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2,3-diphosphoglycerate
hemoglobin
oxygen affinity
oxygen transport
premature infant
respiratory distress syndrome

Postnatal Changes in Oxygen Transport of Term, Premature, and Sick Infants: The Role of Red Cell 2,3-Diphosphoglycerate and Adult Hemoglobin

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Extract

In view of previous studies which did not show a precise relation between the percentage fetal hemoglobin and the position of the oxygen hemoglobin equilibrium curve, this problem was reexamined taking into account both the concentration of fetal hemoglobin and the 2,3-diphosphoglycerate (2,3-DPG) content of the cell.

Forty-eight normal infants weighing 2500 g or more at birth were studied on days 1 and 5 of life and then at 3 and 6–9 weeks, and at 3–4, 5–6, and 8–11 months of age. Fifty-six infants ranging in birth weight from 900 to 2420 g were studied during the first 8 days of life and then at 2- to 3-week intervals until approximately 16 weeks of life. Twelve premature infants who were ill with the respiratory distress syndrome were also studied.

Laboratory procedures consisted of measurement of total hemoglobin, fetal hemoglobin, red cell 2,3-DPG, and oxygen equilibrium curves.

The "functioning DPG fraction" in millimicromoles per milliliter red blood cells (RBC) was obtained by multiplication of the total red cell DPG content (millimicromoles per milliliter RBC) by the percentage of adult hemoglobin.

These studies confirm previous observations that the term infant begins life with blood that has an increased affinity for oxygen. During the first few months of life the oxygen-hemoglobin equilibrium curve gradually shifts to the right and between 4 and 6 months of age becomes similar to that observed in the normal adult.

The change in P_{50} in these infants correlated neither with the change in red cell DPG content alone nor with the decline in fetal hemoglobin alone. Instead, the progressive decrease in oxygen affinity during the first 6 months of life correlated significantly ($r = 0.876$, $P < 0.001$) with the functioning DPG fraction. The term "functioning DPG fraction" is suggested to reflect the fact that both the DPG concentration and the adult hemoglobin concentration within the cell, with which the DPG interacts, are necessary factors in determining the position of the oxygen equilibrium curve.

Infants with respiratory distress appear to have P_{50} s that are lower than those of healthy infants of similar gestational age and birth weight. This appears to be primarily a result of a decrease in red cell DPG concentration. It is this type of infant who may benefit from exchange transfusion with fresh adult blood.

Speculation

It would appear that the fetal red cell with its fetal hemoglobin that is less able to interact with DPG and decrease its affinity for oxygen is well suited for the fetus in its intrauterine environment. The same hemoglobin, however, appears poorly suited to meet the demands of extrauterine stress because of an inability to respond to hypoxia by significantly increasing oxygen unloading capacity. In situations of hypoxic stress the newborn infant might fare better if his blood were replaced with the fresh blood of an adult.

Introduction

In 1930 Anselmino and Hoffman [2] first observed that the oxygen affinity of human fetal blood was greater than that of maternal blood. In 1931 Haselhorst and Stromberger [20] and in 1933 Eastman and associates [17] also demonstrated that the oxygen tension at which hemoglobin is half-saturated, P_{50}, was approximately 6 mm Hg lower in cord blood than in maternal blood.

In 1953 Allen, Wyman, and Smith [1] showed that, although the intact fetal cell possessed a higher affinity for oxygen than did the red cells of normal adults, when adult and fetal hemoglobin solutions were dialyzed against the same surrounding solution the resulting oxygen affinities were identical. They suggested, therefore, that the reported differences in oxygen equilibria may result from differences in the environment of the hemoglobin molecule rather than from intrinsic properties of the molecule itself. These findings were confirmed and extended in 1962 by Schruefer *et al.* [32] and most recently by Bauer *et al.* [7].

Studies of the properties of the intracellular environment and of the membrane have failed to provide an explanation for the differences in oxygen affinity of the two types of cells [12, 22]. In 1967 Benesch and Benesch [9] and Chanutin and Curnish [11] demonstrated that the affinity of a solution of adult hemoglobin for oxygen may be decreased by its interaction with organic phosphates. The two principal organic phosphates of the human erythrocyte, 2,3-DPG, and adenosine triphosphate (ATP) combine reversibly with deoxyhemoglobin and shift the oxygen-hemoglobin equilibrium curve to the right. Since 2,3-DPG comprises approximately 60% of the organic phosphate of the human red cell, it is quantitatively the most important in this regard. Subsequent studies in older children and adults have shown a precise relation between red cell 2,3-DPG content and the position of the oxygen-hemoglobin equilibrium curve [14, 18, 24, 26, 27].

Studies employing fetal hemoglobin have failed to demonstrate this interaction with 2,3-DPG. Both 2,3-DPG and ATP had little effect on altering the oxygen affinity of fetal hemoglobin while their effect on the oxygen affinity of adult hemoglobin was profound [6, 15, 30, 37].

In view of previous studies which did not show a precise relation between the percentage fetal hemoglobin and the position of the oxygen-hemoglobin equilibrium curve [4, 8] this problem was reexamined taking into account both the concentration of fetal hemoglobin and the 2,3-DPG content of the cell.

Premature and term infants were studied sequentially, and evidence will be presented to demonstrate that the oxygen affinity of hemoglobin, as reflected by the P_{50}, is determined neither by the concentration of fetal hemoglobin nor by that of 2,3-DPG alone but by the interaction of 2,3-DPG with the adult hemoglobin present in the red cells of the developing infants. In addition, the consequences of these changes on oxygen delivery and its alterations in neonatal disease will be described.

Materials and Methods

Subjects

Term infants. Forty-eight normal infants weighing 2500 or more at birth were studied on days 1 and 5 of life and then at 3 and 6–9 weeks, 3–4, 5–6, and 8–11 months of age. Some randomly selected healthy infants were also studied at periods ranging from 3 to 11 months of age.

Premature infants. Fifty-six infants ranging in birth weight from 900 to 2420 g were studied during the first 8 days of life and then at 2- to 3-week intervals until approximately 16 weeks of life.

Sick infants. This group was comprised of 12 premature infants who were ill with the respiratory distress syndrome. In four infants exchange transfusions or simple blood transfusions were performed.

Controls. Twenty healthy, nonsmoking adults served as normal controls.

Laboratory Procedures

Six to ten milliliters blood were obtained from each infant anaerobically in well heparinized syringes [41]. The blood was kept chilled in wet ice until the time of analysis.

Total hemoglobin concentration, hematocrit, and reticulocyte counts were performed by standard hematological techniques. The mean corpuscular hemoglobin concentration (MCHC) was obtained from the ratio of hemoglobin to hematocrit.

Fetal hemoglobin was determined by alkali denaturation [35]. Red cell 2,3-DPG was determined by the method of Krimsky [23] as modified by Schröter and Heyden [31] employing the extraction procedure described by Beutler *et al.* [10] for 0.1-ml samples of blood.

The oxygen equilibrium curves were obtained by directly measuring the oxygen tension, pH, and oxygen saturation following equilibration of whole blood (at a constant carbon dioxide tension) at varying oxygen contents. At least three points were obtained for each curve with oxygen saturation ranging from 30 to 60% at a constant temperature of 37°. The P_{50} was then obtained from the regression line drawn through the data points on the steep part of the oxygen equilibrium curve [14]. The Po_2 and Pco_2 were measured with the appropriate electrodes at 37° [34] and the pH with a radiometer glass microelectrode while the oxygen saturation was measured directly by a spectrophotometric technique on lysed whole blood [28]. The n values were calculated using Hill's expression $\log [So_2/100 - So_2] = n \log Po_2 + \log K$. To compare the affinity of the hemoglobin for oxygen in different clinical situations all P_{50}s were corrected to pH 7.40 using the Bohr factor of −0.485 [33].

Oxygen capacity in milliliters of oxygen per 100 ml of blood was calculated by multiplication of the hemoglobin concentration in grams per 100 ml by 1.39 [38]. Where the blood sample was sufficient, oxygen capacity was measured directly by the Van Slyke technique.

The unloading capacity in milliliters of oxygen per 100 ml of blood was calculated from the oxygen equilibrium curve, with oxygen content instead of oxygen saturation on the ordinate. It represents the amount of oxygen that can be extracted from the blood for a given difference in Po_2. As "arterial" point we chose the Po_2 which gave 95% saturation; the "venous" Po_2 was assumed to be 40 mm Hg.

The "functioning DPG fraction" in millimicromoles per milliliter RBC was obtained by multiplication of the total red cell DPG content (millimicromoles per milliliter RBC) by the percentage of adult hemoglobin. The whole blood buffer base in milliequivalents per liter was calculated by the Henderson-Hasselbach equation and corrected for the measured hematocrit [36].

RESULTS

Normal Term Infants

The results of the studies of 48 normal term infants are presented in Table I. The mean P_{50} on the first

Table I. Oxygen transport in term infants

No. of infants	Age	Total Hb, g/100 ml blood	Hct, %	MCHC, %	O_2 capacity, ml/100 ml blood	P_{50} at pH 7.40, mm Hg	2,3-DPG, mμmoles/ml RBC	Fetal Hb, % of total	FFDPG,[1] mμmoles/ml RBC	Reticulocyte count, %
19	1 day	17.8	52.7	34.2	24.7	19.4	5433	77.0	1246	4.7
		±2.0[2]	±7.1	±1.9	±2.8	±1.8	±1041	±7.3	±570	±1.74
18	5 days	16.2	46.9	34.1	22.6	20.6	6580	76.8	1516	2.15
		±1.2	±6.0	±0.8	±2.2	±1.7	±996	±5.8	±495	±1.64
14	3 weeks	12.0	33.5	35.9	16.7	22.7	5378	70.0	1614	0.88
		±1.3	±4.3	±1.2	±1.9	±1.0	±732	±7.33	±252	±0.71
10	6–9 weeks	10.5	30.2	34.9	14.7	24.4	5560	52.1	2670	1.63
		±1.2	±3.9	±0.6	±1.6	±1.4	±747	±11.0	±550	±0.65
14	3–4 months	10.2	30.3	33.8	14.3	26.5	5819	23.2	4470	1.36
		±0.8	±2.4	±1.7	±1.2	±2.0	±1240	±16.0	±1380	±0.45
8	6 months	11.3	34.0	33.4	14.7	27.8	5086	4.7	4840	1.42
		±0.9	±3.6	±0.7	±0.6	±1.0	±1570	±2.2	±1500	±1.15
8	8–11 months	11.4	34.8	32.8	15.9	30.3	7381	1.6	7260	0.82
		±0.6	±1.9	±0.9	±0.8	±0.7	±485	±1.0	±544	±0.27

[1] Functioning fraction of 2,3-diphosphoglycerate.

[2] All values are given as mean ± 1 SD.

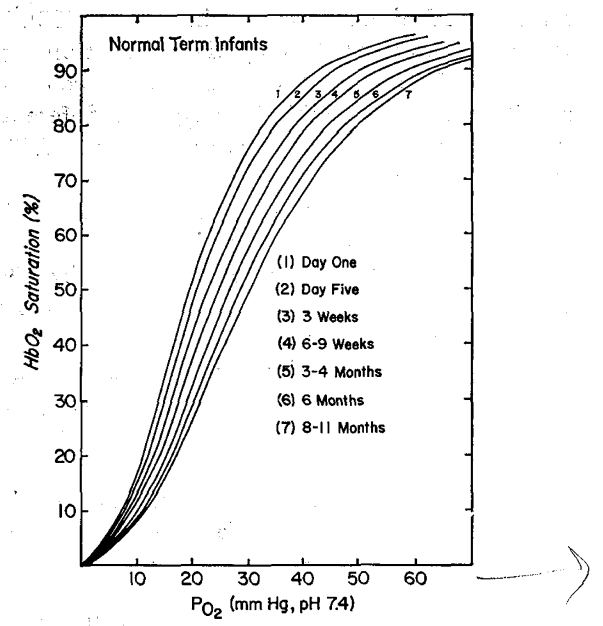


Fig. 1. Oxygen equilibrium curves of blood from term infants at different postnatal ages; each curve represents the mean value of the infants studied in each age group.

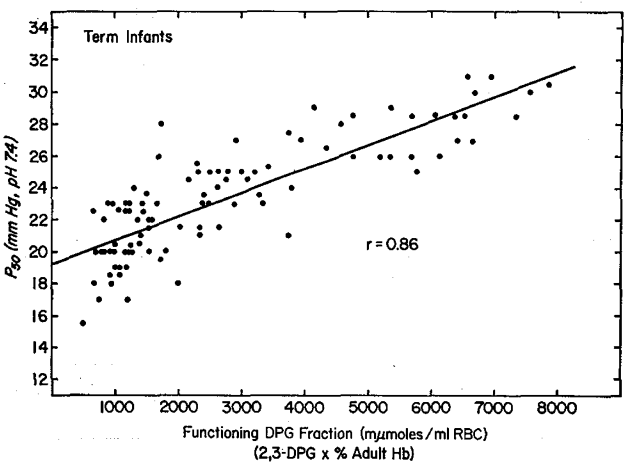
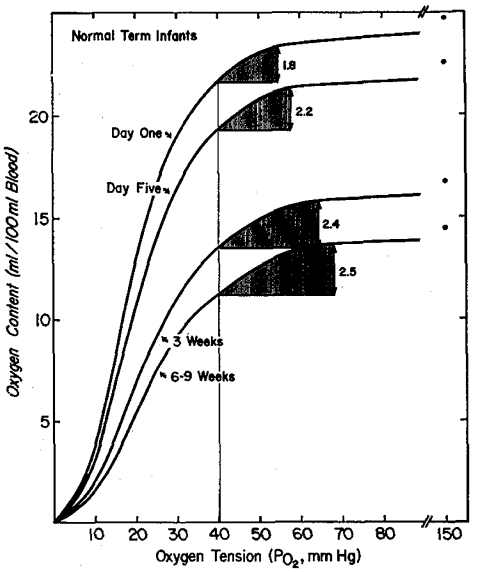


Fig. 2. The P_{50} and functioning DPG fraction of all *term infants* at different postnatal ages.

day of life was 19.4 ± 1.8 mm Hg as contrasted with a value of 27.0 ± 1.1 mm Hg for the normal adults. In these infants the P_{50} rose significantly during the first 5 days of life to 20.6 ± 1.7 mm Hg ($P < 0.05$). From day 5 the P_{50} gradually continued to increase and reached normal adult values by months 4–6 of life (Fig. 1). The red cell DPG on day 1 averaged 5433 ± 1041 mμmoles/ml RBC and thus did not differ significantly from that of the normal adults (5114 ± 418 mμmoles/ml RBC). By day 5 the DPG had increased to 6580 ± 996 mμmoles/ml RBC and then gradually declined. By 8–11 months of age the P_{50} in these infants averaged 30.3 mm Hg and exceeded that of the normal adult. At this age the red cell 2,3-DPG was also considerably elevated while the fetal hemoglobin concentration had decreased to that of the normal adult.



Figs. 3 and 4. Oxygen equilibrium curves of blood from term infants at different postnatal ages. Double arrows represent the oxygen-unloading capacity between a given "arterial" and "venous" P_{O_2}. Points corresponding to 150 mm Hg on the abscissa are the O_2 capacities; each curve represents the mean value of the infants studied in each age group.

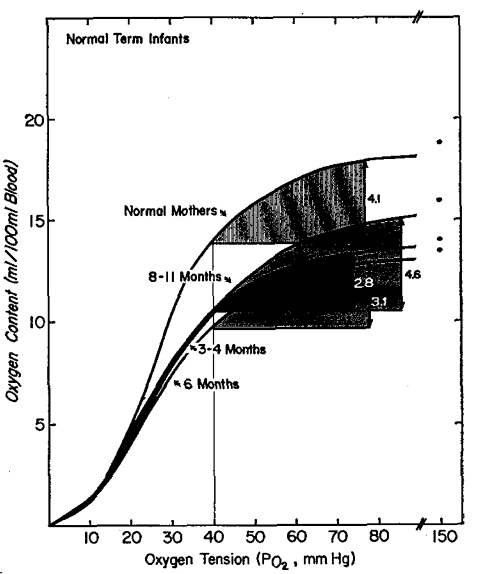


Fig. 4.

The functioning DPG fraction that initially was 1246 ± 570 mμmoles/ml RBC increased to 1516 ± 495 by day 5 and reached the normal adult value of 4000–5000 mμmoles/ml RBC by 4–6 months of age. When the value for P_{50} was related to the red cell DPG alone or the adult hemoglobin concentration alone, no significant correlation was observed. When the value for P_{50} was related to the functioning DPG fraction (Fig. 2), the correlation coefficient was 0.876 ($P < 0.001$). The unloading capacities shown in Figures 3 and 4 increased from day 1 of life to reach adult levels at 6 months.

Normal Premature Babies

The results of the studies obtained from premature infants are grouped according to their birth weight (Table II).

Group I was comprised of infants of less than 1000 g;

Table II. Oxygen transport in premature infants

Age	Total Hb, g/100 ml blood	Hct, %	MCHC, %	O_2 capacity, ml/100 ml blood	P_{50} at pH 7.40, mm Hg	2,3-DPG, mμmoles/ml RBC	Fetal Hb, % of total	FFDPG,[1] mμmoles/ml RBC
Group I (<1000 g)[2]								
2 weeks	17.2	47.0	36.6	23.9	18.0	6255	83.0	1002
4 weeks	8.5	26.0	32.7	11.8	15.0	3923	81.0	761
9 weeks	7.2	22.0	32.7	10.0	15.0	4636	87.1	974
11 weeks	7.7	22.5	34.2	10.7	17.0	5867	78.0	1290
Group II (1001–1,500 g)								
1–2 days	15.1	45.7	33.0	21.0	18.0	4124	86.6	580
	±1.3[3]	±3.7	±0.7	±1.8	±1.7	±1562	±3.1	±287
5–8 days	13.4	41.4	33.5	18.7	18.9	4501	84.4	903
	±1.1	±3.2	±2.9	±1.5	±3.0	±1919	±3.8	±689
2–3 weeks	12.6	33.6	34.2	15.9	21.2	5721	83.3	1119
	±3.1	±6.0	±1.1	±3.1	±1.9	±1375	±5.1	±557
4–5 weeks	8.8	25.3	34.9	12.3	20.5	6095	85.2	931
	±0.9	±1.8	±1.7	±1.3	±1.7	±2081	±2.3	±456
6–9 weeks	9.1	24.5	35.1	11.8	23.4	8734	77.2	1995
	±1.7	±5.8	±2.2	±2.4	±1.1	±1854	±1.9	±480
9–10 weeks[4]	8.2	24.0	34.0	11.1	24.0	9000	77.0	2070
Group III (1501–2000 g)								
1–2 days	16.1	47.8	33.7	22.4	19.3	4475	87.2	703
	±0.9	±1.9	±1.9	±1.2	±0.9	±1174	±3.6	±331
5–8 days	16.8	48.5	34.7	25.3	19.8	5489	79.4	1056
	±3.3	±10.0	±0.5	±4.7	±1.3	±1428	±5.0	±590
2–3 weeks	13.6	40.4	34.4	18.8	21.3	6002	80.6	1184
	±3.0	±9.8	±1.5	±4.0	±1.8	±998	±5.8	±329
4–5 weeks	11.2	31.9	35.5	15.5	20.8	5841	75.8	1569
	±2.8	±9.9	±2.2	±3.8	±1.6	±839	±7.8	±577
6–9 weeks	8.0	22.1	35.9	11.1	24.0	7290	67.5	2457
	±0.7	±1.7	±0.7	±1.0	±0.9	±634	±6.2	±575
Group IV (2001–2500 g)								
1–2 days	15.9	46.2	35.8	21.9	20.2	5306	76.8	1258
	±0.9	±5.8	±1.9	±1.5	±1.6	±1075	±5.4	±392
5–8 days	15.6	47.0	34.2	21.5	21.3	6417	77.7	1457
	±1.7	±5.0	±1.1	±2.4	±3.3	±1527	±6.3	±603
2–3 weeks	12.3	35.1	34.9	17.1	22.0	7145	76.9	1666
	±1.1	±3.2	±0.5	±1.5	±1.3	±1737	±4.7	±472
6–9 weeks[4]	14.0	44.0	34.0	19.5	25.5	7100	43.0	3212

[1] Functioning fraction of 2,3-diphosphoglycerate.
[2] Only one patient.
[3] Values are given as mean ± SD.
[4] Less than five infants.

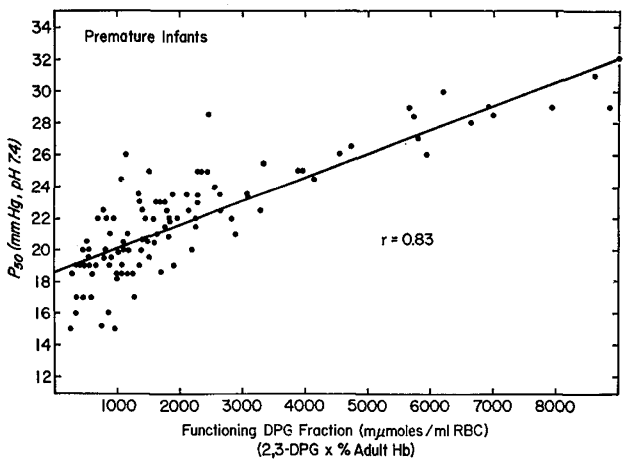


Fig. 5. The P_{50} and functioning DPG fraction of all *premature infants* at different postnatal ages.

group II, 1001–1500 g; *group III,* 1501–2000 g; and *group IV,* infants weighing 2001–2460 g. Where applicable, results were expressed as mean ± 1 SD.

In general the smaller infants had lower red cell DPG, lower P_{50}, and higher fetal hemoglobin concentrations. During the first several weeks of life these small infants had functional DPG fractions that were significantly lower than those of the term infants.

Group I. Only three infants were admitted to the nursery during the study period, of whom only one survived beyond 1 week of age. The results are given in Table II.

Group II. The mean P_{50} during the first 2 days of life was 18 mm Hg, rose to 18.9 at 1 week, and was 21.0 mm Hg for the following 6 weeks after which time there was a significant increase to 23.4 mm Hg. Red cell 2,3-DPG was 4124 mμmoles/ml RBC during the first 2 days of life and gradually increased to 4501 at 1 week, to 5721 at 3 weeks, 6095 at 4–5 weeks, and 8734 mμmoles/ml RBC at 6–9 weeks. Fetal hemoglobin remained unchanged for the first 6 weeks at 84.5 ± 3.0%. The functioning DPG fraction, however, steadily increased from 580 mμmoles/ml RBC during week 1 to 2000 mμmoles/ml RBC by 6–9 weeks of age.

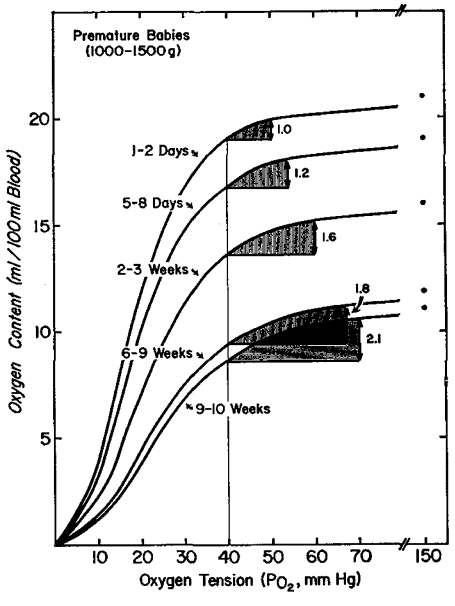
Group III. The mean P_{50} was 19.3 mm Hg during the first 2 days of life and rose to 19.8 at the end of week 1 and to 21.3 mm Hg between weeks 2 and 3; by 6–9 weeks the mean P_{50} was 23.0 mm Hg. Red cell 2,3-DPG initially was 4475 mμmoles/ml RBC and rose to 5489 by the end of week 1 and to 6002 by 2–3 weeks; at 6–9 weeks the red cell 2,3-DPG was 7290 mμmoles/ml RBC. Fetal hemoglobin slowly decreased from 87.2 ± 3.6% at birth to 67.5% by 6–9 weeks of age. Functional DPG fraction increased from 703 at birth to 2457 mμmoles/ml RBC at 6–9 weeks of age.

Group IV. The mean P_{50} was 20.2 mm Hg at 2 days of age and rose to 21.3 at week 1 and to 22.0 mm Hg at 2–3 weeks of age. Red cell 2,3-DPG was 5306 mμmoles/ml RBC at 2 days and rose to 6417 at week 1, and 7145 mμmoles/ml RBC at 2–3 weeks of age. Fetal hemoglobin remained relatively unchanged at 77.0% for the first 3 weeks of age. The functioning DPG fraction increased from 1250 to 1670 mμmoles/ml RBC during the first 3 weeks of life.

For the entire group of premature infants the correlation coefficient between the O_2 affinity and the functioning DPG fraction was 0.867 ($P < 0.001$ (Fig. 5)). For all groups the mean oxygen unloading capacities are depicted in Figures 6, 7, and 8. All the premature infants had smaller unloading oxygen capacities initially than the term infants and did not catch up during the first 3 months of life.

Infants with Respiratory Distress Syndrome

The findings in 12 infants with the respiratory distress syndrome are presented in Table III and contrasted with those of normal premature and term infants. In this group of 12 infants the P_{50}, the red cell



Figs. 6, 7, and 8. Oxygen equilibrium curves of blood from all weight groups of premature infants at different postnatal ages. Double arrows represent the oxygen-unloading capacity between a given "arterial" and "venous" P_{O_2}. Points corresponding to 150 mm Hg on the abscissa are the O_2 capacities; each curve represents the mean value of the infants studied in each age group.

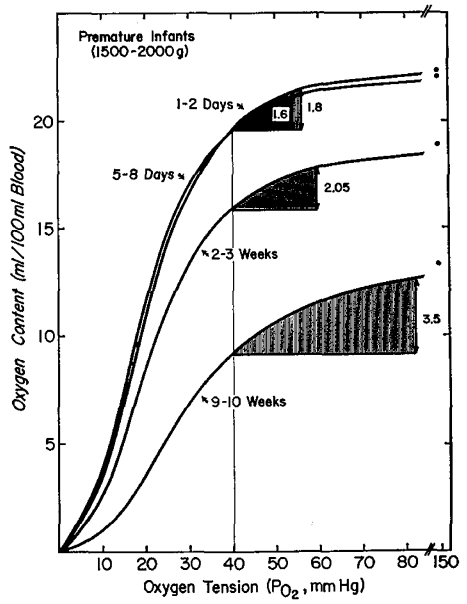


Fig. 7.

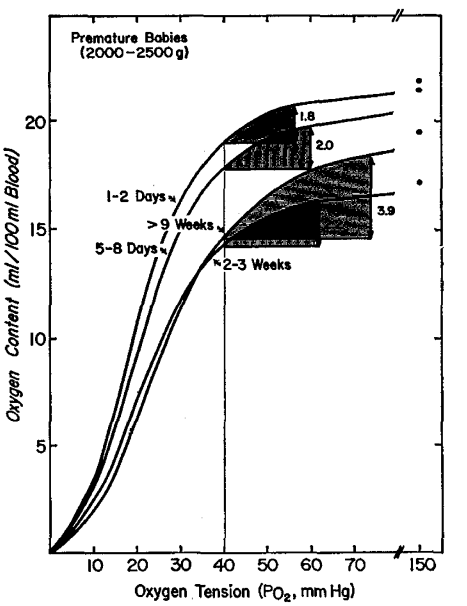


Fig. 8.

2,3-DPG, and the functioning fraction of DPG were all found to be significantly lower. The sequential changes in the P_{50}, the red cell 2,3-DPG, percentage fetal hemoglobin, and the functioning fraction of 2,3-DPG, in four infants who received exchange transfusion are presented in Table IV. In these infants a marked increase in the P_{50} was produced by the exchange transfusion. This was a consequence of a decrease in the fetal hemoglobin concentration and an increase in the functioning fraction of 2,3-PDG.

Discussion

These studies confirm previous observations that the term infant begins life with blood having an increased affinity for oxygen. During the first few months of life the oxygen-hemoglobin equilibrium curve gradually shifts to the right and (between 4 and 6 months of

Table III. Oxygen transport in infants with respiratory distress syndrome

Infant group	Birth wt, g	P_{50} at pH 7.40, mm Hg	2,3-DPG, mμmoles/ml RBC	Fetal Hb, % of total	FFDPG[1], mμmoles/ml RBC
Term	3100	19.4	5433	77.0	1246
	±520[2]	±1.8	±1041	±7.3	±570
Prematures	1500	18.6	4320	86.9	640
	±410	±1.6	±1280	±3.2	±300
Respiratory distress syndrome	1490	16.5	2640	87.3	343
	±240	±.8	±575	±2.8	±187

[1] Functioning fraction of 2,3-diphosphoglycerate.
[2] All values are given as mean ± 1 SD.

Table IV. Sequential changes in oxygen affinity following exchange transfusion of infants with respiratory distress syndrome

Infant	Birth wt, g	P_{50} at pH 7.40, mm Hg	2,3-DPG, mμmoles/ml RBC	Fetal Hb, % of total	FFDPG[1], mμmoles/ml RBC
Before exchange transfusion					
C[2]	1300	17.0	2900	83.5	478
S	1100	19.0	4137	88.6	472
W	1790	19.0	4000	82.3	669
J[3]	2381	19.0	3467	87.2	440
One day after exchange transfusion					
C		21.0	3020	63.1	812
S		23.5	3047	4.1	2922
W		23.5	7535	64.8	2652
J		24.5	4263	4.0	4118
One week after exchange transfusion					
C		22.5	4435	38.9	2700
S		26.0	4791	4.1	4595
W		25.0	7902	60.9	3090
J		29.0	7221	3.9	6939

[1] Functioning fraction of 2,3-diphosphoglycerate.
[2] Simple transfusion of 30 ml fresh heparinized blood.
[3] Infant of a diabetic mother, 36 weeks gestation, ventilated by intermittent positive pressure respiration.

age) becomes similar to that of the normal adult. Sequential studies performed in infants born prematurely reveal that this shift in the oxygen-hemoglobin equilibrium curve is far more gradual for the first 3 months of life, in comparison to the term infant. Adult values are not achieved in *group I* and *II* infants until late in the 1st half-year of life.

This study, like previous studies [4, 8], failed to demonstrate a precise correlation between the decrease in the oxygen affinity of the neonate's blood and the progressive decline in the concentration of fetal hemoglobin ($r = 0.410$). The observation that the P_{50} in the term infant actually increases from a mean of 19.4 to 20.6 during week 1 of life while fetal hemoglobin concentration remains unchanged clearly suggests the influence of other factors.

During this 1st week of life the level of red cell 2,3-DPG rises sharply [21] and then returns to the initial birth level by weeks 2–3 and remains unchanged for the next 6 months. The same pattern was also observed in newborn lambs [5].

In adults the decreased oxygen affinity of hemoglobin in the presence of normal temperature and hydrogen ion concentration seems to be controlled by the concentration of the red cell 2,3-DPG. Increased 2,3-DPG levels and a displacement of the oxygen equilibrium curve to the right have been documented in numerous clinical conditions [14, 18, 24, 26, 27]. In contrast, when the data from both the term and premature infants were evaluated, it was observed that the position of the oxygen-hemoglobin equilibrium curve, as reflected by the P_{50}, was not directly related to the total red cell 2,3-DPG.

Thus the change in P_{50} in these infants correlated neither with the change in red cell DPG content alone nor with the decline in fetal hemoglobin alone. Instead, the progressive decrease in oxygen affinity during the first 6 months of life correlated significantly ($r = 0.876$, $P < 0.001$) with the functioning DPG fraction. The term "functioning fraction" is not intended to imply that a compartmentalized portion of the red cell's 2,3-DPG is in combination with the hemoglobin but instead is introduced to underscore the fact that both 2,3-DPG and adult hemoglobin act in concert to determine the oxygen affinity of the cell.

This relation serves to explain why during week 1 of life infants with similar concentrations of fetal and adult hemoglobin may have marked differences in their P_{50}s. Infants with more adult hemoglobin but less DPG may have a P_{50} similar to that of an infant with a high red cell DPG but increased quantities of fetal hemoglobin.

The oxygen-carrying capacity of the blood decreases during the first 3–4 months of life because of the progressive fall in the total hemoglobin concentration. Despite this fall in the oxygen-carrying capacity the oxygen-unloading capacity is enhanced as a result of the gradual shift to the right of the oxygen-hemoglobin equilibrium curve. In Figures 2 and 3 sequential increases in the ability of blood to deliver oxygen are illustrated. At a mixed venous oxygen tension of 40 mm Hg, arbitrarily selected as the normal venous oxygen tension at rest, the 3-month-old infant is delivering more oxygen to his tissues than the newborn infant despite the fact that his hemoglobin has fallen from 17.0 g/100 ml to approximately 10.5 g/100 ml. The increase in the oxygen-unloading capacity also correlates with the increase in the functioning DPG fraction.

It would appear that exposure to the normal atmospheric environment is not the stimulus for the decrease in fetal hemoglobin concentration. The level of fetal hemoglobin persists in the infants born prematurely for much longer periods of time than is observed in those infants born at term. The maturational factors responsible for this "switch" from fetal to adult hemoglobin synthesis remain unknown.

At about 3 months of age it has been shown that erythropoietin secretion increases and can be detected in the urine [25]. The increase in erythropoietin secretion at this age has been attributed to the anemia that has developed with its resultant hypoxemia. Our findings would suggest that anemia *per se* is not responsible; but at this time increased oxygen demands must be present which then result in increased oxygen utilization, increased oxygen extraction, and a resultant decrease in tissue oxygen tension. This decrease in tissue oxygen tension would then serve as the stimulus for erythropoietin and not merely the fall from 17 to 10.5 g/100 ml in the hemoglobin concentration.

The effects of exchange transfusion or simple transfusions of adult blood clearly illustrate (Fig. 9) the effects of increasing the adult hemoglobin concentration and the functioning DPG fraction on tissue oxygen delivery. Immediately after transfusion the functioning DPG fraction increased, the P_{50} shifted to the right, and the unloading capacity of the blood for oxygen increased. By the following day the oxygen affinity for hemoglobin and the unloading capacity, in most cases, compared with those of normal adults. At this point the functioning DPG fraction had reached

the level of the adult's normal red cell DPG total content.

In sick infants these procedures facilitate oxygen release at higher tissue oxygen tensions. Without this shift to the right, the infant, in times of need, would be forced to drop his tissue oxygen tension or markedly increase his cardiac output in order to extract increased amounts of oxygen. The newborn infant has a limited capacity to increase his cardiac rate. A significant fall in the oxygen tension would result in encroachment upon the ill defined level of "critical oxygen tension." When central venous oxygen tensions drop below this level, oxygen diffusion exchange in the periphery may be impaired because of the narrowed gradient between vessel and cell.

The infants with respiratory distress appeared to have P_{50}s that were lower than those of healthy infants [16, 19] of similar gestational age and birth weight. This appears to be primarily a result of a decrease in red cell DPG concentration. It is this type of infant who may benefit from exchange transfusion with fresh adult blood provided that arterial oxygen tension is also raised to 50–60 mm Hg. The potentially fatal case of *baby J*, an infant with severe respiratory distress, illustrates this point. This infant had a progressive fall in his arterial Po_2 to 16 mm Hg at 12 hr of age and was moribund. In this infant intubation and assisted ventilation were instituted, which raised the arterial Po_2 to 60 mm Hg. Then an exchange transfusion was performed. Infants with this severe degree of hypoxemia associated with the respiratory distress syndrome do not survive, even with assisted ventilation (13). *Baby J* did survive the neonatal period, and his course is illustrated in Figure 9.

To date, most studies of the respiratory distress syndrome in the newborn have focused on arterial oxygenation, a variable of obvious importance, and little attention has been given to an equally important physiologic variable, that of oxygen release. Replacement of blood containing primarily fetal hemoglobin with that containing adult hemoglobin does not hinder arterial oxygenation in the extrauterine environment, providing the arterial oxygen tension does not fall below 50–60 mm Hg. Oxygen unloading, however, is facilitated by this procedure by decreasing the affinity of hemoglobin for oxygen.

Fresh adult blood must be used if the procedure is to be helpful because the P_{50} of adult blood falls rapidly with storage (38).

It will be necessary to measure both arterial and central venous oxygen tension in these infants both before and after exchange transfusion to confirm these theoretical calculations.

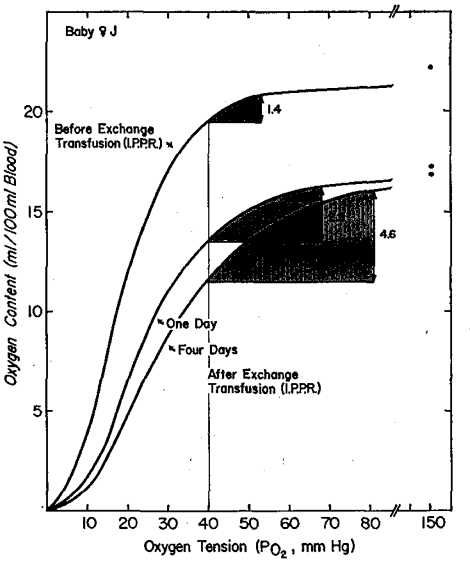


Fig. 9. The sequential oxygen equilibrium curves of the blood of an infant with severe respiratory distress syndrome treated with exchange transfusion and intermittent positive pressure respiration. Double arrows represent the oxygen-unloading capacity between a given "arterial" and "venous" Po_2. Points corresponding to 150 mm Hg on the abscissa are the O_2 capacities. In this infant the oxygen delivery increased from 1.4 to 4.6 ml during the course of 1 week.

It is of considerable interest that the incidence of the respiratory distress syndrome appears decreased in those infants receiving intrauterine exchange transfusions of adult blood [39]. Obviously, other factors may be operative, but the role of adult hemoglobin must be critically examined.

Summary

Sequential studies of the P_{50}, fetal hemoglobin, and red cell DPG concentrations were performed in 48 term and 56 premature infants. In term infants the P_{50} averaged 19.4 mm Hg on day 1; 20.6 on day 5; 26.6 at 3–4 months, and 28.0 at 6 months (normal adult 27.0 ± 1.1 mm Hg). The initial P_{50} of the premature infants was lower, and its change during the first 3 months of age was more gradual. In all babies the P_{50} did not correlate precisely with the percentage fetal hemoglobin alone or the DPG alone but correlated significantly with the product of the red cell DPG content times the percentage adult hemoglobin ("functioning DPG fraction"). Calculations indicated that

the term infant at 3 months of age with a hemoglobin of 11.0 g/100 ml was delivering more oxygen to his tissues at a mean venous Po_2 of 40 mm Hg than the newborn with a hemoglobin of 17.0 g/100 ml blood. Sick infants were found to have lower P_{50}s and DPG levels than normal infants. Infants given either simple or exchange transfusions of fresh adult blood showed an increased functioning DPG fraction, a shift of the oxygen equilibrium curve to the right, and an oxygen-unloading capacity that reached levels of a 6-month-old infant. It is suggested that exchange transfusion with fresh adult blood may be beneficial to these sick infants by raising their functioning DPG fraction and thus increasing their oxygen delivery to tissues at higher venous oxygen tensions.

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