Manual of Pediatric Hematology and Oncology
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Fifth Edition

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In Memory of
my parents – Abe and Lily Lanzkowsky – who instilled in me the importance of integrity,
the rewards of industry, and the primacy of being a mensch

Dedicated to
my devoted and patient wife, Rhona, who appreciates that
the study of medicine is a lifelong and consuming process

and

to our pride and joy our children and grandchildren
Shelley and Sergio – Joshua Abraham and Sara Lily Bienstock;
David Roy – Jessica Anne, Brandon Benjamin, Alexander Michael and
   Elijah Kole Lanzkowsky;
Leora and Alan – Chloe Hannah, Justin Noah, and
       Jared Isaac Diamond;
Marc – Lisa Joy – Jacob Tyler and
   Carly Beatrice Lanzkowsky
Jonathan and Debra Ann – Hana Julia and
   Judah Aiden Lanzkowsky

and

to my patients, students, pediatric house staff, fellows in Pediatric Hematology-Oncology,
and my colleagues, who have taught me so much over the years

Today he can discover his errors of yesterday
And tomorrow he may obtain new light
On what he thinks himself sure of today
Moses Maimonides
Every care has been taken to ensure that various protocols, drugs, and dosage recommendations are precise and accurate, and that generic and trade names of drugs are correct. However, errors can occur and readers should confirm all dosage schedules against the manufacturer's package information data and standard reference sources. Some dosages and delivery methods may not reflect package insert information, due to clinical experience and current usage.

The reader is referred to Appendix 3, which lists the pharmacologic properties and synonyms of the commonly used anticancer drugs.
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Hematologic Manifestations of Systemic Illness, Red Cell Membrane and Enzyme Defects, Extracorpuscular Hemolytic Disease, Management of Oncologic Emergencies, Supportive Care of Patients with Cancer
As the fifth edition of the *Manual of Pediatric Hematology-Oncology* is published, I have reflected on the advances that have occurred since I began practicing hematology-oncology over 50 years ago and since my first book on the subject was published by McGraw Hill in 1980. The present edition is more than double the size of the original book.

Our understanding of hematologic conditions has advanced considerably with the explosion of molecular biology and the management of most hematologic conditions has kept pace with these scientific advances. Our understanding of the basic science of oncology, molecular biology, genetics and the management of oncologic conditions has undergone a seismic change. The previous age of dismal and almost consistent fatal outcomes for most childhood cancers has been replaced by an era in which most childhood cancers are cured. This has been made possible not only because of advances in oncology but because of the parallel development of radiology, radiologic oncology and surgery as well as supportive care such as the pre-emptive use of antibiotics and blood component therapy. It has been a privilege to be a witness and participant in this great evolution over the past 50 years. Yet we still have a long way to go as current advances are superseded by therapy based upon the application of knowledge garnered from an accurate understanding of the fundamental biology of cancer.

In the early days of hematology-oncology practice, hematology dominated and occupied most of the practitioner’s time because most patients with cancer had a short life span and limited therapeutic modalities were available.

Automated electronic blood-counting equipment has enabled valuable red cell parameters such as mean corpuscular volume (MCV) and red cell distribution width (RDW) to be applied in routine clinical practice. This advance permitted the reclassification of anemias
based on MCV and RDW. Previously these parameters were determined by microscopy with considerable observer variability. The attempt at a more accurate determination of any one of these parameters was a laborious, time-consuming enterprise relegated only as a demonstration in physiology laboratories.

Rh hemolytic disease of the newborn and its management by exchange transfusion, which occupied a major place in the hematologists’ domain, has now become almost extinct in developed countries due to the use of Rh immunoglobulin.

The description of the various genetic differences in patients with vitamin B$_{12}$ deficiency has opened up new vistas of our understanding of cobalamin transport and metabolism. Similar advances have occurred with reference to folate transport and metabolism.

Gaucher disease has been converted from a crippling and often disabling disease to one where patients can live a normal and productive life thanks to the advent of enzyme replacement therapy. Replacement therapy has also been developed for other inborn errors of metabolism.

Aplastic anemia has been transformed from a near death sentence to a disease with hope and cure in 90% of patients thanks to immunosuppressive therapies, hematopoietic stem cell transplantation and advanced supportive care. The emergence of clonal disease years later in patients treated medically with immunosuppressive therapy, however, does present a challenge. The discovery of the various genes responsible for Fanconi anemia and other inherited bone marrow failure syndromes has revealed heretofore unimaginable advances in our understanding of DNA repair, telomere maintenance, ribosome biology and other new fields of biology. The relationship of these syndromes to the development of various cancers may hold the key to our better understanding of the etiology of cancer as well as birth defects.

The hemolytic anemias, previously lumped together as a group of congenital hemolytic anemias, can now be identified as separate and distinct enzyme defects of the Embden–Meyerhof and hexose monophosphate pathways in intracellular red cell metabolism as well as various well-defined defects of red cell skeletal proteins due to advances in molecular biology and genetics. With improvement in electrophoretic and other biochemical techniques, hemoglobinopathies are being identified which were not previously possible.

Diseases requiring a chronic transfusion program to maintain a hemoglobin level for hemodynamic stability such as in thalassemia major frequently had marked facial characteristics with broad cheekbones and developed what was called “bronze diabetes” a bronzing of the skin along with organ damage and failure, particularly of the heart, liver, beta cells of the pancreas and other tissues due to secondary hemachromatosis because of excessive iron deposition. The clinical findings attributed to extramedullary hematopoiesis are essentially of historic interest because of the development and widespread use of proper
transfusion and chelation regimens. However, the full potential of the role of intravenous and oral chelating agents is yet to be realized due to the problems of compliance with difficult treatment regimens and also due to failure of some patients to respond adequately. Advances in our understanding of the biology of iron absorption and transport at the molecular level hold out promise for further improvement in the management of these conditions. Curative therapy in thalassemia major and other conditions by hematopoietic stem cell transplantation in suitable cases is widely available today.

In the treatment of idiopathic thrombocytopenic purpura, intravenous gammaglobulin and anti-D immunoglobulin have been added to the armamentarium of management and are useful in specific indications in patients with this disorder.

Major advances in the management of hemophilia have included the introduction of commercially available products for replacement therapy which has saved these patients from a life threatened by hemorrhage into joints, muscles and vital organs. Surgery has become possible in hemophilia without the fear of being unable to control massive hemorrhage during or after surgery. The devastating clinical history of tragic hemophilia outcomes has been relegated to the pages of medical history. Patients with inhibitors, however, still remain a clinical challenge. The whole subject of factors associated with inherited thrombophilia such as mutations of factor V, prothrombin G20210A and 5,10-methylenetetrahydrofolate reductase as well as the roles of antithrombin, protein C and S deficiency and antiphospholipid antibodies in the development of thrombosis has opened new vistas of understanding of thrombotic disorders. Notwithstanding these advances, the management of these patients still presents a clinical challenge.

There are few diseases in which advances in therapy have been as dramatic as in the treatment of childhood leukemia. In my early days as a medical student, the only available treatment for leukemia was blood transfusion. Patients never benefitted from a remission and died within a few months. Steroids and single-agent chemotherapy, first with aminopterin, demonstrated the first remissions in leukemia and raised hope of a potential cure; however, relapse ensued in almost all cases and most patients died within the first year of diagnosis. In most large pediatric oncology centers there were few patients with leukemia as the disease was like a revolving door – diagnosis and death. The development of multiple-agent chemotherapy for induction, consolidation and maintenance, CNS prophylaxis and supportive care ushered in a new era of cure for patients with leukemia. These principles were refined over time by more accurate classification of acute leukemia using morphological, cytochemical, immunological, cytogenetic and molecular criteria which replaced the crude microscopic and highly subjective characteristics previously utilized for the classification of leukemia cells. These advances paved the way for the development of specific protocols of treatment for different types of leukemia. The management of leukemia was further refined by risk stratification, response-based therapy
and identification of minimal residual disease, all of which have led to additional chemotherapy or different chemotherapy protocols, resulting in an enormous improvement in the cure rate of acute leukemia. The results have been enhanced by modern supportive care including antibiotic, antifungal, antiviral therapy and blood component therapy. Those patients whose leukemia is resistant to treatment or who have recurrences can be successfully treated by advances that have occurred with the development of hematopoietic stem cell transplantation. The challenge of finding appropriate, unrelated transplantation donors has been ameliorated by molecular HLA-typing techniques and the development of large, international donor registries. Emerging targeted and pharmacogenetic therapies hold great promise for the future.

Hodgkin disease, originally defined as a “fatal illness of the lymphatics,” is a disease that is cured in most cases today. Initially, Hodgkin disease was treated with high-dose radiation to the sites of identifiable disease resulting in some cures but with major life-long radiation damage to normal tissues because of the use of cobalt machines and higher doses of radiation than is currently used. The introduction of nitrogen mustard early on, as a single-agent chemotherapy, improved the prognosis somewhat. A major breakthrough occurred with the staging of Hodgkin disease and the use of radiation therapy coupled with multiple-agent chemotherapy (MOPP). With time this therapeutic approach was considerably refined to include reduction in radiation dosage and field and a modification of the chemotherapy regimens designed to reduce toxicity of high-dose radiation and of some of the chemotherapeutic agents. These major advances in treatment ushered in a new era in the management and cure of most patients with this disease. The management of Hodgkin disease, however, did go through a phase of staging laparotomy and splenectomy with a great deal of unnecessary surgery and splenectomies being performed. There were considerable surgical morbidity and post-splenectomy sepsis, occasionally fatal, that occurred in some cases. With the advent of MRI and PET scans, surgical staging, splenectomy and lymphangiography have become unnecessary.

Non-Hodgkin lymphoma, previously considered a dismal disease, is another success story. Improvement in histologic, immunologic and cytogenetic techniques has made the diagnosis and classification more accurate. The development of a staging system and multiagent chemotherapy was a major step forward in the management of this disease. This, together with enhanced supportive care including the successful management of tumor lysis syndrome, have all contributed to the excellent results that occur today.

Brain tumors were treated by surgery and radiation therapy with devastating results due to primitive neurosurgical techniques and radiation damage. The advent of MRI scans has made the diagnosis and the determination of the extent of disease more accurate. Major technical advances in neurosurgery such as image guidance, which allows 3D mapping of
tumors, functional mapping and electrocorticography, which allow pre- and intraoperative
differentiation of normal and tumor tissue, the use of ultrasonic aspirators and neuroendoscopy,
have all improved the results of neurosurgical intervention and has resulted in less surgical
damage to normal brain tissue. These neurosurgical advances, coupled with the use of
various chemotherapy regimens, have resulted in considerable improvements in outcome for
some. This field, however, still remains an area begging for a better understanding of the
optimum management of these devastating and often fatal tumors.

In the early days of pediatric oncology Wilms tumor in its early stages was cured with
surgery followed by radiation therapy. The diagnosis was made with an intravenous
pyelogram and inferior venocavogram and chest radiography was employed to detect
pulmonary metastases. The diagnosis and extent of disease were better defined when CT of
the abdomen and chest became available. The development of the clinicopathological
staging system and the more accurate definition of the histology into favorable and
unfavorable histologic types, allowed for more focused treatment with radiation and
multiple chemotherapy agents, for different stages and histology of Wilms tumor, resulting
in the excellent outcomes observed today. The success of the National Wilms Tumor Study
Group (NWTSG), more than any other effort, provided the model for cooperative group
therapeutic cancer trials, which in large measure have been responsible for advances in
treatment of Wilms tumor.

The diagnosis of neuroblastoma and its differentiation histologically from other round blue
cell tumors such as rhabdomyosarcoma, Ewing sarcoma and non-Hodgkin lymphoma was
difficult before neurone-specific enolase cytochemical staining, Shimada histopathology
classification, N-myc gene status, VMA and HVA determinations and MIBG scintigraphy
were introduced. In the future, new molecular approaches will offer diagnostic tools to
provide even greater precision for diagnosis. The existing markers coupled with a staging
system have enabled neuroblastoma to be assigned to various risk group categories with
specific multimodality treatment protocols for each risk group which has improved the
prognosis in this disease. Improvements in diagnostic radiology determining extent of
disease and modern surgical techniques have enhanced the advances in chemotherapy in
this condition. However, despite all the advances that have occurred, disseminated
neuroblastoma still has a poor prognosis.

Major advances have occurred in rhabdomyosarcoma treatment over the years. Early on
treatment of this disease was characterized by mutilating surgery including amputation and
a generally poor outcome. More accurate histologic diagnosis, careful staging, judicious
surgery, combination chemotherapy and radiotherapy have all contributed a great deal to
the improved cure rates with significantly less disability.

Malignant bone tumors had a terrible prognosis. They were generally treated by amputation
of the limb with the primary tumor; however, this was usually followed by pulmonary
metastases and death. The major advance in the treatment of this disease came with the use of high-dose methotrexate and leukovorin rescue which, coupled with limb salvage treatment, has resulted in improved survival and quality-of-life outcomes.

The advances in the treatment of hepatoblastoma were made possible by safer anesthesia, more radical surgery, intensive postoperative management together with multiagent chemotherapy and more recently the increased use of liver transplantation. These advances have allowed many patients to be cured compared to past years.

Histiocytosis is a disease that has undergone many name changes from Letter-Siwe disease, Hand-Schüller-Christian disease and Eosinophilic Granuloma to the realization that these entities are one disease, re-named histiocytosis X (to include all three entities) to its present name of Langerhans Cell Histiocytosis (LCH) due to the realization that these entities have one pathognomonic pathologic feature that is the immunohistochemical presence of Langerhans cells defined in part by expression of CD1a or langerin (CD207), which induces the formation of Birbeck granules. Advances have occurred in the management of this disease by an appreciation of risk stratification depending on number and type of organs involved in this disease process as well as by early response to therapy. Once this was established, systemic therapy was developed for the various risk groups which led to appropriate and improved therapy with better overall results.

Until a final prevention or cure for cancer in children is at hand, hematopoietic stem cell transplantation must be viewed as a major advance. Improved methods for tissue typing, the use of umbilical and peripheral blood stem cells, improved preparative regimens, including intensity-reduced approaches and better management of graft-versus-host disease has made this an almost routine treatment modality for many metabolic disorders, hemoglobinopathies and malignant diseases following ablative chemotherapy in chemotherapy-sensitive tumors. Post-transplantation support with antibiotic, antifungal, antiviral, hematopoietic growth factors and judicious use of blood component therapy has made this procedure safer than it was in years gone by.

The recognition of severe and often permanent damage to organs and life-threatening complications from chemotherapy and radiation therapy has, over the years, led to regimens consisting of combination chemotherapy at reduced doses and reduction in dose and field of radiation with improved outcome. An entire new scientific discipline, Survivorship, has arisen because of the near 80% overall cure rate for childhood cancer. Focusing on the improvement of the quality of life of survivors coupled with research in this new discipline gives hope that many of the remaining long-term effects of cancer chemotherapy in children will be mitigated and possibly eliminated.

Major advances have occurred in the management of chemotherapy-induced vomiting and pain management because of the greater recognition and attention to these issues and the
discovery of many new, effective drugs to deal with these symptoms. The availability of symptom control and palliative care has provided a degree of comfort for children undergoing chemotherapy, radiation and surgery that did not exist only a few years ago.

Hematologist-oncologists today are privileged to practice their specialty in an era in which most oncologic diseases in children are curable and at a time when national and international cooperative groups are making major advances in the management of these diseases and when basic research is at the threshold of making major breakthroughs. The present practice is grounded in evidence-based research that has been and is still being performed by hematologist-oncologists and researchers that form the foundation for ongoing advances. Today we stand on the shoulders of others, which permits us to see future advances unfold to benefit generations of children. While we bask in the glory of past achievements, we should always be cognizant that much work remains to be done until the permanent cure of all childhood malignancies and blood diseases is at hand.

This book encompasses the advances in the management of childhood cancer which have been accomplished to date and which have become the standard of care.

Philip Lanzkowsky, M.B., Ch.B., M.D.,
Preface to the Fifth Edition

The fifth edition of the Manual of Pediatric Hematology and Oncology differs considerably from previous editions but has retained the original intent of the author to offer a concise manual of predominantly clinical material culled from personal experience and to be an immediate reference for the diagnosis and management of hematologic and oncologic diseases. I have resisted succumbing to the common tendency of writing a comprehensive tome which is not helpful to the practicing hematologist-oncologist at the bedside. The book has remained true to its original intent.

The information included at all times keeps “the eye on the ball” to ensure that pertinent, up-to-date, practical clinical advice is presented without extraneous information, however interesting or pertinent this information may be in a different context.

The book differs from previous editions in many respects. The number of contributors has been considerably expanded drawing on the expertise of leaders in different subjects from various institutions in the United States. Increased specialization within the field of hematology and oncology has necessitated including this large a number of contributors in order to bring to the reader balanced and up-to-date information for the care of patients. In addition, the number of chapters has increased from 27, in the previous edition, to 33. The reason for this is that many of the chapters, such as hemolytic anemia and coagulation, had become so large and the subject so extensive that they were better handled by subdividing the chapter into a number of smaller chapters. An additional chapter on the psychosocial aspects of cancer for children and their families, not present in previous editions, has been added.

Some chapters have been extensively revised and re-written where advancement in knowledge has dictated this approach, e.g., Hodgkin lymphoma, neuroblastoma and rhabdomyosarcoma and other soft-tissue sarcomas, whereas other chapters have been only slightly modified. In nearly all the chapters there has been significant change in the management and treatment section reflecting advances that have occurred in these areas.

This edition has retained the essential format written and developed decades ago by the author and, with usage over the years, has proven to be highly effective as a concise, practical, up-to-date guide replete with detailed tables, algorithms and flow diagrams for
investigation and management of hematologic and oncologic conditions. The tables and
flow diagrams included in the book have been updated using the latest information and the
most recent protocols of treatment, which have received general acceptance and have
become the standard of care, have been included. In a book with so many details, errors
inevitably occur. I do not know where they are because if I did they would have been
corrected. I apologize in advance for any inaccuracies that may have crept in inadvertently.

The four previous editions of this book were published when the name of the hospital was
the Schneider Children’s Hospital. Effective April 1, 2010 the name of the hospital was
changed to the Steven and Alexandra Cohen Children’s Medical Center of New York.

I would like to acknowledge Morris Edelman, MB, BCh, B.Sc (Laboratory Medicine) for
his contribution in reviewing the pathology on Hodgkin disease.

I thank Rose Grosso for her untiring efforts in the typing and coordination of the various
phases of the development of this edition.

Philip Lanzkowsky, M.B., Ch.B., M.D.,
Preface to the Fourth Edition

This edition of the *Manual of Pediatric Hematology and Oncology* is the fourth edition and the sixth book written by the author on pediatric hematology and oncology. The first book written by the author 25 years ago was exclusively on pediatric hematology and its companion book, exclusively on pediatric oncology, was written 3 years later. The book reviewers at the time suggested that these two books be combined into a single book on pediatric hematology and oncology and the first edition of the *Manual of Pediatric Hematology and Oncology* was published by the author in 1989.

It is from these origins that this 4th edition arises – the original book written in its entirety by the author was 456 pages – has more than doubled in size. The basic format and content of the clinical manifestations, diagnosis and differential diagnosis has persisted with little change as originally written by the author. The management and treatment of various diseases have undergone profound changes over time and these aspects of the book have been brought up-to-date by the subspecialists in the various disease entities. The increase in the size of the book is reflective of the advances that have occurred in both hematology and oncology over the past 25 years. Despite the size of the book, the philosophy has remained unchanged over the past quarter century. The author and his contributors have retained this book as a concise manual of personal experiences on the subject over these decades rather than developing a comprehensive tome culled from the literature. Its central theme remains clinical as an immediate reference for the practicing pediatric hematologist-oncologist concerned with the diagnosis and management of hematologic and oncologic diseases. It is extremely useful for students, residents, fellows and pediatric hematologists and oncologists as a basic reference assembling in one place, essential knowledge required for clinical practice.

This edition has retained the essential format written and developed decades ago by the author and, with usage over the years, has proven to be highly effective as a concise, practical, up-to-date guide replete with detailed tables, algorithms and flow diagrams for investigation and management of hematologic and oncologic conditions. The tables and flow diagrams have been updated with the latest information and the most recent protocols of treatment, that have received general acceptance and have produced the best results, have been included in the book.
Since the previous edition, some five years ago, there have been considerable advances particularly in the management of oncologic disease in children and these sections of the book have been completely rewritten. In addition, advances in certain areas have required that other sections of the book be updated. There has been extensive revision of certain chapters such as on Diseases of the White Cells, Lymphoproliferative Disorders, Myeloproliferative Disorders and Myelodysplastic Syndromes and Bone Marrow Failure. Because of the extensive advances in thrombosis we have rewritten that entire section contained in the chapter on Disorders of Coagulation to encompass recent advances in that area. The book, like its previous editions, reflects the practical experience of the author and his colleagues based on half a century of clinical experience. The number of contributors has been expanded but consists essentially of the faculty of the Division of Hematology Oncology at the Schneider Children’s Hospital, all working together to provide the readers of the manual with a practical guide to the management of the wide spectrum of diseases within the discipline of pediatric hematology-oncology.

I would like to thank Laurie Locastro for her editorial assistance, cover design and for her untiring efforts in the coordination of the various phases of the production of this edition. I also appreciate the efforts of Lawrence Tavnier for his expert typing of parts of the manuscript and would like to thank Elizabeth Dowling and Patrician Mastrolembo for proof reading of the book to ensure its accuracy.

Philip Lanzkowsky, M.B., Ch.B., M.D.,
This edition of the Manual of Pediatric Hematology and Oncology, published five years after the second edition, has been written with the original philosophy in mind. It presents the synthesis of experience of four decades of clinical practice in pediatric hematology and oncology and is designed to be of paramount use to the practicing hematologist and oncologist. The book, like its previous editions, contains the most recent information from the literature coupled with the practical experience of the author and his colleagues to provide a guide to the practicing clinician in the investigation and up-to-date treatment of hematologic and oncologic diseases in childhood.

The past five years have seen considerable advances in the management of oncologic diseases in children. Most of the advances have been designed to reduce the immediate and long-term toxicity of therapy without influencing the excellent results that have been achieved in the past. This has been accomplished by reducing dosages, varying the schedules of chemotherapy, and reducing the field and volume of radiation.

The book is designed to be a concise, practical, up-to-date guide and is replete with detailed tables, algorithms, and flow diagrams for investigation and management of hematologic and oncologic conditions. The tables and flow diagrams have been updated with the latest information, and the most recent protocols that have received general acceptance and have produced the best results have been included in the book.

Certain parts of the book have been totally rewritten because our understanding of the pathogenesis of various diseases has been altered in the light of modern biological investigations. Once again, we have included only those basic science advances that have been universally accepted and impinge on clinical practice.

I thank Ms. Christine Grabowski, Ms. Lisa Phelps, Ms. Ellen Healy and Ms. Patricia Mastrolembo for their untiring efforts in the coordination of the writing and various phases of the development of this edition. Additionally, I acknowledge our fellows, Drs. Banu Aygun, Samuel Bangug, Mahmut Celiker, Naghma Husain, Youssef Khabbase, Stacey Rifkin-Zenenberg, and Rosa Ana Gonzalez, for their assistance in culling the literature.
I also thank Dr. Bhoomi Mehrotra for reviewing the chapter on bone marrow transplantation, Dr. Lorry Rubin for reviewing the sections of the book dealing with infection, and Dr. Leonard Kahn for reviewing the pathology.

Philip Lanzkowsky, M.B., Ch.B., M.D.,
Preface to the Second Edition

This edition of the *Manual of Pediatric Hematology and Oncology*, published five years after the first edition, has been written with a similar philosophy in mind. The basic objective of the book is to present useful clinical information from the recent literature in pediatric hematology and oncology and to temper it with experience derived from an active clinical practice.

The manual is designed to be a concise, practical, up-to-date book for practitioners responsible for the care of children with hematologic and oncologic diseases by presenting them with detailed tables and flow diagrams for investigation and clinical management.

Since the publication of the first edition, major advances have occurred, particularly in the management of oncologic diseases in children, including major advances in recombinant human growth factors and bone marrow transplantation. We have included only those basic science advances that have been universally accepted and impinge on clinical practice.

I would like to thank Dr. Raj Pahwa for his contributions on bone marrow transplantation, Drs. Alan Diamond and Leora Lanzkowsky-Diamond for their assistance with the neuro-radiology section, and Christine Grabowski and Lisa Phelps for their expert typing of the manuscript and for their untiring assistance in the various phases of the development of this book.

Philip Lanzkowsky, M.B., Ch.B., M.D.,
Preface to the First Edition

The Manual of Pediatric Hematology and Oncology represents the synthesis of personal experience of three decades of active clinical and research endeavors in pediatric hematology and oncology. The basic orientation and intent of the book is clinical, and the book reflects a uniform systematic approach to the diagnosis and management of hematologic and oncologic diseases in children. The book is designed to cover the entire spectrum of these diseases, and although emphasis is placed on relatively common disorders, rare disorders are included for the sake of completion. Recent developments in hematology-oncology based on pertinent advances in molecular genetics, cytogenetics, immunology, transplantation, and biochemistry are included if the issues have proven value and applicability to clinical practice.

Our aim in writing this manual was to cull pertinent and useful clinical information from the recent literature in pediatric hematology and oncology and to temper it with experience derived from active clinical practice. The result, we hope, is a concise, practical, readable, up-to-date book for practitioners responsible for the care of children with hematologic and oncologic diseases. It is specifically designed for the medical student and practitioner seeking more detailed information on the subject, the pediatric house officer responsible for the care of patients with these disorders, the fellow in pediatric hematology-oncology seeking a systemic approach to these diseases and a guide in preparation for the board examinations, and the practicing pediatric hematologist-oncologist seeking another opinion and approach to these disorders. As with all brief texts, some dogmatism and “matters of opinion” have been unavoidable in the interests of clarity. The opinions expressed on management are prudent clinical opinions; and although they may not be accepted by all, pediatric hematologists-oncologists will certainly find a consensus. The reader is presented with a consistency of approach and philosophy describing the management of various diseases rather than with different managements derived from various approaches described in the literature. Where there are divergent or currently unresolved views on the investigation or management of a particular disease, we have attempted to state our own opinion and practice so as to provide some guidance rather than to leave the reader perplexed.

The manual is not designed as a tome containing the minutiae of basic physiology, biochemistry, genetics, molecular biology, cellular kinetics, and other esoteric and abstruse
detail. These subjects are covered extensively in larger works. Only those basic science advances that impinge on clinical practice have been included here. Each chapter stresses the pathogenesis, pathology, diagnosis, differential diagnosis, investigations, and detailed therapy of hematologic and oncologic diseases seen in children.

I would like to thank Ms. Joan Dowdell and Ms. Helen Witkowski for their expert typing and for their untiring assistance in the various phases of the development of this book.

Philip Lanzkowsky, M.D.,
F.R.C.P., D.C.H., F.A.A.P.
Anemia can be defined as a reduction in hemoglobin concentration, hematocrit, or number of red blood cells per cubic millimeter. The lower limit of the normal range is set at two standard deviations below the mean for age and sex for the normal population.*

The first step in diagnosis of anemia is to establish whether the abnormality is isolated to a single cell line (red blood cells only) or whether it is part of a multiple cell line abnormality (red cells, white cells and platelets). Abnormalities of two or three cell lines usually indicate one of the following:

- bone marrow involvement, (e.g., aplastic anemia, leukemia), or
- an immunologic disorder (e.g., connective tissue disease or immunoneutropenia, idiopathic thrombocytopenic purpura [ITP] or immune hemolytic anemia singly or in combination) or
- sequestration of cells (e.g., hypersplenism).

Table 1-1 presents an etiologic classification of anemia and the diagnostic features in each case. The blood smear is very helpful in the diagnosis of anemia. It establishes whether the anemia is hypochromic, microcytic, normocytic, macrocytic or shows specific morphologic abnormalities suggestive of red cell membrane disorders (e.g., spherocytes, stomatocytosis or elliptocytosis) or hemoglobinopathies (e.g. sickle cell disease, thalassemia).

The mean corpuscular volume (MCV) confirms the findings on the smear with reference to the red cell size, e.g., microcytic (<70 fl), macrocytic (>85 fl) or normocytic (72–79 fl). Figure 1-1 delineates diagnosis of anemia by examination of the smear and Table 1-2 lists the differential diagnostic considerations based on specific red cell morphologic abnormalities. The mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are calculated values and generally of less diagnostic

*Children with cyanotic congenital heart disease, respiratory insufficiency, arteriovenous pulmonary shunts or hemoglobinopathies that alter oxygen affinity can be functionally anemic with hemoglobin levels in the normal range.
Table 1-1  Etiologic Classification and Major Diagnostic Features of Anemia in Children

<table>
<thead>
<tr>
<th>Etiologic Classification</th>
<th>Diagnostic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Impaired red cell formation</td>
<td></td>
</tr>
<tr>
<td>A. Deficiency</td>
<td></td>
</tr>
<tr>
<td>Decreased dietary intake</td>
<td>Hypochromic, microcytic red cells; low MCV, low MCH, low MCHC, high RDW, low serum ferritin, high FEP, guaiac positivity</td>
</tr>
<tr>
<td>e.g., excessive cows’ milk</td>
<td></td>
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<tr>
<td>(iron-deficiency anemia), vegan</td>
<td></td>
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<tr>
<td>Increased demand, e.g., Growth (iron)</td>
<td></td>
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<tr>
<td>hemolysis (folic acid)</td>
<td></td>
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<tr>
<td>Decreased absorption</td>
<td></td>
</tr>
<tr>
<td>Specific: intrinsic factor lack (Vitamin B&lt;sub&gt;12&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td>Generalized: malabsorption syndrome (e.g., folic acid, iron)</td>
<td></td>
</tr>
<tr>
<td>Increased loss</td>
<td></td>
</tr>
<tr>
<td>Acute: hemorrhage (iron)</td>
<td></td>
</tr>
<tr>
<td>Chronic: gut bleeding (iron)</td>
<td></td>
</tr>
<tr>
<td>Impairment in red cell formation can result from one of the following deficiencies:</td>
<td></td>
</tr>
<tr>
<td>1. Iron deficiency</td>
<td></td>
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<tr>
<td>2. Folate deficiency</td>
<td></td>
</tr>
<tr>
<td>Macrocystic red cells, high MCV, high RDW, megaloblastic marrow, low serum and red cell folate</td>
<td></td>
</tr>
<tr>
<td>3. Vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency</td>
<td></td>
</tr>
<tr>
<td>Macrocystic red cells, high MCV, high RDW, megaloblastic marrow, low serum B&lt;sub&gt;12&lt;/sub&gt;, decreased gastric acidity; Schilling test positive</td>
<td></td>
</tr>
<tr>
<td>4. Vitamin C deficiency</td>
<td>Clinical scurvy</td>
</tr>
<tr>
<td>5. Protein deficiency</td>
<td>Kwashiorkor</td>
</tr>
<tr>
<td>6. Vitamin B&lt;sub&gt;6&lt;/sub&gt; deficiency</td>
<td>Hypochromic red cells, sideroblastic bone marrow, high serum ferritin</td>
</tr>
<tr>
<td>7. Thyroxine deficiency</td>
<td>Clinical hypothyroidism, low T&lt;sub&gt;4&lt;/sub&gt;, high TSH</td>
</tr>
<tr>
<td>B. Bone marrow failure</td>
<td></td>
</tr>
<tr>
<td>1. Failure of a single cell line</td>
<td></td>
</tr>
<tr>
<td>a. Megakaryocytes</td>
<td></td>
</tr>
<tr>
<td>(1) Amegakaryocytic thrombocytopenic purpura with absent radii (TAR)</td>
<td>Limb abnormalities, thrombocytopenic purpura absent megakaryocytes</td>
</tr>
<tr>
<td>b. Red cell precursors</td>
<td></td>
</tr>
<tr>
<td>(1) Congenital red cell aplasia</td>
<td>Absent red cell precursors</td>
</tr>
<tr>
<td>(Diamond–Blackfan anemia)</td>
<td></td>
</tr>
<tr>
<td>(2) Acquired red cell aplasia (transient erythroblastopenia of childhood – TEC)</td>
<td>Absent red cell precursors</td>
</tr>
<tr>
<td>c. White cell precursors</td>
<td></td>
</tr>
<tr>
<td>(1) Congenital neutropenias</td>
<td>Neutropenia, recurrent infection</td>
</tr>
</tbody>
</table>

(Continued)