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Review

The U.S. Pediatric Cancer Clinical Trials Programmes: International Implications and the Way Forward

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The four national paediatric cancer clinical trials organisations in the United States—the Children's Cancer Group, the National Wilms' Tumor Study Group, the Intergroup Rhabdomyosarcoma Study Group and the Pediatric Oncology Group—were formed in 1955, 1969, 1972 and 1979, respectively. Together, the Children's Cancer Group and Pediatric Oncology Group serve as a national registry of nearly all childhood cancers in the United States, provide a national network of communication for researchers, care providers and families of paediatric patients with malignant disease and conduct laboratory investigations and clinical trials of new treatments of cancers in infants, children, adolescents and young adults. Nearly 95% of patients with cancer in the United States who are below 15 years of age are registered by the Children's Cancer Group and the Pediatric Oncology Group and more than half of American children with cancer are entered into at least one trial by a paediatric group. Improved survival of children receiving treatment according to well-defined protocols in specialised children's centres, in contrast to children who received treatment outside of these centres, has been shown for those with acute lymphoblastic leukaemia, lymphoma, Wilms' tumour, medulloblastoma, rhabdomyosarcoma and Ewing's sarcoma.

By the year 2000, the overall cure rate for United States children and adolescents with cancer should exceed 85%. To reach this goal, the way forward will depend on international collaboration, implementation of global harmonisation, prevention of the erosion of biomedical research and clinical trials by the managed health care industry, increased public and private financial support and continued recruitment into paediatric oncology of brilliant and dedicated young investigators. The specific challenges ahead include: (1) transferring the knowledge, methodologies and technologies to countries that are less fortunate; (2) conducting multinational clinical trials in conjunction with paediatric cooperative groups in other countries; (3) accessing older adolescent patients who currently do not participate in cooperative group trials; (4) merging clinical trials by adult collaborative groups that overlap with the paediatric groups, as in acute lymphoblastic leukaemia, acute myelogenous leukaemia, Hodgkin's disease, osteosarcoma and germ cell tumours; (5) establishing a stable source of funding for national and international cooperative paediatric cancer clinical trials; (6) creating an informatics system that can link paediatric cooperative group operation centres around the world, and the institutions within each collaborative group; and (7) securing the support of the insurance industry and government in covering clinical trials. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

OVER THE past four decades since the cancer clinical-trial cooperative group programme in the United States was initiated, progress in the treatment of children with cancer in the United States has dramatically improved, with a reversal of the outcome from 80% mortality to an estimated 80% survival. For the year 2000, the projected survival curve for persons below 20 years of age in the United States who will be diagnosed with cancer at the turn of the century indicates that

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the cure rate will be 86% among this group (Figure 1) [1–3]. This estimate is obtained from projections of national survival data from the Surveillance, Epidemiology and End Results (SEER) programme of the United States in which annual cohorts of patients diagnosed between 1973 and 1992 have been followed prospectively until 1995. The method has been previously published by the author [4].

How did the nation reach this expectation and what will it take to get there and beyond? Much of the progress at the national level is attributable to the cooperative trial programme among centres of excellence in paediatric cancer. Many challenges remain for the cooperative group enterprise, not the least of which are the remaining 20% of patients who are not currently being cured and the reduction of therapy and its associated toxicities, complications and financial costs in the 80% who are being cured. Also, when expressed as a rate per persons at risk between 1986 and 1991, the incidence of cancer during childhood and adolescence was exceeded in the United States only by cancers of the prostate, lung, breast, colon, rectum and bladder [5]. Moreover, the incidence of cancer is increasing in all age, racial and ethnic subgroups in the United States, and particularly in 15- to 19-year-olds who rank second only to the oldest segment of the United States population in cancer incidence (Figure 2).

Thus, it is appropriate to review the status of the paediatric cooperative groups in the United States, including a focus on the Children's Cancer Group, the nation's first cancer clinical trial cooperative group. This review will extend the summary of the early cooperative-group history written by Gehan and Schneiderman in 1990 [6], with emphasis on the paediatric cooperative groups and recognition of the progress that must be made to eliminate cancer among our young.

THE U.S. CLINICAL TRIALS COOPERATIVE GROUP PROGRAMME

A U.S. Cooperative Group may be defined as a group of investigators who (1) jointly develop and conduct cancer clinical trials in multi-institutional settings, (2) conduct definitive studies of promising versus standard treatments, (3) simultaneously manage a large number of clinical trials, containing large numbers of patients, (4) receive funding that is not linked to any specific trial (unlike other National Institutes of Health [NIH]-supported multi-institutional research), (5) continually generate new trials and (6) accept substantial National Cancer Institute (NCI) staff involvement in investigator-initiated research, under conditions of a mutually-interactive Cooperative Agreement. The goals of the NCI-sponsored Cooperative Group programme are to (1) improve therapy through definitive clinical trials to increase survival, a reasonable surrogate (event-free survival, disease-free survival, progression-free survival, etc.) and/or quality of life, (2) conduct drug development and pilot studies and (3) correlate outcome data with laboratory observations to learn cancer biology, aetiology, pathology, etc.

To achieve these goals, the responsibilities of each Group are (1) to develop, articulate, implement and follow a comprehensive research plan; (2) to prioritise competing ideas; (3) to develop, conduct and report studies; (4) to employ clinical trials methodology that insures valid results; (5) to complete studies rapidly enough to ensure that results are meaningful; (6) to maximise available financial resources; (7) to assure quality control of data and (8) to collaborate with the staff of the NCI via a formal arrangement known as a Cooperative Agreement. The organisational structure of each

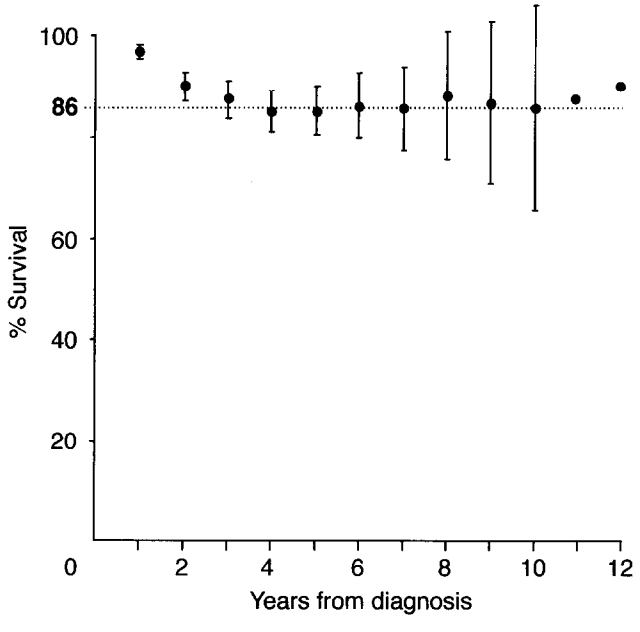

Figure 1. Estimated survival of United States persons less than 20 years of age who will be diagnosed with cancer in the year 2000 as projected from 1975–1992 SEER data. The vertical bars represent 95% confidence intervals.

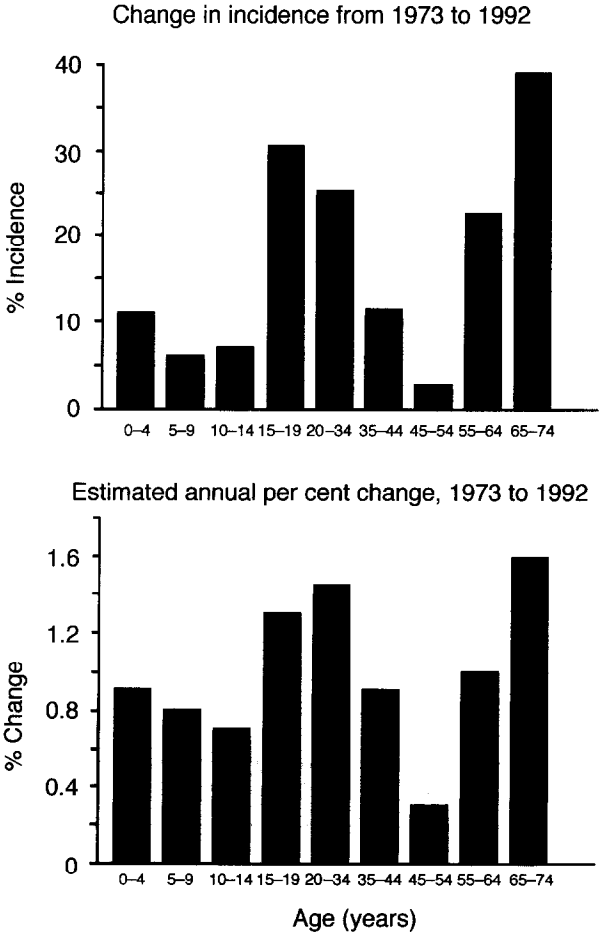

Figure 2. Increasing incidence of cancer in the United States, as a function of age at diagnosis. Data from Kosary and associates [5].

Table 1. *NCI-sponsored clinical trials cooperative groups*

Year founded	Abbrev.	Cooperative group	Group Chair	Group Statistician
1955	CCG	Children's Cancer Group	Archie Bleyer, M.D.	Mark Krailo, Ph.D.
1955	ECOG	Eastern Cooperative Oncology Group	Robert Comis, M.D.	David Harrington, Ph.D.
1956	CALGB	Cancer and Leukemia Group B	Richard Schilsky, M.D.	Stephen George, Ph.D.
1958	SWOG	Southwest Oncology Group	Charles Coltman, M.D.	John Crowley, Ph.D.
1967	RTOG	Radiation Therapy Oncology Group	Walter Curran, Jr., M.D.	Thomas Pajak, Ph.D.
1969	NWTSG	National Wilms' Tumor Study Group	Daniel Green, M.D.	Norman Breslow, Ph.D.
1970	GOG	Gynecology Oncology Group	Robert Park, M.D.	John Blessing, Ph.D.
1971	NSABP	National Surgical Adjuvant Breast & Bowel Project	Norman Wolmark, M.D.	Sam Weiand, Ph.D.
1972	IRS	Intergroup Rhabdomyosarcoma Study Group	Harold Maurer, M.D.	James Anderson, Ph.D.
1977	NCCTG	North Central Cancer Treatment Group	Michael O'Connor, M.D.	Judith O'Fallon, Ph.D.
1979	POG	Pediatric Oncology Group	Sharon Murphy, M.D.	Jonathan Schuster, Ph.D.

group includes the group chair's office, group operations office, statistics and data Centre and participating institutions, which are functionally organised to provide executive leadership, administrative committees, discipline (modality) committees, disease (strategy group, core) committees and study committees.

Clinical trials are the *sine qua non* of the cooperative groups, and translational research is the quintessential component of clinical trials in the modern era. One of the dilemmas created by the rapid advances in molecular biology is that the speed of laboratory research has outpaced the ability of clinical trial mechanisms to take advantage of developments in basic science. Other impediments include regulations based on tradition [7]. Another serious problem is that only approximately 2% of all adults with cancer are entered into NCI-sponsored trials, an unfortunately low rate that has been a national focus for several years. Among the patients who are enrolled, the ethnic and racial distribution has been representative of all patients with cancer in the United States [8].

The NCI Clinical Trials Cooperative Group programme currently includes 11 cooperative groups, of which four are paediatric cooperative groups. The current chairs and head statisticians are listed in Table 1, together with the year of founding and abbreviation of each group. Administration of the Cooperative Group Programme is provided within the NCI by the Division of Cancer Treatment, Diagnosis and Centers (DCTDC) and the Division of Cancer Prevention and Control (DCPC). Within the DCTDC, the Cooperative Groups are managed by the Cancer Therapy Evaluation Program (CTEP). Ancillary programmes of the NCI Cooperative Group Clinical Trials Programme within CTEP are the Quality Assessment Review Center and the Radiologic Physics Centre. The current NCI DCTDC Cooperative Group budget, including institutional indirect costs, is approximately $90 million per year.

THE PAEDIATRIC CLINICAL TRIALS COOPERATIVE GROUPS

The two major paediatric cooperative groups are the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG). The two paediatric disease-specific cooperative groups are the National Wilms' Tumor Study Group (NWTSG) and the Intergroup Rhabdomyosarcoma Study Group (IRSG). The ages of these four groups range from 17 to 41 years, with the POG derived in 1979 from the paediatric divisions of the Cancer and Acute Leukemia Study Group B and the Southwest Oncology Group. Figure 3 displays the DCTDC's annual cooperative group budget for each of the four paediatric groups and collectively for the seven adult cooperative groups.

The paediatric cooperative group expenditures are justified in part by the observation that more than 20% of all therapeutic study entries into clinical trials sponsored by the DCTDC are provided by the paediatric cooperative groups. 22% of all patients accrued to NCI-sponsored cooperative group studies are entered by the CCG and POG (Table 2). In addition to the NCI-defined goals, the CCG and POG have established a national network of the vast majority of American children with cancer, their families and care providers that, with the help of laboratory investigators and translational research made possible by this network, has directly and continuously provided success.

The national childhood cancer mortality rate did not decline until after the formation of the paediatric cooperative groups by the NCI in 1955 (Figure 4). Since then, the mortality rate has declined steadily and linearly, from more than eight cancer deaths per 100 000 patients per year to the current rate of less than three deaths per 100 000 (Figure 4), despite a steady increase in cancer incidence during this interval.

Benefits to the patient and family from participation in the national paediatric cooperative group clinical trials are numerous. There is immediate access to the collective wisdom of experts in the treatment of paediatric cancer; the world's leading authorities on paediatric cancer participate in the cooperative groups. There is access to state-of-the-art

Table 2. *NCI cooperative groups accrual summary,* 1994

	Open studies	Patient entries	
Total therapeutic studies	398	16779	100.0%
Phase III	151	12849	
Phase II	196	3392	
Phase I	51	538	
Children's Cancer Group (CCG)*		2080	12.4%
Pediatric Oncology Group (POG)*		1630	9.7%
CCG + POG		3710	22.1%
Non-therapeutic studies†	94	8586	
Total	492	25365	

*Therapeutic studies. †Correlative, epidemiologic, etc.

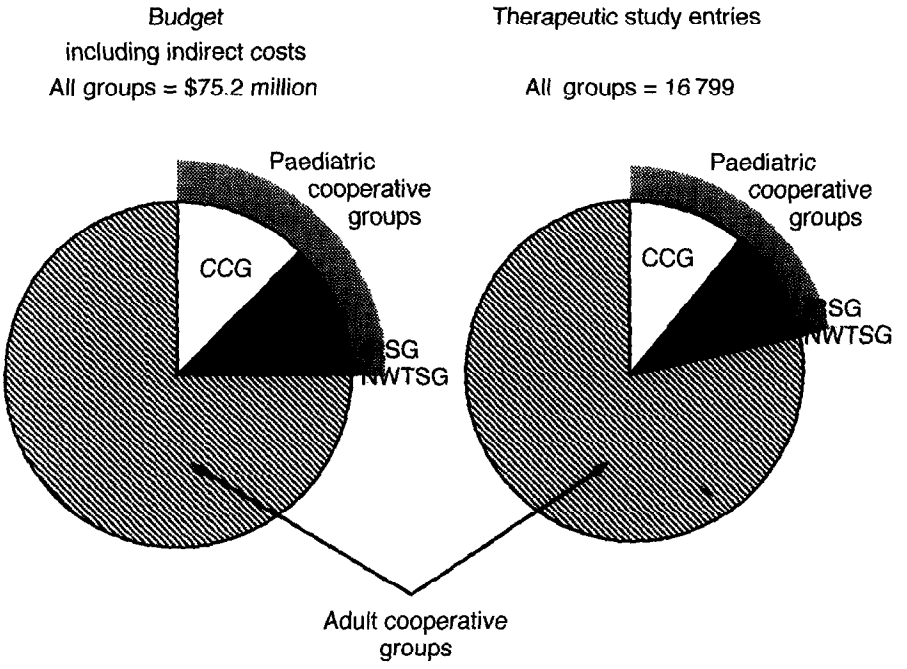

Figure 3. NCI Division of Cancer Treatment, Diagnosis and Centers budget for the cooperative group programme 1994. CCG, Children's Cancer Group; IRSG, Intergroup Rhabdomyosarcoma Group; NWTSG, National Wilms' Tumor Study Group; POG, Pediatric Oncology Group.

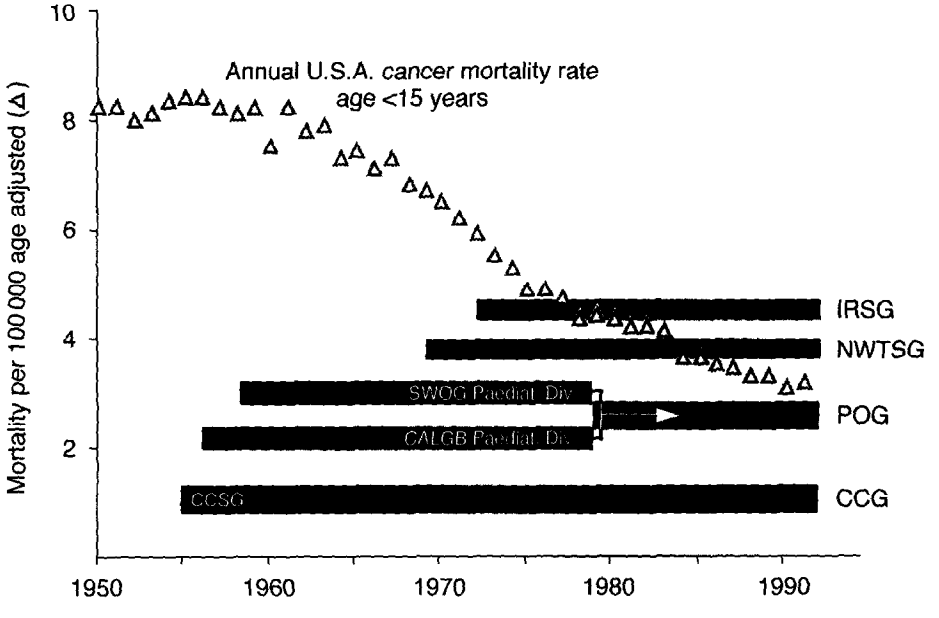

Figure 4. The paediatric cooperative groups and the national decline in rate of deaths before age 15 years among patients with cancer. Mortality data from Kosary and associates [5]. CALGB, Cancer and Acute Leukemia Group B; CCG, Children's Cancer Group; CCSG, Children's Cancer Study Group; IRSG, Intergroup Rhabdomyosarcoma Group; NWTSG, National Wilms' Tumor Study Group; POG, Pediatric Oncology Group.

therapies and technologies. Expertise in translational research is unparalleled; virtually any laboratory advance that may assist in understanding the disease afflicting the patient is available in or via the cooperative group mechanism. The survival rates of children and adolescents with cancer are significantly enhanced by participation in cooperative-group clinical trials. Children and adolescents with acute lymphoblastic leukaemia [9], lymphoma [10], medulloblastoma [11], Wilms' tumour [12] and rhabdomyosarcoma [11] enjoy a significant survival advantage when receiving treatment according to well-defined protocols in specialised tertiary children's centres, compared with paediatric patients not enrolled on protocols and treated outside of paediatric cancer centres [13]. When all ages are considered, children have had by far the greatest reduction in the national mortality rates. The reduction from 1950 to 1991 exceeds 70% for children less than 5 years old and 50% for children 5–14 years old (Figure 5).

Comparisons of the registration of new patients by CCG and POG institutions with the expected incidence of paediatric cancers as projected from the SEER Program of the NCI have shown very few locations in the United States that are

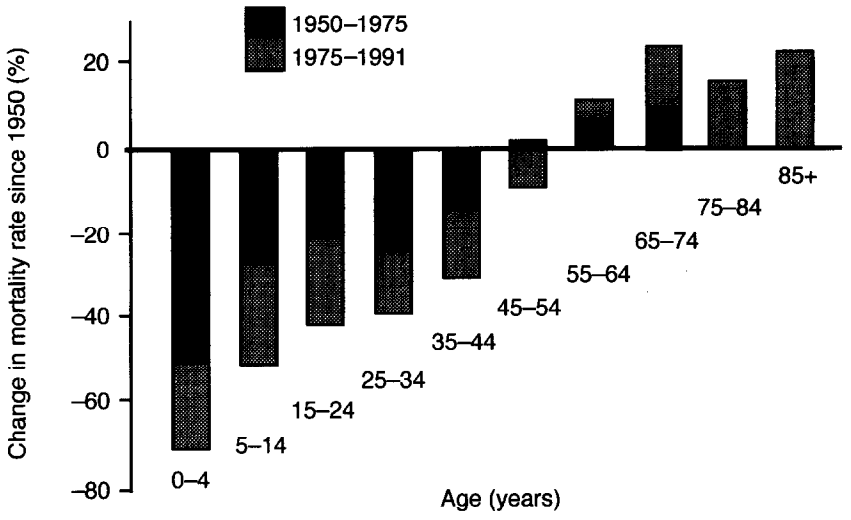

Figure 5. Change in cancer mortality as a function of age at diagnosis after 1950. Data from Kosary and associates [5].

under-represented by the cases accrued by CCG and POG institutions [14, 15]. Minority children have equal or greater access to national paediatric cancer clinical trials whether the trials are sponsored by the DCTDC and primarily therapeutic in nature or are sponsored by the DCPC and primarily for cancer control [16]. Compared with population-based SEER projections, the observed accrual of minority patients by CCG and POG is equal to or greater than expected in virtually every location in the United States [15].

The paediatric and adult groups differ in several major ways. The vast majority of patients with cancer in the United States who are below 15 years of age—nearly 95%—are registered by the two major paediatric groups [14, 15], in contrast to a minority of patients seen by the adult groups. More than 70% of American children with cancer are entered into at least one trial by a paediatric group [8], in contrast to approximately 2% of adult cancer patients. In general, paediatric clinical trial regimens are more complex, more multimodal and involve more agents and phases of treatment and a longer treatment interval than in adult trials. As a result, data acquisition and management are more laborious in paediatric trials than in adult trials. Also, follow-up of paediatric cancer survivors is more problematic than follow-up of adult cancer survivors, with a lifetime of follow-up needed for children in contrast to a median of 10 years for adults.

CHILDREN'S CANCER GROUP

Founded in 1955, the CCG was the first cooperative group formed by the NIH and is the world's largest paediatric cancer research organisation. Over its 42 years, the annual study entry rate in the CCG has increased to the 3000–4000 range (Figure 6). Thirteen different disciplines are represented among the 2500 registered members of CCG, who contribute at least 5% of their time to group activities (Figure 7). Current CCG membership includes 36 full-member institutions, 80 affiliate members and 43 corresponding members (in 23 countries). Because eight of the member institutions are in Canada and cover the entire breadth of the country from Nova Scotia to Vancouver, CCG is in essence a North American cooperative group. In addition, one of the full-member institutions is located in Australia.

In 1994, the year of the most recent NCI update, the CCG accrued more than 2000 therapeutic study entries, which was 12.4% of the total therapeutic study entries (Phase I, II and III) of all of the cooperative groups (Table 2). In 1996, 160 studies were being conducted by CCG, of which 45% were Phase III trials, 24% were new-agent phase I and II trials, 14% were biology studies, 10% were psychology and supportive care studies, and 7% were epidemiology studies. The majority of the studies are translational research, which attempts to link advances in the laboratory with solutions in the patients and vice versa.

Childhood leukaemia is a particularly good example of how progress made by institutions within or without the group has been successfully integrated into CCG studies for the benefit of large numbers of children with this disease. Between 1968 and 1993, 12 921 children with acute lymphoblastic leukaemia were entered into CCG studies; during this time survival improved from less than 10% to greater than 70% (Figure 8(a)). Results in contemporaneous trials of the national paediatric cooperative groups are comparable to the results at single institutions that pioneered therapy in acute lymphoblastic leukaemia (Figure 8(b)). Children in the United States with acute myelogenous leukaemia have also benefited from the cooperative group approach (Figure 8(c)), as have most of the children with solid malignant tumours [17].

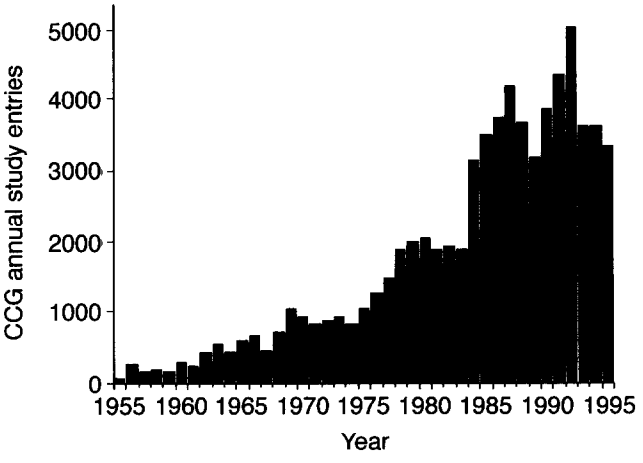

Figure 6. Annual study entries, Children's Cancer Group, 1955–1995. CCG, Children's Cancer Group.

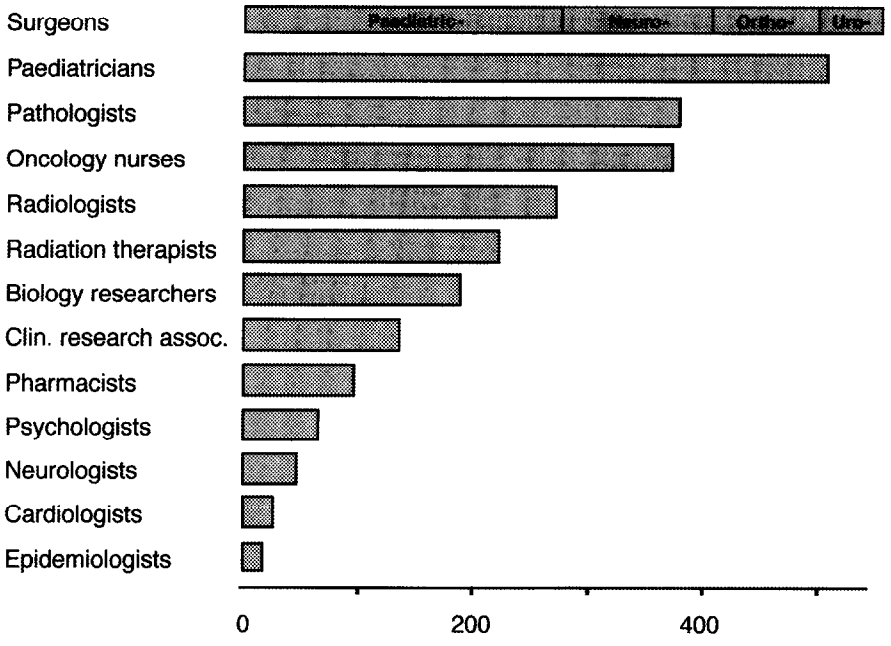

Figure 7. Children's Cancer Group membership by discipline.

NATIONAL AND INTERNATIONAL CHALLENGES FOR THE FUTURE

The divergence of the cancer incidence and mortality curves, which has been occurring in the United States for several decades, captures the essence of the primary challenges for the future. The increasing incidence must be understood and reversed. The rate of declining mortality must be accelerated, or at least continued, until no children and adolescents die of malignant disease. The specific challenges ahead include: (1) transferring the knowledge, methodologies and technologies to countries that are less fortunate; (2) conducting multinational clinical trials in conjunction with paediatric cooperative groups in other countries; (3) accessing older adolescent patients who currently do not participate in cooperative group trials; (4) merging clinical trials by adult collaborative groups that overlap with the paediatric groups, as in acute lymphoblastic leukaemia, acute myelogenous leukaemia, Hodgkin's disease, osteosarcoma and germ cell tumours; (5) establishing a stable source of funding for national and international cooperative paediatric cancer clinical trials; (6) creating an informatics system that can link paediatric cooperative group operations centres around the world, and the institutions within each collaborative group and (7) securing the support of the insurance industry and government in covering clinical trials.

Attempts to overcome the last cited obstacle have recently met with some success in the United States, where military employees and dependents are now covered by CHAMPUS or Tricare for cancer clinical trials sponsored by the NCI, thanks to the efforts of the new Director of the NCI, Richard Klausner, Ph.D., and of the Department of Defense. The BlueCross BlueShield Association has recently formed a paediatric cancer network to insure children and adolescents with cancer, provided that they receive treatment by approved investigators of and at member institutions of, the CCG or the POG [18]. Also, the United States NCI has supported paediatric international trials (see *Global Harmonisation* below), not only in regulatory support but also in funding of institutions in other countries (e.g., Canada, Australia, Switzerland).

The need for an information and telecommunications system that instantaneously permits communication between all members of the network has now become feasible. The Internet is already being used by the CCG to access the Operations Center, register patients, download treatment protocols, submit data and share current information on the Group's clinical trials, all without breaching patient confidentiality while maintaining the security of the data. Eventually, all of the paediatric cancer clinical trial cooperative groups, regardless of location, will be linked by the Internet and telecommunications systems [19].

A particular dilemma is the adolescent gap. As previously reported [20], the progress made in children younger than 15 years of age at diagnosis has not been matched in the older adolescent group of those 15–19 years old. Improvement in survival has been less in the older subgroup than in the younger patients. One factor for the slower rate of progress may be the types of neoplasms that develop in older adolescents. For example, more adolescents develop carcinomas and melanomas than younger persons and both of these types of cancer are generally resistant to the type of therapy that is so effective in younger patients. The place of treatment may be another reason. Relatively few patients in the 15- to 19-year-old bracket gain access to the national clinical trials compared with younger patients. Also, the incidence of cancer has increased more in adolescent patients, which puts relatively more patients in this age range at risk of death.

In 1991, the American Cancer Society sponsored a special conference on children and adolescents with cancer [21]. One of the major findings was the striking under representation of 15- to 19-year-old patients among those registered by the two national paediatric cancer cooperative groups. According to survey data compiled from 1989 to 1991, 92% of American children below the age of 15 years with cancer receive their care at CCG or POG institutions. Among 15- to 19-year-olds, however, this rate was only 21% [13, 14]. This

difference is also manifested in the proportion of patients entered into clinical trials, with greater than 50% of these patients below the age of 15 entered into one or more clinical trials of the paediatric cooperative groups [7], compared with less than 10% of 15- to 19-year-olds. Also, very few older adolescents are registered with the adult cooperative groups; less than 3% of patients below 20 years of age are entered into NCI-sponsored adult cooperative group trials [15]. Yet, adolescents and young adults with cancer including those with acute lymphoblastic leukaemia [22] and sarcomas (R. Sposto, Children's Cancer Group, U.S.A.) who have been entered into paediatric cooperative group studies have also been observed to have a better outcome than those who have not been entered into such trials.

A logical conclusion from these observations is that older adolescents with cancer would benefit from the clinical trials organisations and should be a critical public health target. That the largest private insurance company in the United States supports the NCI-sponsored paediatric cooperative groups indicates that the insurance industry recognises the merit of the national clinical trials programme. Hopefully, other health maintenance organisations, including those with multinational coverage, will follow their lead.

Another conclusion is that the adult and paediatric cooperative groups should work together to solve the adolescent gap dilemma. The highly successful combined adult and paediatric cooperative group trial of acute progranulocytic leukaemia, in which *cis*-retinoic acid was clearly demonstrated

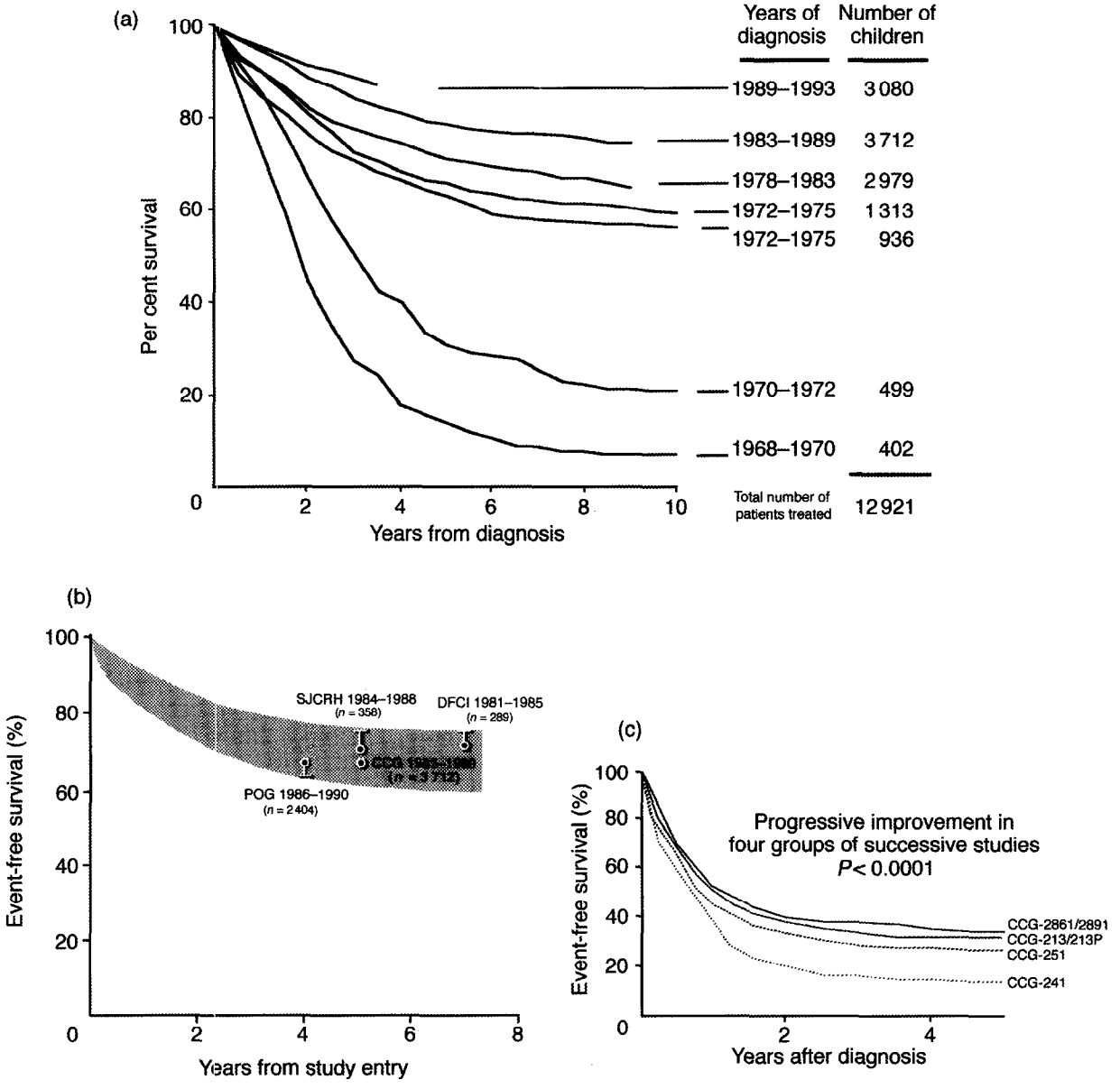

Figure 8. (a) Survival of children with acute lymphoblastic leukaemia on Children's Cancer Group studies, 1968–1993. (b) Survival of children with acute lymphoblastic leukaemia on contemporary studies of the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), the St. Jude Children's Research Hospital (SJCRH) and the Dana Farber Cancer Institute (DFCI). Vertical bars indicate standard deviation for designated studies and the shaded zone approximates a 95% confidence interval for all studies. Institutional data from Pui and Crist [23]. (c) Event-free survival of children with acute myelogenous leukaemia on Children's Cancer Group studies, 1968–1993. CCG, Children's Cancer Group.

to be an effective adjunct to chemotherapy in this disease, is an excellent example of how multiple cooperative groups in both paediatric and medical oncology can successfully conduct a trial together. The CCG has recently proposed to join ranks with two of the adult cooperative groups in studies of malignancies that are common to older adolescents and young adults such as melanoma, Hodgkin's disease, non-rhabdomyosarcoma sarcomas, testicular carcinoma and ovarian carcinoma.

Historically, investment in paediatric cancer research has paid dividends in understanding the basic biology of cancer, treating adults with malignant disease and providing principles of therapy and advances for other diseases in children and adults. A partial list of examples follows. The first demonstration of chemotherapy as a cure for human cancer took place in children. The concept of combination chemotherapy and the principle of multimodal therapy were first effectively tested and demonstrated in children with cancer. Neoadjuvant chemotherapy began for children with Wilms' tumour. Many of the current principles in blood banking were formulated in studies involving children, including platelet and granulocyte transfusions. The two-hit hypothesis was first tested and supported in children with cancer. The first tumour suppresser gene (*RB1*) was discovered in children with retinoblastoma. Because the increasing incidence of cancer in adults will continue for the foreseeable future, the paediatric cooperative groups have expanding opportunities to help adult patients with cancer.

Table 3. United Kingdom Cancer Research Campaign phase I/II clinical trial centres

CRC Clinical Trial Centre at Newcastle General Hospital, Newcastle Upon Tyne
CRC Laboratories at Charing Cross Hospital, London
CRC Beatson Laboratories, University of Glasgow, Bearsden, Glasgow
CRC Clinical Trial Centre at Mount Vernon Hospital, Northwood, Middlesex
CRC Clinical Trial Centre at Western General Hospital, Edinburgh
Christie CRC Research Centre, Manchester
CRC Clinical Trial Centre at University of Cambridge, Cambridge
CRC Clinical Trial Centre at Royal Marsden Hospital, London
CRC Clinical Trial Centre at Bradford Royal Infirmary, West Yorkshire
CRC Institute for Cancer Studies at Queen Elizabeth Hospital, Birmingham
CRC Clinical Trial Centre at City Hospital, Nottingham
CRC Clinical Trial Centre at Royal Infirmary, Glasgow
CRC Clinical Trial Centre at Southampton General Hospital, Southamption
CRC Clinical Trial Centre at University of Leeds, Leeds
CRC Clinical Trial Centre at Clatterbridge Hospital, Wirral, Merseyside
CRC Clinical Trial Centre at St. Bartholomew's Hospital, London
CRC Clinical Trial Centre at Guy's Hospital, London
CRC Clinical Trial Centre at University College, London

GLOBAL HARMONISATION

Finally, the United States has recently instituted a policy change that will facilitate international collaboration. Previously, participation of a United States cooperative group in an international trial required that every institution in the foreign group apply to the United States Office of Protection for Research Risk (OPRR) for human subjects approval assurance and required that a single project assurance was granted by OPRR to cover a specific protocol. This meant that every institution in the trial had to apply to OPRR for approval to participate in the trial and that there was a separate application for each project. In 1996, thanks to a study of B-cell lymphoma that the CCG wanted to conduct with the French Society for Pediatric Oncology (SFOP) and the United Kingdom Childrens Cancer Study Group (UKCCSG) and to NCI–CTEP efforts to promote this study, the United States OPRR agreed to recognise established international standards for protection of human subjects (e.g., the Declaration of Helsinki) and to permit a central body (e.g., a Ministry of Health or central operations office) to represent a group of institutions and thereby make one application to the OPRR on behalf of the entire group. The central body must assure compliance by its member institutions, have formal lines of authority over its members and have or establish a central ethics committee. If these criteria are met, an International Cooperative Project Assurance (ICPA) will cover the entire group, subgroups of members or single-institution members; it will also cover multiple protocols. In January 1977, the first such ICPA was awarded to the Phase I/II Committee of the Cancer Research Campaign (CRC) of the United Kingdom (Table 3). The terms and conditions of the ICPA permits any or all of the CRC institutions covered by the ICPA to participate in phase I and II trials conducted by the United States Cooperative Groups. Once again, paediatric cancer investigators have led the way for all cancer organisations and for patients of all ages.

To continue the legacy, the way forward will depend on international collaboration, prevention of the erosion of biomedical research and clinical trials by managed care, increased public and private financial support and continued recruitment to paediatric oncology of brilliant and dedicated young investigators. Because global harmonisation can assist in all of these needs and has the support of the world community, the future looks bright. The way forward is complicated and treacherous, but the rewards will be tremendous, as aptly described by John Schaar:

> The future is not a result of choices among alternative paths offered by the present, but a place that is created, first in mind, next in will, then in activity. The future is not some place we are going to, but a place we are creating. The paths are not to be discovered, but made, and the activity of making the future changes both the maker and the destination.

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