Blood diseases

OF INFANCY AND CHILDHOOD

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SPECIAL MESSAGE

When the manuscript was completed for this edition, Dr. Carl H. Smith arranged for his associate, Dr. Denis R. Miller, to assist with the remaining details of preparation. Since Dr. Smith's death, Dr. Miller has devoted much time and effort to follow through on the completion of this work. It is with a deep sense of gratitude that especial thanks are expressed to Dr. Miller not only for his untiring work, but for the kind spirit, deep understanding and humility he has displayed.

It is with profound gratitude that acknowledgment is made to Dr. Virginia C. Canale, whose gracious and generous assistance and cooperation expedited the completion of this book. Special thanks and sincere appreciation are expressed to Dr. Canale.

Deep appreciation and thanks are expressed to Mrs. Marvin Tishcoff for her sincere and unwavering dedication to the various tasks involved in the completion of this edition.

Margaret B. Smith

Preface

In this third edition of *Blood Diseases of Infancy and Childhood* the objectives stated in the Preface of the preceding edition remain unchanged. They are to provide an opportunity to introduce newer developments in pediatric hematology, to revise much of the text in the light of newer concepts, and to review current knowledge in this field. New tables and figures have been added to illustrate these advances. The flood of research data and literature in pediatric hematology and related fields has grown to such proportions that only those contributions were chosen that are relevant to the needs of the medical student, pediatrician, family physician, house staff officer, laboratory technologist, and, in many instances, the pathologist. In recent years the introduction of sophisticated investigational techniques and equipment has resulted in a massive proliferation of knowledge concerning biochemical, physiologic, immunologic, and genetic aspects of blood diseases. To facilitate description and formulation of various entities, their pathogenesis and clinical manifestations, as well as management, the technical complexities of the original publications have been minimized without sacrificing essential information. The bibliography has been greatly expanded to aid the student engaged in an investigative problem and includes over 1200 new references. While recent contributions have been incorporated in the present text, some deletions have been made, and several chapters have been thoroughly revised and reorganized.

Among the topics discussed are the recent studies of 2,3-diphosphoglycerate (2,3-DPG) and its role in determining the affinity of hemoglobin for oxygen. The use of phenobarbital as a means of lowering bilirubin in the management of jaundice of the newborn is described, as well as phototherapy as another measure to prevent the damage of hyperbilirubinemia. In the management of hemolytic anemia resulting from Rh incompatibility, the value of amniocentesis and intrauterine blood transfusion is presented. The injection of Rh antibody in the form of Rh immune globulin into unsensitized Rh-negative postpartum women has been proven to be effective in preventing Rh immunization. Amniocentesis is not only a guide in the management of Rh-hemolytic disease, but also can serve as a diagnostic aid in the prenatal detection and management of certain congenital defects.

The differential diagnosis and etiologic factors in the early and late neonatal periods have been further explored in the light of recent investigations dealing with pigments resulting from hemolysis such as hemopoxin.

Since the infant's diet is usually deficient in iron, iron-fortified milk has been recommended for routine use, together with other carefully selected foods to insure adequate iron intake.

The immunologic implications of blood disorders have their impact in almost every aspect of hematology, including those pertaining to allergic disorders, to the autoimmune hemolytic diseases, to viral interactions, to disorders of immunoglobulin metabolism, in transfusion, and in transplantation procedures.

Transfusion therapy has employed the value of essential blood components, of

packed red cells rather than whole blood, the use of frozen-thawed prepared red blood cells, obviating the use of unnecessary plasma infusions. With the use of frozen-thawed prepared red blood cells for transfusion, previous febrile and allergic reactions have been eliminated. In intrauterine transfusions there is the possibility of developing host-versus-graft reaction from the incidental introduction of white blood cells.

The hemolytic anemias have been discussed from the standpoint of three main components of the cell—the membrane, the hemoglobin molecule, and the intracellular enzymes and intermediates of intracellular metabolism—congenital defects of which may have a profoundly adverse effect upon cell function metabolism and survival. Disease is manifested by severe anemia often requiring transfusions. An ever increasing number of red cell enzyme deficiencies have been characterized. These defects result in metabolically abnormal cells and in premature cell death. Recent investigations have demonstrated that the ability of the red cell to perform its various functions is critically dependent upon cell metabolism and that a most important regulator of hemoglobin function (oxygen affinity) and glycolysis (energy production) is 2,3-DPG. It is now possible to pinpoint the large number of enzymopathies and to determine their genetic background and in some instances to determine which will benefit by splenectomy.

The hemoglobinopathies have been dealt with to include investigations of erythrocyte metabolism, survival, organ sequestration, and membrane function. Studies of thalassemia include investigations of the many thalassemia syndromes resulting from deficient alpha, beta, delta, or gamma chain synthesis, as well as an inquiry of the most advantageous treatment with regard to amounts and frequency of blood administration and hemoglobin levels to be achieved. An important group of hemoglobinopathies, the unstable hemoglobin hemolytic anemias or congenital Heinz body anemias have been identified and are caused by amino acid substitutions that alter heme-globin or interchain contacts. Other recently discovered hemoglobinopathies include those associated with increased or decreased oxygen affinity.

Knowledge of the biochemistry and immunology of the leukocyte has been advanced and previously poorly understood diseases associated with increased susceptibility to bacterial diseases have now been related to aberrations of the intricate processes of opsonization, ingestion, and digestion of potentially pathogenic bacteria. One of these, chronic granulomatous disease of childhood, has been related to deficiencies of intracellular enzymes that destroy ingested bacteria.

Recent studies have uncovered a relationship between the Ebstein-Barr virus and infectious mononucleosis and Burkitt's lymphoma.

A vast knowledge has proliferated during the past five years in the field of acute leukemia of childhood. Aided by a greater awareness of the kinetics of leukemic cell proliferation and cell biochemistry, new drugs such as L-asparaginase and cytosine arabinoside and the use of multiple drug combinations have resulted in improved remission rates and prolonged survival in this disease, which less than a quarter of a century ago, before the chemotherapy era, carried a median survival of about four months. Aggressive chemotherapy has effectively decreased the leukemic cell burden. Localized disease, particularly in the central nervous system, has been identified and successfully treated; and supportive therapy, including the use of allopurinol to prevent hyperuricemia, newer antibiotics, and platelet concentrates have in concert prolonged the duration and improved the quality of remission in this disease. The importance of comprehensive support, including the emotional needs of the child, cannot be gainsaid. The eventual complete control, successful treatment, and, hopefully, prevention of leukemia must await further painstaking research efforts.

Improved diagnostic studies, including lymphangiography, the introduction of splenectomy, advanced radiotherapeutic techniques, and new combinations of drugs have improved remission rates and survival in such disorders as Hodgkin's disease. The importance of accurate clinical and pathological staging in determining prognosis has been reviewed. The recognition of an association between immunologic deficiency diseases and lymphoproliferative malignancies has stimulated investigators to redefine the contributions of the reticuloendothelial stimulation and aberrations of lymphoid proliferation and differentiation in these disorders.

The treatment of hemophilia has been aided immensely by the introduction of such new products as cryoprecipitate and amino acid precipitates of purified factor VIII, which when used appropriately have decreased morbidity and permitted children with this disorder to undergo extensive surgery without complications. A modern coagulation scheme, constantly undergoing revision, has been updated to bring into focus the intrinsic and extrinsic systems of coagulation.

The mechanism and etiology of disseminated intravascular coagulation and the laboratory diagnosis and management of this disorder are discussed, as is the fibrinolytic system.

The purpuras are discussed in light of recent advances in platelet metabolism and function. The physiology of the platelet, including platelet adhesiveness, aggregation, and release of thromboplastic materials that initiate clotting are reviewed, and such entities as thrombasthenia and the thrombocytopathy have been given clearer definition and understanding.

Those who have helped immensely in revising and updating this third edition include Drs. Alexander Wiener, Leon Sussman, Julian Schorr, James German, Philip Lanzkowsky, Denis Miller, Virginia Canale, Margaret Hilgartner, Herbert Horowitz, Theo Vats, Richard Silver, George Wantz, Frederick Battaglia, Julius Rutzky, and many others whose generous contributions, photographs, and tables are acknowledged in the text. Mr. Percy W. Brooks, Director of Medical Illustration at Cornell University Medical College, skillfully prepared many of the new illustrations. Miss Denise Berman and Mrs. Bella Mellenhoff provided secretarial assistance, and special praise goes to Mrs. Marvin Tishcoff who typed and retyped much of the manuscript.

Once again, I am particularly grateful to my wife, Margaret, for her encouragement in undertaking another edition. I owe her an enormous debt for her untiring efforts and patience in the multitude of the tasks required in revising the text and index.

Carl H. Smith
April, 1971

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1 ORIGIN AND DEVELOPMENT OF BLOOD CELLS

Blood formation in the fetus. A review of the essential features of prenatal blood development provides a basis for interpreting postnatal abnormalities of the circulating blood elements, their progenitors, and sites of formation. The designation of prenatal hematopoiesis imparts an implication of continuity to the events occurring in the embryo in the first 2 months and in the fetus in the remainder of gestation. Current emphasis on maternal-fetal relationships, which has shed so much light on other systems, conceivably may clarify the etiology of certain of the blood dyscrasias on the same basis. An understanding of the blood changes in the earlier months of life, furthermore, requires some knowledge of embryonic and fetal blood formation.

Sites of blood formation. Blood cells in the embryo arise from the mesenchyme. The first cells produced in the yolk sac become the primitive red corpuscles. Since the mesenchyme is wide-spread throughout the embryo, blood formation begins in multiple sites but eventually becomes specialized in certain organs. With some overlapping, definitive blood centers mainly involving red cell elements appear successively in the yolk sac at the fourth month of gestation.[5] Although the bone marrow makes its appearance in the sixth week of development, it does not become a site of active hematopoiesis until the fourth to fifth month and does not become the exclusive site[5] until 2 to 3 weeks after birth.[28] Until the middle of fetal life the liver is the most actively engaged organ participating in blood formation. It has been stated that the liver as opposed to the marrow represents the principal source of fetal erythrocytes. In this period of hepatic hematopoiesis, fetal hemoglobin is the sole type synthesized. As hematopoiesis wanes in this area, it is assumed by the bone marrow, which exercises this function for the remainder of fetal life. Coincidental activity goes on in the spleen, the lymph nodes, and, to a lesser extent, the thymus.

The bone marrow and spleen provide ideal environments for red cell and hemoglobin formation. In both there are nonanastomosing arterial capillaries emptying into a rich plexus of venous sinusoids. By virtue of sluggish circulation and blood stasis, a relatively high carbon dioxide tension develops, a factor of primary importance in the elaboration of hemoglobin and in formation of the primordial cell.

Appearance of blood elements. The mesenchyme is regarded as the essential blood-forming tissue of the embryo, corresponding to fixed connective tissue cells in the adult organism. The hemocytoblast, a derivative of the mesenchyme, is the primitive totipotent cell, the main function of which is involved in hematopoiesis. This early cell, frequently ameboid in embryos, represents the precursor of red blood cells, granular leukocytes, lymphocytes, and megakaryocytes.[22,28]

There are fluctuations in blood cellular elements relative to placental size. The placenta is six times heavier than the fetus at 1 month and only one-seventh the fetal weight at birth.[5] In the smallest fetus studied by Playfair and associates,[47] 1.9 cm. long, 99% of the red cells were nucleated. By 6 cm. (12 weeks) the nucleated counts varied from 10,000 to 100,000 per cubic millimeter and fell steadily thereafter. At term about 0.2% of the red cells were nucleated. Myelocytes were found in the 1.9 cm. fetus and mature granulocytes in a 4.2 cm. fetus. Eosinophils were found in a 6.4 cm. fetus and increased regularly with the size of the fetus (to 17 cm. at 20 weeks). In the 1.9 cm. fetus 57% of the white cells were lymphocytes, in no way distinguishable from normal adult small lymphocytes. They continued to rise with age until in a fetus of about 17 to 22 cm. (20 to 25 weeks) the highest counts were recorded in some over 10,000 per cubic millimeter. Monocytes were found in the smallest fetuses and at all subsequent ages. Proerythroblasts were seen frequently, as well as the bare nuclei suspicious of megakaryocytes.