The past and future of cancer in the young

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Most people are unaware that cancer is the No. 1 disease killer of children from late infancy through early adulthood.[1] In the US and most economically advantaged nations of the world, cancer kills more children older than age 6 months than any other disease. More than 10% of all deaths in children younger than 15 years of age are caused by cancer. Cancer is the leading medical cause of death in both males and females from 1 to 34 years of age, and in females cancer is the leading cause from age 1 to 75; after age 34 in men (75 in females) heart disease exceeds cancer as the leading cause of mortality. Only accidents exceed cancer as the leading cause of mortality in children and adolescents.

Since 1945, about 170,000 US children have died of cancer before age 15 years.[2] If the average age at diagnosis of these patients was 5 years, and the average life span would otherwise have been 75 years, then 20 million person-years were potentially affected by the diagnosis, either in terms of risk of premature death or compromised quality of life by the disease or its treatment. Of these 20 million person-years, at least 11.5 million person-years of life were lost to premature death.[2] Currently, more than 100,000 person-years of potential life are lost each year among the US children who die of cancer.[2]

The incidence of childhood cancer

By projecting trends predicted from data collected by the Statistics, Epidemiology and End Results (SEER) Program of the National Cancer Institute,[3] the current incidence of cancer in Americans younger than 15 years old is 14 cases per 100,000/year (Fig 1). Teenagers in the 15- to 19-year age bracket have an incidence of about 20 cases per 100,000/year (Fig 2). Thus, approximately 11,000 US children and adolescents younger than 20 years of age are diagnosed to have cancer each year.[2] That means each weekday, 42 children or adolescents are diagnosed to have cancer. That's nearly one in each state, on the average. Since 1945, 280,000 US children have been diagnosed to have cancer before they were 15 years old.[2]

Worldwide, the incidence of cancer may be estimated at 11/100,000 persons < 20 years of age.[4] Since there are approximately 2.1 billion people in this age range, there are probably 260,000 children in the world who are diagnosed with cancer each year. Cancer is 10–20 times more common in children than AIDS in our country.[2] Since 1980, when the AIDS epidemic began, cancer has occurred in more than 70,000 US children, compared with 1,680 cases of AIDS in the same age group over the same period of time.[2]

There is evidence that in the US the incidence of cancer is increasing, not only overall in all age groups but also in children. In fact, it appears that the incidence is increasing among children more than it is in young and middle-age adults (Fig 2).[3]

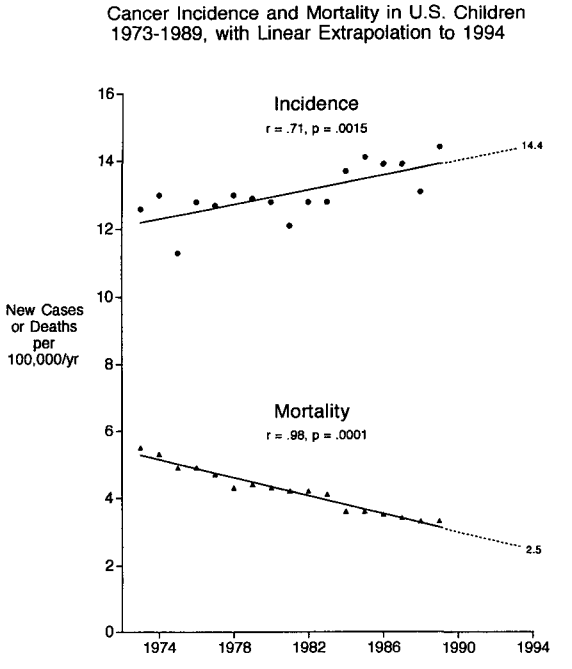

Fig 1. Increasing incidence and declining mortality of cancer during childhood (0–14 years), United States, all races, both sexes, 1973–89. The rates are standardized on age distribution younger than 15 years of 1970 US census population. Data from United States SEER program, as reported in Cancer Statistics Review, 1973–89.[3] Values of statistical significance are based on the F-test applied to linear regression of the data with 13 degrees of freedom.

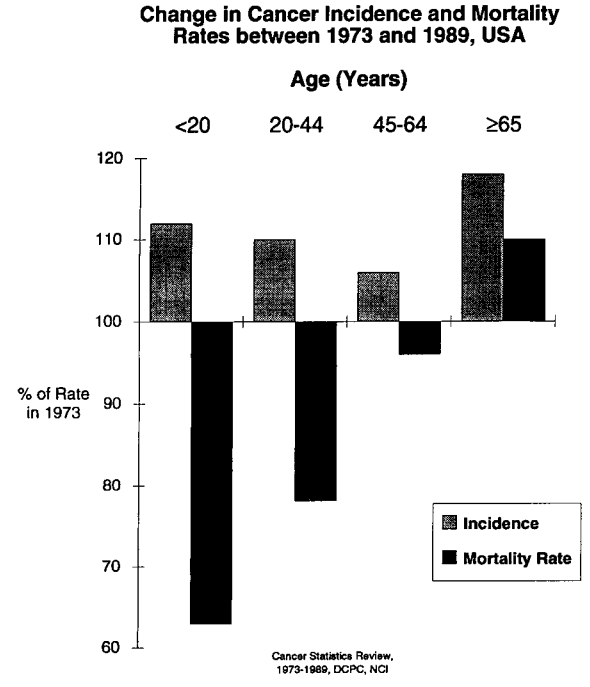

Fig 2. Incidence and mortality rate of cancer in < 20, 20–44, 45–64, and ≥ 65 year-olds, United States, all races, both sexes, 1973–89. The rates are standardized on age distribution of 1970 US census population. Data from United States SEER program, as reported in Cancer Statistics Review, 1973–89.[3]

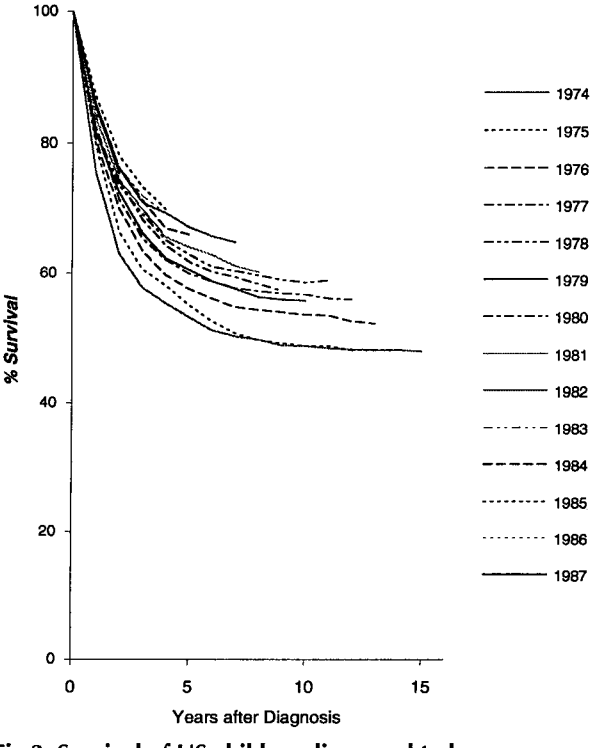

Fig 3. Survival of US children diagnosed to have cancer before 15 years of age, according to 1973–1988 SEER data for both sexes. Data from Cancer Statistics Review, 1973–1989.[3]

Survival of children with cancer

SEER data predict that mortality from cancer in Americans younger than 15 years of age has dropped to 3 cases per 100,000/year in 1993 (Fig 1). The cancer mortality rate has decreased more dramatically in children than in any other age group (Fig 2), with the plateau on the survival curve increasing from 50% in the mid-1970s to 70% by the mid-1980s (Fig 3). Based on projections of SEER data on 11-year survival rates for annual cohorts of patients diagnosed in 1973–80, 10-year survival rates of annual cohorts for 1973–81, 9-year rates of annual cohorts for 1973–82, 8-year rates of annual cohorts for 1973–83, 7-year rates of annual cohorts for 1973–85, 6-year rates of annual cohorts for 1973–84, and the "differential survival" rate determined from comparing concurrent incidence and mortality rates, the long-term survival of Caucasian children diagnosed in 1993 will approach 80% (Table 1, Fig 4).

Although children with cancer represent only about 1% of all persons with cancer, there is a lifetime for every child cured of cancer (in contrast to the median age of 67 years at diagnosis among all persons with cancer[1]). In the US, childhood cancer ranks second in the total number of potential person-years of life saved (Fig 5). If the cure rate is 80%, and the average childhood cancer survivor lives until age 77, the loss of more than 400,000 patient-years of potential life is being averted each year (Fig 5).

At the current survival trend, the total number of childhood cancer survivors can be predicted to be between 180,000 and 220,000 by the year 2000.[2] The trend can be interpreted to predict that the prevalence of cancer survivors among young adults (15–45 years of age) in the US will increase to one in 900 persons in the year 2000, and unless the trend changes, to as many as one in 250 persons in the year 2010.[2]

This dramatic progress is worthwhile only if the quality of survival—the medical, psychosocial, intellectual, emotional, and financial cost of cure—justifies the increased prolongation of life. Epidemiologically, the magnitude of the potential cost may increase steadily as more and more children are cured, and as more inten-

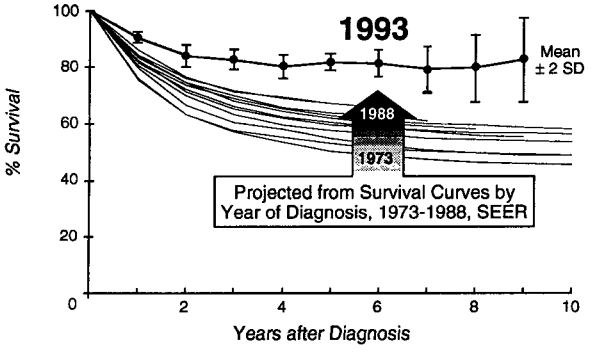

Fig 4. Estimated survival of US children younger than 15 years old diagnosed with cancer in 1993. The projection is based on the data in Table 1.

TABLE 1. SURVIVAL OF CHILDREN WITH CANCER BEFORE AGE 15 YEARS*

Year	4-Year Survival	5-Year Survival	6-Year Survival	7-Year Survival	8-Year Survival	9-Year Survival	10-Year Survival	11-Year Survival
1973	53.4	50.4	49.1	47.5	46.6	46.2	45.2	44.9
1974	55.3	53.2	51.2	50.2	49.7	48.8	48.7	48.4
1975	58.1	55.0	52.6	50.7	49.6	49.2	48.7	48.7
1976	59.7	57.5	56.0	54.7	54.2	53.9	53.5	53.4
1977	62.1	59.9	58.7	57.6	57.1	56.8	56.6	56.0
1978	65.1	62.9	61.0	60.3	59.6	58.9	58.5	57.8
1979	62.3	60.5	58.7	57.5	56.2	55.8	55.6	
1980	64.3	61.8	60.2	59.3	58.3	57.2		
1981	65.5	64.0	62.8	61.1	60.1			
1982	69.2	67.0	65.6	64.7				
1983	69.2	66.9	65.8					
1984	66.8	65.9						
1985	69.8							
1993†	**81.2** (77–85)	**81.3** (77–86)	**82.5** (78–87)	**83.0** (77–90)	**80.9** (71–91)	**81.7** (68–96)	**88.0** (71–)	**89.0** (89–)

SEER Data for 1973–1988 and Linear Extrapolation to Year 1993. Survival rates are relative rates expressed as percents.

* 1973–84 data from reference 3.

† Predicted by linear regression. Values in parentheses represent 95% confidence intervals for slope of linear regression curve.

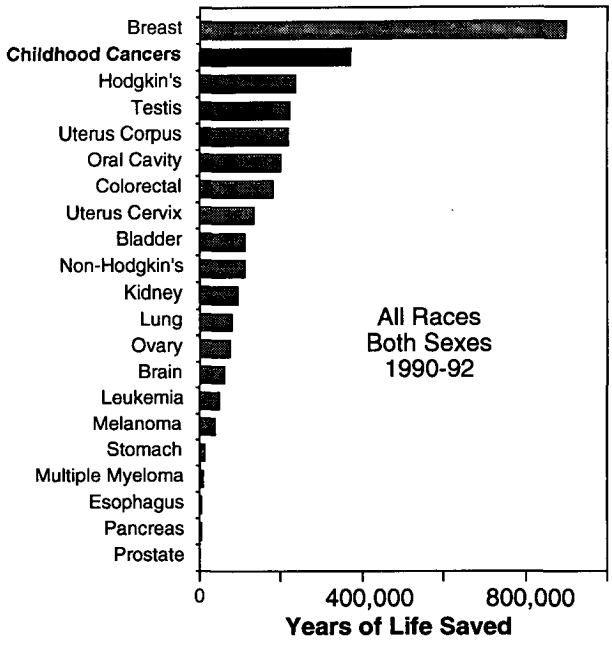

Fig 5. Number of person-years of potential life saved annually in the US among persons diagnosed to have cancer, as derived from an expected life span of 72 years, the median age at diagnosis (67 years),[1] and the maximum number of patients surviving their cancer each year. Person-years = (number of survivors) x (72 – [median age at diagnosis in years]) Survival data were obtained from Cancer Statistics Review, 1973-1989.[3]

sive therapies are used to further increase the cure rate. The problem is underscored by the prediction that within a decade more than 0.1% of the country's young work force can be predicted to be cancer survivors.[2]

Progress in specific childhood cancers

For each of the common cancers of children, there is evidence that the survival rate has increased. The most common childhood cancers and their survival rates are listed below:

1. Acute lymphoblastic leukemia, the most common form of cancer among children, now can be cured in more than 50% of cases and in more than 70% of children with the common type of acute lymphoblastic leukemia, the pre-B-cell (non-T, non-B) type (Fig 6).
2. Brain tumors, the second most frequent cancer, are responding to combined surgery, radiation, and chemotherapy, with nearly half of all children surviving.
3. Non-Hodgkin's lymphomas and Hodgkin's disease, the third most common cancer group in children, are now 50–90% curable, depending on the type and stage (Fig 6).
4. The fourth most common cancer, neuroblastoma, is a highly malignant tumor of the periph-

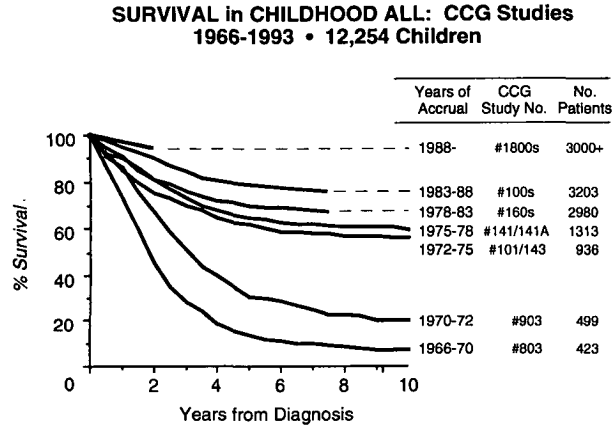

Fig 6. CCG ALL survival.

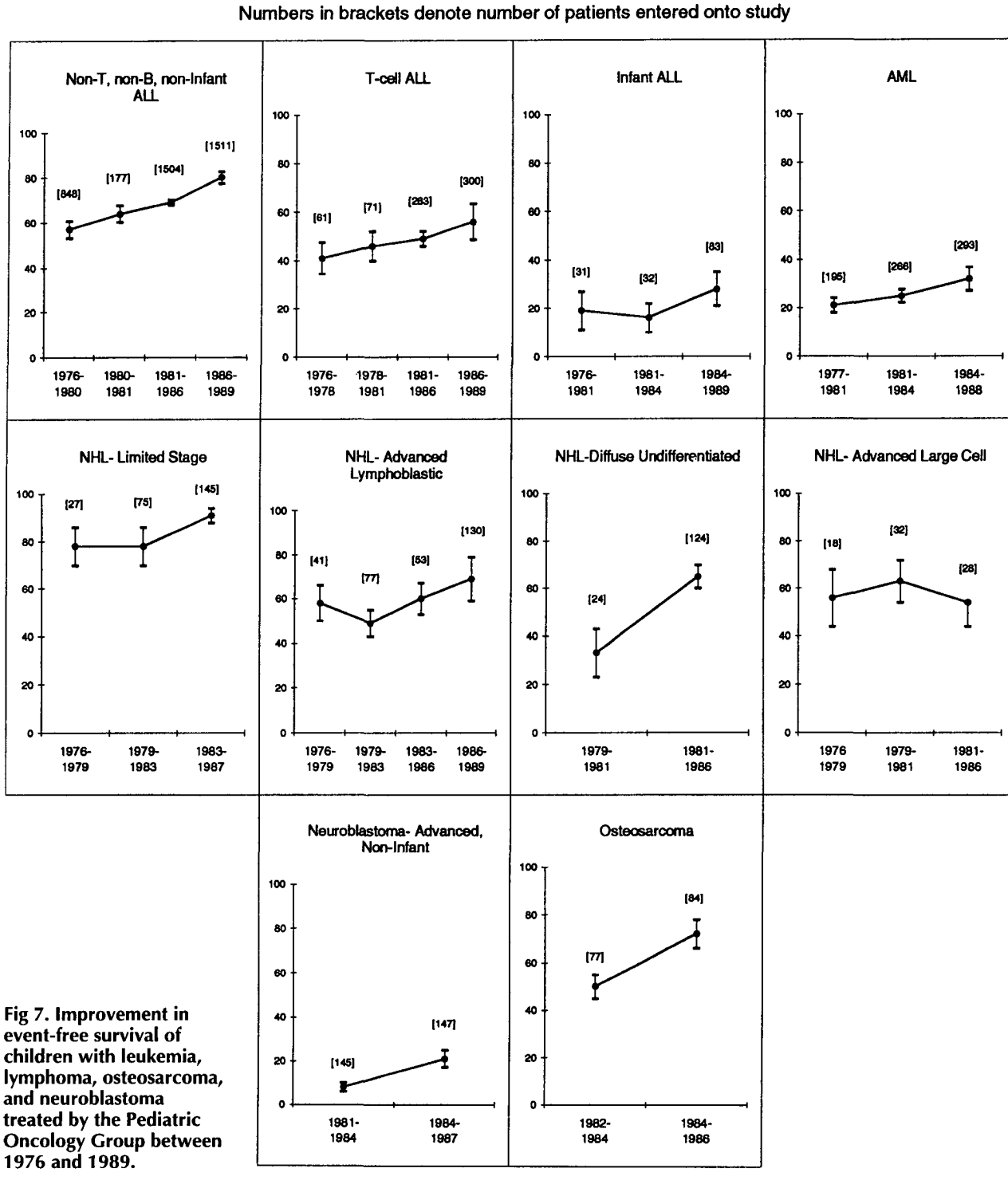

Fig 7. Improvement in event-free survival of children with leukemia, lymphoma, osteosarcoma, and neuroblastoma treated by the Pediatric Oncology Group between 1976 and 1989.

Pediatric Oncology Group: Progress against Childhood Cancer: The Pediatric Oncology Group Experience. Pediat 89:597-600, 1992

eral nervous system. Unfortunately, survival has increased only to approximately 20% in noninfant neuroblastoma cases with evidence for disease dissemination beyond intracavitary nodes (Fig 7).[5]

5. The fifth most common malignancy, Wilms' tumor of the kidney, is now 85–90% curable.
6. Soft-tissue sarcomas, or solid tumors of the connective tissues of the body, comprise the sixth most common cancer group in children. This group of tumors includes rhabdomyosarcoma, fibrosarcoma, and spindle-cell sarcomas. More than 75% of these tumors are now being cured.
7. The seventh most common cancer is osteogenic sarcoma, a malignant bone tumor. This "double tragedy" disease, in that most patients died de-

TABLE 2. ROLE OF CLINICAL TRIALS AND COOPERATIVE GROUP STUDIES IN THE CANCERS OF CHILDREN, 1985*

	Number of Cases in US	*Number of Patients Managed by CCG†*	*Number of Patients Managed by POG‡*	*Percentage of US Patients Managed by CCG and POG*
Leukemia	2257	1300	853	95
CNS	1362	325	270	44
Lymphoma	758	358	358	94
Neuroblastoma	526	260	193	86
Wilms' tumor	444	228	165	89
Bone tumors	312	228	199	—
Rhabdomyosarcoma	228	163	92	—
Other	994	386	336	75
Total	6881	3251	2466	83

* Data from Boyett JM, Vietti TJ: Cancer 56:1894–96, 1985.

† Childrens Cancer Group.

‡ Pediatric Oncology Group.

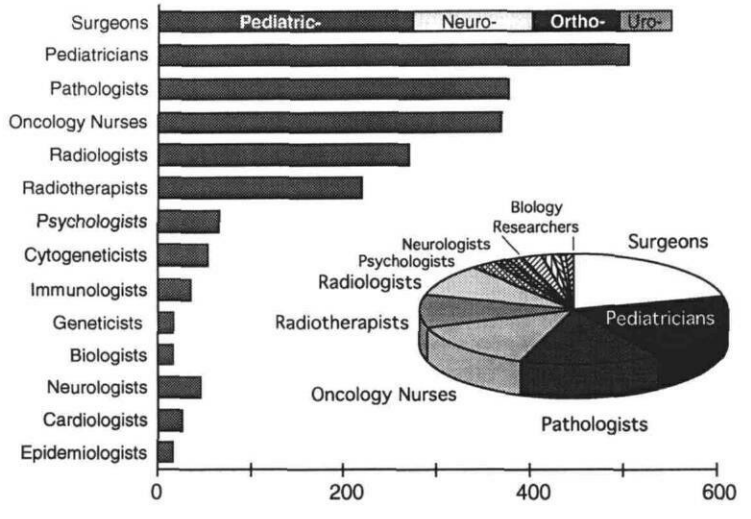

Fig 8. Membership in the Childrens Cancer Group.

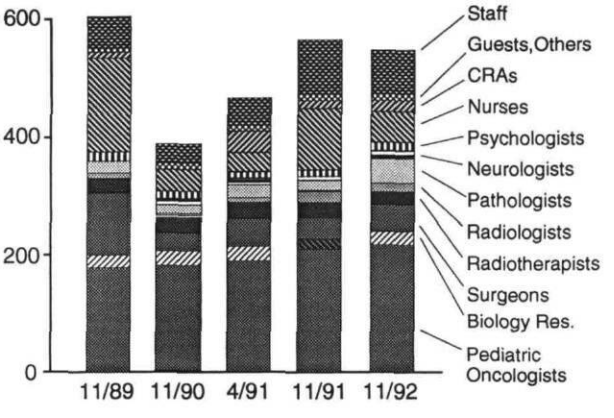

Fig 9. Specialties represented among attendees at Semi-Annual Meetings of the Childrens Cancer Group.

spite amputation of the extremity harboring the tumor, has become significantly less tragic. Survival has improved from 25% in 1970 to at least 50% in the early 1980s and probably 70% in the late 1980s (Fig 7).

8. The eighth most frequent cancer is retinoblastoma, a cancer of the back of the eye, now is curable in more than 90% of cases.

Role of clinical trials and cooperative group studies in pediatric oncology

The treatment of most children with cancer is managed at pediatric cancer centers located throughout the United States. These centers enroll about 4,000 children per year in clinical trials monitored by the National Cancer Institute. Given that the current clinical-trial accrual rate among adults with cancer is about 16,000 per year, children represent 20% of all patients entered onto clinical trials in the US.

Between 80 and 90% of children with cancer are managed at institutions of one of two national collaborative groups: the Childrens Cancer Group (CCG) and the Pediatric Oncology Group (POG) (Table 2). The CCG and POG conduct a variety of studies in most of the malignant diseases of infants, children and adolescents. More than 90% of children younger than 15 years old with diagnosis of malignant disease are seen at an institution that is a member of either the CCG or POG.[5] The highest proportion seen occurs in the youngest (0–4 years) age group, and the proportion declines significantly with increasing age.[6] The groups are truly multidisciplinary, with representation of all the medical and psychosocial specialties necessary for optimum evaluation and care of children with cancer (Fig 8). As many as 600 pediatric oncologists, pediatric surgeons, radiotherapists, pathologists, radiologists, pediatric oncology nurses, psychologists, basic scientists, statisticians, and other professionals meet twice yearly to review the results of current studies and plan new strategies of diagnosis, staging, treatment, and detection as well as prevention of adverse effects of therapy (Fig 9). With 2,500 investigators in the US, Canada, and Australia, the CCG currently is conducting 81 therapeutic trials (open to patient entry or in active followup), and has 39 therapeutic studies under development. In addition, the CCG has 35 nontherapeutic studies that are either open or closed to patient entry, and 10 more nontherapeutic studies being planned. Since 1955 the CCG has accrued more than 60,000 patient entries onto therapeutic and diag-

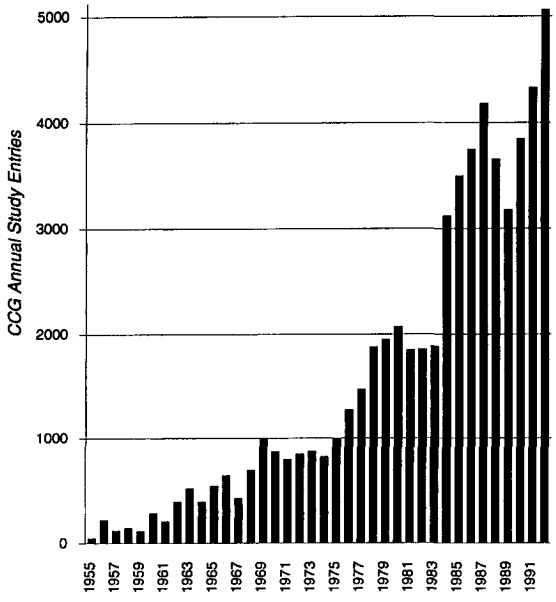

Fig 10. Annual study entries of the Childrens Cancer Group, 1955–1992.

nostic studies (Fig 10). These collaborative efforts are funded by the US National Cancer Institute, Department of Health and Human Services.

Applications to cancer in adults

Many of the principles of therapy used in treating adults with cancer first were tested and developed in children. Examples are the first demonstration of the effectiveness of chemotherapy, combination chemotherapy, multimodal therapy, and adjuvant chemotherapy. The discoveries in children are amplified when they are applied successfully to adult patients; e.g., approximately 2,000 US children develop leukemia each year in comparison to 25,000 new cases of leukemia in adults. Scientifically, pediatric cancers represent "model tumors of unparalleled import,"[7] which have led to major discoveries of significance for cancer in general.

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