discord among scientists, popular publications encouraged the public to remain optimistic that with adequate funds, staff, and facilities a "magic bullet" to cure the disease would surely be discovered.

During the late 1940s and 1950s, research on acute leukemia yielded several unanticipated but promising chemotherapeutic agents—drugs that held the potential to control the growth of or destroy cancer cells throughout the body. In response, physicians and scientists mounted a collaborative, national research program to screen and develop additional chemical therapies.[4] This chapter traces the scientific development of antileukemic agents and considers how the advent and proliferation of cancer chemotherapies profoundly shaped the medical management of the disease. Personal correspondence, memoirs, popular newspaper and magazine articles, and American Cancer Society publications illuminated the evolving relationships between biological disease, pharmaceutical development, and the changing experiences and expectations of young patients with acute leukemia and their families in the postwar period.[5]

Warfare, Chemotherapy, and Acute Leukemia

The discovery and development of mustard gases—chemical warfare compounds that later proved to be effective against cancer—began during World War I.[6] Although many countries had signed the 1925 Geneva Protocol that pledged not to deploy chemical weapons, American military in-

telligence maintained throughout World War II that chemical warfare was a potential threat. Consequently, investigators directed their work toward defensive measures such as creating novel methods to administer existing blistering gases, fabricating new protective masks and clothing, and formulating and testing new chemical agents that could be deployed safely by American troops.[7] Chemical research on trench warfare weaponry returned to World War I studies on mustard gas poisoning that had reported that exposure to this family of gases caused delayed, negative changes in blood and bone marrow.[8] During World War II, under a contract between the Office of Scientific Research and Development and the Department of Pharmacology at Yale University, researchers studied the pharmacological effects of nitrogen mustards, compounds closely related to the substances previously employed.

Wartime research on nitrogen mustard compounds contributed to palliative measures and treatment methods for leukemia, lymphoma, and other diseases of the blood and blood-forming organs. At Yale, Louis S. Goodman, Alfred Gilman, Frederick Philips, and Roberta Allen investigated the cytotoxic properties of the gas and determined that its effects resembled the cellular effects of x-rays on a number of tissues. Encouraged by data from experiments in which nitrogen mustard caused temporary regressions in mouse tumors, the group pursued clinical trials of nitrogen mustard as a cancer chemotherapy agent in humans. In December 1942, nitrogen mustard was injected into a patient suffering with an advanced lymphosarcoma at New Haven Hospital. After his tumors regressed, the compound was administered to additional patients. After observing favorable results in the preliminary studies, clinical trials with nitrogen mustard were begun with cancer patients of varied ages at Memorial Hospital in New York City, the Billings Hospital of the University of Chicago, and the medical school at the University of Utah in Salt Lake City. By 1948, nearly 150 patients with lymphosarcoma, Hodgkin's disease, leukemia, and other related conditions had been treated.

In 1946, Goodman and his colleagues published a report in the *Journal of the American Medical Association* that described the preliminary results of the intravenous nitrogen mustard studies.[9] Many of the patients had already undergone radiation therapy, were resistant to further roentgen irradiation, and were in an advanced or terminal stage of their illness. Despite their poor prognosis, researchers observed dramatic remissions in patients with Hodgkin's disease—partial or complete disappearance of large, numerous tumor masses. Nitrogen mustard also relieved patients' symptoms, reduced fevers, and restored their appetite, weight, and strength, allowing them to tem-

porarily return to work for weeks or months. The investigators called for further research into the optimal dosage, dosage schedule, and combination of mustard agents.[10] C. P. Rhoads, the chairman of the National Research Council's Committee on Growth, issued an official statement in the same prominent journal advocating the use of nitrogen mustards as part of a cancer treatment program.[11] He emphasized that the tumor regressions produced by the nitrogen mustards were only temporary and did not lead to a cure but proposed further laboratory studies on related compounds and on cancers of different structure or physiology. Nitrogen mustards acted as the first step in the development of myleran and other chemotherapy agents that later proved to be valuable in treating children with acute leukemia.

Sidney Farber, Aminopterin, and Mary Sheila

Soon after the nitrogen mustard results were published, Sidney Farber announced his findings. Aminopterin, an antifolic therapy synthesized by Lederle Laboratories and clinically tested by Farber, was the first chemotherapeutic agent to temporarily, but consistently, alter the deadly course of acute leukemia.[12] In her letter to John Gunther, Angela Burns described how Farber's key discovery, ongoing chemotherapeutic research program, and clinical facilities directly affected the course of her daughter's illness. After Mary Sheila's diagnosis, the family physician recommended that they immediately take her to Boston to receive treatment under Farber's supervision. At the hospital, Mary Sheila received blood transfusions and began an aminopterin regimen. The Burnses sought at least a short reprieve for their daughter—a period of health that they hoped would last until the discovery of another new treatment or, ideally, a permanent cure. "In our case," Burns reflected, "there was nothing to lose, and perhaps, miraculously, everything to gain."[13] The Burns family celebrated the dramatic transformation in Mary Sheila's health caused by aminopterin. The drug induced temporary remissions that typically lasted from a few days to several months. Mary Sheila experienced a two- to three-week remission. Although this was only a middling result, her mother wrote joyfully, "She was as well and blooming and normal as she had ever been."[14]

Children cycled from illness, through short periods of remission, and then, inevitably, relapsed. Clinical photographs taken of patients with acute leukemia graphically demonstrated the dreadful manifestations of the disease and its attendant toxic therapies. A long list of complications included: oral

ulcers, leukemic infiltration of the eyes, chronic nosebleeds, uncontrollable hemorrhaging, and life-threatening infections that preyed on children's suppressed immune systems.[15] These conditions debilitated sufferers and necessitated frequent trips to and from the clinic as well as extended hospital stays.

Mary Sheila's condition changed constantly, giving her parents and physicians little relief. The chemotherapy regimen lowered Mary Sheila's white blood cell count and reduced the swelling in her spleen and liver but left her vulnerable to dangerous infections. Daily nausea made her stop eating and, consequently, lose weight. In response, her treatment was stopped so that the nausea would abate. Each time the aminopterin was halted, her leukemia—measured quantitatively through regular blood counts—resurged and additional transfusions were administered. Physicians had to maintain a careful balance between aggressively treating the acute leukemia and limiting its toxic effects—infection, nausea, or bleeding—that could also produce fatal consequences.

In August, only three months after her diagnosis, Mary Sheila's health slowly began to deteriorate. Her mother described her daughter's acute leukemia as a "monstrous disease eating her away" during the fall of 1948.[16] Burns's letter painted a horrific picture of the physical toll of the treatment and of the disease itself. Mary Sheila began to experience uncontrollable nosebleeds. Her bleeding episodes became increasingly frequent and progressed to her mouth, gums, and intestines, all sites of the rapid cell division that aminopterin targeted. The capillaries in her legs began to deteriorate, the small vessels in her entire body weakened, and she was soon covered with bright-colored blemishes from the leaking blood. Throughout her illness, Mary Sheila experienced a dozen severe hemorrhages that threatened her vital organs. In January 1949, she died from uremic poisoning, a condition that occurs when elements that are usually excreted in the urine accumulate in the body and produce a toxic state.

Observing her daughter's health fluctuate between periods of health and sickness was agonizing for Burns, yet she conveyed a sense of satisfaction that they had exhausted the available treatment options, writing candidly, "We did everything humanly possible to save our child's life. Nothing was overlooked, no chance was ignored. Many times, our doctor told us it was curtains this time, and she fooled them."[17] The Burnses aggressively pursued treatment alternatives up to the day of their daughter's death. Physicians had planned a direct transfusion of fresh blood between Mary Sheila and her father as the donor. Burns wrote, "Based on her high white blood cell count and low hemoglobin levels, they wanted to give her a complete transfusion—drawing

off all of her poisoned blood and pumping in 5000 c.c.'s of fresh blood."[18] Her condition, though, was too precarious to attempt the procedure, so they elected to give her extra blood instead of completely replacing her supply. That night, she slipped into a coma and died less than an hour later. At the time of death, a needle remained inserted into a superficial vein in her ankle, awaiting the partial transfusion.

Children, Hospitals, and Total Care

Mary Sheila spent the months between her diagnosis and death traveling between her home and the Children's Cancer Research Foundation's Jimmy Fund Clinic in Boston. Between 1947 and 1957, the clinic treated 800 children with acute leukemia using Sidney Farber's "total care" concept. According to Farber, total care included, "the application of all the techniques of medicine and surgery for the comfort, well-being and prolongation of life of the child with advanced cancer" as well as "attention to the mental peace of the family as well as to their social and economic problems."[19]

Farber, however, had not pioneered this idea of comprehensive service. Richard Cabot, a noted physician at Massachusetts General Hospital, introduced the concept of adding an in-house social service department to the hospital, and in 1909 a full-time, paid social worker joined the doctor, educator, psychologist, minister, and patient in the "team-work" of the medical dispensary.[20] The social worker visited the home and addressed patients' economic, mental or moral needs. In *Social Work: Essays on the Meeting Ground of Doctor and Social Worker,* published a decade later, Cabot claimed that about 200 other hospitals in the United States had added social work programs. By including the social work professional, Cabot insisted that it helped "retain the individuality of the patient" and "conquer dehumanization."[21] In 1952, Farber adhered to this long tradition, hiring Antoinette L. Peironi as full-time social worker. She developed a social services office at the Jimmy Fund Clinic.

The furnishings and structure of the Jimmy Fund building facilitated this patient-centered system of care. Since the mid-1850s, a number of specialized children's hospitals had evolved.[22] First conceived of as a haven for the urban poor, by the early decades of the twentieth century they had become facilities for acutely ill youth of all ages and classes. The recognition of pediatrics as a medical specialty helped bridge these two phases. The modern spaces and amenities available at the Jimmy Fund Clinic was yet another step in the di-

agnosis and treatment of sick children. The clinic's waiting room contained a television set and toys to entertain the young patients, painted murals depicting images from familiar children's stories adorned the walls, a merry-go-round provided distraction before appointments, and tricycles provided kid-sized transportation from the waiting from to the laboratory for blood work. To expedite the transfer of new therapies from bench to bedside, the treatment clinic and research facilities were both housed within the Jimmy Fund building. Farber tightly joined the activities of each staff and encouraged the administration of chemical agents in the clinic directly after they had been studied in the laboratory.[23]

Strategically careful to downplay the fluid boundary between experimentation and treatment in the clinic, Farber stated, "[There] is no research, in the popular sense of the term, conducted on the patient with advanced cancer."[24] Notably, this statement resembled C. P. Rhoads's descriptions in *Reader's Digest* about the close link between research and patient care at Memorial. Rhoads declared that the young patients suffering from leukemia supplied "some of the qualities of a wartime emergency" and likened their treatment to the cooperative efforts within the medical division of the Army's Chemical Warfare Service during the war as a way to dramatize the need for rapid advances.[25] He tried to assure the public, however, that patients treated at Memorial were not experimental subjects, but the *voluntary* recipients of promising new treatments developed by investigators at the Sloan-Kettering Institute. He wrote, "Virtually all patients beyond the help of surgery are willing to have new treatments tried on them."[26] Like Rhoads, Farber stated, "We strongly emphasize our research program to parents. Perhaps the benefits of the next medical advance will come in time to help *their* child. We stress our hope for longer periods of remission."[27] Farber and Rhoads recognized popular fears of medical experimentation, but they tried to distinguish their program of rapidly transferring drugs from bench to bedside from any associations with research held in disrepute. Attempting to dispel concerns, they highlighted patients' willingness to participate and their great need for effective agents as justification for their practices. Dire childhood cancer prognoses and the physical proximity of research and treatment buildings at Memorial and the Jimmy Fund Clinic facilitated this simple transfer from animal model to human patient.

As children's cancer care entered the hospital ward and outpatient clinic, nurses, social workers, psychologists, and recreational therapists were needed

to provide care for critically ill patients and their families. A handbook for nurses published by the American Society for the Control of Cancer in 1940 contained no information about the education, research, or treatment of the care of children with cancer, but literature on acute leukemia and nurses' integral role in childhood cancer sufferers' medical and personal care began to be published with increasing frequency in the 1950s. In an article from *R.N.: A Journal for Nurses,* Farber attributed "shorter exacerbation periods and longer remissions among children with acute leukemia" to "good nursing care and new anti-leukemic drugs."[28] As children began to live longer and require repeated admissions to the hospital, B. A. Crawford, the nursing supervisor at the clinic, described how nurses' duties expanded. Nurses carried out medical procedures such as sternal marrow punctures and transfusions, watched for possible side effects, regulated diet, and were responsible for the day-to-day hygienic care and discipline of children. They also addressed the emotional and mental needs of the patient and family. Crawford summarized the nurses' responsibilities into one major goal: to eliminate fear of the illness and its treatment.

At the Jimmy Fund Clinic, longer, flexible hospital visiting hours enabled parents to remain present during painful or frightening procedures and help reduce children's anxieties. An on-site penthouse also allowed two or three sets of parents with children in serious condition to stay overnight in the medical facility. Farber considered parents key—even central—members of the "total care" team. Such flexibility was still rare in the care of children and even more so for adults. And, the extra allowances did have pitfalls. The close triad between patients, parents, and nurses could create tension regarding the division of medical and personal caretaking duties. "Mothers are apt to resent having others care for their children," wrote nursing student Mary Brodish. "The nurse may often avoid this resentment by working with the mother rather than in supposed competition against her."[29] Nurses at the Jimmy Fund Clinic taught parents to involve them and to impart skills they would need when their children returned home for weeks or months during periods of remission. Mouth ulcers and sore, bleeding gums posed a particular challenge for maintaining health and hygiene. Parents brushed teeth and gums with a cotton-tipped swab and wiped dried blood from their child's lips and noses.[30] Parents also practiced keeping a careful intake and output record for fluid balance, watching for signs of dangerous transfusion reactions, and applying pressure to intravenous sites to prevent life-threatening hemor-

rhaging episodes. As Brodish noted, however, "the nurse can decide when situations warrant the parent's participation and when it would be better, either for the parent or the child, for the parent to leave temporarily."[31]

During the 1950s, psychologists and sociologists began to study the immediate and long-term consequences caused by a child's hospital stay.[32] Children's books such as *Johnny Goes to the Hospital* and *Linda Goes to the Hospital* were tools for parents, nurses, or psychologists to introduce children to unfamiliar situations. Simple stories and illustrations explained visits to the doctor, daily hospital routines, and the process of preparing for and undergoing such common surgeries as tonsillectomies.[33] Nevertheless, little could fully prepare children and parents for childhood cancer treatment.

As psychologists and other members of the medical staff began to study the mental and emotional repercussions of childhood cancer, they focused primarily on the children's parents, not the young cancer patients.[34] In the late 1940s, Mary Bozeman and her colleagues in the rehabilitation and psychiatry department at Memorial began a multiphase study of emotional problems faced by the parents of children suffering from leukemia.[35] At request of the pediatric service, they interviewed twenty mothers to evaluate the impact of a fatal childhood illness and to develop new guidelines for care that would help minimize the illness' traumatic effects. Bozeman found that the unpredictability of the disease's course, the pattern of remission and relapse, the relentless side effects of chemotherapy, and the anticipation of their child's inevitable death combined to torment the children's mothers.

In another study that included fathers' perspectives, Beatrix Cobb, a member of the pediatric staff at the University of Texas M. D. Anderson Cancer Center, interviewed twenty parents six months after their child's deaths from acute leukemia.[36] She asked the parents about four different topics: their retrospective reactions to the long-terminal stage of illness; the impact of enforced separation and disruption of routine family life; the impact of illness on the child's well siblings; and the role of religion in their experience of illness.[37] Despite the stresses associated with acute leukemia care, the parents disclosed that they were grateful for the opportunity to spend time with their child as long as his or her illness and suffering were properly controlled. Significantly, Cobb's focus on illness and the whole family circle also extended to other children in the family. Parents had major concerns regarding the well-being of the ill child's siblings when they responded negatively to the sickness and death, for example, losing weight or worrying excessively about their own health.

In one exception, another study focused more directly on young acute leukemia sufferers. The pediatricians wrote, "Hospital practice is increasingly concerned with the management of children with potentially fatal diseases and their families," yet observed, "It is striking to note that so little has been written concerning this aspect of pediatric practice."[38] They found that children felt isolated and depressed during their illness but did not seem openly concerned about death. Still, they cautioned medical professionals that a child's reaction to illness depended on his or her age and cancer type and advised them to evaluate each case individually. To address and assuage both children and their parents, they counseled hospitals to allow parents to serve as partners in the physical care of their children, a system like the one employed at the Jimmy Fund Clinic. The M. D. Anderson model, however, advocated only limited parental involvement. "Because of the considerable anxiety which parents of a child with a malignant disorder faced," they advised it was "undesirable to add to this anxiety by leaving decisions concerning treatment to them."[39] Parental decision making was viewed as guilt inducing, not lending a sense of empowerment or control like physical care. In the 1960s and 1970s, psychological inquiry into patient experience intensified as the development of advanced supportive care, additional chemotherapeutic agents, and effective treatment protocols for acute leukemia ensured years of survival and, in select cases, a cure.

Hormones and 6-Mercaptopurine

Following Farber's discovery of aminopterin in 1947, investigators searched for other agents that would induce partial or complete leukemic remissions, a period after the administration of treatment when the number of white blood cells and other blood cells in the blood and bone marrow were normal (hematological remission) and the patient displayed no signs or symptoms of leukemia (clinical remission). Researchers soon found that two additional groups of drugs induced rapid, temporary remissions in children with acute leukemia—hormones and antimetabolites. In 1949, despite the limited production of cortisone and adrenocorticotropic hormone (ACTH), both hormones were under scrutiny for their possible medical applications.[40] In October 1949, three years after Armour Laboratories first made a preparation of ACTH, researchers gathered at the First Clinical ACTH Conference to give a brief status report. Those assembled represented a variety of research interests and promoted the application of ACTH to patients with gout, nephrosis,

rheumatoid arthritis, and other related diseases. Sidney Farber offered the case of a six-year-old boy whose bone marrow was dominated by immature cells called blast forms. The boy complained of pain in his arms and legs, bled from his mouth, and had lost weight. Despite his advanced disease, he had achieved a complete remission with ACTH after nine days of therapy.[41]

In 1950, the availability of ACTH had increased markedly for investigative and therapeutic uses and, in December 1950, Armour sponsored a second meeting. Farber presented the outcomes of seventy-four children treated with either ACTH or cortisone alone or one of the hormones in sequence with folic acid antagonists such as aminopterin.[42] In this investigation, he found that ACTH and cortisone produced the same result. The patients responded in three distinct categories: clinical improvement with hematological improvement, clinical improvement only, and failure. Children who experienced remissions achieved them quickly and improved for between two and thirty-six weeks. The research group observed the optimum results when cortisone or ACTH was administered in sequence with folic acid antagonists. Farber downplayed the harm of "toxic effects" from the therapy, arguing that they could be controlled through measured use of the drugs. In the discussion session following Farber's presentation, physicians from the New England Medical Center in Boston, the Memorial Center for Cancer and Allied Diseases, the Mayo Foundation in Rochester, Minnesota, and others added positive results from their institutions. There was now conclusive evidence that hormones and folic acid antagonists could be used in combination to effectively treat acute leukemia. Farber was confident that these results provided an answer for the frequently heard question, "Should one prolong life in a child with acute leukemia?" The discovery of folic acid antagonists, ACTH, and cortisone gave physicians at research centers the ability to "return the child to a state indistinguishable from normal for a period of weeks or months, and even, in a few instances now, more than 2 years, with the eventual outcome still unchanged."[43] He urged the conference participants to prolong young patient's lives as long as possible, use any available new therapies, prescribe necessary transfusions and antibiotics, and attend to the emotional and social aspects of the disease through a coordinated program of total care.

Less than two years later, experimental results reported by researchers at Memorial Hospital confirmed that the lives of acute leukemia victims were extended by administering hormones and anti–folic acid chemicals consecutively.[44] By using the second agent after cells had become resistant to the first, children lived an average of three to four months longer. The *CA News-*

letter from the same month lauded this form of combination chemotherapy as one of the most intriguing experimental treatment efforts of the time.[45]

Newspaper coverage of these new chemotherapeutic agents differed from the scientific literature, which reported only moderate gains in remission rates and length of survival. Reporters ebulliently described children's journeys from their hometowns to cancer centers for treatment with ACTH. To aid the search for a miracle cure or at least a longer life for these young patients, airlines donated airfare, communities raised funds, and parents accompanied their ill children to specialized treatment and research facilities. "Happy to Be Going Home" declared the caption atop a 1950 photograph of Billy Anderson and Gerald Dunaway, patients at Bellevue Hospital in New York City, waving goodbye to the institution's security guard.[46] Both Billy, an eight-year-old from Summerland, Mississippi, and Gerald, a seven-year-old from Indianapolis, Indiana, had been admitted to the hospital with advanced cases of acute leukemia. In less than two months, physicians had halted the progress of their fatal disease with ACTH and cortisone, calling these drugs the "only medical hope" remaining for these children. Gerald's mother had also turned to her faith, reporting, "We prayed so much I thought the heavens would burst" in hope that spiritual intervention would aid her son.[47] Mrs. Dunaway knew that a miracle would be required to save her son; less than a year before, Gerald's five-year-old sister had been diagnosed and died of leukemia. Mrs. Dunaway urged the reporter to take a close look at Gerald, insisting, "Isn't he the picture of health?"[48] The article ended with the two boys walking hand in hand through the hospital door and "out into the air and light."[49] Although no follow-up story relayed the outcome of their treatment, a short article printed about five-year-old Donna Jean Soderberg only two months later reported the inevitable end to the boys' illness.

In May 1950, the death of Soderberg, the poster girl of the Leukemia Research Foundation, exemplified the brief cycle of treatment and remission associated with these chemotherapeutic agents. Like Gerald and Billy, Donna responded initially to ACTH, was able to return home for Easter, and lived almost a year after her initial diagnosis. After she became resistant to ACTH, physicians attempted to use the hormone a second time, but she did not show signs of improvement and died shortly thereafter.[50] These children's journeys personalized the search for chemotherapeutic agents and lent a sense of hope and urgency to research related to acute leukemia.

The research and development of new drugs and pathways spanned the university medical center, research hospital, government facility, and phar-

maceutical industry laboratory. In some cases, collaboration between investigators yielded the most promising results. In 1953, several scientific publications described 6-mercaptopurine (6-MP), an antimetabolite that interfered with cancer cells' ability to manufacture nucleic acids and continue cell reproduction.[51] Developed in a joint research program between biochemists George H. Hitchings and Gertrude B. Elion of the Wellcome Research Laboratories in Tuckahoe, New York, the Southern Research Institute of Birmingham, Alabama, and Sloan-Kettering Institute, preliminary analyses showed that 6-MP was active in some children who were refractory. The term "refractory" designated those patients who failed to go into remission following treatment.[52]

In a 1953 clinical evaluation of 6-MP at Memorial, of eighty-seven children with acute leukemia, forty-one had clinical and hematologic remissions, sixteen experienced partial remissions, and in thirty children the agent was considered a failure.[53] Remissions lasted from one to ten months and researchers found that children were still responsive to other drugs after relapse. Thus, 6-MP could be incorporated into a plan of sequential therapy. The researchers concluded that young acute leukemia patients should receive antimetabolites such as amethoperin and 6-MP first, while cortisone and ACTH should be reserved for emergency situations when a faster acting agent was needed or when the patient became resistant to the initial treatment.[54] The research demonstrated that with no treatment 5 percent of patients lived a year or longer, with cortisone and amethoperin 29 percent survived for the same period, and by staggering amethopterin, cortisone, and 6-MP, the figure rose to 52 percent.[55]

The media covered these developments with keen interest. A science journalist in the *New York Times* boasted, "It looks as if 6-MP is the most useful compound ever discovered for the treatment of leukemia."[56] At a meeting of the American Pharmaceutical Manufacturers' Association, C. P. Rhoads expressed confidence that by refining 6-MP a more specific antileukemic agent could be produced, saying, "Following these principles, it will be surprising if means of cancer control are not found in the foreseeable future."[57] The rapid development of effective chemotherapeutic agents in the laboratory and the cancer clinic led to enthusiastic claims by journalists and investigators alike, but uncertainty remained whether these promises would be fulfilled. And, some asked, at what price to young patients and their beleaguered families?

National Cancer Institute, Cancer Chemotherapy, and Cooperative Groups

In the early 1950s, only a fraction of leukemia patients responded to therapy, and the short, temporary remissions did not significantly extend patients' lives. The announcement of each new agent, however, raised new enthusiasm for this small area of cancer research. The screening program for promising anticancer drugs at the Sloan-Kettering Institute—already responsible for screening about 75 percent of the 2,000 substances tested in the United States—was unable to accommodate the testing of additional compounds supplied by industrial sources.[58] In response, pressure for an expanded program grew among a body of interested investigators and gained force in Congress.[59] A series of special meetings between 1952 and 1954 evaluated the necessity for an expanded chemotherapy program, the best screening methods, an efficient structure for the program, and its financial requirements.[60] The conclusions from these discussions were presented to congressional appropriations committees by National Cancer Institute leaders and other expert witnesses.

Sidney Farber extended his influence beyond the walls of his Jimmy Fund Clinic by entering the national political debate over research priorities and funding. According to a colleague, Farber tirelessly promoted the idea that "the child was the father of the man." In his testimony, he graphically demonstrated that clinical advances in cancer research commonly occurred in pediatrics first and were then translated into similar treatments for adults. Flanked by Mary Lasker and Rhoads and armed with dramatic photographs of a child with leukemia before and after treatment, Farber asked Congress to allocate money for leukemia research. Congress responded this request by appropriating a million dollars to the cause and proposing a new approach to chemotherapy research. Congressional appropriations for new facilities and staff members devoted to cancer, especially chemotherapeutic research and clinical cancer trials, insured a secure place for leukemia and, consequently, all cancers on the national health agenda throughout the 1950s and 1960s. During this period, the annual budget for the Bethesda, Maryland–based National Cancer Institute increased more than $100 million.

In April 1955, the legislative body asked officials at the National Cancer Institute to manage a directed, comprehensive research program targeting acute leukemia.[61] National Cancer Institute was charged with defining the pro-

gram's research goals and then dividing the tasks into separate contracts for external laboratory and clinical groups housed in universities, at research hospitals, and in the pharmaceutical industry. In *Science News Letter,* the organizational structure of the program was compared to "wartime researches that gave us radar, the atom bomb and other winning developments."[62] Estimating that government, private agencies, and industries had spent approximately $12–15 million identifying and screening chemotherapeutic agents for cancer, they hoped to direct and refine the drug identification process.[63] In response, Kenneth Endicott established the Cancer Chemotherapy National Service Center as a support system for chemotherapy research throughout the country—from the acquisition of chemicals to be tested, through bioassay, into clinical trials. At the National Cancer Institute, the program's center, scientists screened thousands of agents. Each year they tested between 35,000 and 40,000 agents, using mouse models to test the drugs' action against three animal tumor systems: Law's leukemia L1210, sarcoma 180, and mammary adenocarcinoma 755.[64] Congress appropriated $5 million to the project in 1955, $19 million in 1956, and by the following year the national program to promote voluntary cooperative research in cancer chemotherapy represented nearly half of the National Cancer Institute's budget.[65] This level of funding and the vast work it supported indicated the scientific and governmental support for chemotherapeutic research. Only four years later, it was reported that eighty-five chemical compounds had exhibited antitumor activity in animal testing and had been administered to cancer patients to determine humans' biological resistance to the drugs and the agents' toxicity.[66] Work under the auspices of the chemotherapy program and the Cancer Chemotherapy National Service Center investigated chemotherapeutic agents for cancers affecting all age groups but achieved some of its most dramatic results in the fast-growing cancers particular to children.

In 1955, Gordon Zubrod, the clinical director of the National Cancer Institute, and his associates James Holland, Emil Frei III, and Emil J. Freireich directed the medicine branch of the center toward therapeutic research projects on acute leukemia.[67] Holland, Frei, and Freireich founded the Eastern Study Group, and the clinical researchers at Memorial Hospital under Joseph Burchenal were organized as the Leukemia Group. After James Holland relocated to Roswell Park Cancer Center in Buffalo, New York, in 1954, Frei, the administrator of the hospital's leukemia service, and his colleagues at the National Cancer Institute continued their cooperative studies under the title Leukemia

At the National Cancer Institute, clinical research related to pediatric cancers became a very active, yet controversial, part of the program. Despite the resistance that early investigators such as Tom Frei (shown) encountered, child-friendly spaces and special programs to serve this young population and their families grew. Reprinted with permission of the National Library of Medicine.

Group B (later renamed Cancer and Leukemia Group B). The establishment of a formal network enabled the investigators to compare drugs or protocols with very similar remission rates that necessitated a large number of patients in order to detect minute differences. Endicott noted, "A single hospital can rarely make enough observations in . . . highly selected patients to give adequate data in a reasonable time; hence, collaborative research becomes essential."[68] Clinical groups organized patients at the National Cancer Institute Clinical Center, Memorial Sloan-Kettering, M. D. Anderson, the Children's Cancer Research Foundation, and Roswell Park into large-scale, cooperative studies. During their initial study, a comparison of a single and a combina-

tion chemotherapy regimen initially studied in a mouse model by National Cancer Institute investigator Lloyd Law, the researcher groups deliberated over proper clinical trial design and statistical analysis.[69]

An addition to Bethesda's facilities furthered clinical research on pediatric acute leukemia patients. Although the National Cancer Institute did not have a pediatrician on staff from 1953 to 1958, children occupied beds in the general clinic. In 1957, the National Institutes of Health added a twenty-bed pediatrics unit to the National Cancer Institute's chemotherapy section for intensive research in cancer in children.[70] Children treated in the large unit ranged from infancy to fifteen years old. Most of the patients only traveled to the unit from the neighboring Washington, D.C., area, but private physicians from across the country also referred their young cancer patients to the facility for further treatment. Children with inoperable Wilm's tumors, osteosarcoma (bone tumors), nasopharyngeal tumors (nose and throat tumors), and neuroblastoma (cancers of the nervous system) were admitted to the unit, but the majority of the patients suffered from acute leukemia and benefited from the unit's emphasis on this area of cancer chemotherapy development.[71] The young patients entered a rigorous research environment at the National Cancer Institute. As Zubrod explained, "Patients are admitted for purposes of total research, not for general care or diagnostic work-up" and in all cases given "the most individualized treatment the unit can offer" during their stay.[72] Under the direction of Frei, a multidisciplinary team of physicians and allied health workers including nurses, dietitians, social workers, and occupational therapists met twice weekly. At the first meeting, the team addressed the case history of each child and the particular problems of the family, including the effects of hospital life and terminal illness on each child and his or her family. At the second meeting, the team and members of the medical staff met to review the clinical findings.

Parents' wish to find new treatments and their desperate hope for a cure sometimes complicated the standardized clinical evaluation of active compounds by specialists. Endicott wrote that maintaining strictly controlled trials was made more difficult by "the urgent need and constant pressure to do something for the hundreds of thousands of patients dying of advanced cancer." "The moment a new drug shows activity in man," he continued, "public and professional pressure is exerted to bring the compound into general use before careful studies can be completed."[73] The authority of the clinical researcher, the integrity of the clinical trial, the risks and benefits to advanced cancer patients, and parents' decisions all had to be constantly negotiated. The

clinical studies panel of the Cancer Chemotherapy National Service Center recommended that "the patient's care should be under the complete control of the investigator."[74] Such conflicts over children's care certainly erupted between physicians and parents in hospitals and research centers with recourse to experimental therapies. During a decade when chemotherapy represented a last hope for young acute leukemia victims and their parents, some families encountered unexpected barriers.

Constraints on Care

Angela Burns generally praised her daughter's care at the Jimmy Fund Clinic, but her letter also suggests the toll Mary Sheila's illness and treatment took on the family. She recounted their daily trips from Fall River, Massachusetts, to Boston: "This child made a trip to Boston, 50 miles away, and back, *every day,* and while at clinic, we often had to wait an hour for our turn."[75] In the midst of several trips Mary Sheila's nose had begun to bleed uncontrollably and they had to rush to Boston before she went into shock. The family relied on the Red Cross for a portion of their medical transportation, but as Mary Sheila became frail, she could no longer endure the trip without the comfort of a private car. The Burns struggled to meet the financial demands of her care. Angela Burns wondered how those who traveled from greater distances for treatment could manage, noting, "Everyone must pinch and starve to keep these children with their mothers in a large city like Boston."[76] After Mary Sheila's death, the family established a transportation and hospitalization fund to assist other ill children in the region.[77]

Two other case studies clearly illustrated the role of financial and geographic factors in shaping patients' and families' experiences of acute leukemia in the 1950s. The Jacksons, a working-class family from New York, endured a substantial financial burden during their young son's illness. In his "About New York" regular column in the *New York Times,* Meyer Berger described the Jackson's struggle and New Yorkers' generous response to the medical tragedy.[78] In the second case, the experiences of the Bush family demonstrated how geography impeded some young acute leukemia victims from receiving the latest treatment options, even if that family came from a privileged background. Although the Bush's personal circumstances allowed them to travel from Midland, Texas, to New York City for medical care for their daughter, Robin, few other families living far from noted cancer research centers could have had the resources to pursue similar care for their child.

In 1946, Bill Jackson, like many young G.I.s, returned from duty in the Navy in the South Pacific and married a neighborhood girl. In a few years, the couple had a son, William Sherman Jackson, III, who they nicknamed Skipper. In 1955, his three-year-old son, who was widely known for his lively personality and frenzied pace, abruptly fell ill. The newspaper story explained that a slight slip of his hand while tying his shoe had caused an ugly black eye. Physicians diagnosed acute leukemia. The boy's care—doctor visits, hospitals, tests, and transfusions—drained the family's budget and forced them to borrow heavily to meet the demands of both their household expenses and Skipper's medical care. Although Jackson did not talk openly about his son's illness or the strains on his family at his job as head airfreight agent for American Airlines, the staff at LaGuardia Airport slowly gleaned facts about their trying times. Jackson's coworkers agreed to give a dollar out of each paycheck to help the family and made unsolicited blood donations. Six days later, an article in the *New York Times* announced that Skipper had died in his sleep at the Long Island Jewish Hospital, his maternal grandmother at his side.[79]

Berger's article did not provide detailed information about Skipper's diagnosis or therapy, but it did highlight the demands placed on the family during their only child's illness. Skipper's mother stayed at the hospital full time, and his grandmother provided additional help. The young boy lived only a short time after his diagnosis, but his medical treatment placed an enormous financial burden on the family. From 1943 to 1947, Senator Robert F. Wagner of New York, Senator James Murray of Montana, and Representative John Dingell of Michigan sponsored four bills that supported a national health insurance plan as a component of the Social Security Act.[80] Under this proposal, coverage would have been compulsory, universal, and comprehensive; it would have alleviated the Jackson's financial worries. Under the leadership of Morris Fishbein, editor of the *Journal of the American Medical Association,* however, the AMA vehemently opposed government involvement in payment for medical care. A "socialized" system, he and some of his colleagues maintained, would undermine the entire physician-patient relationship and negatively impact the current practice of medicine. And, there was a second, equally formidable obstacle to overcome. As Jonathan Engel, a scholar of health policy and history, has argued, "Despite the inability of millions to afford necessary medical and hospital services, Americans simply did not want national health insurance." Lacking fundamental support, reformers' campaigns failed.

Although families used a number of alternatives including industrial

health plans, prepaid union health plans, mutual hospital plans such as Blue Cross, and private, voluntary medical insurance to help manage their medical costs, those without adequate coverage continued to struggle to pay for their household bills and mounting medical charges. Childhood cancers, like other major catastrophic illnesses, placed an enormous strain on a family budget. Berger's description made it clear that cancer presented a significant hardship for the Jackson family.

Living in a remote area created different burdens on families with children stricken with cancer. Families who lived outside urban areas may not have had access to the experimental therapies available at specialized cancer centers or major research hospitals. An article published in *Southwestern Medicine* advised physicians to learn about the latest chemotherapeutic agents: "The family physician may be called upon to use these products in patients unable to travel to radiological centers because of illness or because of the expense involved."[81] For many patients with acute leukemia, symptomatic treatment and death at home or the local hospital may have been the only suitable options. The Bush family—scions of American politics—confronted some of these challenges when their five-year-old daughter Robin was diagnosed with acute leukemia in 1953.

Former first lady Barbara Bush recalled the obstacles the family faced as they tried to procure medical treatment for Robin.[82] She had scheduled an appointment with the family's pediatrician, Dorothy Wyvell, after her daughter stubbornly insisted that she wanted to remain in bed all day or simply lie in the yard. After analyzing the results from Robin's examination and blood work, Wyvell requested that Barbara and her husband, George, return to her office for a conference. She informed the young parents that their daughter had leukemia. Confronted with the bleak news, they asked the physician for her professional opinion regarding Robin's treatment. In Barbara's recollection, Wyvell encouraged the parents "to tell no one, go home, forget that Robin was sick, make her as comfortable as we could, love her and let her gently slip away. She said this would happen very quickly, in several weeks."[83] Rather than accept this advice, the couple clung to the hope that a second opinion would be different. They asked Wyvell to call John Walker, a relative and physician at Memorial, to inquire whether anything more could be done for their daughter. Walker encouraged them to bring Robin to New York City for immediate treatment by Joseph Burchenal, Lois Murphy, and Charlotte Tan, leading researchers in the field, though he warned them that the therapy would only temporarily extend her life while the search for a cure continued.

Unlike the Jacksons, the Bushes had considerable economic resources. They were able to fly from Texas to New York the next day and admit Robin to the hospital. Both parents divided their time between the Walker home and their daughter's hospital room. The Bushes relied heavily on family and friends for support and the ample blood supply needed for Robin's constant transfusions. Unlike the Jacksons, they also carried medical insurance that would have covered every expense. Memorial Sloan-Kettering (like the Jimmy Fund Clinic) offered free treatment, but the added costs of meals, child care, transportation, and lodging for family members staying near the hospital quickly mounted. They also met parents of other children on the ward who had encountered serious financial problems. When Robin was able to return home for a short stay, Memorial's physicians depended on Wyvell to provide any necessary medical care and Barbara depended on Midland friends for companionship. Bush recalled, "Leukemia was not a well-known disease. Many people thought it was catching and did not let their children get near Robin."[84] Over time, the medicine used to control Robin's leukemia caused side effects that led to a coma. In October 1953, only two months before celebrating her fourth birthday, Robin died. Her parents donated Robin's body to research with the hope that further studies would help lead to a cure for others suffering from this dread disease.[85]

The "One-Boy Whirlwind"

Despite the tragic deaths of Mary Sheila Burns, Skipper Jackson, Robin Bush, and thousands of others, the cancer establishment celebrated gains in the short-term survival of patients with acute leukemia and other cancers. Although few of the American Cancer Society's educational materials directly addressed cancer in children, their fundraising campaigns increasingly used photographs and stories of young cancer sufferers and survivors to encourage donations to the organization's annual drives. In the nineteenth and early twentieth centuries, children had been increasingly used to advertise consumer goods, raise support for child-centered health and welfare reforms, and heighten lay awareness of specific diseases in the popular press and in materials produced and distributed by voluntary health agencies.[86] In the 1940s, March of Dimes campaigns used sentimental images of poster children to direct parental concern toward polio prevention and treatment and to raise funds for their rehabilitation programs.[87] Polio epidemics, not childhood cancer cases, incited the greatest amount of concern in American parents.[88]

Poliomyelitis affected thousands of children across the country as improvements in hygiene and sanitation made children more susceptible to its reach.[89] In an effort to prevent transmission of the disease, parents forbade their children from swimming in public pools, visiting local movie theaters, or playing with neighborhood friends. Leg braces, crutches, iron lungs, and other rehabilitative tools became common symbols of polio's drastic effects. In his study of children's lives during World War II, William Tuttle found that many children had witnessed the effects of the disease firsthand in their classmates and feared polio and the paralysis that often followed more than they feared war. President Franklin Delano Roosevelt, working together with the National Foundation for Infantile Paralysis, wrote that polio eradication was a war goal, "The dread disease that we battle at home, like the enemy we oppose abroad, shows no concern, no pity for the young. It strikes—with its most frequent and devastating force—against children."[90] In keeping with Roosevelt's phrasing, newspaper and magazine stories used war-related terms such as battle, attack, victory, and unconditional surrender to describe polio research programs.[91]

By the late 1940s, John F. Enders, an infectious disease expert at Boston Children's Hospital, had completed preliminary experiments to grow and maintain poliovirus in human tissue cells. From this work, researchers learned that an immunization was needed to protect against three different polio strains. Jonas Salk developed a vaccine and large-scale trials were conducted on children to test its efficacy. In trying to maintain the life and health of child populations, scientists and physicians exposed children "volunteers" to experimental risks.[92] As scientists attempted to translate these results into an effective immunization, American Cancer Society materials began spotlighting a set of lesser-known killers—childhood cancers—to raise funds for education and research. Like polio, a disease widely feared for its crippling effects and periodic, epidemic spread, American Cancer Society images suggested that cancer (often a less visible disease in everyday life) could also harm their children.

In 1953, five cancer patients—two children and three adults—stood on a platform before the American Cancer Society annual fundraising convention as their physicians provided testimony about their cancer treatment. Of the five patients, four-year-old leukemia patient Jennifer McCollum garnered the most attention from the American Cancer Society publicity office. Treated with aminopterin, ACTH, and an unidentified drug provided by Memorial Hospital, Jennifer was promoted as a symbol of the developments in cancer

chemotherapy research in the late 1940s and early 1950s. Organizers hoped that her story would inspire those gathered in Chicago to raise the $18 million needed for its 1953–1954 programs.[93]

Two years later, as physician scientists reported on new experimental techniques to the chairpersons and officials at the national meeting, patients who had benefited from the treatments dramatized the potential results. The national meeting in Cleveland, Ohio, was designed to stimulate enthusiasm for the American Cancer Society's April fundraising crusade. At the meeting, two boys afflicted with different cancers demonstrated the current status of cancer research and treatment. Donald Lewis Marteeney from Kansas City, Missouri, had undergone twenty-one surgeries for neuroblastoma before he was two years old, but by the time he was seven, he had been tumor-free for five years and was considered cured. Four-year-old Thomas Nagy of Cleveland was diagnosed with acute leukemia and was treated with cortisone to induce a remission. When he relapsed a few weeks before the meeting, he was treated with a combination of cortisone and aminopterin and experienced a second remission. Farber supplemented the boy's story with slides of patients with leukemia, Hodgkin's disease, and lymphoma who had measurable responses to chemotherapeutic treatment. In their publicity photograph, the boys stood shoulder to shoulder brandishing oversized Swords of Hope while Nagy held a sign printed with the year's slogan, "Strike back at cancer, man's cruelest enemy."[94]

Enthusiasm about the progress made against acute leukemia quickly extended to other childhood cancers that responded to treatment. Throughout the 1950s, children played a key role in motivating fundraisers and articulating the society's educational message. The plight of seven-year-old cancer survivor Leroy Curtis from Denver, Colorado, played a prominent, ongoing role in several cancer campaigns. The story of his diagnosis and treatment was the topic of an article published in Denver's *Rocky Mountain News.* Curtis's journey began when a doctor felt a strange lump in the boy's abdomen at his first checkup. At three months, surgeons removed a malignant tumor near his left kidney. After the operation and ten months of x-ray treatment and hospitalizations, no trace of the cancer remained. To mark his fourth birthday and the probable end of his illness, Leroy had a party with his neighborhood friends, ate cake and chocolate ice cream, and wore a new cowboy outfit.[95]

In 1955 he opened the American Cancer Society's annual crusade by presenting the organization's Sword of Hope to President Dwight Eisenhower. A film of the event was broadcast on television and at movie theaters across the

United States. The chairman of the society's board of directors announced, "We chose Leroy, because we think he is a fine youngster and an excellent example of what can so often be done today to save lives from cancer through early diagnosis and prompt, proper treatment."[96] During a promotional weekend trip to New York City on behalf of the American Cancer Society, Leroy visited the children's ward at Memorial Hospital and joined in a party for the child patients that included two clowns from the Ringling Brothers and Barnum and Bailey Circus. He also appeared on several television shows, toured the Central Park Zoo, and spoke with Meyer Berger about all of his adventures.[97] In 1956, he returned to the national campaign meeting in Cincinnati to pose for pictures and star in the afternoon program led by the year's national campaign chairman, Ed Sullivan.[98] Called the "one-boy whirlwind" in an American Cancer Society article, he led off the show by singing a song while sitting atop the piano. Famous figures, lesser-known cancer survivors, and physicians and scientists participated in the conference and show, but Leroy and his personal experiences with cancer were prominently featured in American Cancer Society publications. Leroy represented the American Cancer Society model of cancer success that included prompt diagnosis, treatment, and cure through conventional medical means. As a survivor of a common childhood tumor that responded to surgery, Leroy and other young children who had been cured of cancer were able to provide a hopeful, sentimental story to motivate fundraising volunteers and inspire benefactors to give generous donations for the research and treatment of all cancers—especially those that required other types of therapies.

Some testimonials, however, were stories that ended in pleas for help. The parents of seven-year-old leukemia sufferer Darya Flagg described their personal experiences in a half-hour radio appeal for the American Cancer Society. From the living room of their farm home, they recorded an unscripted show that was aired nationwide. Darya's grandmother, the principal of Darya's school, their minister, and neighbors also spoke on her behalf. Called "a real-life drama of parents who have refused to give up hope," they mounted a campaign asking listeners to support the cancer crusade and to find a cure for the girl's illness.[99] Unlike Leroy's far-reaching crusade, messages of frank desperation for a cure, not an enthusiastic promotion of the American Cancer Society warning signals, characterized appeals by acute leukemia sufferers and their families who faced inevitable death despite heeding advice about early detection or prompt treatment.

Although American Cancer Society fundraising campaigns broadcast chil-

dren's stories widely, few educational materials published or approved by the society discussed young cancer sufferers and survivors. This may have been because of the intractable nature of many pediatric cancers. In one exception, *Look* magazine produced an informative booklet on cancer that that was to be widely distributed through companies' employee reading racks. The first article in the booklet featured many children stricken with cancer, the "child killer." In the forward, Charles S. Cameron, medical and scientific director of the American Cancer Society, blamed the rising mortality from cancer on a growing population, an increase in older age brackets, and the growing rate of lung cancer cases but stated that early detection had slowed the rate of increase.[100] He extended his argument to cancer in the young by claiming that raising parents' awareness of the disease would lead to reduced mortality in children—a message repeated from popular articles published in the 1940s.

The examples given in the article, however, challenged the plausibility and benefits of accurate, early detection. Bobby Giampa's parents initially ignored his fatigue, attributing it to his recent entrance into the first grade. After four-month-old Patty Porrine ceaselessly screamed and cried, her mother took her to three doctors before they discovered that she had a tumor in her leg. One physician had dismissed Ms. Porrine's concerns saying, "You modern mothers spoil your children. Just let her cry."[101] Six-month-old Linda Wreith's physician thought that an insect bite may have caused her eye to swell, but when her mother took her to a specialist, x-ray images revealed that several bone tumors had caused the unusual bump. As in the 1940s, experts admonished both parents and private physicians against remaining ignorant of childhood cancers, its symptoms, and the availability of treatment options and cures. Regular physical examinations and constant attention to suspicious pains or lumps were advocated as optimal, though problematic, detection methods.

The *Look* article differed from earlier publications in that it contained a list of therapeutic agents and procedures for treating local and systemic cancers in children. The limited but growing list included: cell "poisons" such as nitrogen mustard, metabolic substitutes such as antifolics and purine and pyrimidine derivatives, experimental therapies using viruses to target and kill cancer cells, hormones such as cortisone and ACTH, and radioactive chemicals to destroy cancerous thyroid cells. Atop the final three pages of the article, phrases proclaimed, "ANGUISH for those who wait for death," "MIRACLES of medicine give parents the will to act," and "HOPE grows that drugs and viruses will stop all cancer." These words and the stories of Bobby, Patty,

and Linda demonstrated the dichotomy of helplessness and hopefulness that had characterized childhood cancer in the 1940s and continued to shadow this set of diseases.[102]

The pamphlet also included the rest of Bobby's, Patty's, and Linda's stories. After administering the experimental drug amethopterin, physicians sent Bobby home six days before Christmas in 1951. In July, he returned to Memorial Hospital, where they tried experimental SK 5356 (later renamed 6-mercaptopurine) that permitted him to attend school for four months. He relapsed and died soon after he returned to the hospital for further treatment. Nicknamed the "Hope Child" by her physicians at Memorial Hospital, Patty underwent x-ray treatments to destroy her tumor. Her tumor regressed, but she had to wear a lift on one foot to counteract the side effects of the radiation. When Linda was admitted to St. Luke's Hospital on December 21, 1947, it was the first of thirteen hospital stays for the five-year-old. Surgeons could remove only a portion of her tumors, so physicians tried x-ray therapy and nitrogen mustard to reduce the swelling and control the tumors' growth. The article claimed, "Linda promises to score another victory for chemistry," and her mother added, "I call it a miracle." Despite this hopefulness, a physician at Memorial cautioned, "We never completely discharge a patient."[103] Bobby, Patty, and Linda illustrated how children's experiences with cancer varied widely. All children with acute leukemia died within a year of diagnosis, many children with cancer underwent extensive procedures or experimental chemotherapy treatments, some experienced debilitating side effects from the therapy, and most faced uncertain outcomes.

Experimentation versus Treatment

Angela Burns recognized that her child been in treatment for an incurable disease at the same time she was serving as a research subject for Farber's cancer studies. "Frankly," she wrote, "they were experimenting and they needed children to carry on their work."[104] Research on new chemotherapeutic agents required young acute leukemia patients to endure additional painful procedures and toxic side effects, but parents still sought experimental therapies in hopes of prolonging their child's life and aiding a larger population of young cancer sufferers.[105] When the two-year-old Van Lopik twins from Grand Rapids, Michigan, were diagnosed with acute leukemia, physicians told their parents that there was "no chance" for Eileen Sue's survival and "little chance" to save their daughter Kathleen Jo, who showed signs of

leukemia only three months after her sister. Mrs. Van Lopik acknowledged that she and her husband had accepted Eileen Sue's prognosis, saying, "We have given doctors permission to make any type of test they wish or use any attempt at a cure for the benefit of research. Maybe it will help others—even Kathleen."[106] Newspaper articles reported Eileen Sue's death two days later and Kathleen's later in the spring.[107] Statements made by the Burns and Van Lopik families revealed that their decisions required a difficult calculus between the possible risks and benefits for their child.

A series of articles and a letter to the editor in the *New York Times* introduced another example of medical experimentation into a highly visible, public forum. This case involved two distinct populations—children and prisoners—and incited a debate about research ethics among physicians. In June 1949, Louis Boy, a convict in New York's Sing Sing prison, participated in a secret medical experiment. The two physicians involved in the experiment hoped that, by exchanging the prisoner's healthy blood with the leukemic blood of eight-year-old Marcia Slater, they would transfer an unidentified factor that would combat leukemia and, eventually, cure the young girl. They also believed that the prisoner might develop an antileukemic substance during the exchange that could then be used to fight leukemia in other patients. Physicians directly transferred half a pint of affected blood from the ill child to the veins of the convict through a piece of rubber tubing. They then gave the child a pint of his blood. The exchange continued for five hours a day on four consecutive days until approximately eighteen pints had been exchanged between Boy and Slater.[108] Physicians regularly used transfusions to strengthen leukemia patients and to make them more comfortable, but newspaper articles describing the experiment claimed that the recipient's blood had never been added back to the donor's veins. After the extensive transfusions, the prisoner remained under guard in a ward at the Ossining, New York, hospital while the girl rested in a private room. By the end of the week, initial tests on the prisoner recorded no abnormalities in his blood and bone marrow and a small improvement in the young cancer patient. The experiment, a last resort for Slater, did not succeed in saving the girl's life.[109]

In interviews with the press, physicians involved with the procedure publicly justified the experiment's possible dangers and benefits. Slater's doctor, Harry Wallerstein, a physician at Jewish Memorial Hospital in New York, stated that he conducted this experiment with a prison volunteer because he needed to enroll a subject who was willing to take risks.[110] Although previous experiments of this nature carried out on laboratory animals had shown

that it was not possible to transmit the disease through an exchange of blood, an authority declared, "I would not care to have leukemic blood pumped into my own veins."[111] Wallerstein and James B. Murphy, head of the cancer division of the Rockefeller Institute for Medical Research, confirmed that Boy had volunteered without the promise of reward and with full knowledge of the possible fatal risks including a "very, very remote" chance that he could contract leukemia. For the next year, physicians planned to monitor his blood for the presence of leukemic cells. The researchers' statements and subsequent actions suggested a level of uncertainty regarding the experiment's effects on both Slater and Boy.[112]

The Boy-Slater experiment raised moral questions regarding the acceptable levels of risk to research subjects in medical experiments. On June 8, a letter to the *New York Times* from Ludwig Gross, a physician and the chief of cancer research at Veterans' Administration Hospital in New York, fiercely censured the experiment, calling it "open to considerable criticism from both a scientific and also from a purely humanitarian point of view."[113] Likening leukemia to a death sentence that could only be temporarily delayed by new chemotherapeutic agents and radioisotopes, he asked whether the prisoner was properly informed of the dangers that would result if he contracted this disease during the transfer. Unlike Wallerstein and Murphy, Gross also claimed that similar transfusion experiments had been conducted previously between leukemia sufferers and those with terminal illnesses. Gross was outraged by the vast amounts of infected blood that were transferred to a healthy human volunteer. He condemned the experiment, saying that Slater would gain only the temporary improvement she would have received from a standard transfusion, a small chance remained that an experimental accident could also kill Boy, and the transfusion had few significant benefits to science or medicine. Test results from Boy's final medical examination at Jewish Memorial Hospital showed that Boy had not been harmed in the experiment.[114]

Why did the Slater-Boy experiment stimulate such a volatile response? In his editorial, Gross focused on issues surrounding Boy, the healthy prisoner "volunteer," but also briefly addressed the considerations required when experimenting on a child—specifically, a child suffering from a terminal illness. By the time of this debate, there had already been a long history of children serving as research subjects.[115] In the early twentieth century, accusations of "human vivisection" and the use of children as "guinea pigs" prompted debate over the limits of acceptable human experimentation. The success of

medical research in the 1930s and the benign picture of investigation (that physicians used only their own bodies and those of volunteers) obscured the more complex realities of the research activities in the 1940s.[116] Physicians involved in this experiment and in all clinical research on acute leukemia had to meet two interconnected, yet often opposing, goals—the pursuit of new medical knowledge through experimentation and the responsibility to protect children from harm.

Despite the creation of the Nuremberg Code, a document composed of ten key ethical principles that was drafted in response to Nazi medical experiments, there continued to be little consensus among American researchers of the limits of medical research.[117] The use of dying children reflected an uneasy, constantly negotiated union of experimentation and therapy. At a time when few formal guidelines or professional criticism restricted institutional human experiments, several factors may have spurred Gross's reaction: the child participant, her particular disease, few therapeutic benefits, or the direct blood transfusion from a male prisoner to a young girl. The experiences of Mary Sheila and Marcia Slater poignantly demonstrate that the overlap between childhood cancer research and treatment merits a careful scrutiny, both to expose past abuses and to illuminate present and future concerns of patients, parents, and practitioners.

In 1952, Farber boasted, "If the problem of resistance, either initial or acquired, of the leukemic cell to the folic acid antagonist could be solved, the usefulness of the antagonists in acute leukemia could be compared with justice to that of insulin in diabetes."[118] He repeated this belief again four years later, expanding the problem of resistance to all antileukemic agents developed during the subsequent four-year period.[119]

This obstacle prevented the cure for acute leukemia promised by select physicians, promoted by the popular media, and expected by the public; however, children with cancer were living longer. In the 1940s, fewer than 5 percent of children with acute leukemia survived one year following their diagnosis. By 1956, more than half of the children receiving treatment for acute leukemia survived a year from clinical diagnosis of the disease because of the aggressive use of chemical agents and the addition of adjunct therapy such as transfusions of whole blood, antibiotics, and maintenance of fluid and electrolytes.[120] Yet, these changing forms of medical management created new challenges for physicians and allied health practitioners, children, and parents. By the mid-1950s, some children were able to take their pills at home and

come to the outpatient clinic only once or twice a week for general examinations and bone marrow aspirations to monitor their leukemic cell counts.[121] This relieved physicians and nurses of the child's daily care, but parents were now charged with administering medications, checking for signs of toxicity, stopping a dangerous hemorrhage, guarding against infections, and shuttling the child to frequent medical appointments. These responsibilities multiplied as children neared the end of their lives. In the next decade, parents' duties continued to expand as two collaborative groups—Leukemia Group B and the Acute Leukemia Task Force—produced consistent, lengthy remissions for most children and provided proof that chemotherapy could cure acute leukemia.