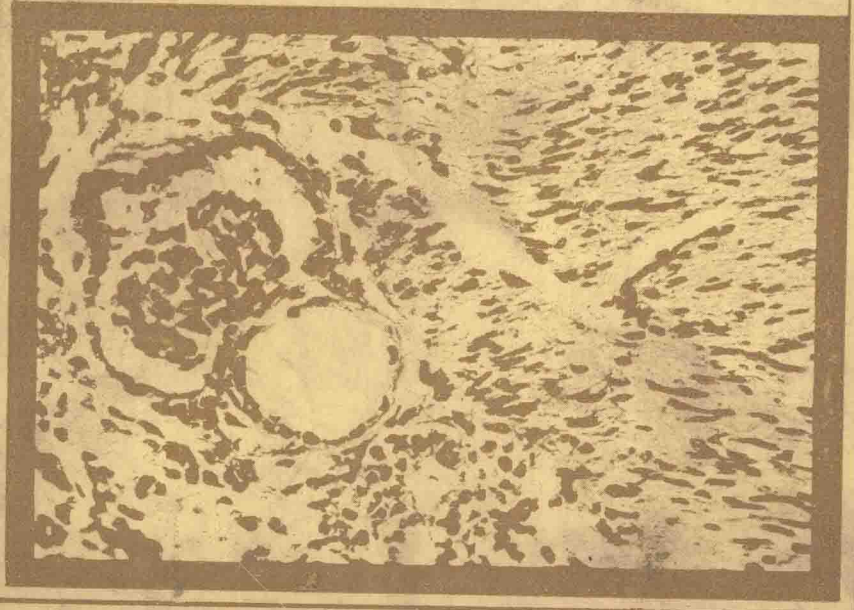
CLINICAL MANAGEMENT OF CANCER IN CHILDREN

Edited by
Carl Pochedly



CLINICAL MANAGEMENT OF CANCER IN CHILDREN

Carl Pochedly, M.D., Editor
Director, Pediatric Hematology, Nassau County Medical Center,
East Meadow, N.Y.
Associate Professor of Pediatrics, School of Medicine,
State University of New York at Stony Brook

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Robert L. Baehner, M.D.
Director, Pediatric Hematology-Oncology, and Associate Professor of Pediatrics, Indiana University School of Medicine, Indianapolis, Ind.
Established investigator of the American Heart Association

Joseph H. Burchenal, M.D.
Director of Clinical Investigation, Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Professor of Medicine, Cornell University Medical College

Robert R. Chilcote, M.D.
Fellow in Hematology-Oncology, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Ind.

Mark Edelstein
Research Assistant, Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis, Mo.
Candidate to receive M.D. and Ph.D. degrees in May 1975

John M. Falletta, M.D.
Research Hematology Laboratory, Texas Children's Hospital, Texas Medical Center
Assistant Professor of Pediatrics, Baylor College of Medicine, Houston, Tex.

Donald J. Fernbach, M.D.
Professor of Pediatrics, Baylor College of Medicine
Director, Research Hematology Laboratory, Texas Children's Hospital, Houston, Tex.

Warren A. Heffron, M.D.
Director, Family Practice Program, Assistant Professor, Department of Family and Community Medicine, School of Medicine, University of New Mexico, Albuquerque, N. Mex.

Lawrence Helson, M.D.
Associate Attending Physician, Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Gussie R. Higgins, M.D.
Associate Hematologist, Division of Hematology-Oncology and Director, Cancer Chemotherapy Program and Cancer Control Program, Children's Hospital of Los Angeles, Los Angeles, Calif.
Assistant Professor of Hematology, University of Southern California School of Medicine

Robert E. Hittle, M.D.
Associate Radiologist and Director of Radiotherapy, Children's Hospital of Los Angeles, Los Angeles, Calif.
Assistant Clinical Professor of Radiology, University of Southern California School of Medicine

Norman Jaffe, M.D.
Administrative Chief, Out-Patient Tumor Therapy Clinics, Children's Cancer Research Foundation, Boston, Mass.
Associate Professor of Pediatrics, Harvard Medical School, Cambridge, Mass.

André D. Lascari, M.D.
Pediatric Hematologist and Professor of Pediatrics, School of Medicine, Southern Illinois University, Springfield, Ill.

Sanford Leikin, M.D.
Director, Hematology-Oncology, Children's Hospital, Washington, D.C.
Professor of Child Health and Development, George Washington University School of Medicine

Alvin M. Mauer, M.D.
Medical Director, St. Jude Children's Research Hospital, Memphis, Tenn.
Professor of Pediatrics, School of Medicine, University of Tennessee

Gerhard Nellhaus, M.D.
Director, Pediatric Neurology and Associate Professor of Pediatrics and Neurology, University of Colorado Medical Center, Denver, Colo.

Darleen R. Powars, M.D.
Associate Professor of Pediatrics, Division of Hematology-Oncology, University of Southern California School of Medicine, Los Angeles, Calif.

Charles B. Pratt, M.D.
Associate Member in Chemotherapy, St. Jude Children's Research Hospital, Memphis, Tenn.

Kenneth A. Starling, M.D.
Associate Professor of Pediatrics, Baylor College of Medicine
Associate Director, Research Hematology Laboratory, Texas Children's Hospital, Houston, Tex.

Norah duV. Tapley, M.D.
Radiotherapist, Department of Radiotherapy, M.D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex.

Jerome M. Vaeth, M.D.
Chief, Department of Radiation Oncology, St. Mary's Hospital and Medical Center, San Francisco, Calif.
Director, West Coast Cancer Foundation

Teresa J. Vietti, M.D.
Professor of Pediatrics, Washington University School of Medicine, St. Louis, Mo.
Director, Division of Hematology and Oncology, St. Louis Children's Hospital

John L. Ziegler, M.D.
Chief, Pediatric Oncology Branch, National Cancer Institute, Bethesda, Md.

One of the greatest joys in the practice of pediatrics is the opportunity to watch children grow and develop from the moment they are born—through infancy, childhood, and adolescence. This opportunity differs in large part from hospital pediatrics in which the focus is on the abnormalities of childhood, whether they result from trauma, infection, congenital defect, glandular dysfunction, blood dyscrasias, tumors, nephritis, or nephrosis, among others.

The practicing pediatrician is dedicated to protecting and guiding the child through the years of growth and development. The practicing pediatrician cares for the whole child, not only physically, but emotionally as well. He or she treats the child's illnesses and traumas and becomes an important part of the child's life—and often serves as guidance counselor for the parents.

There was a time, as many of us still remember, when deaths of children were not infrequent. Each year every pediatrician was faced with the possibility of deaths among his or her patients from numerous uncontrollable diseases. Poliomyelitis, scarlet fever, nephrosis, empyema, blood stream infections, erysipelas, appendicitis, and tuberculosis were some of the more common dangers. The practicing pediatrician had many moments of anxiety and distress.

Today most of these threats have disappeared, due largely to a combination of preventive vaccines, antibiotic therapy, and medical and surgical advances.

But a few life-threatening conditions remain, and, of those still encountered by the modern pediatrician, none is more pernicious than cancer. Fortunately, it is comparatively rare during infancy and childhood, but, when it does occur, it usually presents the pediatrician with one of the most difficult and critical problems he or she is ever called upon to handle.

As we all know, cancer has a much better prognosis today than only a few years ago. This is due to a combination of treatment by surgery, steroids, x-ray therapy, and chemotherapy. And since children under treatment and in remission are home so much of the time, the role of the child's pediatrician has greatly increased. He or she must understand fully not only the signs and symptoms of the disease but also the complications that at times are related to the treatment.

How should the pediatrician tell the parents of the diagnosis? How much should he or she tell the parents of the probable prognosis? Should he or she be at all optimistic?

During this first discussion with the parents after the diagnosis has been made, it is important that both parents be told of the condition together—to support each other in their anxiety, shock, and potential tragedy. The parents should be given a complete outline of the whole situation, the prognosis, and the modern method of treatment, with emphasis on the results of combination therapy. The discussion must not be hurried, and the parents should be encouraged to ask questions. They must be given honest answers, with full and accurate information.

Throughout the course of the child's treatment, there must always be time to

give the parents the emotional support they seek. The pediatrician must always be compassionate, sympathetic, and understanding.

Too many pediatricians faced with the possibility of caring for a dying child shy away from this terrible and heartbreaking ordeal, withdrawing completely and turning the child over to a specialist. Desertion by the pediatrician during this crucial and terrifying period is to be condemned. Although the child may be sent to a special center for specialized treatment and follow-up, the child and the parents have learned to depend on the pediatrician for care and understanding and have built up a relationship of trust. Under modern methods of treatment, the prognosis for most malignancies is so improved that the pediatrician will serve a most important part in the course of treatment and follow-up.

It is to give the practicing pediatrician a better understanding of the modern approach to cancer that *Clinical Management of Cancer in Children* is presented.

Dr. Carl Pochedly, author of *The Child with Leukemia* and coeditor of *Major Problems in Childhood Cancer*, has brought together an eminent group of contributors from authorities in the field.

In the first of three initial commentaries, Dr. Joseph H. Burchenal of the Memorial Sloan-Kettering Cancer Center provides an overview of the advances made in the treatment of childhood cancer during the past 30 years. Dr. Alvin M. Mauer then presents his argument for specialized treatment centers. The third commentary, by Dr. Jerome M. Vaeth, is devoted to a discussion of keeping radiation at the lowest possible therapeutic level to avoid causing permanent tissue damage.

The first chapter of *Clinical Management of Cancer in Children*, presented by Drs. Donald J. Fernbach and Kenneth A. Starling of the Baylor College of Medicine, is devoted to a report on acute leukemia—how much longer and with less morbidity affected children are living under modern methods of therapy. A suggested treatment regimen is detailed. The wealth of these authors' experience is demonstrated by a study of 1,024 children with acute leukemia who have been followed by the Southwest Cancer Chemotherapy Group.

In Chapter 2, on Wilms' tumor, Dr. Darleen R. Powars of the University of Southern California School of Medicine differentiates between the true Wilms' tumor and the benign mesoblastic nephroma so frequently mistaken for it. This differentiation is most important, Dr. Powars points out, because intense radiation of an infant or young child may have very serious after effects. Under current methods of management, children with Wilms' tumor now have a better prognosis for long-term survival than children with any of the major malignant disorders of childhood.

"Infection in Childhood Cancer," by Drs. Robert R. Chilcote and Robert L. Baehner of Indiana University School of Medicine, is a further contribution of great importance to the practicing pediatrician if he or she is to aid in the care of children during their treatment for cancer. As the authors point out, mild infections may become life-threatening infections during periods of therapeutic immunosuppression or myelosuppression with severe granulocytopenia. The portions of the chapter relating to clinical management of such infections and the general prophylactic procedures

are of extreme importance to the pediatrician working closely with the oncologist or hematologist in the care of the child with cancer.

In Chapter 4, "Lymphosarcoma," Dr. André D. Lascari of the Southern Illinois University School of Medicine notes that, although lymphosarcoma has always been one of the most dangerous cancers in children, the combination of radiotherapy and chemotherapy has resulted in increased survival. The section on differential diagnosis and the section defining the anatomic stage of the disease are of greatest value to all pediatricians who suspect the condition in any of their patients.

The subject of neuroblastoma is covered in Chapter 5 by Dr. Lawrence Helson of the Memorial Sloan-Kettering Cancer Center. Dr. Helson emphasizes that early diagnosis in the first two years of life (before dissemination) is indispensable for a good prognosis. This places a most important responsibility on the shoulders of the child's pediatrician, for once the neuroblastoma is disseminated the results of treatment are poor.

In Chapters 6, 8, and 9—"Childhood Rhabdomyosarcoma" by Dr. Charles B. Pratt, "Retinoblastoma" by Dr. Norah duV. Tapley, and "Hodgkin's Disease in Children" by Drs. Robert E. Hittle and Gussie R. Higgins—each author emphasizes the significance of diagnosing the condition in its early stages. The recent approach of classifying malignant tumors into various stages relating to the size, distribution, and spread has provided the physician with a fair indication of prognosis under modern treatment, for the combination treatment of surgery, radiation therapy, and chemotherapy has given evidence that many cancers treated in their early stages may be suppressed and even cured.

Dr. Gerhard Nellhaus, in Chapter 7, clearly defines the special problems of diagnosing brain tumors in children, in whom the softness of the brain, open sutures, and incomplete myelinization of the brain and spinal cord add to the usual problems of diagnosis. Dr. Nellhaus stresses the essential role of the pediatrician before and after the operation for removal of the tumor.

Dr. John M. Falletta's chapter on "Immunotherapy of Childhood Cancer" presents exciting prospects of future therapy for malignancies. This is a paper well worth reading, for it demonstrates that there is a definite possibility of building up antigens against cancer, in response to the intervention of foreign proteins such as BCG, irradiated tumor cells, or lysed tumor cells. This is just the beginning of a whole new approach to the treatment of cancer, but it gives hope of eventually perfecting the build-up of a person's immune response against cancer.

In Chapter 11, "Malignant Bone Tumors," Dr. Norman Jaffe gives an excellent review of this important subject. Although these tumors are comparatively uncommon, the mortality rate is exceedingly high. Dr. Jaffe emphasizes the importance of a careful and painstaking evaluation and presents not only a differential diagnosis of bone tumors, benign and malignant, but also details the principles of treatment of each of these pathologic types.

Burkitt's lymphoma, a malignant condition, was first described in Uganda in 1961. It is found primarily in children of tropical countries but is occasionally found

in the United States, as well. This malignancy is reviewed in Chapter 12 by Dr. John L. Ziegler of the National Cancer Institute. Burkitt's lymphoma is of particular importance for it is not only the most rapidly growing human neoplasm but the most responsive to chemotherapy. Dr. Ziegler reports that, of the patients who have small or localized multiple or small tumor deposits or where there has been extensive surgical removal, one-third achieve first remissions and never relapse when treated by chemotherapy and radiation. The prognosis is dependent on the initial response to chemotherapy.

The histiocytoses are discussed by Dr. Sanford Leikin. These are among the most difficult tumors to diagnose, to differentiate benign and malignant, and to match with effective treatment regimens. Dr. Leikin reports the results of the Children's Cancer Study Group. It is evident here that the age of onset of the condition is the greatest factor in determining the prognosis, and that the results of treatment regimens differ with the age levels treated. This contribution is a clear, well-organized summary of the present-day knowledge of a complex disease.

The chapter on "Pediatric Chemotherapy" by Dr. Teresa J. Vietti and Mark B. Edelstein is a clear and beautiful review of a rapidly advancing science of interest to all pediatricians. In this discussion the authors review the most commonly used agents with proved effectiveness as well as certain new and promising drugs. The action, toxicity, and method of administration of these agents is detailed.

In the fifteenth and final chapter, Dr. Warren A. Heffron covers group therapy sessions, a new and important aspect in the emotional care of children with cancer. Staff members are included as part of the group, and there are group meetings of parents, as well. There are also staff meetings of all who are involved in the treatment of these children.

Milton I. Levine, M.D.
Emeritus Clinical Professor of
Pediatrics, Cornell University
Medical College
Consultant Pediatrician,
New York Hospital
Editorial Director,
Pediatric Annals

Introduction

In the recent past, when no effective therapy could be offered to children with cancer, pediatricians were naturally depressed by their helplessness and tended to reject these children and to put aside their distraught parents with the assertion, "There is nothing anyone can do." Now that children with cancer often can be treated successfully or even cured, we have a brand new perspective. Along with an upsurge of scientific interest and research in cancer, therapeutic optimism has grown.

Because of the great scientific progress recently made in the treatment of cancer, the pediatrician can no longer withdraw from active, even aggressive, treatment and compassionate management of children with cancer. There is now a real contribution he or she can make. As treatment of various kinds of childhood cancer becomes more clearly understood and better established, pediatricians will be able—and will be expected—to take an ever increasing role in the care and treatment of these children.

The treatment of childhood cancer is still a complex process involving several medical disciplines and specialties. Successful treatment often depends on close cooperation among pediatrician, hematologist, radiotherapist, and surgeon, but the role of the pediatrician in this cooperative effort is becoming ever more primary and central. Not only may the pediatrician be called upon to administer the various aspects of the child's chemotherapy and to recognize possible side effects resulting from it, but he or she must also be able to communicate with the family by discussing the child's condition, expected needs for future care, and prognosis. In addition, the pediatrician must provide the personal support that is important to any family with a seriously ill child. A fairly comprehensive knowledge of current techniques of diagnosis and therapy and an understanding of the prognosis of various types of cancer are needed for the pediatrician to effectively play his or her central role in the care of children with cancer.

The material on cancer contained in this book has been selected on the basis of its clinical usefulness and relevance to practicing pediatricians. Emphasis is on what the pediatrician *can do*. The chapters are clinically oriented and are not intended to be comprehensive reviews of the topics discussed.

Even children who cannot be cured of their cancer can often be greatly helped by being given conscientious and thorough pediatric care. When they are avoided or neglected because of the pediatrician's personal bias that the condition is "hopeless," any hope these children have for prolonged survival or cure is lost. An important side effect or fringe benefit of the recent explosion of interest in, and improvement in, therapy of

childhood cancer has been a new optimism, enabling children with cancer to receive a full measure of the same conscientious, compassionate, and thorough pediatric care their physicians routinely give to any other sick children.

The following chapters give us many specific and sound reasons for the new optimism that has been growing among those most active in the treatment of children with cancer. This will increasingly enable the pediatrician to affirm his or her central and vital role in the treatment of children with cancer, just as he or she customarily does with any other seriously ill children.

Carl Pochedly, M.D.

CURRENT COMMENTARY I

Childhood Cancer, 1944 to 1974

Joseph H. Burchenal, M.D.

Progress made in treatment of childhood cancer in the past 30 years has been tremendous. We need only examine the survival statistics of 30 years ago and compare them to those of the present to realize the great strides that have been made.

This progress can be ascribed to many different factors, including:

1. A better knowledge of the natural history and course of the disease, leading to earlier and more thorough surgical treatment

2. The development of high-energy radiation, again combined with knowledge of the spread of the disease, which has contributed significantly to the treatment of Hodgkin's disease and the lymphomas

3. The use of intensive, intermittent, short-course chemotherapy, usually with combinations of drugs, both as adjuvant to surgery and radiation or given alone in stage III and stage IV disease, which has markedly increased survival and produced cures in many cases.

ACUTE LEUKEMIA

The most common neoplastic disease in childhood is acute lymphoblastic leukemia. Before the introduction by Farber in 1948[1] of specific therapy

with folic acid antagonists, the median survival time from the first symptom of the disease until death was between four and five months.[2] In 107 cases reported from Memorial Hospital ~~prior~~ to ~~1948~~, only 1 survived more than a year, and that patient died at 14 months.[3]

With the accession of many new agents,[4–13] the discovery by Whiteside[14] of the efficacy of intrathecal methotrexate against meningeal leukemia, and the introduction of intensive, intermittent combination chemotherapy,[15] the outlook for long-term survival and perhaps cure has altered drastically. In a current series of patients observed following treatment, Pinkel[16] and Simone[17] are projecting a five-year survival rate of over 50 percent. These patients were induced into remission with vincristine and prednisone, treated prophylactically with craniospinal irradiation or cranial irradiation and intrathecal methotrexate, and maintained on oral dosages of mercaptopurine daily and cyclophosphamide and methotrexate weekly. Similarly, the recent reported study of Acute Leukemia Group B has shown an overall survival rate of 40 percent at four years in 426 patients. By life-table analysis, several selected regimens of this multiphasic study are expected to produce more than 50 percent survivors at five years.[18]

In previous studies of cases collected from hematologists all over the world, it was demonstrated that cases of acute leukemia surviving five years have a 50 percent chance of continuing free of disease for an indefinite period of time.[19] Of these 158 patients, 93 are living and well with no evidence of disease 10 to 21 years after diagnosis. Since many of the patients in this series had one or more relapses of leukemia prior to five years, it is likely that intensively treated cases in the recently reported series, who have continued for five years in continuous remission, will have a much higher rate of indefinite disease-free survival than the previous less intensively treated series.

BURKITT'S TUMOR

In Burkitt's tumor in Africa,[20] Burkitt and O'Conor in 1961 reported a median survival time of as little as four to six months from the first symptom of the disease.[21] In contrast, Ziegler[22] is now able to report 50 percent overall long-term survival, and as high as 73 percent long-term survival in stage I and stage II disease. Since relapses after two years of unmaintained remission are extremely rare in this disease, it is probable that these long-term remissions are nearly synonymous with cure. The treatment consisted of massive doses of cyclophosphamide (40 mg/kg), repeated every two to three weeks, with intrathecal methotrexate and/or cytosine arabinoside for CNS (central nervous system) complications. The combination of vincristine and methotrexate followed by a five-day

course of cytosine arabinoside was also used, with or without cyclophosphamide.

The diagnosis of Burkitt's tumor in a nonendemic area such as the United States is difficult; such cases are rare. Previously these cases were grouped in with the non-Hodgkin's lymphomas. Thirty years ago the survival of the generalized disease was extremely poor (three to six months). Only patients with completely-localized, extranodal or nodal lesions treated by surgery or massive irradiation had any chance of long-term survival. Now Carbone[23] has recently reported that 9 out of 20 patients with American Burkitt's tumor, treated with repeated massive doses of cyclophosphamide, have survived more than two years; 3 of these have no evidence of disease at five years. In a larger total series of 29 patients, there has been a decrease in survival of less than 4 percent after the first 12 months.

LYMPHOMAS

Recent studies by Wollner[24,25] have produced striking results in the non-Hodgkin's lymphomas, nodal or extra-nodal, in children by using a massive dose of cyclophosphamide (40 mg/kg IV), followed immediately by a regimen used for acute lymphoblastic leukemia. This regimen consists of vincristine, prednisone, and daunomycin induction, intrathecal methotrexate for prophylaxis of CNS involvement, radiation therapy to any localized disease, three courses of cytosine arabinoside and thioguanine, followed by thrice-weekly *l*-asparaginase for four weeks as consolidation, and then six-week cycles of maintenance therapy. Out of 35 patients (19 with lymphosarcoma and 16 with reticulum cell sarcoma), 32 patients (27 in stage III and IV) had complete regression of all measurable tumor, and 29 remain with no evidence of disease from over 3 to over 28 months from the start of treatment. Studies from the same hospital, before the initiation of this massive combination treatment regimen, had shown 14 of 18 patients relapsing at a median of 4 months.[26]

In Hodgkin's disease 30 years ago, even in stage I and II disease, repeated palliative radiotherapy resulted in occasional long-term survival, but rarely in cures. The generalized disease was synonymous with a sentence of death. The great improvements in massive-dose and extended-field radiotherapy initiated by Easson, Peters, and Kaplan have increased tremendously the cure rate in localized disease. The epoch-making development by DeVita[27,28] of the intermittent intensive combination chemotherapy program with nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone (MOPP), in two-week courses, every month for six months, has revolutionized the treatment of stage III and IV Hodgkin's disease.

WILMS' TUMOR

Wilms' tumor is one of the common solid tumors in infants and children; it may be present at birth. Klapproth,[29] surveying the literature, found the cure rate between 1940 and 1958 to be between 17 and 23 percent. In 1966, Farber[30] was able to report that by the use of early radical surgery, locally administered radiotherapy, and actinomycin D, 47 out of 53 patients with no demonstrable metastases on admission were alive with no evidence of tumors, from two to nine years later. In 18 of 31 patients who had pulmonary metastases, radiotherapy and actinomycin D destroyed the tumor. These 18 patients were alive and well with no evidence of disease two years or more following therapy. Thus, the cure rate with multidisciplinary therapy in both early and far-advanced Wilms' tumor has improved immeasurably in the past 30 years.

EWING'S TUMOR

In Ewing's tumor, treated either by surgery or radiation, a five-year survival of approximately 10 percent was to be expected 30 years ago, and most patients showed evidence of metastases within 2 years. Recently, Hustu[31] reported 11 of 15 patients surviving with no evidence of disease over 4 to over 91 months after diagnosis. These patients were treated with massive local irradiation to the primary tumor and with prophylactic vincristine and cyclophosphamide once weekly for four to six doses, as tolerated, and then every two weeks for two years. Similarly, the recent studies of Rosen et al.,[32] using massive local radiation to the primary Ewing's tumor and a four-drug adjuvant chemotherapy protocol consisting of actinomycin D, adriamycin, cyclophosphamide, and vincristine, repeated every three months, showed 7 out of 8 patients without evidence of disease over 26 to over 48 months from the start of therapy.

RHABDOMYOSARCOMA

The disappointing results of radiation or surgical treatment of rhabdomyosarcoma in children, with an overall survival rate of about 10 percent, have changed markedly in recent years. Pratt[33] reported 20 children with embryonal rhabdomyosarcoma treated with multidisciplinary therapy consisting of surgery, radiotherapy, and combination chemotherapy. Of the 20 children, 15 developed complete regression of the tumor, and 7 are now tumor-free from 2 to 39 months on maintenance combination chemotherapy with vincristine, actinomycin D, and cyclophosphamide. In rhabdomyosarcoma of the head and neck, Donaldson[34] reported no evi-

dence of disease in 14 of 19 children with the use of surgical excision, when possible, combined with radiation and combination chemotherapy with vincristine, actinomycin D, and cyclophosphamide. Twelve of these children have been disease-free for more than two years.

In the treatment of neuroblastoma, marked palliation and temporary complete remissions can be achieved with chemotherapy, but long-term remissions or cures are rare, except in patients under one year of age. Similarly, in metastatic osteogenic sarcoma, the use of supra-lethal doses of methotrexate by continuous infusion, followed by rescue with leucovorin, has produced occasional striking regressions. The use of chemotherapy as adjuvant to surgery in this disease is very exciting, but it is too early to discuss definitive results. In brain tumors, although certain of the nitrosoureas have been shown to cross the blood-brain barrier, and methotrexate has been used intrathecally and intraventricularly, progress has been less impressive than with the previously mentioned group of tumors.

Thus, there has been tremendous progress in the treatment of childhood tumors in the past 30 years, due to the development of multidisciplinary therapy and intensive intermittent combination chemotherapy. But much remains to be done to achieve the goal of the complete control of childhood cancer.