PEDIATRIC CANCER THERAPY

EDITED BY CARL POCHEDLY

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Foreword

The investigation and treatment of children's tumors is increasingly rewarding, not only because of the much improved outlook for these children, but also because of the contribution that the discipline of pediatric oncology is making to the subject of malignant disease in general. No one can deny the importance of the subject: malignant disease is now the most common cause of death in children over the age of one year in the United States and in the United Kingdom. Quite apart from the distress to the child and his family, the loss of their young lives and of their economic value to our nations cannot be tolerated.

There is, therefore, increasing need for good, authoritative accounts of the modern management of malignant disease in children, now that so much can be accomplished. This book is directed to the general pediatrician, not to stimulate him to manage these children on his own, but to demonstrate how well the children may do when they are treated in special centers by experienced teams. To help such a team in the management of these children, the pediatrician will need the basic knowledge provided by this book, which is produced to the high standards we have come to expect from its editor, Carl Pochedly. He has gathered together a number of American authors who are experts in the field they cover. In an exciting subject like pediatric oncology, which is notable for international collaboration, it is fitting that this book should appear in the International Year of the Child.

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Preface

This book directs the attention of pediatricians and family practitioners to current concepts and technology in the management of cancer in children. New diagnostic techniques, new drugs, and new approaches to management have been introduced in recent years. Also, our understanding of the biology of tumors in children has increased considerably. We have tried in this book to clearly reflect this change and progress as it has affected the clinical management of children with cancer.

Every effort has been made to select material that is clinically relevant and useful to the clinician in practice. This is especially important now that more and more pediatricians and family practitioners are assuming meaningful roles in the management of children with cancer, and therefore have greater interest and expertise in this field. It is the attitude of leading children's cancer centers that families of children with cancer should maintain close contact with their pediatrician or family practitioner. This physician should be fully informed of the therapy and progress of the child, as well as being actively involved in the general pediatric management.

The steady improvement in the overall survival rate of children with cancer has done much to dispel pessimism and has given rise to a new era of cautious optimism. During the past 20 years many effective drugs have been found, and we have slowly learned how to use them.

In addition, improved results have come from applying a multidisciplinary approach, integrating the talents of the pediatrician or family practitioner, oncologist, radiotherapist, and surgeon. Finally, this new optimism enables children with cancer to receive a full measure of the same conscientious, compassionate, and thorough care that physicians routinely give to any other sick child.

This book contains detailed descriptions of recommended therapy regimens for management of the various childhood malignancies. It should be emphasized, however, that these complex multimodal therapy protocols should be carried out only under the close personal supervision of a pediatric oncologist. In addition, this therapy should be carried out only in the appropriate clinical setting, where necessary support services and personnel are readily available.

The chapters of this book focus on the American experience in the treatment of cancer in children. This is not meant to minimize or to detract from the many important contributions made by investigators and study groups in the United Kingdom and elsewhere in the world, which have contributed greatly to progress in therapy of these diseases. A high degree of international cooperation exists among pediatric cancer investigators in various parts of the world. It is gratifying to see the ease with which communication can occur between oncologists of different countries on vital matters of mutual scientific concern.

I am very grateful for the participation of the authors of the various chapters, all of whom are established investigators and acknowledged leaders in the field. Among them, they have reviewed all major aspects in the management of childhood cancer with clarity and authority. We hope the chapters of this book will enhance the pediatrician's and family practitioner's understanding of childhood cancer, stimulate interest, and lead to benefit of children.

Finally, I am very grateful to Mr. Alfred Arsenault, President of Insight Publishing Company, for giving his kind permission and complete cooperation in re-publishing material that originally appeared in *Pediatric Annals*. Also, Ms. Joan Sanow of University Park Press was uncommonly efficient and continually supportive during all the phases in the complex process of producing this book.

Contents

ACUTE LYMPHOID LEUKEMIA

Jeanne M. Lusher, M.D., and
Yaddanapudi Ravindranath, M.B.B.S.

The acute leukemias are a group of neoplasms that are manifest in the bone marrow. They are the most common form of cancer in children, accounting for 30 to 45 percent of all pediatric malignancies.

Acute leukemias arise either in the lymphoid tissue or from the marrow hematopoietic stem cell or its progeny. An example of the latter, acute myeloid leukemia, is discussed by Dr. Necheles in the following chapter.

Acute lymphoid leukemia (ALL), the subject of this article, is the predominant form in childhood, accounting for 75 to 85 percent of all cases. Once considered uniformly fatal, ALL can now be eradicated in a significant number of children. In just the past 25 years the prognosis has changed from hopeless to optimistic, and today there is a better-than-50 percent chance of disease-free, long-term survival.

However, optimum care of the child with leukemia requires a well-organized and coordinated treatment program carried out by experienced personnel in a well-equipped center.

INCIDENCE AND ETIOLOGY

Age, Sex, and Racial Differences

The risk a Caucasian child has of developing acute leukemia during the first decade of life is 1 in 2,880.[1] The peak age of onset is one to five years; in acute lymphoid leukemia, the peak age is three to four years. Almost all of the series reported have shown a slight but significant predominance of males (55 percent).* There also appears to be a slightly higher incidence among Caucasian chil-

*This may be a reflection of the greater number of boys developing one form of ALL, the T-cell variety, which is described in the following pages.

dren in the U.S. than in black children, although there is some evidence to support the theory that this apparent racial difference is really a reflection of socioeconomic factors.

Etiology

Despite a great deal of research, few specific factors have been directly linked to the causation of acute leukemia. There is no indication that a transmissible infectious agent from either man or animal is responsible for leukemia in human beings. While ionizing irradiation has been clearly implicated, the mechanism or mechanisms by which it causes malignant transformation are still not fully understood. The mechanism may be an indirect one, such as the activation of a latent oncogenic virus. An attractive hypothesis, the oncogenic hypothesis, is that certain cells carry information for malignant transformation but require activation by an intracellular event, probably related to environmental factors, such as irradiation, chemical carcinogens, or perhaps even viruses.[2]

There is increased risk of leukemia associated with pre-existing chromosomal abnormalities. The probability that a child with Down's syndrome will develop leukemia is about 1 in 200, which is 15 times the normal rate. The risk of developing leukemia is quite high in two other genetically transmitted diseases: Bloom's syndrome and Fanconi's anemia, both of which are characterized by chromosomal fragility in cell culture. In the latter two syndromes the risk of leukemia is 1 in 10, and it usually occurs in adolescence or early adult life. While leukemia developing in Fanconi's anemia is almost always of the acute monomyelogenous type, approximately two-thirds of the leukemias developing in Down's syndrome are ALL.[3]

PATHOGENESIS

The bone marrow is presumed to be the site of origin of leukemia, although many organs (spleen, liver, lymph nodes, kidneys, etc.) are frequently affected at the time of diagnosis.

The mechanism by which leukemic cells replace normal marrow cells is not entirely clear. The most widely accepted theory is that a clone of leukemic cells develops. This clone of slowly dividing cells does not produce an end-stage cell, such as the mature granulocytes or erythrocytes, and thus the leukemic cells gradually accumulate and replace the normal elements.[2] Replacement of

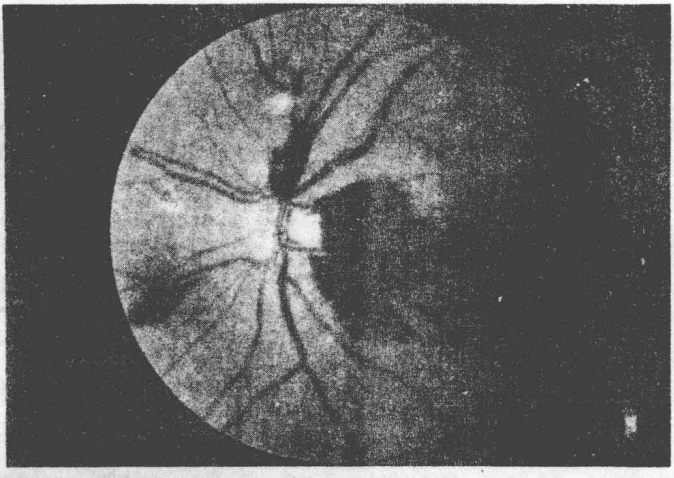

FIGURE 1. Optic fundus of a newly diagnosed child with ALL showing retinal hemorrhages resulting from severe thrombocytopenia.

normal marrow elements by leukemic cells eventually results in peripheral pancytopenia.

Presenting Complaints

Most often the child's presenting complaints will reflect this paucity of normal blood cells. Thus, pallor and excessive fatigability result from anemia; purpura, epistaxis, or other bleeding manifestations (Figure 1) result from thrombocytopenia; and fever and other signs of bacterial infection (Figure 2) result from granulocytopenia (Table 1). The onset may be insidious or abrupt, and any or all of these signs may be present when the child is first seen.

In addition, many patients have generalized lymphadenopathy and hepatosplenomegaly. Bone pain is frequent and results from leukemia infiltration of the cortex and periosteum[4] (Figure

TABLE 1. Common presenting complaints in the child with acute lymphoid leukemia

Fever
Pallor
Purpura and other bleeding
Anorexia, listlessness
Bone and/or joint pain
Lymphadenopathy
Weight loss

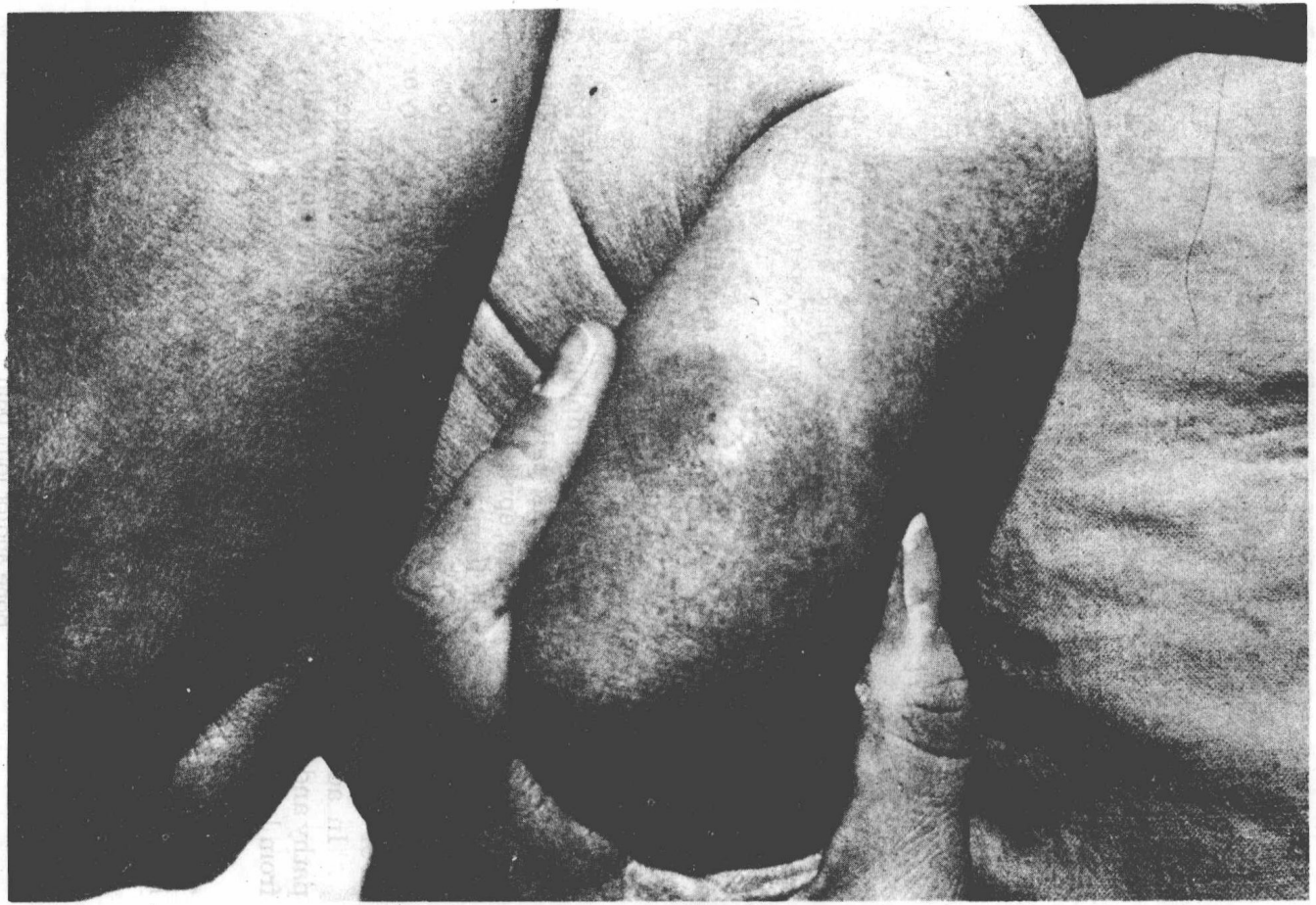

FIGURE 2. Typical skin lesion of *Pseudomonas* sepsis in child with ALL who had severe neutropenia.

3). Joint pain and swelling occur in 5 to 10 percent of children; cortical and periosteal leukemic infiltrates adjacent to the joint capsule result in joint effusion and in pain that may mimic rheumatoid arthritis. While leukemic involvement of the central nervous system and testes may be apparent at the time of diagnosis, these sites are most commonly affected at a later date.

In most instances examination of a well-stained peripheral blood film reveals the presence of leukemic cells (Figure 4). In

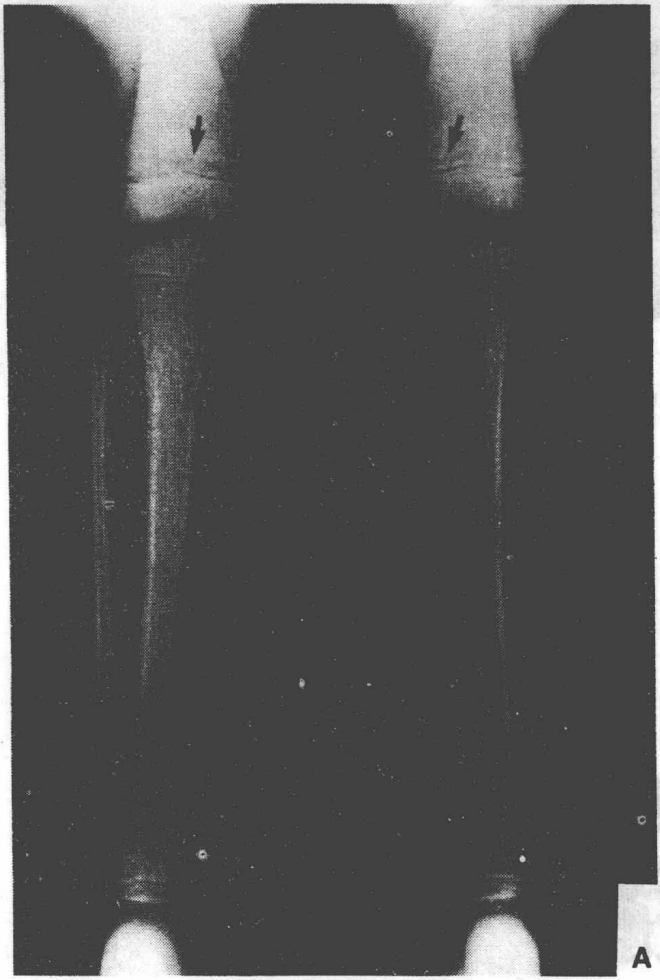

FIGURE 3. Bone changes are frequent in ALL. A: Submetaphyseal rarefaction in lower ends of femurs and tibias.

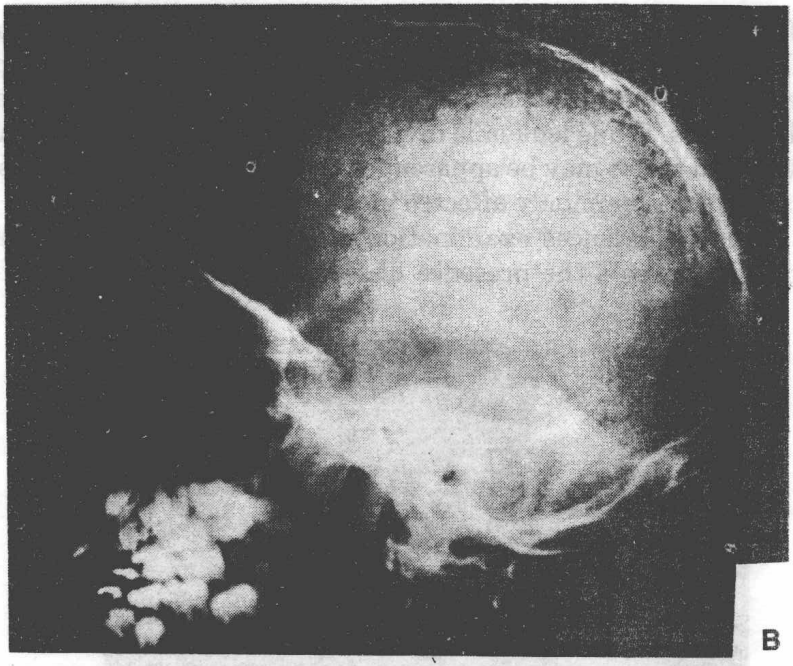

FIGURE 3. Bone changes in ALL. B: Moth-eaten appearance of skull resulting from multiple small lytic lesions.

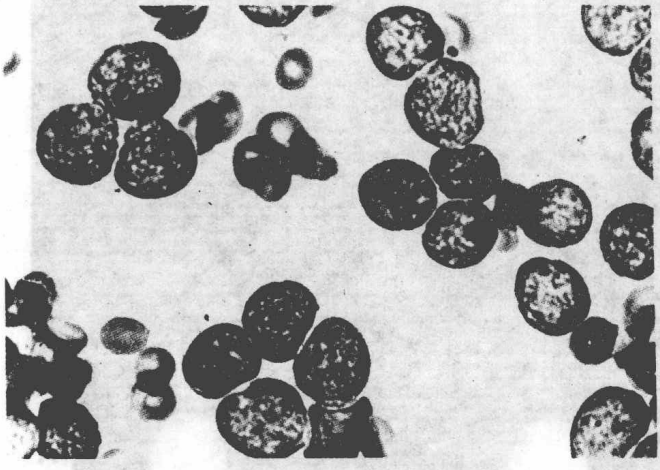

FIGURE 4. Lymphoblasts are characterized by scanty cytoplasm and indistinct nucleoli that are few in number.

some children no definite blast forms are seen in the peripheral blood even though the bone-marrow aspirate demonstrates almost total replacement of normal elements by leukemic cells. Needle aspiration of the marrow almost always provides a sample adequate for diagnosis, although occasionally one must resort to needle biopsy (using a Jamshidi needle)[5] if the aspirated sample is inadequate.

Cytology

In our experience, the differentiation between ALL and other cell types can best be made by careful examination of a well-prepared Leishman-Giemsa–stained bone-marrow aspirate. Lymphoblasts characteristically have very scanty cytoplasm, which stains deep blue in color, and indistinct nucleoli that are few in number (Figure 4). In those instances where the cell type is not readily apparent, the application of cytochemical methods (PAS, Sudan black, peroxidase, and esterase stains) may be helpful.[6-8] However, even with these stains there remain some cases that cannot be classified with certainty.

Heterogeneity of Acute Lymphoid Leukemia

ALL has long been recognized to be a heterogeneous disease on the basis of clinical features at the time of diagnosis and response to therapy. Approximately 10 to 20 percent of children have a mediastinal mass at the time of diagnosis (Figure 5). These patients, the majority of whom are boys, have an extremely poor prognosis; we have shown that this poor prognosis is independent of the high initial leukocyte count that is generally observed in this group.[9]

Within the last few years it has been established that the leukemic blast cells from such patients have properties of thymus-derived lymphocytes. They form E-rosettes with sheep erythrocytes (Figure 6) and lack surface-bound immunoglobulin (Ig).[10-14] In contrast, the leukemic blast cells from the majority of children with ALL possess neither the T-cell markers mentioned above nor B-cell markers (surface-bound Ig), thus giving rise to the subdivision of ALL into T-cell and "null"-cell ALL. (It has recently been shown in our laboratory, however, that these "null" cells express either B- or T-cell antigens when tested with T- and B-cell antisera and thus are not really "null" cells.[15]) Thus, accurate classification of ALL can best be accomplished by combining such markers as