Clinical pediatric oncology

EDITED BY

WATARU W. SUTOW, M.D.

TERESA J. VIETTI, M.D.

DONALD J. FERNBACH, M.D.

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WATARU W. SUTOW, M.D.

Pediatrician and Professor of Pediatrics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

TERESA J. VIETTI, M.D.

Professor of Pediatrics, Mallinckrodt Department of Pediatrics, Washington University School of Medicine; Associate Pediatrician, Barnes and Associated Hospitals; Director, Division of Hematology and Oncology, St. Louis Children's Hospital, St. Louis, Missouri

DONALD J. FERNBACH, M.D.

Professor of Pediatrics, Baylor College of Medicine; Chief, Hematology and Oncology Service at Texas Children's Hospital; Director, Research Hematology Laboratory, Texas Children's Hospital, Houston, Texas

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Contributors

Alberto G. Ayala, M.D.

Assistant Pathologist and Assistant Professor of Pathology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Virginia M. Badger, M.D.

Assistant Professor of Orthopedic Surgery, Washington University School of Medicine; Assistant Surgeon, Barnes Hospital and St. Louis Children's Hospital; Assistant Surgeon, Shriners Hospital for Crippled Children; Associate, Missouri State Crippled Children's Program; Chief of Orthopedic Surgery, St. Louis City Hospital, St. Louis, Missouri

Daisilee H. Berry, M.D.

Associate Professor of Pediatrics, University of Arkansas School of Medicine; Assistant Director of Clinical Research and Attending Pediatrician, University of Arkansas Medical Center; Attending Pediatrician, Arkansas Children's Hospital, Little Rock, Arkansas

James J. Butler, M.D.

Associate Pathologist and Associate Professor of Pathology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

George W. Clayton, M.D.

Professor of Pediatrics and Chief, Endocrine Section, Department of Pediatrics, Baylor College of Medicine; Chief, Endocrine Service, Texas Children's Hospital, Houston, Texas

Milton H. Donaldson, M.D.

Associate Professor of Pediatrics, University of Pennsylvania School of Medicine; Senior Physician and Associate Director of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

John W. Duckett, M.D.

Assistant Professor of Urology, University of Pennsylvania School of Medicine; Senior Surgeon, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Donald J. Fernbach, M.D.

Professor of Pediatrics, Baylor College of Medicine; Chief, Hematology and Oncology Service at Texas Children's Hospital; Director, Research Hematology Laboratory, Texas Children's Hospital, Houston, Texas

Lillian M. Fuller, M.D.

Radiotherapist and Associate Professor of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Mary Ellen Haggard, M.D.

Professor of Pediatrics and Director, Division of Pediatric Hematology and Oncology, The University of Texas Medical Branch, Galveston, Texas

Martin Hrgovcic, M.D., D.Sc.(Med.)

Formerly Faculty Associate in Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, and the Diagnostic Clinic of Houston, Houston, Texas

David H. Hussey, M.D.

Associate Radiotherapist and Associate Professor of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Oscar Y. King, M.D.

Project Investigator in Pediatrics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Vita J. Land, M.D.

Assistant Professor of Pediatrics, Washington University School of Medicine; Assistant Pediatrician, St. Louis Children's Hospital, St. Louis, Missouri

Daniel M. Lane, M.D., M.S.(Peds.), Ph.D.

Associate Professor of Pediatrics, Tulane University School of Medicine, New Orleans, Louisiana

Derrick Lonsdale, M.B., B.S.(London)

Staff Pediatrician, Cleveland Clinic, Cleveland, Ohio

Richard G. Martin, M.D.

Surgeon and Professor of Surgery and Chief, Section of General Surgery, The M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Robert W. Miller, M.D.

Chief, Epidemiology Branch, National Cancer Institute, Bethesda, Maryland; Clinical Professor of Pediatrics, Georgetown University, Washington, D. C.

S. Grant Mulholland, M.D.

Assistant Professor of Urology, University of Pennsylvania School of Medicine; Urologist, Graduate Hospital of the University of Pennsylvania; Chief, Department of Urology, Philadelphia General Hospital, Philadelphia, Pennsylvania

Carlos A. Perez, M.D.

Professor of Radiology and Chief, Clinical Section, Division of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

Abdelsalam H. Ragab, M.D.

Assistant Professor of Pediatrics, Washington University School of Medicine; Assistant Pediatrician, St. Louis Children's Hospital, St. Louis, Missouri

Felix Rutledge, M.D.

Gynecologist-in-Chief and Professor of Gynecology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Julian P. Smith, M.D.

Gynecologist and Associate Professor of Gynecology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

James B. Snow, Jr., M.D.

Professor and Chairman, Department of Otorhinolaryngology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Kenneth A. Starling, M.D.

Assistant Professor of Pediatrics, Baylor College of Medicine; Associate Hematologist and Oncologist, Texas Children's Hospital and Research Hematology Laboratory, Houston, Texas

Herman D. Suit, M.D.

Chief, Department of Radiation Medicine, Massachusetts General Hospital; Professor of Radiation Therapy, Harvard Medical School, Boston, Massachusetts

Margaret P. Sullivan, M.D.

Associate Pediatrician and Associate Professor of Pediatrics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Wataru W. Sutow, M.D.

Pediatrician and Professor of Pediatrics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Jerry J. Swaney, M.D.

Associate in Pediatrics, Northwestern University; Director, Pediatric Oncology, Children's Memorial Hospital, Chicago, Illinois

Norah duV. Tapley, M.D.

Radiotherapist and Professor of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas

Jessie L. Ternberg, M.D., Ph.D.

Head, Division of Pediatric Surgery, St. Louis Children's Hospital; Professor of Surgery, Washington University School of Medicine; Associate Surgeon, Barnes Hospital and St. Louis County Hospital, St. Louis, Missouri

Patricia Tretter, M.D.

Associate Attending Radiologist and Associate Clinical Professor of Radiology, The Presbyterian Hospital in the City of New York at the Columbia-Presbyterian Medical Center, New York, New York

Frederick Valeriote, Ph.D.

Associate Professor of Radiology and Head, Section of Cancer Biology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

Teresa J. Vietti, M.D.

Professor of Pediatrics, Mallinckrodt Department of Pediatrics, Washington University School of Medicine; Associate Pediatrician, Barnes and Associated Hospitals; Director, Division of Hematology and Oncology, St. Louis Children's Hospital, St. Louis, Missouri

Jordan R. Wilbur, M.D.

Director, Children's Oncology Program, Children's Hospital at Stanford, Palo Alto, California

Thomas E. Williams, M.D.

Associate Professor of Pediatrics and Pathology, The University of Texas Medical School at San Antonio, San Antonio, Texas

Preface

This book represents the composite synthesis of the interest and experience of the many investigators and consultants who comprise the Pediatric Division of the Southwest Cancer Chemotherapy Study Group. The text was designed and written primarily for the clinician; correspondingly there has been less emphasis on the histopathology except as it relates to the recognition, behavior, and management of each disease entity.

Advances in the treatment of malignant neoplastic diseases are being reported with increasing regularity in all age groups, but especially in children. There has been a significant reversal of the mortality rate in some instances, a significant prolongation of the survival time in others, and effective palliation in general.

The order of the chapters was arbitrarily determined to present first the general aspects of the care of the child with cancer and to follow this with detailed discussions of the major disease entities. No attempt has been made to be all-inclusive or to provide specific modes of therapy. Our major objective was to review the status of cancer in children and to acquaint the reader with the current progress in each area.

The steady improvement in the overall survival rate of children with cancer has done much to dispel pessimism and has spawned a new era of cautious optimism. This improvement exceeds the concept of any single "wonder" drug and is, for the most part, the result of a dogged multidisciplinary approach that integrates the talents of the clinical oncologist, radiotherapist, and surgeon. By functioning in well-equipped centers they are able to extend the capability of the practicing clinician, whose increased awareness and prompt attention are still ultimately critical to the successful management of these complex problems.

As a result of the years of experience provided within the atmosphere of a collaborative group, it is obvious that the era of empirical therapy is dissipating as knowledge of the natural history of tumors, mechanisms of drug action, cellular kinetics, molecular biology, cell differentiation, and immunology continues to accumulate. The pediatric oncologist is now deeply committed in a dynamic period of experimental and investigational therapy that promises even greater benefits within the foreseeable future.

Throughout the text the reader will detect areas of overlapping material. Because of the nature of this book and an awareness of the many existing controversies, we allowed the contributing authors the freedom to express individual opinions wherever this seemed to be appropriate and desirable.

The manuscripts for many of the chapters were generously reviewed and criticized, favorably or otherwise, by our colleagues at a number of institutions.

Their assistance, as well as that of the clerks, secretaries, and others whose efforts have made this book possible, is gratefully acknowledged. We regret that all of the referring physicians, staff, and others who participated in the care of the patients involved cannot be listed here, but it is hoped that our sincere expression of appreciation will be acceptable to all. Those to whom special thanks are due include Drs. R. Cumley, D. DeVivo, C. Griffin, J. Grisham, F. Harberg, M. Ibanez, A. Kaplan, J. Kissane, G. LePage, E. Montague, and M. Smith, and especially our families.

Wataru W. Sutow
Teresa J. Vietti
Donald J. Fernbach

CHAPTER 1

General aspects of childhood cancer*

WATARU W. SUTOW

CHILDHOOD CANCER

The nature and incidence of cancer in the childhood population can be estimated from several sources such as death certificates, tabulations from cancer centers, and reports of tumor registries. Although each of these bodies of data contains serious inherent biases, tabulations of the figures from the total group provide information on the relative incidence of specific types of cancer in children. Age/sex/race predilections of different types of tumors will be discussed separately in the chapter devoted to each type.

Incidence

Table 1-1 shows the combined incidence of specific types of cancer in children as reported by two cancer centers: the Memorial Hospital for Cancer and Allied Diseases in New York City[4] and The University of Texas M. D. Anderson Hospital and Tumor Institute in Houston.[18] Also shown in Table 1-1 is the report of the Manchester (England) Children's Tumour Registry,[17] covering a 10-year period (1953-1963) in a general childhood population of approximately 1 million.

Data obtained from hospital sources may reflect specialized interests of the hospital. Thus the relative infrequency of tumors of the brain and retinoblastomas in the two cancer hospitals shown in Table 1-1 suggests that many patients with these tumors were referred to other centers concentrating on the care of such patients.

The incidence rates of childhood cancer are more difficult to determine than the mortality rates. A report based on the New York state registry data, covering all of New York State exclusive of New York City (about 2,769,000 children in 1960), showed an overall rate of 11.33 per 100,000 children under 15 years of age for 1941-1943, 12.05 for 1949-1951, and 11.67 for 1958-1960.[12]

The incidence of childhood cancer within a geographically limited region (Harris County, Texas, which includes Houston) has been determined from a study of hospital records between 1958 and 1970.[13] During this period, 672 cases were recorded. Based on the 1960 and 1970 census reports, rates for the 0- to 15-year age group per 100,000 population per year have been calculated for a number of childhood malignant diseases (Table 1-2).

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Table 1-1. Relative incidence of specific types of cancer in children under 15 years of age

Type of cancer	Relative frequency (%)	
	Cancer center data*	Manchester (England) Tumour Registry data†
Leukemia	31	29
Lymphoma—Hodgkin's disease	10	9
Soft tissue sarcoma	14	12
Bone sarcoma	13	2 (Ewing's sarcoma)
Neuroblastoma	9	8
Wilms' tumor	7	5
Brain tumors—retinoblastoma	6	20
Miscellaneous	10	15
Total	100	100
Total number of cases	(2248)	(994)

*Data from Dargeon[1] and Sutow.[18]
†Data from Marsden and Steward.[17]

Table 1-2. Incidence of specific malignant diseases in children (0 through 14), Harris County, Texas, 1958-1970*

Type of neoplasm	Rate per 100,000 per year
Leukemia	3.72
Lymphoma	1.25
Central nervous system	1.85
Neuroblastoma	0.90
Wilms' tumor	0.85
Bone sarcoma	0.48
Rhabdomyosarcoma	0.27
Retinoblastoma	0.24
All others	1.23
Total	10.79

*Data from Texas Center for Disease Control.[13]

Table 1-3. Mortality rates in the United States for malignant tumors in children

	Mortality rate (per 100,000 population)*		
	Age under 1 yr	Ages 1-4 yr	Ages 5-14 yr
1940	4.4	4.8	3.0
1950	8.7	11.7	6.7
1960	7.2	10.9	6.4
1966†	5.6	8.3	6.4
White	5.9	8.8	6.7
Nonwhite	3.9	5.5	5.0
Male	5.2	8.8	7.3
Female	6.0	7.7	5.5

*Data from Grove and Hetzel.[11]
†Data from Public Health Service.[19]

Mortality

Cancer kills more children at the present time than does any other disease in the age group of 1 through 14 years, ranking second to accidents as a major cause of death.[19] The American Cancer Society estimates that in 1972 cancer will take the lives of approximately 4000 children under the age of 15.[1] Mortality figures extracted from U. S. Vital Statistics for the past three decades have been tabulated in Table 1-3.

Miller[15] has analyzed all (29,457) death certificates in the United States for children under the age of 15 years who died during the period 1960-1966, as well as the death certificates (2487) for those 15 to 19 years of age who died in 1965 and 1966. The relative incidence of specific types of cancer and their respective mortality rates have been summarized from Miller's report in Table 1-4.

Table 1-4. Mortality from childhood cancer*

Type of cancer	Ages under 15 yr (1960-1966)		Ages 15-19 yr (1965-1966)	
	Total deaths (%)	Rate*	Total deaths (%)	Rate*
Leukemia	48	3.45	30	2.63
Brain tumor	16	1.13	11	1.01
Lymphoma	8	0.54	17	1.54
Neuroblastoma	7	0.50	1	0.10
Wilms' tumor	5	0.38	1	0.07
Bone cancer	4	0.28	13	1.19
Rhabdomyosarcoma	2	0.15	3	0.25
Liver	1	0.08	1	0.10
Retinoblastoma	1	0.05	–	0.004
Teratoma	1	0.05	2	0.17
Miscellaneous	7	0.53	21	1.81

*Per 100,000 per year, based on data from Miller.[15]

Table 1-5. Relative incidence of specific types of cancer in children and adults

Tumor types	Children 0-14 yr*	All types of cancer (%) all ages	
		Dorn and Cutler†	Griswold and associates‡
Leukemia/lymphoma	41	6	7
Sarcomas	27	3	3
Embryonal tumors	16	1	1
Neural tumors	6	2	1
Carcinomas and adenocarcinomas	5	85	86
All others	5	3	2
Number of cases	2248	45,311	29,260
Number of children included	2248	594	425

*Data from Dargeon[4] and Sutow.[18]
†Data from Dorn and Cutler.[5]
‡Data from Griswold, Wilder, Cutler, and Pollack.[9]

Data from death certificates are subject to variations in completeness of reporting and accuracy of diagnosis. Moreover, mortality figures cannot provide a precise estimate of the actual incidence of specific types of cancer having significant cure rates.

Comparison of childhood cancer with cancer in adults

The spectrum of types of cancer in children differs strikingly from that in adults. The types that most often affect children are the leukemias, embryonal tumors, and sarcomas. Adenocarcinomas and carcinomas, which constitute the majority of cancers in adults, are rare in children. Data from several reports have been tabulated to provide a comparison between childhood and adult cancers (Table 1-5). Although these data were obtained by various means from several tumor populations, the vast differences in the types of cancer prevalent among children as compared to those in the general population (predominantly adult) are immediately apparent.

TEAM APPROACH AND TOTAL CARE

The optimum care of children with cancer now includes the application of all known modes of therapy, particularly the multimodal and interdisciplinary approach. This is the total care concept so effectively developed by Farber.[8] Such collaboration among specialists should involve every aspect of patient care, from the diagnostic procedures through definitive therapy and family support.

That this type of organized and coordinated treatment program carried out by experienced physicians in well-staffed and well-equipped medical centers is effective has been demonstrated in published statistics. The survival rate of 89% among 53 children who were treated entirely by Farber and his group for nonmetastatic Wilms' tumor was significantly better than the survival rate of 39% among 54 children whose treatment was started elsewhere and was continued at Farber's institution.[7]

The survival times of 220 children with acute leukemia who were treated in England and Wales from 1963 through 1967 by physicians specializing in childhood leukemia (study group) were compared with those of 1025 children who were treated for this disease by other physicians (comparison group). In a report to the Medical Research Council, the Committee on Leukaemia and the Working Party on Leukaemia in Childhood concluded that the children in the study group had a considerably longer life expectancy than did the children in the comparison group.[6] It is suggested that during the period covered by the study, the "improvement in survival is due not so much to the details of the therapeutic regimens as to the availability of special facilities and expertise."[6]

The use of sensitive and sophisticated diagnostic procedures increases the likelihood, not only of establishing the proper diagnosis, but also of delineating more precisely the extent of the disease. The latter aspect may be vital in the application of effective therapy such as surgery and irradiation. Diagnostic procedures developed in recent years include lymphangiography, angiography, xerography, isotope scanning, electron microscopy, and tissue culture techniques.

Every helpful approach should be considered and used, if appropriate, in the diagnosis and treatment. If adequate facilities and personnel are not avail-

able, the patient should be referred promptly to a university clinic or cancer center wherein such help can be obtained. Surely, a child with cancer and his parents should expect and receive no less.

PERIOD OF RISK AND CURE

After diagnosis and definite therapy, when can a child with a given type of cancer be presumed to be cured? Consideration in this section will be limited to solid tumors. The reader is referred to the chapters on acute leukemia, Hodgkin's disease, lymphomas, and histiocytosis for discussions of long-term survival and cure of those diseases.

Utilizing data from published cases of Wilms' tumor and other sources, Collins[2] introduced the concept of a *period of risk* in the prognosis of solid tumors in 1955. Since a tumor in a given patient could have been present (and growing) no longer than the patient's chronologic age at the time of diagnosis plus the 9 months of gestation, it was postulated that any occult residual tumor present at the time of definitive treatment (assuming an unchanged growth rate) should reach the same size as the primary tumor in the same length of time (that is, the patient's age plus 9 months). Collins concluded that if no evidence of recurrence or metastases became apparent during this time, called the *period of risk*, the patient could be considered cured.[3] Subsequently, other independent reports appeared to substantiate the validity of this concept.[14] In fact, observations based originally on data from patients with Wilms' tumor seemed to hold also for patients with neuroblastoma and rhabdomyosarcoma.[14]

Gross[10] had commented that in children with Wilms' tumor, a fixed post-therapy period of 1 to 1½ years seemed to distinguish those who would remain free of the disease. Platt and Linden,[16] using the California Tumor Registry, compared the two criteria for survival: the period of risk as proposed by Collins and the fixed interval of 2 years. They concluded that the survival rates for the variable interval (Collins) and the fixed interval of 2 years were almost identical.

Although exceptions are uncommon, the application of any rule of this type to a single case carries a risk of being unreliable; nevertheless, these concepts are useful in discussing the prognosis with the parents. Such guidelines are also necessary for the planning and evaluation of long-term continuation therapy.

The recent development of newer antineoplastic drugs has resulted in a more prolonged control of several types of tumor, even though the patient is not cured. An example of this is the significant increase in the duration of remissions in children with acute leukemia following currently employed chemotherapeutic regimens (Chapters 9 and 10). Similar improvements in the results of chemotherapy could well be anticipated in children with some types of solid tumors.[18] If, however, the growth rate of the tumor is appreciably retarded by these agents, modifications in the concept of the risk period will become necessary.

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CHAPTER 2

Etiology of childhood cancer

ROBERT W. MILLER

It is understandable that in the bustle of medical practice physicians will focus their attention on diagnosis and treatment rather than exploring clues to etiology. In consequence, new clinical observations of possible research value go unnoticed or unrecorded. Such observations may concern environmental exposures, therapy, preexistent diseases in the patient, or familial disorders—any of which may portend an increased risk of certain cancers. Recognition of high-risk factors is of value in the prevention and early detection of certain neoplasms.

ENVIRONMENTAL FACTORS

A variety of environmental exposures have been described that are oncogenic in man,[10] but only one of these—ionizing radiation—has induced cancer in children.[44] In part, this difference is due to the much smaller exposure of children to oncogenic agents, which adults encounter at work or by habit.

Drugs during childhood. There is no doubt that (1) drugs containing radioisotopes and (2) immunosuppressive therapy after renal transplantation are related to an increased frequency of cancer in man.[7, 54, 58] Cancer in adults may be induced by a few other drugs, as indicated by case reports (e.g., leukemia after the use of chloramphenicol[57] or melphalan[27, 32]). There is much better evidence of chemical carcinogenesis in man caused by occupational exposures than by drug therapy.

Drugs during fetal life. A monumental finding in human oncology was announced in April, 1971: heavy doses of stilbestrol given to pregnant women to prevent abortion were implicated as the cause of adenocarcinoma of the vagina in their daughters 14 to 22 years later.[26] The initial report describing 7 cases in Boston was quickly confirmed by a search of the New York State Tumor Registry, which revealed 5 more.[23] Adenocarcinoma of the vagina is extremely rare so early in life, and these clusters of cases could not be attributed to chance. Had a more common neoplasm such as lymphoma or neuroblastoma been involved, the excess of cases would probably have gone undetected. Studies are now in progress to determine if stilbestrol during pregnancy induces other cancers or disorders in the offspring and to determine if other drugs may do the same. Sensitivity may be greater in the fetus than in later life. Indeed, there is better evidence for oncogenicity after fetal exposure to stilbestrol than there is for any drug taken later in life.

Viruses. An important development in cancer research has been the invention of statistical techniques for determining dispassionately whether the frequency with which a rare event clusters in time and space exceeds normal expectation.[41] There is no doubt that after examining the distribution of cases on a scatter

map, one can identify individual clusters of rare diseases by inspection and can draw tight boundaries around them. The question is not "Do rare events cluster?" but "Do they cluster excessively?" To date, the application of these new statistical procedures in studies of leukemia has provided no solid evidence of an excess suggesting an infectious mode of spread.[20, 21] In contrast, the application of one of these techniques to data for Burkitt's lymphoma in the West Nile District of Uganda has shown considerable evidence of clustering.[56] For this reason among others, an infectious origin is far more likely for African lymphoma than for leukemia.

Tests of various hypotheses concerning the infectious transmission of leukemia have been made, and the findings were negative. For example, if there is an infectious transmission, it might be detectable among persons having the closest contact with the neoplasm. Leukemia has not been found, however, to occur excessively among marital partners of leukemic persons[43] or in children born of women with leukemia during pregnancy.[13]

Leukemia in mice can be experimentally transmitted to the young by viruses in breast milk.[24, 33] Is there a human counterpart to this laboratory observation? The answer is no. The histories of breast-feeding among 541 children with leukemia under 15 years of age were compared with those for a similar number of neighborhood control children. No significant differences in the frequency or duration of breast-feeding were found.[49]

The hypothesis that the leukemia virus may be widely prevalent in blood but of low pathogenicity is not supported by observations in man. In the series of children just described, there was no significant difference between cases and controls in the frequency of exchange transfusion for blood type incompatibility in the newborn period, when immunologic defenses are low.[44] The claim that a slow virus may be responsible for human leukemia, as is presumed to be true for kuru (cerebellar ataxia in New Guinea), meets difficulty when comparison is made of the epidemiology for the two diseases. Deaths from kuru cluster in villages and in time, but deaths from leukemia do not. Evidence for vertical transmission from mother to child is substantial for kuru, but absent for leukemia. Overall, epidemiologic studies support the belief that kuru is infectious and that leukemia is not.[49]

These observations do not exclude the possibility of a viral role in leukemogenesis. They do indicate that if viruses are involved, their mode of transmission is too subtle to be detected by methods available at present.

HOST FACTORS

Mortality rates in children with specific forms of cancer exhibit dynamic changes by single year of age. These variations must reflect important etiologic influences. Among white children in the United States, the mortality rate for acute lymphocytic leukemia exhibits a huge peak at 4 years of age that is absent among nonwhite children.[48] There is no such peak for children with acute myelogenous leukemia. Thus there must be racial differences in exposure or susceptibility to some agent that induces acute lymphocytic leukemia but not acute myelogenous leukemia.

In children about 4 years of age, there are also peaks in mortality from Wilms' tumor[34] and neuroblastoma[53]—cancers whose intrauterine origins are suggested

by their occurrence in very young patients and by the high frequency with which they are found in situ (microscopically) at autopsy in patients younger than 3 months of age, but not thereafter.[59] The same age pattern is exhibited for primary liver cancers,[17] retinoblastoma,[30] ependymoma,[52] and presacral teratoma.[52] These tumors may be linked with or distinguished from one another by the specific congenital malformations with which they are associated.

Leukemia. Leukemia is at times determined prezygotically. It occurs excessively in Down's syndrome,[50] which in 95% of all cases is due to trisomy 21, in consequence of meiotic nondisjunction.[38] The probability that a child with Down's syndrome will develop leukemia is about 1 in 200—about fifteen times the normal rate.[50] The risk of developing leukemia is substantially higher in two genetically transmitted diseases, Bloom's syndrome and Fanconi's aplastic anemia.[46] The numbers of persons with these syndromes *and* leukemia, although small, indicate that the neoplasm occurs in adolescence or early adulthood and in Fanconi's anemia is limited to the acute myelomonocytic type.[11] The magnitude of the risk of leukemia in these syndromes appears to be almost 1 in 10. Both syndromes are characterized by chromosomal fragility in cell culture.

In addition, there is a high rate of leukemia among atomic bomb survivors in Japan,[29] persons occupationally exposed to benzene,[22] and patients with multiple myeloma treated with melphalan (L-phenylalanine mustard) or cyclophosphamide.[27, 32] Groups at high risk of leukemia have in common a chromosomal abnormality, although not of a single type—congenital aneuploidy in Down's syndrome, chromosomal fragility in Bloom's and Fanconi's syndromes, and long-lasting complex chromosomal aberrations after exposure to ionizing radiation, benzene, melphalan, or cyclophosphamide.[9, 46, 60]

Persons with high probability of developing leukemia do not carry a similar risk of lymphoma, a neoplasm that is associated instead with inborn, immunologic, cell-mediated deficiencies (congenital thymic alymphoplasia, Wiskott-Aldrich syndrome, and ataxia-telangiectasia).[18] Thus the constellation of diseases associated with leukemia is different from that associated with lymphoma.

Wilms' tumor. In an entirely different orbit is Wilms' tumor, adrenocortical neoplasia, and primary liver cancer, which are associated with several congenital growth excesses.[48] Each of the three neoplasms occurs excessively with congenital hemihypertrophy; the neoplasms and hemihypertrophy are independently associated with large pigmented or vascular nevi, among other hamartomas, and with the visceral cytomegaly syndrome to which Beckwith has recently called attention (Fig. 2-1). The syndrome consists of omphalocele, macroglossia, and cytomegaly of visceral organs, including the three in which neoplasia has been observed in association with hemihypertrophy.[5, 28]

Wilms' tumor also occurs excessively with congenital aniridia. This ocular defect, bilateral absence of the iris, is ordinarily extremely rare. Its frequency in children with Wilms' tumor is about a thousand times greater than normal.[16] Ordinarily aniridia is due to an autosomal dominant gene, and two thirds of the cases have a familial history of the defect. When present with Wilms' tumor, aniridia has been nonfamilial, with the exception of 1 case out of 30, indicating that the eye defect and the tumor are due to a new genetic mutation or to an environmental agent that mimics the action of a gene.

It should be noted that the malformations associated with the three categories