

## Historical Review

### A HISTORY OF ST JUDE CHILDREN'S RESEARCH HOSPITAL

The entertainer Danny Thomas founded St Jude Children's Research Hospital in Memphis, Tennessee, in 1960 and opened its doors in 1962 to serve children in need through research and medical care. Dr Donald Pinkel, the first director, initiated the 'Total Therapy' series of studies of acute lymphoblastic leukaemia (ALL), which subsequently demonstrated that the disease was curable in a significant percentage of children. Pioneering studies in childhood cancer and high-quality basic biological research served as key ingredients in creating an environment of scientific excellence and interdisciplinary activity. During its 40 years, the institution has grown in scientific stature and programmatic depth, both made possible by the skill of its investigators, and by its physical and financial growth. This growth reflects not only the faculty's ability to compete for research grants, but also the tireless and remarkably successful fund-raising of the American Lebanese Syrian Associated Charities (ALSAC), founded by Danny Thomas for the sole purpose of supporting St Jude.

St Jude Children's Research Hospital opened its doors in 1962 in Memphis, Tennessee. How it came to be and its ascendance to prominence in a relatively short time is a remarkable story of good will, perseverance, gifted leadership, determined focus and a dash of good fortune. This brief history describes the institution's beginnings, its studies of childhood cancer that first brought it to international recognition and its evolution to a mature research institute. This is largely a personal and necessarily incomplete historical view, based mainly on what I learned and observed during my tenure at St Jude from 1967 to 1992.

#### BEGINNINGS

Danny Thomas was born in Toledo, Ohio, of Lebanese immigrant parents in 1912 (Fig 1). He became an entertainer and, after the customary struggles and near despair, got his break with a successful tenure as a comedian and storyteller in a Chicago nightclub. He subsequently appeared on the stage and in movies, and is probably best known for his long-running television show 'Make Room For Daddy'.

In the 1950s, after he had become successful, he began the process of keeping a vow to St Jude Thaddeus, patron saint of hopeless causes, which he made in the depths of his professional struggles. He vowed, 'Show me my way in life and I will build you a shrine.' He sought advice from

Cardinal Samuel Stritch, then Catholic archbishop of Chicago, whom Thomas had met when the former was a bishop in Toledo. Stritch dissuaded him from building a shrine, saying there were plenty already. They subsequently agreed that a children's hospital for the needy was a better tribute, something like the Shriner's hospitals in the USA, where disabled children received free care. Thomas favoured locating the hospital in Chicago where he got his show business start. Stritch persuaded him that Chicago already had good children's facilities and that he should find a place in greater need. Stritch suggested Memphis, Tennessee, where he had been a parish priest and, being a practical sort, because he was a good friend of a civic leader in Memphis who might be able to smooth the way.

Thomas received a cool reception in Memphis at first, but three Memphians stepped forward to help him and all three proved instrumental in making St Jude what it is today. Mr Edward Barry, a good friend of Stritch and a highly esteemed businessman, and Dr Gilbert Levy, an eminent paediatrician in Memphis who cared for the children of many prominent citizens, smoothed the way with politicians and civic leaders. Barry was to serve as chairman of the St Jude board of directors for 25 years. The third, and scientifically propitious, was Dr Lemuel Diggs (Fig 2). Diggs, then a professor at the University of Tennessee College of Medicine, was a distinguished haematologist best known for his pioneering and productive studies of sickle cell disease for more than five decades. He was the first to clearly distinguish sickle cell trait from sickle cell anaemia (Diggs *et al.* 1933). Diggs advised Thomas and the trustees to change the plans and build a research facility for the study and treatment of blood diseases and cancer in children; they accepted his recommendation.

After 7 years of planning and fundraising, ground was broken for the 85 000 square foot research hospital in 1960 (Fig 3), and the search for a director began. It proved a challenge to attract a leader to an unknown institution with no track record, uncertain finances, an unfinished building, no employees or faculty, and to a provincial, racially segregated southern city. The only serious candidate was Dr Donald Pinkel (Fig 4), a 34-year-old paediatric oncologist who had spent a year with Sidney Farber in Boston before becoming the first chief of paediatrics at the Roswell Park Cancer Institute in Buffalo, New York. He met with Barry and Mr Michael Tamer, a friend of Thomas who had become the chief executive of the American Lebanese Syrian Associated Charities (ALSAC). After the three of them spent a full day in a room at the Conrad Hilton Hotel in Chicago discussing each other's philosophies and ideas, Pinkel was hired with a handshake. Leaving his wife and

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Fig 1. Danny Thomas, founder of St Jude Children's Research Hospital, c. 1956, when he began raising funds.



Fig 2. Lemuel Diggs, MD, c. 1957, when he advised the trustees to build a research hospital.

seven children in Buffalo until he could secure housing, he arrived in Memphis in the summer of 1961 to an unfinished building, no employees and no payroll department, so his first compensation was a personal cheque from Barry.

Pinkel's appointment was yet another of the many critical steps of good judgement and good fortune that proved essential to the success St Jude would later enjoy. Pinkel laid the foundation for what St Jude would come to embody: an environment of basic science intertwined with a scientifically rigorous system of clinical research, a collegial atmosphere, and pride in a strong sense of mission. Throughout his tenure as director, he proved to be an inspiring leader, an able recruiter and a selfless mentor, all the while remaining actively engaged in research.

#### TOTAL THERAPY STUDIES OF ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

From the beginning, St Jude engaged in studies of all paediatric cancers and some haematological disorders. St Jude received its first research grant for a study of sickle cell disease, and it carried out pioneering studies in solid tumours (James *et al*, 1965; Hustu *et al*, 1968; Pratt, 1969), as well as in the development of new chemotherapeutic agents and treatment regimens (Pinkel, 1962; Pratt *et al*, 1968). However, the institution had its greatest initial impact with, and perhaps is best known for, a series of studies of children with ALL.

Before arriving in Memphis, Pinkel had been engaged in a variety of leukaemia studies at Roswell Park and also served as a member of a national co-operative group formed to study leukaemia. In addition to Pinkel, the group included such well-known figures as Emil (Tom) Frei, III, and Emil (Jay) Freireich, who were then at the National Cancer Institute, and James Holland. The group carried out the first controlled clinical trials in leukaemia, most notably demonstrating that the simultaneous administration of methotrexate and mercaptopurine produced longer remissions than either agent alone or when given sequentially after the first of the two had failed (Frei *et al*, 1965). However, all the patients eventually relapsed and died. Another disappointing outcome was the discovery that as remissions lengthened, the more frequent the occurrence of symptomatic leukaemic involvement of the central nervous system (CNS). The symptoms included headache and vomiting due to increased intracranial pressure, as well as cranial nerve palsies and epileptiform seizures. This complication could be controlled for a time by the intrathecal injection of methotrexate, but recurred and became virtually impossible to eradicate, even with external beam irradiation.

Thus, when St Jude opened in 1962, childhood leukaemia remained a universally fatal disease despite some signs of progress: tantalizing, though temporary, responses to several chemotherapy agents; the early definition of proper experimental design and parameters of success in leukaemia trials; the emergence of a small cadre of clinical oncology investigators; and growing research support from the



Fig 3. St Jude Children's Research Hospital in 1962, the year it was founded and received its first patient.



Fig 4. Donald Pinkel, MD, the first director of St Jude Children's Research Hospital, c. 1962.

National Cancer Institute. The latter proved important, and probably critical, to the early growth and success of the studies at St Jude.

#### *Total therapy studies I-IV*

These early studies, which accrued patients from 1962 to 1967, employed a variety of chemotherapy combinations and dosages of methotrexate, mercaptopurine, vincristine, prednisone and cyclophosphamide (George *et al*, 1968; Pinkel, 1971; Pinkel *et al*, 1971, 1972; Simone *et al*, 1972a). They had several important features and outcomes that proved decisive in the design of later, more successful, studies. In addition to combination chemotherapy, patients in Studies I-III received 'prophylactic' craniospinal radiation at two dosage levels, 500 cGy or 1200 cGy. The rationale for this regimen was as follows.

CNS leukaemia often emerged while the bone marrow and blood remained free of detectable leukaemia. This suggested that, as with antibiotic therapy, there was a barrier to penetration of chemotherapy from the blood to the meninges, which pathology and animal studies determined to be the main focus of leukaemic infiltration. As ALL was widespread at the time of diagnosis, it was deduced that giving radiation early in the course of disease might eliminate the asymptomatic and presumably small infiltration, and thus prevent CNS relapse. The results of the pilot Studies I and II, which used 500 cGy of craniospinal irradiation, became available while Study III was in progress. They showed that the 500 cGy had no discernable effect on the relapse rate. Furthermore, two additional problems emerged: the radiation had increased myelosuppression and the chemotherapy regimen proved only modestly effective. Thirteen of 15 patients attained remission, and the median duration of complete remission was 8 months.

Study III added a 1-week 'intensive phase' of daily, high-dosage intravenous chemotherapy immediately after successful remission induction, in turn followed by 1200 cGy craniospinal irradiation and then combination chemotherapy. The patients in Study III fared better. The median duration of complete remission of the 24 patients who attained remission was 15 months. However, 12 of 24 patients suffered initial relapses in the CNS. This was the first time that initial relapses in the CNS outnumbered those in the bone marrow. The chemotherapy prolonged remission, but the radiation was ineffective at controlling leukaemia in the CNS.

While Study III was underway, an important pharmacological issue influenced the design of Study IV. The results ultimately established a principle of therapy that persists today. The rationale for administration of multiple agents simultaneously mimicked the successful use of antibiotics for tuberculosis: attack the leukaemia at multiple points of cellular metabolism to achieve an additive or

synergistic effect and reduce the emergence of strains resistant to any one agent. However, giving four agents during remission in various combinations in 'full' dosage, as in Studies I–III, often caused dangerous myelosuppression. Could one achieve the same antileukaemia effect by giving all four agents in reduced dosage? The design of Study IV was as follows: patients were randomized after successful remission induction to receive either conventional 'full-dosage' chemotherapy with modification of the dosage to achieve an observable biological target, principally a leucocyte count of  $2-3 \times 10^9/l$ , or 'half dosage' of the same agents on the same schedule. The leucocyte counts were monitored weekly. Patients were given no radiation because of the disappointing results of the previous studies. The study had two important outcomes. After a relatively short time, the relapse rate in the half-dose group was significantly greater, and ultimately the median duration of complete remission was 6 months in the half-dose group and 15 months in the full-dose group. The frequency of primary relapse in the CNS was high in both; 15 of 21 patients in the half-dose group and 10 of 21 in the full-dose group. The first conclusion of the study was that full, maximally tolerated doses of chemotherapy are necessary for control of the systemic leukaemia. But the study also demonstrated that inadequate doses of chemotherapy led to an earlier and higher frequency of CNS relapse. This suggested that some chemotherapy crossed the blood–CNS barrier in a dose-dependent manner and that strong systemic chemotherapy was necessary for controlling, though insufficient for eradicating, CNS leukaemia.

An unexpected positive result gradually emerged from these early studies. Two of the 15 patients who entered Studies I–II and five of 26 patients from Study III proved to have long-term complete remissions. This provided a glimmer of hope for future studies and led to the design of Study V. Although it would not be known until years later, these patients were destined to become leukaemia-free survivors after all therapy had been discontinued. They were cured.

#### *Total therapy study V*

This study of only 35 patients provided the proof of principle that the St Jude investigators had hoped for (Aur *et al*, 1971a). The design retained the initial features of Study IV – remission induction with prednisone and vincristine followed by a 1 week course on high-dosage intravenous chemotherapy – but the remainder of therapy was modified. Preventive CNS therapy was reinstated because of the growing incidence of CNS relapse, with three modifications: (1) only the cranium was irradiated to avoid the broader marrow damage caused by spinal irradiation; (2) the dosage was increased to 2400 cGy because it was thought to be a lymphocidal dose at that time and because it was double the ineffective 1200 cGy dosage given in Study III, an attempt to test whether any practical radiation dose would be effective; and (3) in the absence of spinal irradiation, five doses of intrathecal methotrexate were given during the 18-d course of radiation. Subsequent therapy was given in maximum tolerated dosage and consisted of mercaptopurine daily, and methotrexate and cyclophosphamide weekly, with a 2-week course of vincristine and prednisone 'reinduction' every 10 weeks.

The results were dramatic. Among the 32 of 35 patients who attained remission, there were no relapses in the first 5 months of remission and the relapse rate remained significantly lower than in previous studies. Only three children relapsed initially in the CNS. Ultimately, half the patients went on to complete 3 years of therapy. All remained in remission after cessation of therapy, became long-term survivors and were eventually declared cured. A subsequent randomized study confirmed the value of preventive CNS therapy (Aur *et al*, 1978).

The Total Therapy Studies have continued until today, testing many modifications, teasing out the important, trivial and dangerous aspects of treatment, and achieving a progressive improvement in the cure rate, now nearing 80% (Pui & Evans, 1998) (Fig 5). These well-documented studies have provided fertile ground for progressive innovations and discoveries. Early studies separated patients into prognostic categories based on clinical observations (Simone, 1976),

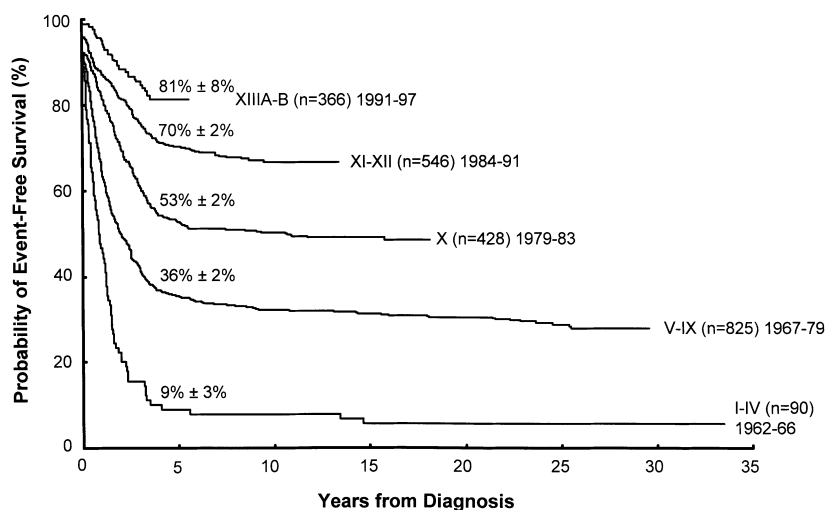


Fig 5. Graph showing the progressive improvement in the cure rate of acute lymphoblastic leukaemia in children (Pui & Evans, 1998. Published with permission. Copyright © 1998 Massachusetts Medical society. All rights reserved).

while Dr Luis Borella was the first to report that some leukaemia cells had immunological features of normal T cells (Borella & Sen, 1974, 1975), thus identifying a group of patients destined at that time to suffer a poor outcome. Dr Dorothy Williams continued this tradition of work in leukaemia biology with her pioneering cytogenetic studies of childhood leukaemia (Williams *et al.*, 1982). Current studies from St Jude use sophisticated microarray analysis of lymphoblast genetic patterns to more accurately predict the response to a given therapy (Yeoh *et al.*, 2002).

The St Jude Total Therapy Studies also provided the opportunity for remarkable studies of *Pneumocystis carinii* pneumonia (PCP), a frequent cause of death in remission in the 1970s, by Dr Walter Hughes and colleagues. Hughes developed the first animal model of PCP, and demonstrated the therapeutic value of trimethoprim and sulphamethoxazole (Hughes *et al.*, 1973). He then carried out a randomized, double-blind study which clearly demonstrated that PCP could be prevented by giving children with leukaemia prophylactic treatment with those agents (Hughes *et al.*, 1975, 1977). The frequency and mortality from PCP subsequently dropped to virtually zero. This work provided the basis for treatment and prevention of PCP in the acquired immunodeficiency syndrome epidemic that began some years later.

#### OTHER CLINICAL CONTRIBUTIONS

In this brief review, it is possible to offer only a sample of the many other important clinical studies carried out at St Jude. Over the years, St Jude investigators have published numerous studies on the management of the complete array of paediatric solid tumours, most notably Hodgkin's disease, rhabdomyosarcoma, neuroblastoma and Ewing's sarcoma of bone. These investigators made one of the first attempts to treat non-Hodgkin's lymphoma (then called lymphosarcoma) as a systemic rather than a localized disease using antileukaemia chemotherapy (Aur *et al.*, 1971b), which proved to be a decisive step, leading to a cure rate that today approaches 80%. The same team carried out some of the first studies to identify leukaemic children with clinical features associated with a poor outcome and manage them differently (Aur *et al.*, 1971c; Simone *et al.*, 1975). This work was a forerunner of the application of the modern genetic and pharmacological techniques used today (Yeoh *et al.*, 2002). St Jude was among the first to publish systematic studies of the side-effects of CNS chemotherapy and radiation (Aur *et al.*, 1978), and the problem of deaths during remission of leukaemia (Simone *et al.*, 1972b). Its investigators also published the first studies showing a much lower frequency of ALL in American southern black children (Hernandez & Tokuhata, 1966) and the especially poor prognosis of this group of patients when compared with whites (Walters *et al.*, 1972). Remarkably, the latter difference had disappeared when re-examined decades later (Pui *et al.*, 1995), probably due to better access to contemporary, protocol-based therapy, and improvements in nutrition and socio-economic status following federal civil rights and food supplement programs (see below).

#### NUTRITIONAL SUPPLEMENTS FOR POOR CHILDREN

In 1968, the year Martin Luther King, Jr, was assassinated in Memphis, St Jude began investigating the health of poor children in a black ghetto in nearby South Memphis. After studies by Dr Paul Zee showed that 26% of children had a haemoglobin concentration below 11 g/dl and retarded growth (Zee *et al.*, 1970), he led a programme that started with a free clinic for the children. St Jude then obtained regular shipments of large quantities of surplus foods free of charge from the American Department of Agriculture, which were received and distributed to needy families by members of that same South Memphis community. The programme proved to be a humanitarian and medical success. It eventually became a national political success because it led to the formation of the nationwide Women, Infants and Children (WIC) programme by the American government to support needy families.

#### BASIC RESEARCH

From its beginnings, St Jude had an active and successful cadre of basic scientists working on a variety of problems. Early studies of the viral aetiology of cancer, a widely investigated process in the 1960s, spearheaded a broad research programme in virology and immunology led by Dr Allan Granoff. His own work focused on a carcinogenic frog virus that developed intriguing temperature-sensitive mutants (Granoff *et al.*, 1966). Dr David Kingsbury carried out pioneering studies on RNA replication that anticipated the discovery of reverse transcriptase (Kingsbury, 1966). Dr George Cheung discovered and described the function of calmodulin (Cheung, 1980). Dr Robert Webster has studied the immunology of influenza virus, and the geographical source of pandemics in China and elsewhere (Webster, 1970), efforts that led to his election to the American National Academy of Science (Academy) in 1998. Dr Peter Doherty, who joined St Jude in the 1980s, subsequently received the Nobel Prize in Physiology or Medicine in 1996. He shared the prize with Dr Rolf Zinkernagel for their work on the specificity of the immune reaction to infectious agents (Doherty *et al.*, 1974; Zinkernagel & Doherty, 1974). Dr Charles Sherr, who left the National Cancer Institute in 1983 to become head of tumour cell biology at St Jude, subsequently was named a Howard Hughes Investigator, and in 1995 was elected to the Academy for his discovery of the *C-FMS* oncogene receptor (Sherr *et al.*, 1985), and for his later work on cyclin D and the cell cycle. Dr James Ihle also left the National Cancer Institute to accept the St Jude chair of biochemistry. He was named a Howard Hughes Investigator in 1997 for his large body of work, which was focused mainly on signal transduction pathways in haematopoietic cells.

#### LEADERSHIP AND GROWTH

Donald Pinkel stepped down as director of St Jude in 1973. Dr Alvin Mauer succeeded him and was followed by Dr Joseph Simone in 1983. Dr Allan Granoff, the chairman of



**Fig 6.** St Jude Children's Research Hospital campus in 2002.

virology since St Jude began, served as interim director in 1992–1993 until the arrival of Dr Arthur Nienhuis, who remains the director today. Each director brought his own style and programmatic emphasis to St Jude and contributed to its growth as a scientific leader in oncology, cell and molecular biology, immunology, and virology, as well as research in infectious disease and the physical and psychosocial consequences of cancer and its treatment.

St Jude has experienced remarkable growth and diversification. From a faculty of 25, a budget of \$1.5 million (\$1 million from ALSAC) and one building of 85 000 square feet in 1965, it has grown to faculty of 180, with about 2550 employees, an annual budget of more than \$270 million (69% from ALSAC) and multiple buildings totalling 1 863 187 square feet (Fig 6). It now conducts major programmes in neuroscience, stem cell research and bone marrow transplantation, and has developed an extensive international outreach programme for helping oncologists in Brazil, Chile, China, El Salvador, Guatemala, Honduras, Costa Rica, Ecuador, Jordan, Lebanon, Mexico, Morocco, Russia, Syria and Venezuela to provide better care for their patients. St Jude has never required payment from patients and, in fact, had no billing department in its first decade. After long discussions, Danny Thomas finally agreed to allow St Jude to collect insurance but no direct payment, on the condition that patients would not be asked if they had insurance before admission. That remains the policy today. St Jude patients have come largely from the lower third of the socio-economic ladder, and the hospital has supported families in many ways during such a stressful time, usually paying for transportation to and from Memphis. Around 1970, St Jude began to rent blocks of hotel rooms in Memphis, where families could stay at no charge.

#### HOW DID THIS HAPPEN?

St Jude's improbable rise to international scientific eminence in its first decade offers instructive lessons. Others may point to luck, timing or other explanations, but I believe the

following factors to be central to the early success. First, Donald Pinkel personally and continually communicated to all faculty and employees a clear and noble vision, which was vocally and materially supported and reinforced by Danny Thomas and the trustees. Second, Pinkel's charismatic leadership instilled a spirit of missionary zeal and daring, especially among clinicians that was reflected in their clinical studies. Third, there was no university or other large, conservative, change-averse institutional structure to struggle against. St Jude had virtually no bureaucracy, just Pinkel and a few lieutenants. Fourth, the leaders and small staff worked shoulder-to-shoulder in the trenches – Pinkel and his lieutenants saw patients and did research with the others – creating an environment of solidarity, enabling them to take risks and move quickly with new ideas. Pinkel led a few platoons, not an army.

Danny Thomas died in 1991 and, following his wishes, was buried in the grounds of St Jude because, in his words, 'St Jude was my greatest accomplishment in life'. Many of us who had the privilege of working at St Jude and sharing in Danny's noble enterprise feel the same way.

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#### ACKNOWLEDGMENTS

I wish to thank Ms Lois Young, Mr John Gilbert and Dr Donald Pinkel for their editorial suggestions and help in gathering information.

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**Keywords:** St Jude, childhood cancer, leukaemia, Danny Thomas, Donald Pinkel.