HEMATOLOGIC PROBLEMS IN THE NEWBORN

Third Edition

By

Frank A. Oski, M.D.

J. Lawrence Naiman, M.D.

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Foreword

The previous two editions of this monograph, published in 1966 and 1972, were classics in the field of neonatal hematology. They were the only resource in which a lucid and comprehensive discussion of blood disorders of the newborn could be found. The current edition promises to be of even greater value.

In the 10 years that have elapsed since the last edition, there have been remarkable advances in all of neonatology, including the areas of special interest to the authors of this volume. Drs. Oski and Naiman have assimilated the new knowledge and have again presented the information in a clear and readable fashion. The literature has been exhaustively reviewed and each chapter contains a great deal of new material. For example, more than 150 additional references are cited in the chapter on Erythroblastosis Fetalis. This chapter includes a discussion of newer methods of treatment, e.g., plasmapheresis, and a much expanded section on prevention of hemolytic disease, including antenatal prophylaxis. New sections have also been added on the hematologic disorders unique to the premature and other high risk infants, who are now surviving in greater numbers than ever before.

This edition has chapters by two new contributors. The chapter on Disorders of Hemoglobin Synthesis and Metabolism has been extensively revised by Dr. Howard Pearson, a world authority on the subject. Genetic mechanisms causing hemoglobin variants, the different syndromes caused by these variants, and those that can be diagnosed antenatally are reviewed. Dr. James Stockman has updated the chapter on Disorders of Leukocytes. During the past decade, much has been learned about neutrophil function, the role of T and B lymphocytes, and responses of the neonates to infections, still a major cause of death in this age group.

This book is a unique reference for the hematologist, neonatologist, and practicing physician. It is both a repository of scientific information and a practical source for the clinical and laboratory data needed to make a correct diagnosis as well as the optimal methods of treatment.

MILTON MARKOWITZ

Preface to the Third Edition

A decade has now elapsed since the publication of the second edition of our monograph. Our book has become slightly larger, although the neonates with hematologic problems have become increasingly smaller. The third edition of this book, still designed with the pediatrician and the pediatric house officer in mind, has attempted to focus on the changing spectrum of problems confronted in the newborn nursery and the neonatal intensive care unit.

We have expanded, and revised extensively, the portions of the book dealing with polycythemia, the anemia of prematurity, the bleeding and thrombocytopenic newborn, and the hematologic manifestations of sepsis. The problem of erythroblastosis has changed dramatically during the past ten years. Prenatal detection of disorders of hemoglobin is now possible. We hope that we have accurately portrayed the status of these two clinical problems.

We have enlisted the help of two hematology colleagues for this third edition — Drs. Howard A. Pearson and James A. Stockman, III. Dr. Pearson has utilized his considerable knowledge of hemoglobinopathies for the preparation of Chapter Nine and Dr. Stockman deals with leukocytes in Chapter Eight. We owe them a large debt of appreciation for their contributions. We also wish to express our thanks to Marjorie Gillette, Brenda Mitchell, and Alice Marr for their valuable secretarial assistance and to Mary Cowell of the W. B. Saunders Company for her editorial guidance.

We hope that you, the reader, will enjoy the Third Edition — more important, we hope that you will find this book useful in dealing with the common, and not so common, hematologic problems in the newborn.

F.A.O.
J.L.N.

Preface to the First Edition

During the first few weeks of life, there are more diagnostic problems with hematologic aspects than at any time thereafter. The pediatrician is asked to distinguish inherited disorders from acquired disease and the consequences of maternal-fetal interaction, all at a time when normal physiologic processes are in a state of rapid change. As Dr. Clement Smith has stated, "This is a time during which life is more dynamic than static, for in no other equally brief span of existence do such profound alterations and adjustments occur as in the weeks, or even the days or hours following birth."

It is the purpose of this book to provide in a single source much of what is known concerning both the normal and abnormal hematologic processes of the first month of life and the effects of prenatal factors on them. We hope this book will provide a useful guide to all who care for, or are interested in, the newborn infant — those who are continually confronted with infants who are bleeding, anemic, jaundiced, or purpuric. We also hope that this discussion of what is known regarding the normal, the hematologic manifestations of the maternal-infant relationship, the disorders of the formed elements of the blood, and the coagulation process will serve as a stimulus to others to explore the areas in which little is as yet known.

It should not be forgotten in this era of mass screening tests for the unusual diseases that a well taken history, a careful physical exam, and a few well chosen laboratory tests can still disclose many common yet serious disturbances. In this book we have indicated how important information can be obtained in an easy manner to aid in the diagnosis and treatment of infants with hematologic disorders.

We regret that all who have made observations relevant to the topics included in this book could not be cited in the text; their numbers are legion and to all we are grateful. In each chapter an attempt has been made to cite the work of the original observer and to bring these observations into focus, based on the most recent work. The chapter on erythroblastosis fetalis clearly illustrates the shortcomings of this approach. So much has been done and is being done that only a summary could be made within the confines of this book.

To Dr. Louis K. Diamond goes much of the credit for nurturing our interest in the field of pediatric hematology. We have benefited from his many years of experience. His own work in these areas has been a beacon, facilitating the studies of others. We are also indebted to Dr. Lewis A. Barness

for stimulating our curiosity and providing the necessary encouragement and wisdom for the completion of this task.

We wish to thank Dr. Alexander Schaffer for providing us with an opportunity to assemble this information and for his helpful criticism at each step along the way.

As in all endeavors of this nature, we wish to express special thanks to those who only sit and work — our typists, Miss Loretta Plunkett and Mrs. George Seeley; our artist, Mrs. Libby Rudnick; and our photographer, Mr. Edward Glifort.

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Contents

Chapter One

NORMAL BLOOD VALUES IN THE NEWBORN PERIOD

Because birth represents only one temporal event in the development of the infant, the interpretation of the blood picture in the newborn requires an understanding of the maturational processes that precede it.

HEMATOPOIESIS IN UTERO

Hematopoiesis in the embryo and fetus can be conveniently divided into three periods: mesoblastic, hepatic, and myeloid (Wintrobe, 1961). All blood cells are derived from the embryonic connective tissue — the mesenchyme — and blood formation can first be detected about the nineteenth day of gestation (Fig. 1–1). At this time, blood islands in the yolk sac can be observed to differentiate in two directions. Peripheral cells in the islands form the walls of the first blood vessels, and centrally located cells become the primitive blood cells or hemocytoblasts (Maximow, 1924; Bloom and Bartelmez, 1940). By the twenty-second day of gestation, similar blood is-

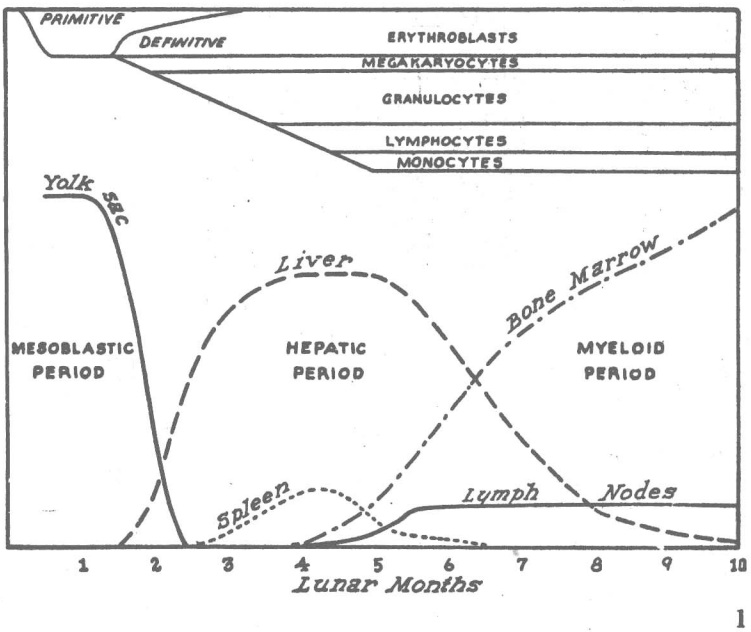

Figure 1–1. The stages of hematopoiesis in the developing embryo and fetus indicating the time of appearance and the comparative participation of the chief centers of hematopoiesis. (From Wintrobe, M.: Clinical Hematology. 5th ed., Philadelphia, Lea & Febiger, 1961.)

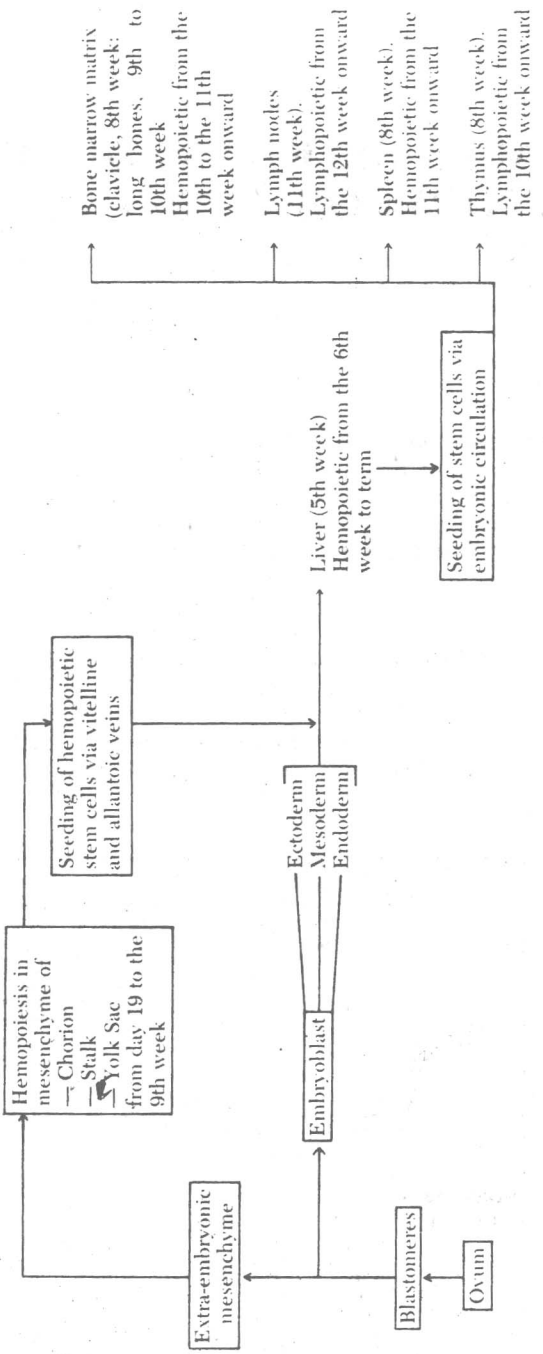

Figure 1–2. The development of intraembryonic hematopoiesis. (Modified from Keleman et al., 1979.)

lands may be observed scattered throughout the mesodermal tissues of the body stalk. By the sixth week of gestation, the activity of this intravascular, mesoblastic stage of erythropoiesis begins to decline, and by the end of the third fetal month it can no longer be observed (Gilmour, 1941).

It has been proposed (Metcalf, 1977; Kelemen et al., 1979) that the development of intraembryonic hematopoiesis is a result of migration to suitable microenvironments, and colonization by stem cells derived from the yolk sac. The timing of these events and their consequences are illustrated in Figure 1–2.

During the fifth week of gestation blood formation begins in the liver. Erythroid elements constitute the predominant hematopoietic cell type in the liver, although a small number of granulocytic and megakaryocytic cells can be found in even the earliest stages of hepatic hematopoiesis (Fukuda, 1974). During the third to fifth months of gestation, erythroid precursors represent approximately 50 per cent of the total nucleated cells of this organ (Thomas and Yoffey, 1964). The liver is the chief organ of hematopoiesis from the third to the sixth fetal month and continues to produce formed elements into the first postnatal week. During the third fetal month, hematopoiesis also can be detected in the spleen and thymus, and shortly afterward in the lymph nodes. Blood cell formation can still be observed in the spleen during the first week of postnatal life.

The myeloid period of hematopoiesis commences during the third to fourth fetal months and becomes quantitatively important by the sixth fetal month. During the last three months of gestation, the bone marrow is the chief site of blood cell formation. Marrow cellularity becomes maximal at about the thirtieth gestational week, although the volume of marrow occupied by hematopoietic tissue continues to increase until term (Kalpaktsoglu and Emery, 1965). Following birth, the amount of marrow tissue continues to grow with no apparent increase in cellular concentration. The only way for an infant to increase cell production is to effect a more rapid turnover of cells or to increase the volume of hematopoietic tissue. This increase in tissue produces the marrow expansion that is most readily observed in the calvarium.

Erythropoiesis

The first true blood cells produced by the embryo belong to the red cell series. They are preceded by macrophages, which can be identified in the fetal liver by 4.5 weeks (Kelemen and Janossa, 1980). Two distinct generations of erythrocytes can be observed in the developing embryo. Red cells arise as a result of either primitive, megaloblastic erythropoiesis or definitive normoblastic erythropoiesis. Both types of cells apparently derive from similar-appearing hemocytoblasts and develop through roughly similar but morphologically distinct series of erythroblasts. In the very early embryo, the red cells arise from the primitive erythroblasts. These cells were termed megaloblasts by Ehrlich (1880) because of their resemblance to the erythroid precursors found in patients with pernicious anemia. Megaloblasts are large cells with abundant polychromatophilic cytoplasm, and they possess a nucleus in which the chromatin is fine and widely dispersed. Megaloblasts give rise to large, irregularly shaped, somewhat hypochromic erythrocytes. The primitive erythroblasts arise primarily from intravascular sites; as development continues, these cells gradually are replaced by smaller cells of the definitive or normoblastic series. Bizarre nuclear shapes and multinucleated erythroid precursors are not normally observed, but evidence of dyserythropoiesis may be pronounced in samples derived from nonfresh material. If delivery follows intrauterine death of the fetus, dyserythropoietic cells appear within a few hours and may increase to 50 per cent of all nucleated red cells. The degree of dyserythropoiesis does not change significantly after delivery in samples stored for as long as 24 hours in the refrigerator; however, dyserythropoiesis increases within 2 hours at 37°C (Kelemen et al., 1979).

Normoblastic erythropoiesis begins about the sixth gestational week and by the tenth week of development accounts for more than 90 per cent of the circulating erythrocytic cells. Maturation of normoblastic erythroid cells resembles that seen in postnatal life and is primarily extravascular.

From the studies of numerous investigators (Wintrobe and Schumacker, 1935; Mugrage and Andresen, 1936; Javert, 1939;

Table 1–1. Mean Red Cell Values During Gestation

Age (In Weeks)	*Hb (g./dl.)*	*Hematocrit (%)*	*RBC (10^6/mm.^{3})*	*Mean Corpusc. Vol. (fl)*	*Mean Corpusc. Hb (pg.)*	*Mean Corpusc. Hb Conc. (g./dl.)*	*Nuc. RBC (% of RBC's)*	*Retic. (%)*	*Diam. (μ)*
12	8.0–10.0	33	1.5	180	60	34	5.0–8.0	40	10.5
16	10.0	35	2.0	140	45	33	2.0–4.0	10–25	9.5
20	11.0	37	2.5	135	44	33	1.0	10–20	9.0
24	14.0	40	3.5	123	38	31	1.0	5–10	8.8
28	14.5	45	4.0	120	40	31	0.5	5–10	8.7
34	15.0	47	4.4	118	38	32	0.2	3–10	8.5

Walker and Turnbull, 1953; and Thomas and Yoffey, 1962), a general pattern of red cell changes is evident. In the early embryo, the red cell count, hemoglobin concentration, and packed cell volume are very low in comparison to those of the term infant or adult. However, the red cells are very large. Most of them are nucleated, and they contain large amounts of hemoglobin. As the fetus develops, the number of red cells, the hemoglobin concentration, and the volume of packed cells increase; the mean size of the cells, their mean corpuscular hemoglobin, and the proportion of circulating immature erythrocytes decrease. The mean cell thickness, which is determined from the mean cell volume and the mean cell diameter, also undergoes a progressive decrease throughout gestation. In the first trimester it averages 2.36 μ; in the second trimester, 2.29; and at term, 2.14, as contrasted with the normal adult value of 1.98 μ (Schulman, 1959). Despite these changes the mean corpuscular hemoglobin concentration remains relatively constant.

By the tenth gestational week, the red cell count ranges from 500,000 to 1,500,000 per mm.^{3} At this time, 5 to 10 per cent of all the circulating erythrocytes are nucleated and the reticulocyte count is approximately 80 per cent. The reticulocytes have a mean diameter of 10.5 μ and a mean cell volume of 250 fl. The hemoglobin concentration ranges from 6 to 9 g./dl., and the hematocrit ranges from 20 to 30 per cent.

By the twenty-fourth week of gestation, the hemoglobin has risen to approximately 14 g./dl., the hematocrit is 40 per cent, and the red blood cell count is 3,500,000. From this period until the termination of gestation at the fortieth week, there is a slow rise in hemoglobin, hematocrit, and red blood cell count. At the twenty-fourth week only 0.3 to 0.5 per cent of the circulating erythrocytes are nucleated, and the reticulocyte count has decreased to 10 per cent or less. Table

Table 1–2. Red Cell Values on First Postnatal Day*

	Gestational Age (weeks)							
	24–25 (7)†	*26–27 (11)*	*28–29 (7)*	*30–31 (25)*	*32–33 (23)*	*34–35 (23)*	*36–37 (20)*	*Term (19)*
RBC × 10^6	4.65‡ ± 0.43	4.73 ± 0.45	4.62 ± 0.75	4.79 ± 0.74	5.0 ± 0.76	5.09 ± 0.5	5.27 ± 0.68	5.14 ± 0.7
Hb (g./dl.)	19.4 ± 1.5	19.0 ± 2.5	19.3 ± 1.8	19.1 ± 2.2	18.5 ± 2.0	19.6 ± 2.1	19.2 ± 1.7	19.3 ± 2.2
Hematocrit (%)	63 ± 4	62 ± 8	60 ± 7	60 ± 8	60 ± 8	61 ± 7	64 ± 7	61 ± 7.4
MCV (fl.)	135 ± 0.2	132 ± 14.4	131 ± 13.5	127 ± 12.7	123 ± 15.7	122 ± 10.0	121 ± 12.5	119 ± 9.4
Reticulocytes (%)	6.0 ± 0.5	9.6 ± 3.2	7.5 ± 2.5	5.8 ± 2.0	5.0 ± 1.9	3.9 ± 1.6	4.2 ± 1.8	3.2 ± 1.4
Weight (g.)	725 ± 185	993 ± 194	1174 ± 128	1450 ± 232	1816 ± 192	1957 ± 291	2245 ± 213	

*From Zaizov, R. and Matoth, Y.: Am. J. Hematol. 1:276, 1976.
†Number of infants.
‡Mean values ± S.D.

1–1 summarizes the changes observed during gestation.

Red cell values obtained on the first day of life from infants at varying gestational ages are presented in Table 1–2. These data, compiled by Zaizov and Matoth (1976), are based on capillary blood samples.

Both mature erythroid cells from different erythropoietic sites in the fetus (Wood and Weatherall, 1973) and erythroid progenitors found in the liver, bone marrow, or peripheral blood of the fetus (Stamatoyannopoulos et al., 1979) produce identical quantities of fetal hemoglobin. The quantities produced in erythroid cultures reflect the gestational age of the fetus from which the sample is obtained.

Myelopoiesis

The production of leukocytes in the parenchyma of the liver and in various connective tissues such as the meninges, mesentery, and stroma of the lymph plexuses has been observed in the five to seven week embryo, but significant leukocyte production does not take place until the myeloid period of hematopoiesis. Marrow in the clavicle is the first to produce leukocytes (Gilmour, 1941). Granulocytes and granulocyte precursors represent 30 to 40 per cent of the cellular elements found in the bone marrow during the period between the tenth and twentieth weeks of gestation (Kelemen et al., 1979).

The observations of Thomas and Yoffey (1962) and Playfair et al. (1963) indicate that there are very few circulating granulocytes during the first half of gestation. Granulocyte counts in excess of 1000 per mm.^{3} were not observed during this period. During the last trimester of pregnancy, the granulocyte count seems to rise rapidly, and at birth the count is greater than in the adult.

Lymphopoiesis

Lymphopoiesis can be observed in the fetal liver and lymph plexuses at the seventh week of gestation. Between the seventh and tenth weeks, lymphopoiesis is present in the thymus and gut-associated lymphoid tissue. Lymphocytes are demonstrable in the spleen and bone marrow between the tenth and twelfth weeks of gestation (Kyriazis and Esterley, 1970; Jones, 1976; Kelemen et al., 1979). Circulating lymphocytes are detectable in fetal blood between 7 and 8 weeks. After their appearance, their number increases rapidly and by the twentieth week of gestation may reach a high of 10,000 per mm.^{3} During the second half of intrauterine life, the number of lymphocytes decreases slowly to approximately 3000 per mm.^{3} at term (Playfair et al., 1963).

T-lymphocytes have been identified as early as the seventh week of gestation. B-lymphocytes with IgG markers are observed in the eighth week of gestation, and by the sixteenth week of gestation more than 90 per cent of all lymphocytes in both the thymus and blood have T or B characteristics (Prindull, 1974; Wybran et al., 1973).

The time of appearance of monocytes is

Table 1–3. The First Appearance of Different Blood Cell Types in Hematopoietic Organs and in Circulating Blood, Given by Fertilization Age in Weeks*

	Extra-embryonic †	*Liver*	*Thymus*	*Spleen*	*Lymph Nodes*	*Bone Marrow*	*Blood*
Primitive erythroblasts	3–4	5		8		8–9	3–4
Definitive erythroblasts	6–7‡	5	10	8	11	8	6–7
Granulocytes	3–4§	5	10	8	12	8–9	7–8
Monocytes (classic)		?	18	11	12–13	11	7–8
Histiocytes, macrophages	3–4	5	10	8	11	8–9	3–4
Megakaryocytes, platelets	5‡	5	14	11		8–9	6–7
Lymphocytes	6	6	8	8	9–12	10–12	7–9
Mast cells‖							

*From Kelemen et al., 1979.
†Yolk sac, chorion, allantois, and body stalk.
‡From the circulating blood?
§Maternal origin is possible.
‖The bone marrow was the only site where substantial amounts of mast cells were distinguished.

variable. Monocytes were seen for the first time during the fifth fetal month by Knoll (1949), while Playfair and associates (1963) observed them as early as the fourth gestational week.

Megakaryocytes

Between the fifth and sixth weeks of gestation, megakaryocytes can be observed in the yolk sac, and from this time until the conclusion of gestation they also can be seen in the liver. Gilmour (1941) noted that after the third fetal month megakaryocytes were consistently present in the bone marrow. Platelets can be observed in the blood by the eleventh gestational week (Bleyer et al., 1971). By the thirtieth gestational week, megakaryocytic activity and the platelet count are similar to those of the adult (Kalpaktsoglou and Emery, 1965).

A summary of the first appearance of different blood cells in the various hematopoietic organs is provided in Table 1–3. These findings are derived from the work of Kelemen and associates (1979), who studied 190 human embryos and fetuses. For the reader who is interested in this topic their atlas should be consulted because it contains marvelous photomicrographs that vividly illustrate human hematopoietic development.

THE HEMATOLOGIC PICTURE AT BIRTH

Several important factors influence what is described as the normal blood picture in the newborn infant. The site of sampling, the time of sampling, the treatment of the umbilical vessels at the time of delivery, the gestational age of the infant, and the possibility of previous fetal-to-maternal or maternal-to-fetal transfusions all influence the so-called normal blood picture. These factors primarily affect hemoglobin and hematocrit values and the red cell count.

Site of Sampling

Capillary samples obtained by skin prick, generally from the heel or toe, have a higher hemoglobin concentration than simultaneously collected venous samples. Oettinger and Mills (1949) found that during the first hour of life the hemoglobin concentration of capillary blood averaged 20.3 g./dl., while blood obtained from the jugular vein averaged 16.7 g./dl. In some infants the difference in hemoglobin concentration amounted to 8 g./dl. Vahlquist (1941) observed that immediately after birth the hemoglobin concentration of heel prick samples was about 10 per cent greater than that taken at the same time from the femoral vein; Mollison (1961) observed only a 5 per cent difference in capillary and venous samples obtained a few hours after birth. Oh and Lind (1966) demonstrated that the capillary-venous hematocrit differences were greater in infants whose umbilical cord was clamped after all arterial pulsations had ceased. During the first five days of life, those infants who received a large placental transfusion maintained a greater capillary-venous hematocrit difference than the infants in whom the cord was clamped immediately after birth. Stasis of blood in the peripheral vessels, because of sluggish circulation with resultant transudation of plasma, is believed to be responsible for the discrepancy in the samples obtained from the different sites, which results in the higher capillary hemoglobin.

Even on the fifth day of life, Oettinger and Mills (1949) found that capillary samples had hemoglobin concentrations 12 per cent higher than those of venous blood, although Vahlquist (1941) could only demonstrate a 2.5 per cent difference on the sixth day of life.

One may conclude that in virtually all infants the capillary/venous hematocrit ratio will be greater than 1.0. The highest ratios, often in excess of 1.2, are observed in infants born before 30 weeks of gestation, in infants with blood pH values below 7.20, in infants with hypotension, and in infants with a red cell mass of less than 35 ml./kg. (Linderkamp et al., 1977). In other words, the capillary hemoglobin and hematocrit values are falsely elevated in the sickest infants — infants with disturbances in their microcirculation. These are the same infants in whom an accurate determination of hemoglobin concentration is most important for clinical management.

The capillary/venous hematocrit ratio gradually falls with increasing gestational age (Linderkamp et al., 1977). Infants born between 26 and 30 weeks of gestation have an average ratio of 1.21; infants born between 31 and 32 weeks, 1.12; infants born

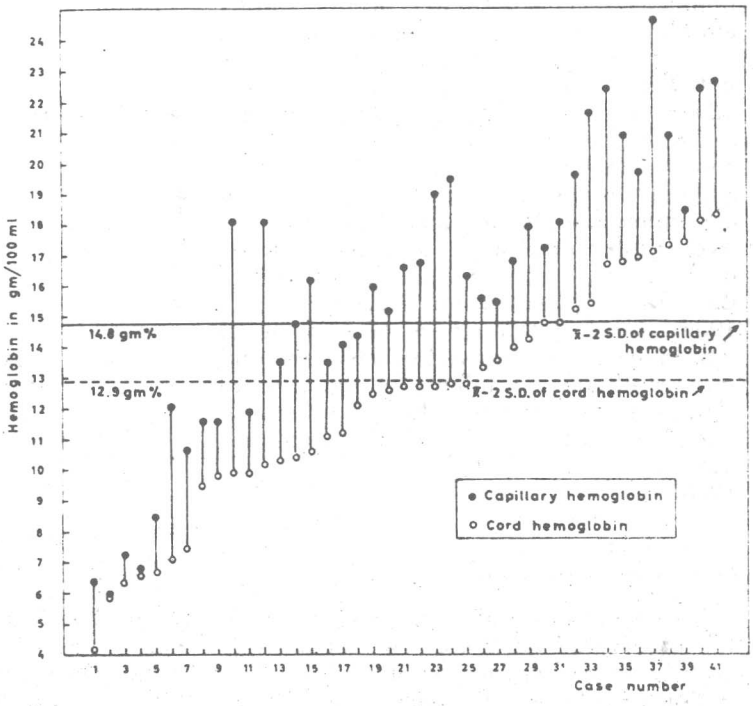

Figure 1–3. Umbilical cord and capillary hemoglobin values in 41 patients who required exchange transfusion. (From Moe, J.: Acta Paediatr. Scand. 56:391, 1967.)

between 33 and 35 weeks, 1.16; and infants born between 36 and 41 weeks, 1.12.

Significant capillary-venous differences in hematocrit and hemoglobin values persist into the third month of life and appear most related to postconceptual age. Infants with birth weights of less than 1500 g. have a mean venous-capillary difference of approximately 5 per cent at 12 weeks of age (Rivera et al., 1982).

The clinical importance of the site of sampling was illustrated by Moe (1967). In his study of 54 infants with erythroblastosis fetalis, cord blood and capillary blood specimens were obtained for hemoglobin and hematocrit determinations. Forty-one infants eventually required exchange transfusions for hyperbilirubinemia. Of these 41 infants, 25 were found to be anemic based on determinations performed on cord blood samples, while only 14 could be considered anemic according to values obtained from capillary samples. The discordant results from the two sampling sites are illustrated in Figure 1–3.

Differences in hemoglobin concentration between venous and capillary blood can be minimized by first warming the extremity before skin prick, obtaining good spontaneous blood flow, and discarding the first few drops before obtaining the samples (Moe, 1970). Capillary values should not be compared to previously obtained cord venous blood values when one is looking for changes in hemoglobin concentration during the first week of life. For this purpose venous blood should be obtained whenever possible. The selection of the vein is unimportant, for blood drawn from the external jugular, internal jugular, femoral, and scalp vein gives similar results (Gairdner et al., 1952a; Oh and Lind, 1966).

Time of Sampling

During the first few hours after birth, an increase in hemoglobin concentration takes place. In some infants this rise may be as great as 6 g./dl. This increase is partially a result of the placental transfusion that occurs at the time of delivery. The total blood volume of the infant rapidly adjusts after birth, decreasing in plasma volume while red cell volume remains essentially unchanged (Usher et al., 1963). This results in an increase in red cell count, hematocrit, and hemoglobin concentration. Gairdner et al. (1958) have shown that an increase in

hemoglobin concentration occurs shortly after birth even when the cord was clamped "as soon as conveniently possible." They noted that the hemoglobin increased from 16.6 to 19.1 g./dl. during a period of eight hours. At the same time, the plasma protein concentration increased from 6.5 to 7.0 g./dl. Although this increase in hemoglobin concentration after birth appears to be a relatively uniform phenomenon, the magnitude of the increase depends on the amount of the placental transfusion (Oh and Lind, 1966). Increased numbers of endothelial fenestrae can be observed in the peripheral skin capillaries of infants in whom cord clamping was delayed. This provides anatomic evidence for increased plasma extravasation in such babies (Pietra et al., 1968).

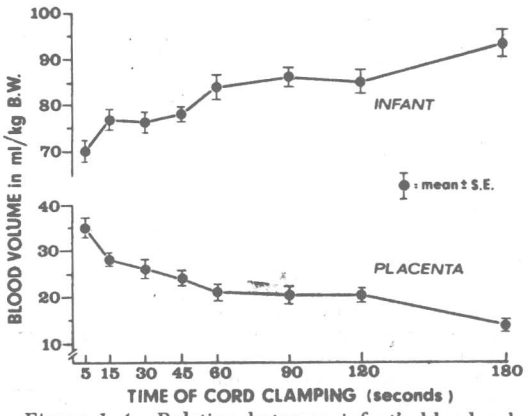

Figure 1–4. Relation between infant's blood volume and placental residual volume at various times of cord-clamping. (From Yao et al.: Lancet 2:891, 1969b.)

Treatment of the Umbilical Vessels

The manner in which the umbilical vessels are treated influences the hematologic values obtained during the first week of life and may even exert an effect throughout the first year of life. Both the hematologic and physiologic consequences of the placental transfusion have been extensively, and lucidly, reviewed by Yao and Lind (1974).

At birth the blood volume of the infant may be increased by as much as 61 per cent by allowing complete emptying of the placental vessels before the cord is clamped (Usher et al., 1963; Yao et al., 1969). It has been estimated that the placental vessels contain 75 to 125 ml. of blood at birth — or one-quarter to one-third the fetal blood volume (Hasselhorst and Allmeling, 1930; Goodall et al., 1938; Demarsh et al., 1942; and Colozzi, 1954). Under normal circumstances, about one-quarter of the placental transfusion takes place within 15 seconds of birth and one-half by the end of the first minute (Usher et al., 1963; Yao et al., 1969). The percentage ratio of blood between the infant's and the placenta's circulation has been found to average 67:33 at birth, 80:20 at one minute, and 87:13 at the end of the placental transfusion (Fig. 1–4). The placental transfusion occurs more rapidly in women who receive ergotamine derivatives at the onset of the third stage of labor (Yao et al., 1968).

The umbilical arteries generally constrict shortly after birth, so that no blood flows from the infant to the mother, although the umbilical vein remains dilated, permitting blood to flow in the direction of gravity. Infants held below the level of the placenta will continue to gain blood; infants held above the placenta may bleed into it (Gunther, 1957). Yao and associates (1969a) demonstrated that hydrostatic pressure, produced by placing the infant 40 cm. below the mother's introitus, hastened placental transfusion to virtual completion in 30 seconds. When the infant was held above the introitus the placental transfusion was either markedly reduced or completely prevented. In infants born by cesarean section, it would appear advisable to keep the baby at least 20 cm. below the placenta for approximately 30 seconds before clamping the cord, in order to insure a partial placental transfusion. This recommendation does not apply when dealing with infants suspected of having erythroblastosis fetalis. In this situation the cord should be clamped promptly in order to minimize the transfer of sensitized cells. Although Redmond et al. (1965) have presented evidence to indicate that the time of cord clamping in relation to the onset of respiration determines the amount of placental transfusion, the studies of Usher and associates (1963) and those of Yao et al. (1969) have failed to confirm their findings.

Results from reports on the effects of placental transfusion on the total blood volume of the infant show wide variability. This is partially because of the techniques employed and partially because of the time