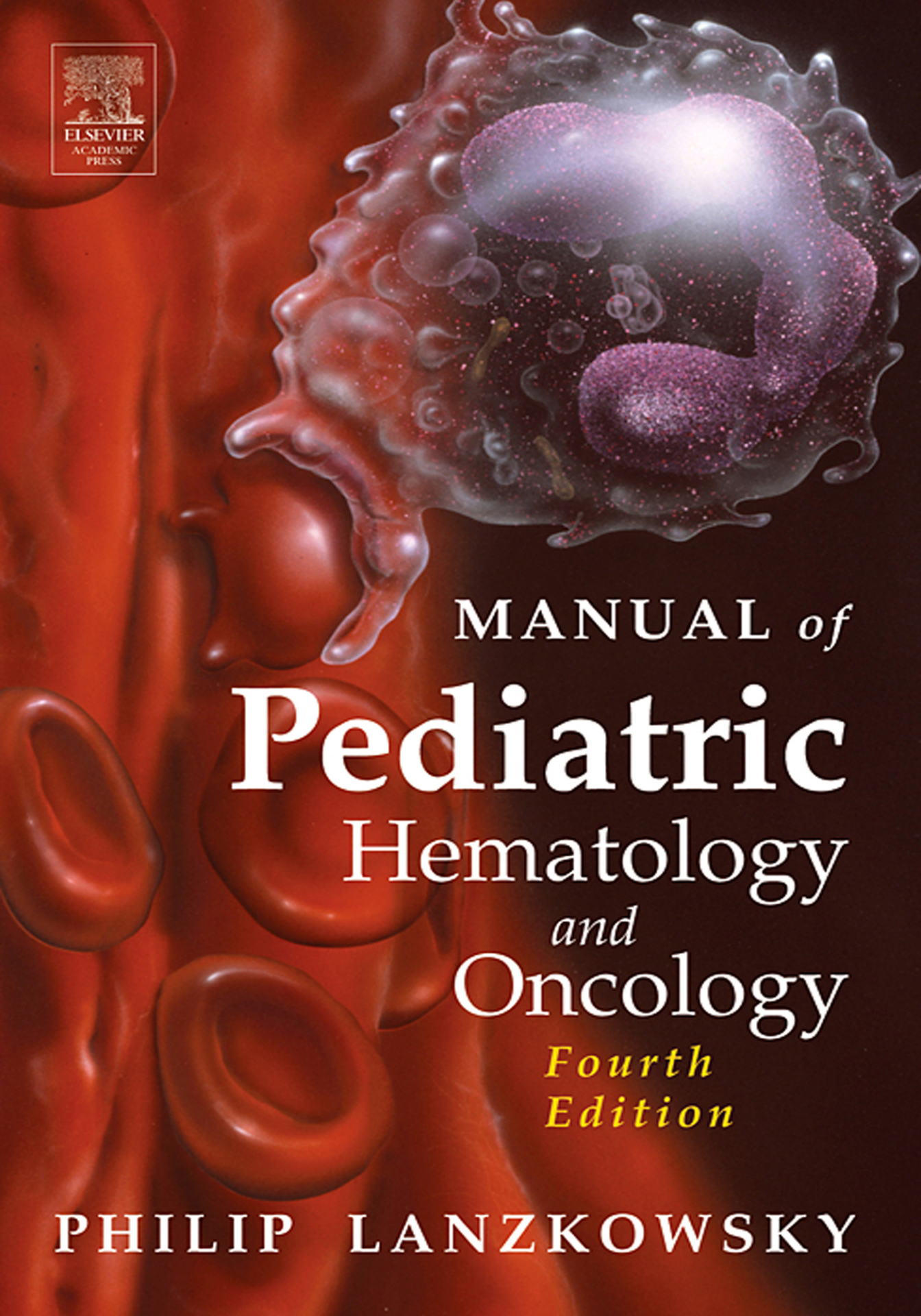
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MANUAL of
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PHILIP LANZKOWSKY

MANUAL OF

Pediatric Hematology AND Oncology

FOURTH EDITION

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MANUAL OF
Pediatric Hematology AND Oncology
FOURTH EDITION

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Elsevier Academic Press
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
84 Theobald's Road, London WC1X 8RR, UK

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Library of Congress Cataloging-in-Publication Data
Lanzkowsky, Philip, 1932-
Manual of pediatric hematology and oncology / Philip Lanzkowsky. – 4th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-12-088524-7 (alk. paper)
1. Pediatric hematology–Handbooks, manuals, etc. 2. Tumors in children–Handbooks, manuals, etc.
[DNLM: 1. Hematologic Diseases–Child. 2. Hematologic Diseases–Infant. 3. Neoplasms–Child. 4. Neoplasms–Infant. WS 300 L297m 2005] I. Title.
RJ411.L35 2005
618.92'15–dc22 2004027550

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 0-12-088524-7

For all information on all Academic Press publications
visit our Web site at www.academicpress.com

Printed in the United States of America
05 06 07 08 09 9 8 7 6 5 4 3 2 1

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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, and Alex Lanzkowsky;
Leora and Alan – Chloe Hannah, Justin Noah, and Jared Isaac Diamond;
Marc and 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 4, which lists the pharmacologic properties and synonyms of the commonly used chemotherapy agents.

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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 Disorders 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 it's 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 this 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 Patricia Mastrolembo for proof reading of the book to ensure its accuracy.

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PREFACE TO THE THIRD EDITION

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 represents 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 Khabbaze, 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.

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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.

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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 the 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.

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1

CLASSIFICATION AND DIAGNOSIS OF ANEMIA DURING CHILDHOOD

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.*

When a patient presents with anemia, it is important 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, or macrocytic and it also 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, for example, 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 value. The MCH usually parallels the MCV. The MCHC is a measure of cellular hydration status. A high value (>35 g/dL) is characteristic of spherocytosis and a low value is commonly associated with iron deficiency.

The MCV and reticulocyte count are helpful in the differential diagnosis of anemia (Figure 1-2). An elevated reticulocyte count suggests chronic blood loss or hemolysis; a normal or depressed count suggests impaired red cell formation.

*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

Etiologic classification	Diagnostic features
I. Impaired red cell formation	
A. Deficiency	
Decreased dietary intake (e.g., excessive milk-iron-deficiency anemia, vegan-vitamin B_{12} deficiency	
Increased demand, e.g., growth (iron) hemolysis (folic acid)	
Decreased absorption	
Specific: intrinsic factor lack (Vitamin B_{12})	
Generalized: malabsorption syndrome (e.g., folic acid, iron)	
Increased loss	
Acute: hemorrhage (iron)	
Chronic: gut bleeding (iron)	
Impairment in red cell formation can result from one of the following deficiencies:	
1. Iron deficiency	Hypochromic, microcytic red cells; low MCV, low MCH, low MCHC, high RDW[a], low serum ferritin, high FEP, guaiac positivity
2. Folate deficiency	Macrocytic red cells, high MCV, high RDW, megaloblastic marrow, low serum and red cell folate
3. Vitamin B_{12} deficiency	Macrocytic red cells, high MCV, high RDW, megaloblastic marrow, low serum B_{12} decreased gastric acidity; Schilling test positive
4. Vitamin C deficiency	Clinical scurvy
5. Protein deficiency	Kwashiorkor
6. Vitamin B_6 deficiency	Hypochromic red cells, sideroblastic bone marrow, high serum ferritin
7. Thyroxine deficiency	Clinical hypothyroidism, low T_4, high TSH
B. Bone marrow failure	
1. Failure of a single cell line	
a. Megakaryocytes[b]	
(1) Amegakaryocytic thrombocytopenic purpura with absent radii (TAR)	Limb abnormalities, thrombocytopenic purpura absent megakaryocytes
b. Red cell precursors	
(1) Congenital red cell aplasia (Diamond–Blackfan anemia)	Absent red cell precursors
(2) Acquired red cell aplasia (transient erythroblastopenia of childhood)	Absent red cell precursors
c. White cell precursors[b]	
(1) Congenital neutropenia	Neutropenia, recurrent infection

(Continues)

Table 1-1. (*Continued*)

Etiologic classification	Diagnostic features
2. Failure of all cell lines (characterized by pancytopenia and acellular or hypocellular marrow)	
a. Constitutional	
(1) Fanconi anemia	Multiple congenital anomalies, chromosomal breakage
(2) Familial without anomalies	Familial history, no congenital anomalies
(3) Dyskeratosis congenita	Marked mucosal and cutaneous abnormalities
b. Acquired	
(1) Idiopathic	No identifiable cause
(2) Secondary	History of exposure to drugs, radiation, household toxins, infections; associated immunologic disease
3. Infiltration	
a. De novo (e.g., leukemia)	Bone marrow: morphology, cytochemistry, immunologic markers, cytogenetics
b. Secondary (e.g., neuroblastoma, lymphoma)	VMA, skeletal survey, bone marrow
c. Dyshematopoietic anemia (decreased erythropoiesis, decreased iron utilization)	
(1) Infection	Evidence of systemic illness
(2) Renal failure and hepatic disease	BUN and liver function tests
(3) Disseminated malignancy	Clinical evidence
(4) Connective tissue diseases	Rheumatoid arthritis
II. Blood loss	Overt or occult guaiac positive
III. Hemolytic anemia	
A. Corpuscular	Splenomegaly, jaundice
1. Membrane defects (spherocytosis, elliptocytosis)	Morphology, osmotic fragility
2. Enzymatic defects (pyruvate kinase, G6PD)	Autohemolysis, enzyme assays
3. Hemoglobin defects	
a. Heme	
b. Globin	
(1) Qualitative (e.g., sickle cell)	Hb electrophoresis
(2) Quantitative (e.g., thalassemia)	HbF, A_2 content
B. Extracorpuscular	
1. Immune	Coombs' test
a. Isoimmune	
b. Autoimmune	
(1) Idiopathic	Coombs' test, antibody identification

(Continues)

Table 1-1. (*Continued*)

Etiologic classification	Diagnostic features
(2) Secondary	
Immunologic disorder (e.g., lupus)	Decreased C_3, C_4, CH_{50} positive ANA
One cell line (e.g., red cells)	Anemia: Coombs' positive
Multiple cell line (e.g., white blood cells, platelets)	Neutropenia-immunoneutropenia, thrombocytopenia-ITP
2. Nonimmune (idiopathic, secondary)	

Abbreviations: FEP, free erythrocyte protoporphyrin; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; ITP, idiopathic thrombocytopenic purpura; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red cell distribution width (see definition in footnote a); VMA, vanillylmandelic acid.

[a] RDW = coefficient of variation of the RBC distribution width (normal between 11.5% and 14.5%).

[b] Not associated with anemia.

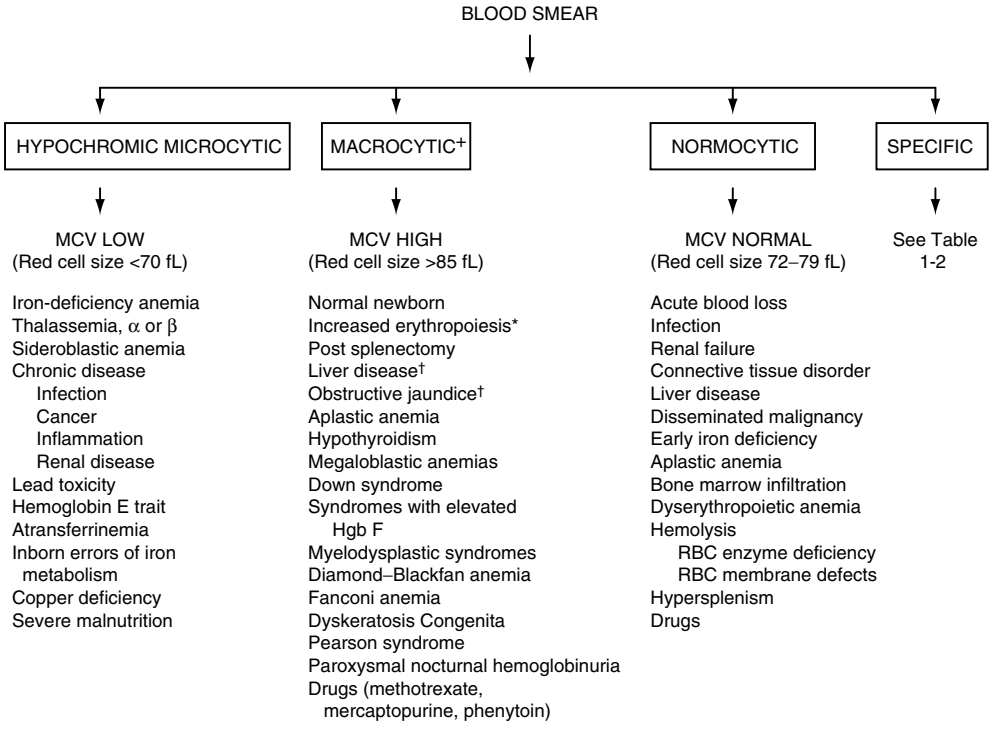

Fig. 1-1. An approach to the diagnosis of anemia by examination of the blood smear.
+Spurious macrocytosis (high MCV) may be caused by macroagglutinated red cells (e.g., *Mycoplasma pneumonia* and autoimmune hemolytic anemia).
*Increased number of reticulocytes.
†On the basis of increased membrane, resulting in an increased membrane/volume ratio. Increased membrane results from exchanges between red cell lipids and altered lipid balance in these conditions.

Table 1-2. Specific Red Cell Morphologic Abnormalities

I. Target cells
Increased surface/volume ratio
- Thalassemia
- Hemoglobinopathies
  - Hb AC or CC
  - Hb SS, SC, S-Thal
- Liver disease
- Postsplenectomy or hyposplenic states
- Severe iron deficiency
- Hb E (heterozygote and homozygote)
- LCAT deficiency: congenital disorder of lecithin/cholesterol acyltransferase deficiency (corneal opacifications, proteinuria, target cells, moderately severe anemia)
- Abetalipoproteinemia

II. Spherocytes
Decreased surface/volume ratio, hyperdense (>MCHC)
- Hereditary spherocytosis
- ABO incompatibility: antibody-coated fragment of RBC membrane removed
- Autoimmune hemolytic anemia: antibody-coated fragment of RBC membrane removed
- Microangiopathic hemolytic anemia (MAHA): fragment of RBC lost after impact with abnormal surface
- SS disease: fragment of RBC removed in reticuloendothelial system
- Hypersplenism
- Burns: fragment of damaged RBC removed by spleen
- Posttransfusion
- Pyruvate kinase deficiency
- Water-dilution hemolysis: fragment of damaged RBC removed by spleen

III. Acanthocytes (spur cells)*
Cells with 5–10 spicules of varying length; spicules irregular in space and thickness, with wide bases; appear smaller than normal cells because they assume a spheroid shape
- Liver disease
- Disseminated intravascular coagulation (and other MAHA)
- Postsplenectomy or hyposplenic state
- Vitamin E deficiency
- Hypothyroidism
- Abetalipoproteinemia: rare congenital disorder; 50–100% of cells acanthocytes; associated abnormalities (fat malabsorption, retinitis pigmentosa, neurologic abnormalities)
- Malabsorptive states

IV. Echinocytes (burr cells)*
10–30 spicules equal in size and evenly distributed over RBC surface; caused by alteration in extracellular or intracellular environment
- Artifact
- Renal failure
- Dehydration
- Liver disease
- Pyruvate kinase deficiency
- Peptic ulcer disease or gastric carcinoma
- Immediately after red cell transfusion
- Rare congenital anemias due to decreased intracellular potassium

*May be morphologically indistinguishable

(Continues)

Table 1-2. (*Continued*)

V. Pyknocytes*
Distorted, hyperchromic, contracted RBC; can be similar to echinocytes and acanthocytes

VI. Schistocytes
Helmet, triangular shapes, or small fragments. Caused by fragmentation on impact with abnormal vascular surface (e.g., fibrin strand, vasculitis, artificial surface in circulation)
- Disseminated intravascular coagulation (DIC)
- Severe hemolytic anemia (e.g., G6PD deficiency)
- Microangiopathic hemolytic anemia
- Hemolytic uremic syndrome
- Prosthetic cardiac valve, abnormal cardiac valve, cardiac patch, coarctation of the aorta
- Connective tissue disorder (e.g., SLE)
- Kasabach–Merritt syndrome
- Purpura fulminans
- Renal vein thrombosis
- Burns (spheroschistocytes as a result of heat)
- Thrombotic thrombocytopenia purpura
- Homograft rejection
- Uremia, acute tubular necrosis, glomerulonephritis
- Malignant hypertension
- Systemic amyloidosis
- Liver cirrhosis
- Disseminated carcinomatosis
- Chronic relapsing schistocytic hemolytic anemia

VII. Elliptocytes
Elliptical cells, normochromic; seen normally in less than 1% of RBCs; larger numbers occasionally seen in a normal patient
- Hereditary elliptocytosis
- Iron deficiency (increased with severity, hypochromic)
- SS disease
- Thalassemia major
- Severe bacterial infection
- SA trait
- Leukoerythroblastic reaction
- Megaloblastic anemias
- Any anemia may occasionally present with up to 10% elliptocytes
- Malaria

VIII. Teardrop cells
Shape of drop, usually microcytic, often also hypochromic
- Newborn
- Thalassemia major
- Leukoerythroblastic reaction
- Myeloproliferative syndromes

IX. Stomatocytes
Has a slit-like area of central pallor
- Normal (in small numbers)
- Hereditary stomatocytosis
- Artifact
- Thalassemia

*May be morphologically indistinguishable

(Continues)

Table 1-2. (*Continued*)

Acute alcoholism
Rh null disease (absence of Rh complex)
Liver disease
Malignancies

X. Nucleated red blood cells
Not normal in the peripheral blood beyond the first week of life
Newborn (first 3–4 days)
Intense bone marrow stimulation
Hypoxia (especially postcardiac arrest)
Acute bleeding
Severe hemolytic anemia (e.g., thalassemia, SS hemoglobinopathy)
Congenital infections (e.g., sepsis, congenital syphilis, CMV, rubella)
Postsplenectomy or hyposplenic states: spleen normally removes nucleated RBC
Leukoerythroblastic reaction: seen with extramedullary hematopoiesis and bone marrow replacement; most commonly leukemia or solid tumor—fungal and mycobacterial infection may also do this; leukoerythroblastic reaction is also associated with teardrop red cells, 10,000–20,000 WBC with small to moderate numbers of metamyelocytes, myelocytes, and promyelocytes; thrombocytosis with large bizarre platelets
Megaloblastic anemia
Dyserythropoietic anemias

XI. Blister cells
Red cell area under membrane, free of hemoglobin, appearing like a blister
G6PD deficiency (during hemolytic episode)
SS disease
Pulmonary emboli

XII. Basophilic stippling
Coarse or fine punctate basophilic inclusions that represent aggregates of ribosomal RNA
Hemolytic anemias (e.g., thalassemia trait)
Iron-deficiency anemia
Lead poisoning
Pyrimidine 5′-nucleotidase deficiency

XIII. Howell–Jolly bodies
Small, well-defined, round, densely stained nuclear-remnant inclusions; 1 μm in diameter; centric in location
Postsplenectomy or hyposplenia
Newborn
Megaloblastic anemias
Dyserythropoietic anemias
A variety of types of anemias (rarely iron-deficiency anemia, hereditary spherocytosis)

XIV. Cabot's Ring bodies
Nuclear remnant ring configuration inclusions
Pernicious anemia
Lead toxicity

XV. Heinz bodies
Denatured aggregated hemoglobin
Thalassemia
Asplenia
Chronic liver disease
Heinz-body hemolytic anemia

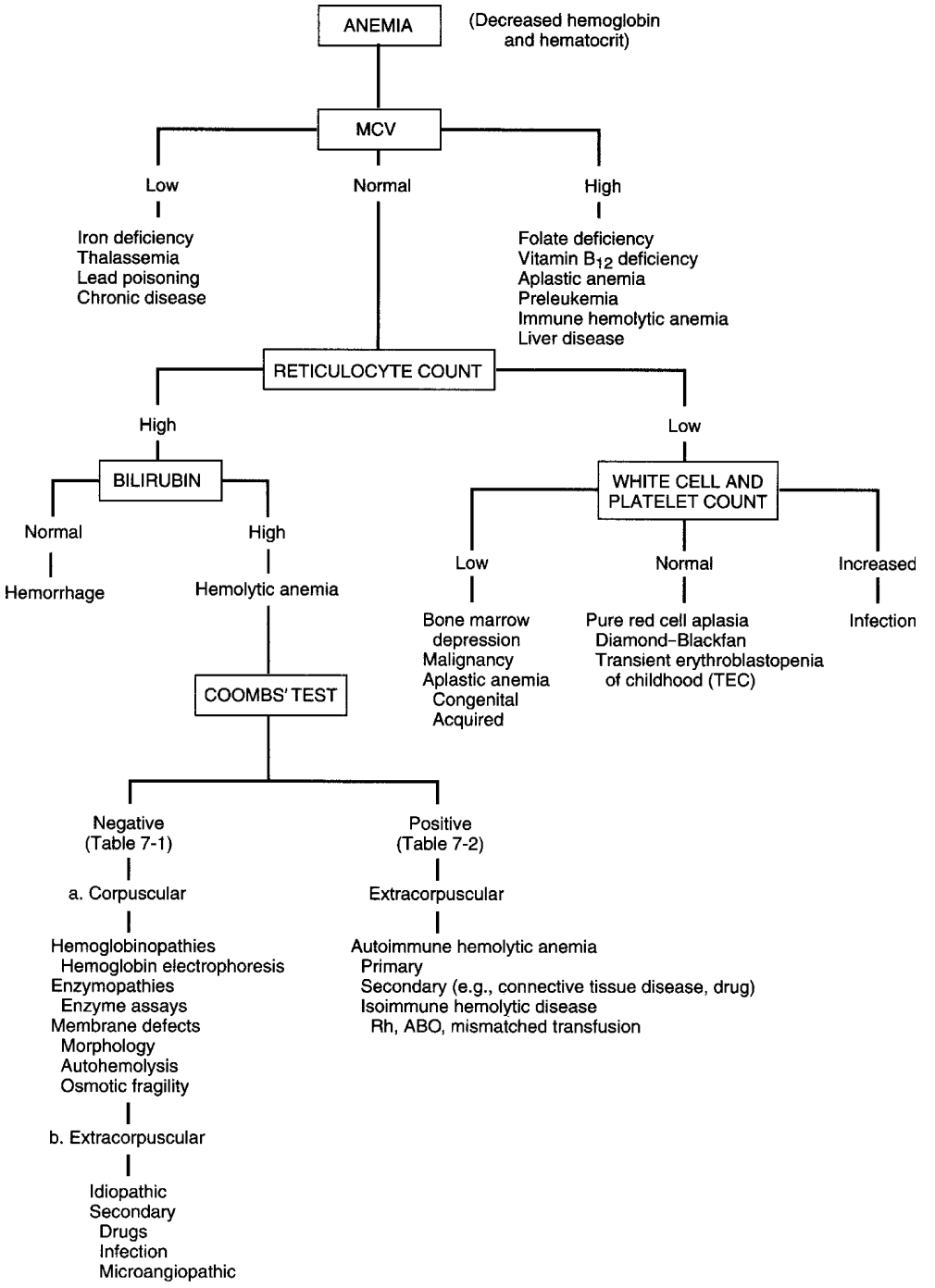

Fig. 1-2. Approach to the diagnosis of anemia by MCV and reticulocyte count.

The reticulocyte count must be adjusted for the level of anemia to obtain the reticulocyte index,* a more accurate reflection of erythropoiesis. In patients with bleeding or hemolysis, the reticulocyte index should be at least 3%, whereas in patients with anemia due to decreased production of red cells, the reticulocyte index is less than 3% and frequently less than 1.5%.

Mean corpuscular volume and red cell distribution width (RDW) indices, available from automated electronic blood-counting equipment, are extremely helpful in defining the morphology and the nature of the anemia and have led to a classification based on these indices (Table 1-3).

In more refractory cases of anemia, bone marrow examination may be indicated. A bone marrow smear should be stained for iron, where indicated, to estimate iron stores and to diagnose the presence of a sideroblastic anemia. Bone marrow examination may indicate a normoblastic, megaloblastic, or sideroblastic morphology. Figure 1-3 presents the causes of each of these findings.

Table 1-4 lists various laboratory studies helpful in the investigation of a patient with anemia. The investigation of anemia entails the following steps:

1. Detailed history and physical examination (see Table 1-1)
2. Complete blood count, to establish whether the anemia is only due to one cell line (e.g., the red cell line only) or is part of a three-cell-line abnormality (abnormality of red cell count, white blood cell count, and platelet count)
3. Determination of the morphologic characteristics of the anemia based on blood smear (Table 1-2) and consideration of the MCV (Figures 1-1 and 1-2) and RDW (Table 1-3) and morphologic consideration of white blood cell and platelet morphology

Table 1-3. Classification of Nature of the Anemia Based on MCV and RDW

	MCV low	MCV normal	MCV high
RDW normal	Microcytic homogeneous	Normocytic homogeneous	Macrocytic homogeneous
	Heterozygous thalassemia Chronic disease	Normal Chronic disease Chronic liver disease Nonanemic hemoglobinopathy (e.g., AS, AC) Chemotherapy Chronic myelocytic leukemia Hemorrhage Hereditary spherocytosis	Aplastic anemia Preleukemia
RDW high	Microcytic heterogeneous	Normocytic heterogeneous	Macrocytic heterogeneous
	Iron deficiency S β-thalassemia Hemoglobin H Red cell fragmentation	Early iron or folate deficiency Mixed deficiencies Hemoglobinopathy (e.g., SS) Myelofibrosis Sideroblastic anemia	Folate deficiency Vitamin B_{12} deficiency Immune hemolytic anemia Cold agglutinins

Abbreviations: MCV, mean corpuscular volume; RDW, red cell distribution width, which is the coefficient of variation of RBC distribution width (normal: 11.5–14.5%).

*Reticulocyte index = reticulocyte count × (patient's hematocrit/normal hematocrit). For example, for a reticulocyte count of 6% and hematocrit of 15%, the reticulocyte index = 6 × (15/45) = 2%.

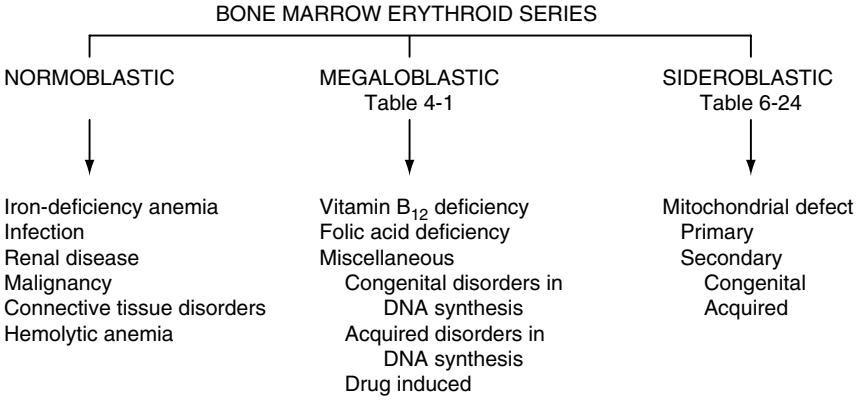

Fig. 1-3. Causes of normoblastic, megaloblastic, and sideroblastic bone marrow morphology.

Table 1-4. Laboratory Studies Often Helpful in the Investigation of a Patient with Anemia

Usual initial studies
Hemoglobin and hematocrit determination
Erythrocyte count and red cell indices, including MCV and RDW
Reticulocyte count
Study of stained blood smear
Leukocyte count and differential count
Platelet count
Suspected iron deficiency
Free erythrocyte protoporphyrin
Serum ferritin levels
Stool for occult blood
^{99m}Tc pertechnetate scan for Meckel's diverticulum—if indicated
Endoscopy (upper and lower bowel)—if indicated
Suspected vitamin B_{12} or folic acid deficiency
Bone marrow
Serum vitamin B_{12} level
Serum folate level
Gastric analysis after histamine injection
Vitamin B_{12} absorption test (radioactive cobalt) (Schilling test)
Suspected hemolytic anemia
Evidence of red cell breakdown
Blood smear
Serum bilirubin level
Urinary urobilinogen
Hemoglobinuria
Serum haptoglobin
Evidence of red cell regeneration
Reticulocyte count
Blood smear
Skeletal radiographs
Evidence of type of hemolytic anemia: corpuscular
Membrane
Blood smear
Osmotic fragility test
Autohemolysis test

(Continues)

Table 1-4. (*Continued*)

Hemoglobin
Sickle test
Hemoglobin electrophoresis
Hemoglobin F determination
Kleihauer–Betke smear
Heat-stability test
Enzymes
Enzyme assay
Evidence of type of hemolytic anemia: extracorpuscular
Immune
Antiglobulin test
Acid serum lysis test
Sucrose lysis test
Donath–Landsteiner antibody
ANA
Suspected aplastic anemia or leukemia
Bone marrow (aspiration and biopsy)—cytochemistry, immunologic markers, chromosome analysis
Skeletal radiographs
Other tests often used especially to diagnose the primary disease
Viral serology, e.g., HIV
ANA, complement, CH_{50}
Blood urea, creatinine, T_4, TSH
Tissue biopsy (skin, lymph node, liver)

4. Bone marrow aspiration, if required, to examine erythroid, myeloid, and megakaryocytic morphology to determine whether normoblastic, megaloblastic, or sideroblastic erythropoiesis is present and to exclude marrow pathology (e.g., aplastic anemia, leukemia, and benign or malignant infiltration of the bone marrow) (Figure 1-3)
5. Determination of underlying cause of anemia by additional tests (Table 1-4).

SUGGESTED READINGS

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2

ANEMIA DURING THE NEONATAL PERIOD

Anemia during the neonatal period is caused by:

- *Hemorrhage:* acute or chronic
- *Hemolysis:* congenital hemolytic anemias or due to isoimmunization, usually associated with indirect hyperbilirubinemia
- *Failure of red cell production:* Diamond–Blackfan anemia (pure red cell aplasia).

Table 2-1 lists the causes of anemia in the newborn.

HEMORRHAGE

Blood loss may occur during the prenatal, intranatal, or postnatal period. Prenatal blood loss may be transplacental, intraplacental, or retroplacental or may be due to a twin-to-twin transfusion.

Prenatal Blood Loss

Transplacental Fetomaternal

In 50% of pregnancies, fetal cells can be demonstrated in the maternal circulation, and in 1% of cases this is of sufficient magnitude to produce anemia in the infant. Transplacental blood loss may be acute or chronic. Table 2-2 lists the characteristics of acute and chronic blood loss in the newborn. Blood loss may be secondary to procedures such as diagnostic amniocentesis or external cephalic version. Fetomaternal hemorrhage is diagnosed by demonstrating fetal red cells by the acid-elution method of staining for fetal hemoglobin (Kleihauer–Betke technique) in the maternal circulation. The optimal timing for demonstrating fetal cells in maternal blood is within 2 hours of delivery and no later than the first 24 hours following delivery.

Intraplacental and Retroplacental

Occasionally, fetal blood accumulates in the substance of the placenta (intraplacental) or retroplacentally, and the infant is born anemic. Intraplacental blood loss from the fetus may occur when there is a tight umbilical cord around the neck or body or when there is delayed cord clamping. Retroplacental bleeding from abruptio placenta is diagnosed by ultrasound or at surgery.

Table 2-1. Causes of Anemia in the Newborn

I. Hemorrhage
- A. Prenatal
  1. Transplacental fetomaternal (spontaneous, traumatic amniocentesis, external cephalic version)
  2. Intraplacental
  3. Retroplacental
  4. Twin-to-twin transfusion
- B. Intranatal
  1. Umbilical cord abnormalities
     a. Rupture of normal cord (unattended labor)
     b. Rupture of varix or aneurysm of cord
     c. Hematomas of cord
     d. Rupture of anomalous aberrant vessels of cord (not protected by Wharton's jelly)
     e. Vasa previa (umbilical cord is presenting part)
     f. Inadequate cord tying
  2. Placental abnormalities
     a. Multilobular placenta (fragile communicating veins to main placenta)
     b. Placenta previa—fetal blood loss predominantly
     c. Abruptio placentae—maternal blood loss predominantly
     d. Accidental incision of placenta during cesarean section
- C. Postnatal
  1. External
     a. Bleeding from umbilicus
     b. Bleeding from gut
     c. Iatrogenic (diagnostic venipuncture, post-exchange transfusion)
  2. Internal
     a. Cephalhematomata
     b. Subaponeurotic hemorrhage
     c. Subdural or subarachnoid hemorrhage
     d. Intracerebral hemorrhage
     e. Intraventricular hemorrhage
     f. Retroperitoneal hemorrhage (may involve adrenals)
     g. Subcapsular hematoma or rupture of liver
     h. Ruptured spleen

II. Hemolytic anemia (see Chapter 7)
- A. Congenital erythrocyte defects
  1. Membrane defects (with characteristic morphology)
     a. Hereditary spherocytosis (pages 143–147)
     b. Hereditary elliptocytosis (pages 147–148)
     c. Hereditary propoikilocytosis (pages 148–149)
     d. Hereditary stomatocytosis (pages 149–150)
     e. Hereditary acanthocytosis (page 150)
     f. Hereditary xerocytosis (pages 150–151)
     g. Infantile pyknocytosis[a]
  2. Hemoglobin defects
     a. α-Thalassemia[b]
     b. γ β-Thalassemia
     c. Unstable hemoglobins (Hb Köln, Hb Zürich[b]) (pages 180–181)
  3. Enzyme defects
     a. Embden–Meyerhof glycolytic pathway
        (1) Pyruvate kinase
        (2) Other enzymes
     b. Hexose-monophosphate shunt
        (1) G6PD (Caucasian and Oriental) with or without drug exposure[b]
        (2) Enzymes concerned with glutathione reduction or synthesis[b]

(Continues)

Table 2-1. (*Continued*)

B. Acquired erythrocyte defects
   1. Immune
      a. Rh disease, ABO, minor blood groups (M, S, Kell, Duffy, Luther)
   2. Nonimmune
      a. Infections (cytomegalovirus, toxoplasmosis, herpes simplex, rubella, syphilis, bacterial sepsis, e.g., *Escherichia coli*)
      b. Microangiopathic hemolytic anemia with or without disseminated intravascular coagulation: disseminated herpes simplex, coxsackie B infections, gram-negative septicemia, renal vein thrombosis
      c. Toxic exposure (drugs, chemicals) ± G6PD ± prematurity[b]: synthetic vitamin K analogues, maternal thiazide diuretics, antimalarial agents, sulfonamides, naphthalene, aniline-dye marking ink, penicillin
      d. Vitamin E deficiency
      e. Metabolic disease (galactosemia, osteopetrosis)

III. Failure of red cell production
   1. Congenital (Chapter 6)
      Diamond–Blackfan anemia (pure red cell aplasia)
      Dyskeratosis Congenita
      Fanconi anemia
      Congenital dyserythropoietic anemia
   2. Acquired
      Viral infection (hepatitis, HIV, CMV, rubella, syphilis, parvovirus)
      Anemia of prematurity

[a]Not permanent membrane defect but has characteristic morphology.
[b]All of these conditions can be associated with Heinz-body formation and in the past were grouped together as congenital Heinz-body anemia.

Table 2-2. Characteristics of Acute and Chronic Blood Loss in the Newborn

Characteristic	Acute blood loss	Chronic blood loss
Clinical	Acute distress; pallor; shallow, rapid, and often irregular respiration; tachycardia; weak or absent peripheral pulses; low or absent blood pressure; no hepatosplenomegaly	Marked pallor disproportionate to evidence of distress; on occasion signs of congestive heart failure may be present, including hepatomegaly
Venous pressure	Low	Normal or elevated
Laboratory		
Hemoglobin concentration	May be normal initially; then drops quickly during first 24 hours of life	Low at birth
Red cell morphology	Normochromic and macrocytic	Hypochromic and microcytic Anisocytosis and poikilocytosis
Serum iron	Normal at birth	Low at birth
Course	Prompt treatment of anemia and shock necessary to prevent death	Generally uneventful
Treatment	Normal saline bolus or packed red blood cells; if indicated, iron therapy	Iron therapy

From Oski FA, Naiman, JL. Hematologic problems in the newborn. 3rd ed. Philadelphia: Saunders, 1982, with permission.

Twin-to-Twin Transfusion

Significant twin-to-twin transfusion occurs in at least 15% of monochorionic twins. The hemoglobin level differs by 5 g/dL and the hematocrit by 15% or more between individual twins. The donor twin is smaller, pale, may have evidence of oligohydramnios, and may show evidence of shock. The recipient is larger and polycythemic with evidence of polyhydramnios and may show signs of congestive heart failure (Chapter 8).

Intranatal Blood Loss

Hemorrhage may occur during the process of birth as a result of various obstetric accidents, malformations of the umbilical cord or the placenta, or a hemorrhagic diathesis (due to a plasma factor deficiency or thrombocytopenia) (Table 2-1).

Postnatal Blood Loss

Postnatal hemorrhage may occur from a number of sites and may be internal (enclosed) or external. Hemorrhage may be due to:

1. Traumatic deliveries (resulting in intracranial or intra-abdominal hemorrhage)
2. Plasma factor deficiencies (see Chapter 11)
   a. Congenital—hemophilia or other plasma factor deficiencies
   b. Acquired—vitamin K deficiency, disseminated intravascular coagulation
3. Thrombocytopenia (see Chapter 10)
   a. Congenital—Wiskott–Aldrich syndrome, Fanconi anemia
   b. Acquired—isoimmune thrombocytopenia, sepsis.

Clinical and Laboratory Findings

Anemia—pallor, tachycardia, and hypotension (if severe, i.e., ≥20 mL/kg blood loss)
Liver and spleen not enlarged (except in chronic transplacental bleed)
Jaundice absent
Coombs' test negative
Increased reticulocyte count
Polychromatophilia
Nucleated RBCs raised
Fetal cells in maternal blood (in fetomaternal bleed)

Treatment

1. Severely affected
   a. Administer 10–20 mL/kg packed red blood cells (hematocrit usually 50–60%) via an umbilical catheter.
   b. Cross-match blood with the mother. If unavailable, use group O Rh-negative blood or saline boluses (temporarily for shock).
   c. Use partial exchange transfusion with packed red cells for infants in incipient heart failure.
2. Mild anemia due to chronic blood loss
   a. Ferrous sulfate (2 mg elemental iron/kg body weight 3 times a day) for 3 months.

HEMOLYTIC ANEMIA

Hemolytic anemia in the newborn is usually associated with unconjugated hyperbilirubinemia. The hemolytic process is often first detected as a result of the investigation of jaundice during the first week of life. The causes of hemolytic anemia in the newborn are listed in Table 2-1.

Congenital Erythrocyte Defects

Congenital erythrocyte defects involving the red cell membrane, hemoglobin, and enzymes are listed in Table 1-2 and discussed in Chapter 7. Any of these conditions may occur in the newborn and manifest clinically as follows:

Hemolytic anemia (low hemoglobin, reticulocytosis, increased nucleated red cells, morphologic changes)
Unconjugated hyperbilirubinemia
Coombs' test negative.

Infantile Pyknocytosis

Infantile pyknocytosis (see Table 1-2) is characterized by:

1. Hemolytic anemia—Coombs' negative (nonimmune).
2. Distortion of as many as 50% of red blood cells with several to many spiny projections (up to 6% of cells may be distorted in normal infants). Abnormal morphology is extracorpuscular in origin.
3. Disappearance of pyknocytes and hemolysis by the age of 6 months. This is a self-limiting condition.
4. Hepatosplenomegaly.
5. Pyknocytosis may occur in glucose-6-phosphate dehydrogenase (G6PD) deficiency, pyruvate kinase deficiency, vitamin E deficiency, neonatal infections, and hemolysis caused by drugs and toxic agents.

Anemia in the Newborn Associated with Heinz-Body Formation

Red cells of the newborn are highly susceptible to oxidative insult and Heinz-body formation. This may be congenital or acquired and transient.

Congenital

Hemolytic anemia associated with Heinz-body formation occurs in the following conditions:

1. Unstable hemoglobinopathies (e.g., Hb Köln or Hb Zürich)
2. α-Thalassemia, for example, hemoglobin H (β-chain tetrameres)*
3. Deficiency of G6PD, 6-phosphogluconic dehydrogenase, glutathione reductase, glutathione peroxidase.

Acquired

Hemolytic anemia associated with Heinz-body formation occurs transiently in normal full-term infants without red cell enzyme deficiencies if the dose of certain drugs

*β-chain hemoglobinopathies such as sickle cell disease or β-thalassemia are generally not apparent until 3–6 months of age when synthesis of the β-globin chain increases, whereas α-chain hemoglobinopathies are evident during fetal life and at birth.

or chemicals is large enough. The following have been associated with toxic Heinz-body formation: synthetic water-soluble vitamin K preparations (Synkayvite), sulfonamides, chloramphenicol, aniline dyes used for marking diapers, and naphthalene used as mothballs.

Diagnosis

1. Demonstrate Heinz bodies on a supravital preparation.
2. Perform specific tests to exclude the various congenital causes of Heinz-body formation mentioned earlier.

Acquired Erythrocyte Defects

Acquired erythrocyte defects may be due to immune (Coombs'-positive) or nonimmune (Coombs'-negative) causes. The immune causes are due to blood group incompatibility between the fetus and the mother, for example, Rh (D), ABO, or minor blood group incompatibilities (such as anti-c, Kell, Duffy, Luther, anti-C, and anti-E) causing isoimmunization.

Rh Isoimmunization

Clinical Features

1. Anemia, mild to severe (if severe, associated with hydrops fetalis)
2. Jaundice (indirect hyperbilirubinemia)
   a. Presents during first 24 hours.
   b. May cause kernicterus
      (1) Exchange transfusion should be carried out whenever the bilirubin level in full-term infants rises to, or exceeds, 20 mg/dL.
      (2) Factors that predispose to the development of kernicterus at lower levels of bilirubin, such as prematurity, hypoproteinemia, metabolic acidosis, drugs (sulfonamides, caffeine, sodium benzoate), and hypoglycemia, require exchange transfusions below 20 mg/dL.
   c. Table 2-3 lists the various causes of unconjugated hyperbilirubinemia. Figure 2-1 outlines an approach to the diagnosis of both unconjugated and conjugated hyperbilirubinemia.
3. Hepatosplenomegaly; varies with severity.
4. Petechiae (only in severely affected infants). Hyporegenerative thrombocytopenia and neutropenia may occur during the first week.

Table 2-3. Causes of Unconjugated Hyperbilirubinemia

I. "Physiologic" jaundice: jaundice of hepatic immaturity
II. Hemolytic anemia (see Chapter 7 for more complete list of causes)
A. Congenital erythrocyte defect
1. Membrane defects: hereditary spherocytosis, ovalocytosis, stomatocytosis, infantile pyknocytosis
2. Enzyme defects (nonspherocytic)
a. Embden–Meyerhof glycolytic pathway (energy potential): pyruvate kinase, triose phosphate isomerase, etc. (pages 152–153)
b. Hexose monophosphate shunt (reduction potential): G6PD (pages 153–157)
3. Hemoglobin defects
Sickle cell hemoglobinopathy[a]

(Continues)

Table 2-3. (*Continued*)

- B. Acquired erythrocyte defect
  1. Immune: allo-immunization (Rh, ABO, Kell, Duffy, Lutheran)
  2. Nonimmune
     - a. Infection
       - (1) Bacterial: *Escherichia coli*, streptococcal septicemia
       - (2) Viral: cytomegalovirus, rubella, herpes simplex
       - (3) Protozoal: toxoplasmosis
       - (4) Spirochetal: syphilis
     - b. Drugs: penicillin
     - c. Metabolic: asphyxia, hypoxia, shock, acidosis, vitamin E deficiency in premature infants, hypoglycemia

III. Polycythemia (see Table 8-1 for more complete list of causes)
- A. Placental hypertransfusion
  1. Twin-to-twin transfusion
  2. Maternal–fetal transfusion
  3. Delayed cord clamping
- B. Placental insufficiency
  1. Small for gestational age
  2. Postmaturity
  3. Toxemia of pregnancy
  4. Placenta previa
- C. Endocrinal
  1. Congenital adrenal hyperplasia
  2. Neonatal thyrotoxicosis
  3. Maternal diabetes mellitus
- D. Miscellaneous
  1. Down syndrome
  2. Hyperplastic visceromegaly (Beckwith–Wiedemann syndrome), associated with hypoglycemia

IV. Hematoma

Cephalhematoma, subgaleal, subdural, intraventricular, intracerebral, subcapsular hematoma of liver; bleeding into gut

V. Conjugation defects
- A. Reduction in bilirubin glucuronyl transferase
  1. Severe (type I): Crigler–Najjar (autosomal recessive)
  2. Mild (type II): Crigler–Najjar (autosomal dominant)
  3. Gilbert disease
- B. Inhibitors of bilirubin glucuronyl transferase
  1. Drugs: novobiocin
  2. Breast milk: pregnane-3α, 20β-diol
  3. Familial: transient familial hyperbilirubinemia

VI. Metabolic

Hypothyroidism, maternal diabetes mellitus, galactosemia

VII. Gut obstruction (due to enterohepatic recirculation of bilirubin)
(e.g., pyloric stenosis, annular pancreas, duodenal atresia)

VIII. Maternal indirect hyperbilirubinemia
(e.g., homozygous sickle cell hemoglobinopathy)

IX. Idiopathic

[a]Not usually a cause of jaundice in the newborn because of the predominance of Hgb F (unless associated with concomitant G6PD deficiency).

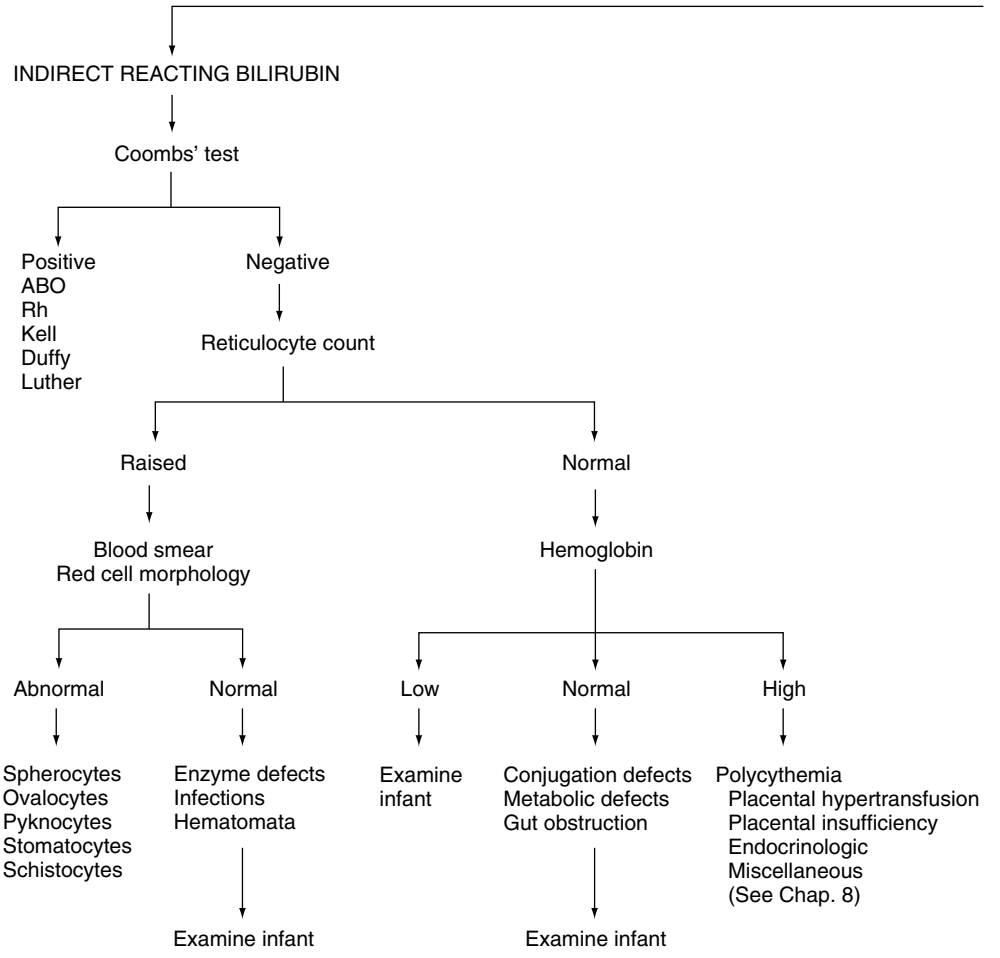

Fig. 2-1. Approach to investigation of jaundice in the newborn.

(*Continues*)

5. Severe illness with birth of infant with hydrops fetalis, stillbirth, or death *in utero* and delivery of a macerated fetus.
6. Late hyporegenerative anemia with absent reticulocytes. This occurs occasionally during the second to the fifth week and is due to a diminished population of erythroid progenitors (serum concentration of erythropoietin is low and the marrow concentrations of BFU-E and CFU-E are not elevated).

Laboratory Findings

1. Serologic abnormalities (incompatibility between blood group of infant and mother; direct Coombs' test positive in infant; mother's serum has the presence of immune antibodies detected by the indirect Coombs' test)
2. Decreased hemoglobin level, elevated reticulocyte count, smear-increased nucleated red cells, marked polychromasia, and anisocytosis
3. Raised indirect bilirubin level.

Management

Antenatal

Patients should be screened at their first antenatal visit for Rh and non-Rh antibodies. Figure 2-2 shows a schema of the antenatal management of Rh disease. If an

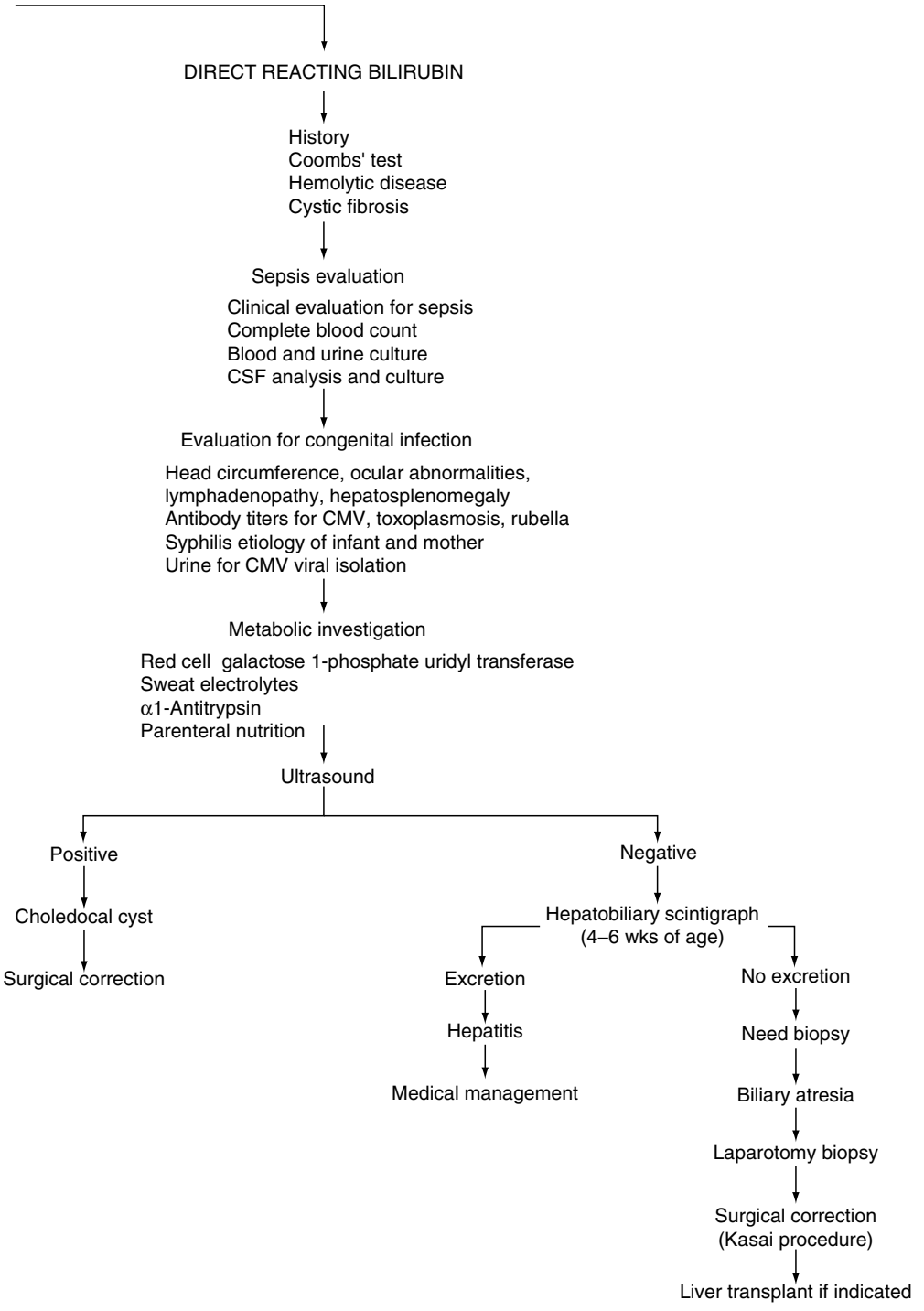

Fig. 2-1. (*Continued*)

immune antibody is detected in the mother's serum, proper management includes the following:

1. Obtain past obstetric history and outcome of previous pregnancies.
2. Determine blood group and conduct indirect Coombs' test (to determine the presence and titer of irregular antibodies). Most irregular antibodies can cause

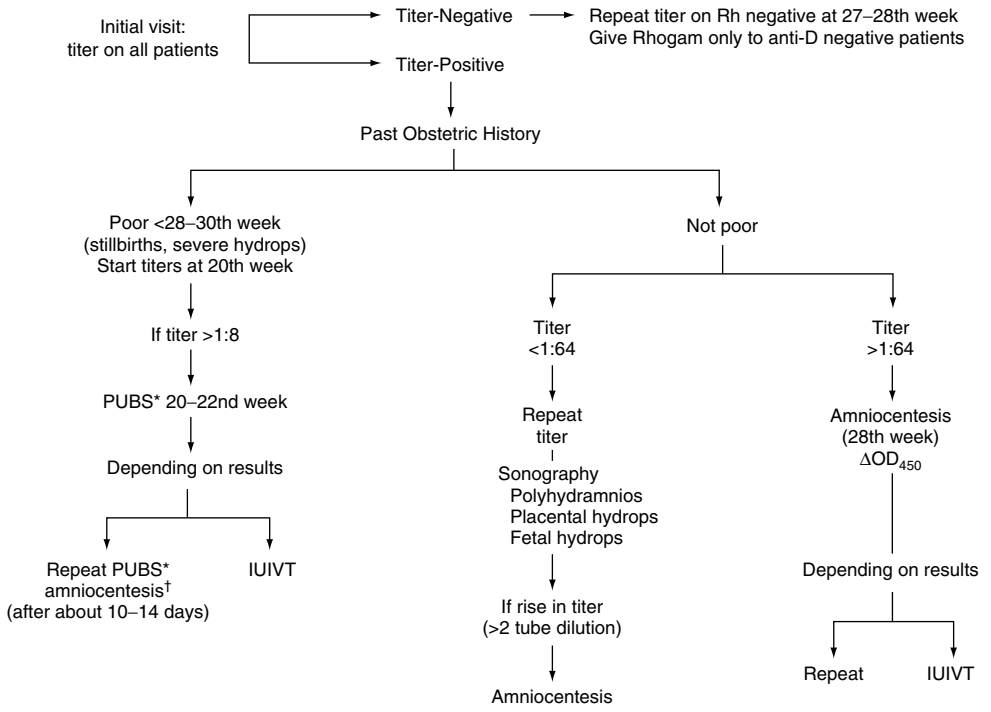

Fig. 2-2. Schema of antenatal management of Rh disease.
Abbreviation: IUIVT, intrauterine intravenous transfusion.
*Percutaneous umbilical vein blood sampling.
†Amniotic fluid analysis is less reliable prior to the 26th week of gestation, and PUBS is recommended.

erythroblastosis fetalis; therefore, screening of maternal serum is important. Titers should be determined at various weeks of gestation (Figure 2-2). The frequency depends on the initial or subsequent rise in titers. Theoretically, any blood group antigen (with the exception of Lewis and I, which are not present on fetal erythrocytes) may cause erythroblastosis fetalis. Anti-Le^a, Le^b, M, H, P, S, and I are IgM antibodies and rarely, if ever, cause erythroblastosis fetalis and need not cause concern.

3. Determine zygosity of the father: If the mother is Rh negative and the father is Rh positive, the father's zygosity becomes critical. If he is homozygous, all his future children will be Rh positive. If the father is heterozygous, there is a 50% chance that the fetus will be Rh negative and unaffected. The Rh genotype can be accurately determined by the use of polymerase chain reaction (PCR) of chorionic villus tissue, amniotic cells, and fetal blood when the father is heterozygous or his zygosity is unknown. Mothers with fetuses found to be Rh D negative (dd) can be reassured and further serologic testing and invasive procedures can be avoided. Fetal zygosity can thus be determined by molecular biological means without invading the fetomaternal circulation. It has recently been demonstrated that fetal Rh D genotyping can be performed rapidly on maternal plasma in the second trimester of pregnancy. This is performed by extracting DNA from maternal plasma and analyzing it for the Rh D gene with a fluorescent-based PCR test sensitive enough to detect the Rh D gene in a single cell. The advantage of this test is that neither the mother nor the fetus is exposed to the risks of amniocentesis or chorionic villus sampling.

4. Examination of the amniotic fluid for spectrophotometric analysis of bilirubin. Past obstetric history and antibody titer are indications for serial amniocentesis and spectrophotometric analyses of amniotic fluid to determine the condition of the fetus. Amniotic fluid analysis correlates well with the hemoglobin and hematocrit at birth ($r = 0.9$), but does not predict whether the fetus will require an exchange transfusion after birth. The following are indications for amniocentesis:
   a. History of previous Rh disease severe enough to require an exchange transfusion or to cause stillbirth.
   b. Maternal titer of anti-D, anti-c, or anti-Kell (or other irregular antibodies) of 1:8 to 1:64 or greater by indirect Coombs' test or albumin titration and depending on previous history. An assessment of the optical density difference at 450 μm (ΔOD_{450}) at a given gestational age permits reasonable prediction of the fetal outcome (Figure 2-3). Determination of the appropriate

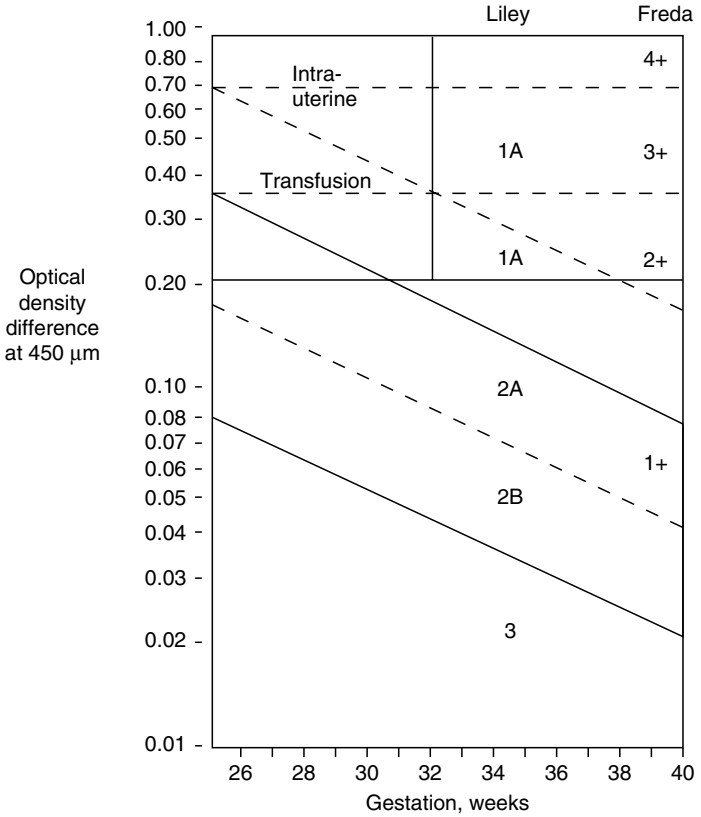

Fig. 2-3. Assessment of fetal prognosis by the methods of Liley and of Freda. Liley's method of prediction: *Zone 1A:* Condition desperate, immediate delivery or intrauterine transfusion required, depending on gestational age. *Zone 1B:* Hemoglobin less than 8 g/dL, delivery or intrauterine transfusion urgent, depending on gestational age. *Zone 2A:* Hemoglobin 8–10 g/dL, delivery at 36–37 weeks. *Zone 2B:* Hemoglobin 11.0–13.9 g/dL, delivery at 37–39 weeks. *Zone 3:* Not anemic, deliver at term. Freda's method of prediction: *Zone 4+:* Fetal death imminent, immediate delivery or intrauterine transfusion, depending on gestational age. *Zone 3+:* Fetus in jeopardy, death within 3 weeks, delivery or intrauterine transfusion as soon as possible, depending on gestational age. *Zone 2+:* Fetal survival for at least 7–10 days, repeat amniocentesis indicated, possible indication for intrauterine transfusion, depending on gestational age. *Zone 1+:* Fetus in no immediate danger. (From Robertson JG. Evaluation of the reported methods of interpreting spectrophotometric tracings of amniotic fluid analysis in Rhesus isoimmunization. Am J Obstet Gynecol 1966;95:120, with permission.)

treatment depends on the ΔOD_{450} of the amniotic fluid, the results of the fetal biophysical profile scoring,* and the assessment of the presence or absence of fetal hydrops (seen on ultrasound) and amniotic phospholipid determinations (lung profile):

Features of lung profile	Immature fetus	Mature fetus
Lecithin/sphingomyelin	<2.0	>2.0
ratio	<45%	>50%
Phosphatidylinositol	Absent	Absent
Phosphatidylglycerol	Present (small amounts)	Present (prominent)

If the amniotic fluid ΔOD_{450} indicates a severely affected fetus and phospholipid estimations indicate lung maturity, the infant should be delivered. If the ΔOD_{450} indicates a severely affected fetus and the phospholipid estimations indicate marked immaturity, maternal plasmapheresis and/or intrauterine intravenous transfusion (IUIVT) should be carried out. IUIVT has many advantages over intraperitoneal fetal transfusions and is the procedure of choice. This decision is made in conjunction with the biophysical profile score.

Intensive maternal plasmapheresis antenatally using a continuous-flow cell separator can significantly reduce Rh antibody levels, reduce fetal hemolysis, and improve fetal survival in those mothers carrying highly sensitized Rh-positive fetuses. This procedure together with IUIVT should be carried out when a high antibody titer exists early before a time when the infant can be safely delivered.

If the risk of perinatal death resulting from complications of prematurity is high, then an IUIVT should be carried out. Percutaneously, the umbilical vein is used for blood sampling (PUBS) and venous access and permits a fetal transfusion via the intravascular route (IUIVT). With the availability of high-resolution ultrasound guidance, a fine (20-gauge) needle is inserted directly into the umbilical cord, either at the insertion site into the placenta or into a free loop of cord. This allows the same blood sampling as is available postnatally in the neonate. Temporary paralysis of the fetus with the use of pancuronium bromide (Pavulon) facilitates the procedure, which may be applied to fetuses from 18 weeks' gestation until the gestational age when fetal lung maturity is confirmed. The interval between procedures ranges from 1 to 3 weeks.

The risks of IUIVT include:

Fetal loss (2%)
Premature labor and rupture of membranes
Chorioamnionitis
Fetal bradycardia
Cord hematoma or laceration
Fetomaternal hemorrhage.

The overall survival rate is 88%. Intraperitoneal transfusion can be performed in addition to IUIVT to increase the amount of blood transfused and to extend the interval between transfusions.

Modern neonatal care, including attention to metabolic, nutritional, and ventilatory needs and the use of artificial surfactant insufflation, makes successful earlier delivery possible. The need for IUIVT and intraperitoneal transfusion is rarely, if ever, indicated.

*Ultrasound for the assessment of gestational age must be done early in pregnancy. The fetal biophysical profile scoring uses multiple variables: fetal breathing movements, gross body movements, fetal tone, reactive fetal heart rate, and quantitative amniotic fluid volume. This scoring system provides a good short-term assessment of fetal risk for death or damage *in utero*.

Postnatal

Hyperbilirubinemia is the most frequent problem and can be managed by exchange transfusion. Phototherapy is an adjunct rather than the first line of therapy in hyperbilirubinemia due to erythroblastosis fetalis. Postnatal management and criteria for exchange transfusion have changed over the years. We currently use the following management:

1. In hydropic infant at birth:
   a. Adequate ventilation must be established.
   b. Partial exchange transfusion may be necessary to correct severe anemia.
   c. Double-volume exchange transfusion may be required later.
2. A rapid increase in the bilirubin level of greater than 1.0 mg/h and/or a bilirubin level approaching 20 mg/dL at any time during the first few days of life in the full-term infant is an indication for exchange transfusion. In preterm or high-risk infants, exchange transfusion should be carried out at lower levels of bilirubin (e.g., 15 mg/dL).
3. Clinical signs suggesting kernicterus at any time at any bilirubin level are an indication for exchange transfusion.

Prevention of Rh Hemolytic Disease

Rh hemolytic disease can be prevented by the use of Rh immunoglobulin at a dose of 300 μg, which is indicated in the following circumstances:

1. For all Rh-negative, Rh_0 (D^u)-negative mothers who are unimmunized to the Rh factor. In these patients Rh immunoglobulin is given at 28 weeks' gestation and within 72 hours of delivery. Antenatal administration of Rh immunoglobulin is safe for the mother and the fetus
2. For all unimmunized Rh-negative mothers who have undergone spontaneous or induced abortion, particularly beyond the seventh or eighth week of gestation
3. After ruptured tubal pregnancies in unimmunized Rh-negative mothers
4. Following any event during pregnancy that may lead to transplacental hemorrhage, such as external version, amniocentesis, or antepartum hemorrhage in unimmunized Rh-negative women
5. Following tubal ligation or hysterotomy after the birth of an Rh-positive child in unimmunized Rh-negative women
6. Following chorionic villus sampling at 10–12 weeks' gestation. In these patients 50 μg of Rh immunoglobulin should be given.

ABO Isoimmunization

Clinical Features

1. Jaundice (indirect hyperbilirubinemia) usually within first 24 hours; may be of sufficient severity to cause kernicterus
2. Anemia
3. Hepatosplenomegaly.

Table 2-4 lists the clinical and laboratory features of isoimmune hemolysis due to Rh and ABO incompatibility.

Diagnosis

1. Hemoglobin decreased
2. Smear: spherocytosis in 80% of infants, reticulocytosis, marked polychromasia