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Physiologic Factors Affecting Respiratory Stability in Premature Infants

Author
Ertel-Howley, Joan K

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By

Joan K. Ertel-Howley

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THESIS

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PHYSIOLOGIC FACTORS AFFECTING RESPIRATORY STABILITY IN PREMATURE INFANTS

by

Joan Ertel-Howley

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I wish to thank my colleagues at Kaiser San Francisco, all my friends who have been so supportive, and my family--especially my mother who helped me build the mattress and has given me more than just a little encouragement in my mid-life trek to doctorhood. I also want to thank my friend Anne Parker and my partner Penney Magrane who play essential roles in my life and without whom this process would be dull indeed. It is to them that this work is dedicated.

TABLE OF CONTENTS

		page
I.	Introduction	1
II.	Background	3
	A. History	3
	B. Epidemiology	6
	C. Cost of Care	7
	D. Major Problems of Prematurity	8
III.	Premature Versus Full-Term Birth	11
	A. Gestational Age Determinations	11
	B. SGA	15
	C. LGA	16
	D. LBW and VLBW	16
IV.	Change From Fetal Circulation	23
	A. Change in Circulation at Birth	23
	B. Persistent Fetal Circulation	27
V.	From Fetus to Neonate	28
	A. Fetal Lung Development	28
	B. Neonatal Physiology	30
VI.	First Breath	35
VII.	Role of Surfactant, The Laplace Principle	
	$P = 2T/r$	40

		page
VIII.	Ventilation and Perfusion	50
IX.	Gas Exchange	55
	A. Transition to Hemoglobin A	55
	B. Oxygenation of Hemoglobin	57
	C. Oxygen-Hemoglobin Dissociation	58
X.	Normal Oxygen Transport	61
XI.	Factors Affecting the Affinity of Hemoglobin for Oxygen	63
	A. Content and Type of Hemoglobin	64
	B. 2,3-DPG	68
	C. ATP	73
	D. pH	74
	E. CO_2	75
	F. Temperature	76
XII.	Effects of the Environment on Gas Exchange in Premature Infants	78
	A. Thermal Environment	78
	B. Nursery Activity	85
XIII.	Respiratory Distress Syndrome	88
	A. Definition	88
	B. Incidence	89

page

C. Pathogenesis 90

D. Treatment 92

E. Complications: Hypoxia, Oxygen Toxicity, RLF, BPD, IVH 99

F. Prevention 103

XIV. A Proposal for a Noninvasive Technique to Decrease the Lability of PaO_2 107

XV. Conclusion 144

Bibliography 147

I

INTRODUCTION

The transition from fetal to extrauterine life is a critical period and one associated with many potential hazards. When birth is premature or the infant at birth is dysmature, the potential for both morbidity and mortality is increased. Neonatal-Perinatal medicine has evolved as a discipline out of the need to focus attention on this critical period.

Within the broad field of neonatology my own interest has centered on respiratory physiology and the transition from the intrauterine to extrauterine environment and establishment of respiration. The successful change from placental gas exchange to breathing is impeded when the architecture of the lung is immature. Establishment of respiration is a complicated process which requires anatomic, physiologic, and biochemical components of the system to be intact and properly functional. In order to understand the deviations in these mechanisms that occur in respiratory distress syndrome (RDS) in premature infants, it is necessary to understand the normal physiology. I have presented a rather in-depth review of these mechanisms in the following chapters which culminate in an overview of RDS.

Many of the complications of premature birth that produce serious handicaps are the result of RDS and an immature respiratory system. Serious complications are associated both

with the failure to adequately oxygenate the brain and vital organs and as a result of treatment complications and toxic effects of oxygen.

Clearly the best treatment of RDS is the prevention of prematurity. For the time being, I leave this to the obstetricians and perinatologists. I focus instead on the prevention of the complications of treatment. I have, in this thesis, proposed a noninvasive technique to reduce the incidence and sequelae of hypoxia and oxygen toxicity by altering the premature infant's microenvironment to reduce noxious stimuli, provide positive proprioceptive stimulation, reduce thermal lability, reduce nonpurposeful gross motor activity, and conserve heat and energy. The principles of this new technique have been successfully applied by others but I offer as support the basis of these principles in basic science.

II

BACKGROUND

A. History

Early statistics on the incidence and survival of premature infants are sketchy since birth weights have only been recorded in a regular way in more recent time and estimations of gestational age were based solely on maternal dates until Lubchenco, Dubowitz (175, 89) and others devised accurate measurement tools. Some early estimates of preterm birth are available from Tarnier and Budin's days at the Maternité in France around 1880 (66). From 1879 to 1880 mortality of babies weighing less than 2000 grams was about 68%. From 1880 to 1882 mortality at the Maternité dropped 42% with the introduction of the incubator. France was the leader in the care of prematures at the turn of the century.

Until the conclusion of World War II, little research or resources were directed toward improving generally poor neonatal survival rates. In the first quarter of the century statistics on the incidence of premature birth are scarce and vary between institutions from 5-25% (224). The most frequent cause of premature birth at this time was chronic disease of the mother. Few women were delivered in hospitals and most neonatal care was provided at home (256). This trend persisted into the 1930s and early 1940s. Gradually maternity units expanded, incubators became accepted by pediatricians providing care for low birth

weight (LBW) infants and premature centers began to emerge.

After World War II there was a sudden boom in the birth rate and, at least in the United States, increased economic resources available for advancing the quality of perinatal care. Two serious diseases were prominent; hyaline membrane disease (later to be renamed Respiratory Distress Syndrome), and retrolental fibroplasia, both associated with premature birth although the former as a pathologic entity and the latter a sequelae of treatment.

Prematurity now, instead of the result of chronic disease in the mother, began to be seen as associated with other maternal risk factors such as adolescence, substance abuse, poor maternal nutrition, and low socioeconomic status. This fact had political and economic repercussions. Accurate statistics indicated unacceptable levels of perinatal mortality and morbidity among high risk populations (59). Nutritional supplement programs were developed and special emphasis was aimed at improving perinatal outcome in the segment of the population at greatest risk of mortality (58).

Newborn intensive care units began to flourish in the 1960s, but care was conservative until the advent of the technology of the 1970s which provided the beginning of advanced life support techniques used today. The incidence of premature birth varies between 5% and 10% of live births and varies tremendously from country to country and within geographic regions (104).

An average incidence of 8% accounts for 75% of perinatal deaths. Even a small decline in the incidence of prematurity would have tremendous impact on mortality.

Since respiratory distress syndrome (RDS) is the most common problem associated with prematurity, advances in the care of this disease have had major impact on morbidity and mortality rates in the neonatal period. Table 2-1 provides the chronology of some of the important advances in this area (95).

Table 2-1.

Chronology of advances in understanding of pulmonary surfactant and RDS

Date	Observations and research trends
1902	Initial description of pulmonary hyaline membranes (PHM)
1923	First English description of PHM in association with neonatal pneumonia
1929	Discovery of the effects of surface forces at the air-water interface of the lung
1930-1949	Prevailing view that PHM resulted from aspirated amniotic sac contents
1936-1942	Description of structural features of fetal lung development, including three stages *(glandular, canalicular, and alveolar)*
1949	Proposal that an interval of air breathing was prerequisite to development of PHM
1950	Association of PHM with prematurity, fetal anoxia, maternal diabetes, and cesarean section
1950	Description of the clinical respiratory abnormalities associated with PHM
1951	PHM considered to be a secondary phenomenon resulting from tissue damage
1953-1955	Roentgenographic description of the reticulogranular pattern in generalized atelectasis
1954-1959	Elucidation of major pulmonary function abnormalities in RDS
1955-1957	Discovery of surfactant in pulmonary edema foam and lung extracts
1955-1958	Proposal that atelectasis is significant factor in respiratory distress with PHM
1955-1960	Clarification of the clinical pattern of RDS
1959	Demonstration of pulmonary surfactant deficiency in infants succumbing to RDS
1961	Identification of phosphatidylcholine (lecithin) as the major surfactant component
1961-1965	Lowered RDS mortality with intensive respiratory and metabolic care
1962-1967	Description of the timing of lung surfactant appearance during late gestation
1965-1967	Observation that lung phosphatidylcholine concentrations are decreased in RDS
1965-1970	Demonstration that aggressive mechanical ventilation improves survival in severe RDS but causes bronchopulmonary dysplasia
1971	Discovery of the predictability of amniotic fluid lecithin/sphingomyelin ratios, allowing prevention of *iatrogenic RDS*
1971	Improved oxygenation with continuous positive airway pressure
1971-1973	Discovery of the physiologic and biochemical effects of corticosteroids on the fetal lung
1971-1975	Demonstration of enhanced neonatal care via regionalized perinatal programs
1972	Direct demonstration by electron microscopic autoradiography of the role of type II pneumonocytes
1972	Prevention of RDS with antenatal corticosteroid administration
1974	Clarification of pathways for de novo biosynthesis of lung phosphatidylcholine
1975	Discovery of phosphatidylglycerol as a significant component of surfactant
1975-1980	Growing interest in surfactant secretion and turnover
1981-1985	Exogenous surfactant therapy by airway instillation
1983-1985	Emphasis on lung injury and repair (pathogenesis of bronchopulmonary dysplasia, lung antioxidants, new modes of mechanical ventilation)
1985-	Molecular biology of surfactant components being defined, including apoprotein

B. Epidemiology

Low birth weight (LBW) infants have the greatest risk of mortality and morbidity in infancy and childhood (Fanaroff). LBW infants (<2500 grams) have a 40 times higher mortality rate than infants with normal birth weights. The relative risk of neonatal mortality is 200 times greater for very low birth weight (VLBW) infants, weighing up to 1500 grams (95).

At the beginning of this century two-thirds of infant mortality occurred in the neonatal period and was primarily due to infectious disease. By 1950, 7.5% of live born infants were LBW and still two-thirds of infant deaths occurred in the neonatal period. Instead of mortality due to infectious disease, the major culprits were birth trauma, asphyxia, congenital malformations, and prematurity (30).

From 1965 to 1980 the infant mortality rate decreased significantly due to increased survival of LBW infants. This decrease has been attributed to the increased proportion of care to LBW infants being delivered in tertiary perinatal centers. By the early 1980s LBW still accounted for two-thirds of the neonatal mortality but VLBW infants accounted for half of this number (31).

The biggest mortality rates were shifted to the lower birth weight infants and surviving LBW infants remained more likely to have untoward neurologic sequelae. The risk of morbidity increases as birth weight decreases. This fact was supported by

two recent studies on the outcome of VLBW infants (149, 225). Both studies looked at neontal morbidity and mortality in infants 500 to 1000 grams. Mortality rates in this group varied from 35% to 74.6%. The percentage of survivors with handicaps remains unacceptably high. The incidence of functional handicap has been assessed at 23% to 50% of survivors with birth weights less than 1000 grams. There is increased incidence of handicap in the lowest birth weight infants.

C. Cost of Care

Advances in neonatal intensive care have significantly reduced overall neonatal morbidity and mortality (53, 167, 194). But a short time ago even the most highly technological unit rarely salvaged very low birth weight (VLBW) infants, less than 1500 grams, intact. Infants with birth weights less than 1000 grams still have mortality and morbidity that are significantly higher than infants of other weight categories (193, 215, 260). These very tiny premature infants require prolonged and often repeated hospitalizations if they do survive and frequently survive with varying degrees of handicaps.

Walker and associates (260) performed a cost-benefit analysis of infants weighing between 500 and 999 grams at birth and found a 68% mortality rate. Ten percent of survivors had moderate neurodevelopmental handicaps. Sixteen percent had severe handicaps. Walker analyzed cost of care for survivors and found costs in 1982 dollars of $362,992 per survivor for those weighing

600 to 699 grams. Costs declined as birth weight increased. Her conclusion was that intensive care may not be economically justifiable for infants weighing less than 990 grams at birth.

The medical costs of neonatal intensive care continue to climb. The cost of hospitalization in an intensive care nursery (ICN) has been reported to range from $16,000 to $250,000 (31, 260, 217, 214). Approximately 40% of VLBW survivors require subsequent hospitalizations (181, 130). Shankaran et al. (232) studied total medical costs of care from ICN discharge to age 3 years and found costs increased proportionally with severity of handicap. The U.S. Department of Agriculture estimated the medical costs of childrearing at home to range from $22 to $27 per month. Shankaran states the cost of raising an ICN infant in an institution is $1216 per month. The cost of home care for ICN survivors with moderate to severe handicaps was $109 $\pm$ $59 for outpatient care and $542 $\pm$ $737 for inpatient care.

In all the studies reviewed, ICN care and increased severity of handicap are associated with astronomical medical costs. Life long costs were least for those survivors of the ICN with the least neurodevelopmental handicaps.

D. Major Problems of Prematurity

The major handicapping sequelae of premature birth are the results of socioeconomic and cultural influences superimposed on genetic, metabolic, and physiologic intrauterine and extrauterine environmental effects. Cerebral palsy, mental retardation,

sensory and cognitive disabilities, and diminished ability to adapt socially, psychologically, and physically to the environment are problems associated with prematurity and LBW infants. LBW survivors have an increased incidence of disability from a broad range of conditions including neurodevelopmental handicaps, congenital anomalies, respiratory illnesses, and the iatrogenic complications of neonatal intensive care (95).

In Saigal's 1984 study of LBW survivors (225), 74% had RDS, 45% had bronchopulmonary displasia (BPD), 77% had patent ductus arteriosus (PDA), 42% had clinical sepsis, 20% had necrotizing enterocolitis, 21% had intraventricular hemorrhage (IVH), and 9% had seizures requiring anticonvulsant therapy. Percentages may vary slightly in other studies of LBW survivors, but clearly survival is associated with high levels of serious sequelae and potential for handicap.

Of the potentially serious results of prematurity and LBW, there are differences which are dependent upon both birth weight and maturity and their correlation. Chapter III covers these distinctions which are necessary to appreciate if efforts at prevention are to be properly directed. Certain causes of premature birth may be avoided and identification of high risk pregnancy may provide appropriate intervention at a stage when complications may be avoided. Of particular interest to me is the definition of which problems are the results of neonatal intensive care and which, with appropriate understanding of

the pathophysiology, may be diminished by altered methods of care.

III

FULL-TERM VERSUS PRETERM BIRTH

A. Gestational Age Determination

In the 1960's there was a surge in perinatal research. Gruenwald (130), among others, demonstrated convincingly that infants of low birth weight (LBW), that is less than 2500 grams, were not all simply premature as they had always been previously classified. LBW infants may be prematurely born, less than 37 weeks gestation, or may be full-term infants who are small for their gestational age (SGA). Both groups of infants have associated increased morbidity although SGA infants have less mortality than very premature infants.

The distinction of SGA versus prematurity was difficult to make until a tool was developed to accurately define the gestational age of the infant. Neurologic evaluation of gestational age was elucidated between 1962 and 1968 by the works of several French researchers (7, 156, 226). In 1970 Dubowitz (89) published a scale that provided a reliable scoring system for evaluating neurologic findings and physical characteristics.

Three techniques are most commonly used to determine gestational age. These are:

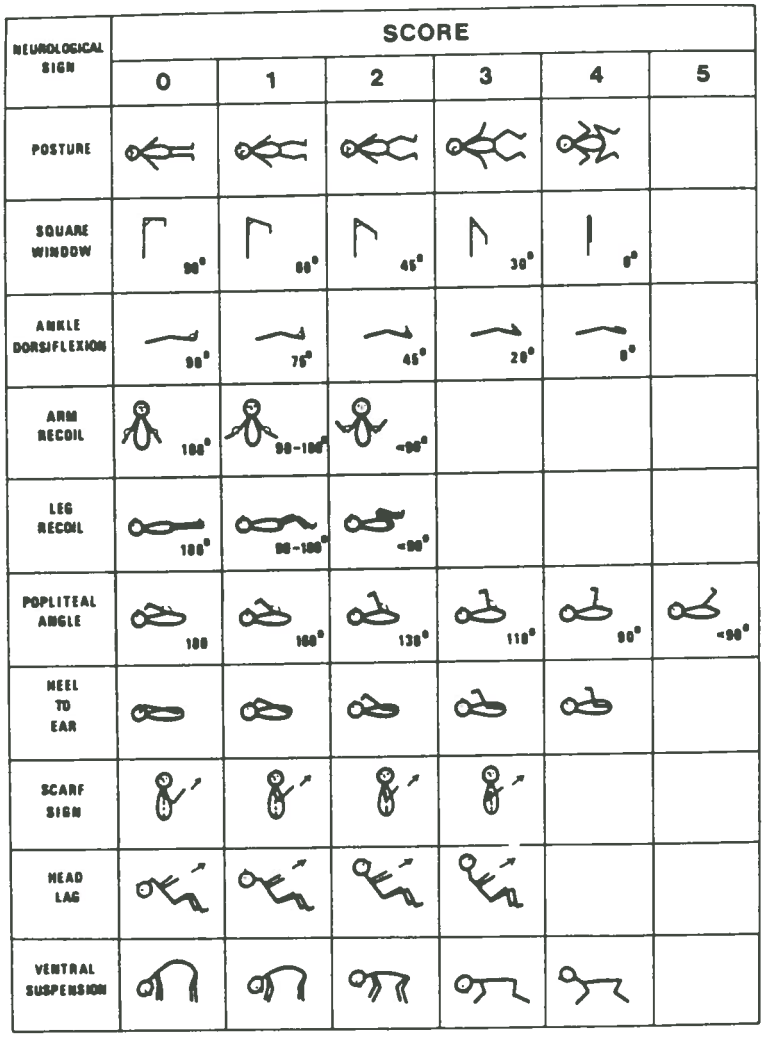
1. The assessment of external physical characteristics;
2. The neurologic evaluation;
3. Scoring systems which combine the external physical

characteristics and the neurologic evaluation (175).

An example of this type of scoring system is provided in Figure 3-1 and Table 3-1 (89, 7).

An abbreviated version of the Dubowitz system was developed by Ballard (21) and does not require the infant to be vigorous or alert (Figure 3-2) (8).

Figure 3-1.



The scoring of neurologic findings according to Dubowitz et al. from Amiel-Tison.

Table 3-1.

TECHNIQUES OF NEUROLOGIC ASSESSMENT*

Posture
With the infant supine and quiet, score as follows:

arms and legs extended	= 0
slight or moderate flexion of hips and knees	= 1
moderate to strong flexion of hips and knees	= 2
legs flexed and abducted, arms slightly flexed	= 3
full flexion of arms and legs	= 4

Square Window
Flex the hand at the wrist. Exert pressure sufficient to get as much flexion as possible. The angle between the hypothenar eminence and the anterior aspect of the forearm is measured and scored according to Figure 4-4. Do not rotate the wrist.

Ankle Dorsiflexion
Flex the foot at the ankle with sufficient pressure to get maximum change. The angle between the dorsum of the foot and the anterior aspect of the leg is measured and scored as in Figure 4-4.

Arm Recoil
With the infant supine, fully flex the forearm for five seconds, then fully extend by pulling the hands and release. Score the reaction according to:

remain extended or random movements	= 0
incomplete or partial flexion	= 1
brisk return to full flexion	= 2

Leg Recoil
With the infant supine, the hips and knees are fully flexed for five seconds, then extended by traction on the feet and released. Score the reaction according to:

no response or slight flexion	= 0
partial flexion	= 1
full flexion (less than 90° at knees and hips)	= 2

Popliteal Angle
With the infant supine and the pelvis flat on the examining surface, the leg is flexed on the thigh and the thigh fully flexed with the use of one hand. With the other hand the leg is then extended and the angle attained scored as in Figure 4-4.

Heel-to-Ear Maneuver
With the infant supine, hold the infant's foot with one hand and move it as near to the head as possible without forcing it. Keep the pelvis flat on the examining surface. Score as in Figure 4-4.

Scarf Sign
With the infant supine, take the infant's hand and draw it across the neck and as far across the opposite shoulder as possible. Assistance to the elbow is permissible by lifting it across the body. Score according to the location of the elbow:

elbow reaches the opposite anterior axillary line	= 0
elbow between opposite anterior axillary line and midline of thorax	= 1
elbow at midline of thorax	= 2
elbow does not reach midline of thorax	= 3

Head Lag
With the infant supine, grasp each forearm just proximal to the wrist and pull gently so as to bring the infant to a sitting position. Score according to the relationship of the head to the trunk during the maneuver:

no evidence of head support	= 0
some evidence of head support	= 1
maintains head in the same antero-posterior plane as the body	= 2
tends to hold the head forward	= 3

Ventral Suspension
With the infant prone and the chest resting on the examiner's palm, lift the infant off the examining surface and score according to the posture shown in Figure 4-4.

*According to Dubowitz et al from Amiel-Tison

Figure 3-2.

Neuromuscular Maturity

	0	1	2	3	4	5
Posture						
Square Window (wrist)	 90°	 60°	 45°	 30°	 0°	
Arm Recoil	 180°		 100°-180°	 90°-100°	 <90°	
Popliteal Angle	 180°	 160°	 130°	 110°	 90°	 <90°
Scarf Sign						
Heel to Ear						

Apgars _____ 1 min _____ 5 min

Age at Exam _____ hrs

Race _____ Sex _____

B.D. _____

LMP _____

EDC _____

Gest. age by Dates _____ wks

Gest. age by Exam _____ wks

B.W. _____ gm. _____ %ile

Length _____ cm. _____ %ile

Head Circum. _____ cm. _____ %ile

Clin. Dist. None _____ Mild _____

Mod. _____ Severe _____

PHYSICAL MATURITY

Skin	gelatinous red, transparent	smooth pink, visible veins	superficial peeling &/or rash few veins	cracking pale area rare veins	parchment deep cracking no vessels	leathery cracked wrinkled
Lanugo	none	abundant	thinning	bald areas	mostly bald	
Plantar Creases	no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases cover entire sole	
Breast	barely percept.	flat areola no bud	stippled areola 1–2 mm bud	raised areola 3–4 mm bud	full areola 5–10 mm bud	
Ear	pinna flat, stays folded	sl. curved pinna; soft with slow recoil	well-curv. pinna; soft but ready recoil	formed & firm with instant recoil	thick cartilage ear stiff	
Genitals ♂	scrotum empty no rugae		testes descending, few rugae	testes down good rugae	testes pendulous deep rugae	
Genitals ♀	prominent clitoris & labia minora		majora & minora equally prominent	majora large minora small	clitoris & minora completely covered	

MATURITY RATING

Score	Wks
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Assessment of gestational age, University of Cincinnati. (With thanks to Dr. J. Ballard

The determination of weight compared to length of gestation has identified two other groups of infants at risk besides those who are premature. These are the small for gestational age (SGA) neonates and large for gestational age (LGA) neonates.

B. SGA

SGA babies may be full-term but small, less than 2500 grams, and dysmature rather than premature. SGA is most often the result of intrauterine growth retardation (IUGR). Failure to grow in utero may be due to maternal, placental, or fetal circumstances and is a complex problem worthy of separate discussion. The outcome of SGA infants is compounded by prematurity. Because dismature infants have different perinatal adaptation problems than low birth weight (LBW) premature babies, identification of SGA is important in the immediate newborn period (Table 3-2) (255).

FACTORS IMPLICATED IN THE ETIOLOGY OF INTRAUTERINE FETAL GROWTH RETARDATION

Fetal Factors
Chromosomal disorders (e.g., autosomal trisomies)
Chronic fetal infections (e.g., cytomegalic inclusion disease, congenital rubella, syphilis)
Radiation injury
Multiple gestation
Pituitary failure (?)
Placental Factors
Decreased placental weight or cellularity or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Twin transfusion syndrome (parabiotic syndrome)
Localized transfer lesions (?)
Maternal Factors
Toxemia
Hypertensive or renal disease or both
Hypoxemia (high altitude, cyanotic, cardiac, or pulmonary disease)
Malnutrition or chronic illness
Sickle cell anemia
Experimental Factors
Maternal uterine ischemia – rat
Fetal placental ischemia – sheep and monkey
Maternal protein deprivation – rat, guinea pig, and pig

C. LGA

LGA infants are macrosomic, greater than 4000 grams, and often the progeny of diabetic mothers. Prevalence of overt diabetes complicating pregnancy has been estimated to approximate 0.5% of all gestations in the United States. An additional 3% of women demonstrate some kind of biochemical abnormality that occurs transiently and is unmasked only during pregnancy (201). Without appropriate care perinatal mortality is 10 times higher in diabetic women than the normal population. Gestational diabetics have a twofold increased risk over the normal population (183).

Insulin has been implicated as the primary growth hormone for intrauterine development. When insulin is absent there is marked intrauterine growth retardation. Conversely, maternal and fetal hyperglycemia and increased maternal levels of amino acids and free fatty acids results in fetal hyperinsulinism producing the anabolic actions of insulin. This results in increased protein synthesis and excessive deposition of fat and glycogen which accounts for the macrosomic infant of diabetic mothers (136). These infants are at risk for complications of hypoglycemia, hypocalcemia, hyperviscosity, and hyperbilirubinemia.

D. LBW and VLBW

LBW (low birth weight) infants weighing up to 2500 grams who are born prematurely or are retarded in intrauterine growth are 40 times more likely to die than normal term infants. VLBW (very

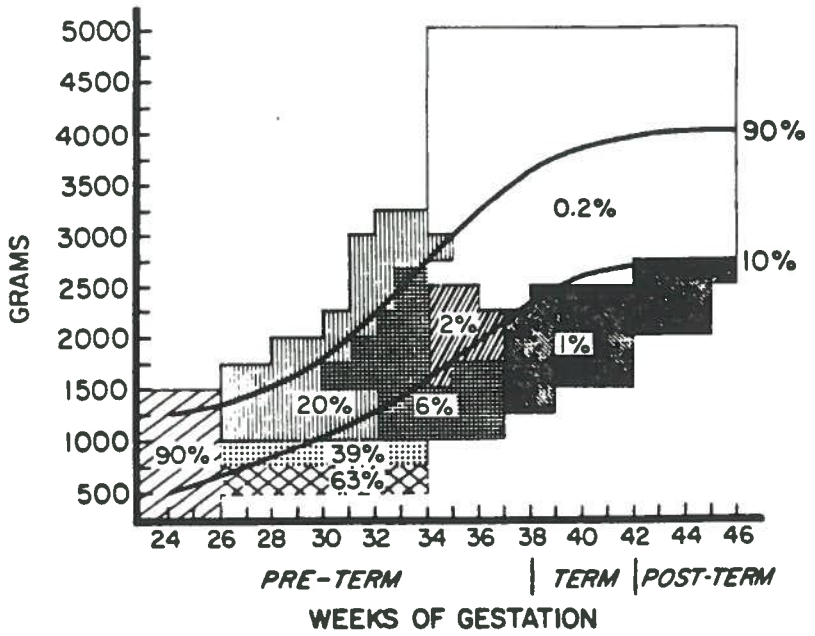
low birth weight) infants, weighing up to 1500 grams have a neonatal death rate 200 times greater than normal infants (31). Epidemiology and risk factors associated with LBW have already been discussed.

LBW infants have a greater risk of perinatal morbidity and mortality than normal term infants. The most common causes of death are respiratory distress syndrome, intraventricular hemorrhage, septicemia, asphyxia, birth injuries, and malformations (32).

VLBW infants account for approximately 1% of all births. Survival in this group is directly related to birth weight. Only 2% of infants weighing 500 to 600 grams survive, while 85% to 95% of infants survive when birth weights are 1250 to 1500 grams (30). Surviving VLBW infants do not have an increased morbidity as a result of decreasing mortality rates. These infants do, however, have an increased incidence of rehospitalization in their first year of life. Subsequent hospitalizations are for such causes as inguinal hernias, infection, and treatment of chronic sequelae of prematurity (30).

Mortality risk comparisons of birth weight and gestational age have been studied in detail by Sweet (Figure 3-3). Although neonatal mortality has decreased over the past 15 years, the incidence of LBW has only decreased a small amount. Behrman's 1985 data show a modest decline in LBW but essentially no decline

Figure 3-3.



Mortality risk according to birth weight–gestational age relationship. (From Sweet, A.Y.: Classification of the low birth weight infant. In Klaus, M.H., and Fanaroff, A.A., editors: Care of the high-risk neonate, ed. 3, Philadelphia, 1986, W.B. Saunders Co.)

in VLBW infants. The relative risk of LBW birth is highest for blacks, teen mothers, and those who fail to obtain prenatal care. It is important to realize there is more than a 200% difference between blacks and whites in the incidence of LBW birth in the United States (31) (Table 3-3).

Table 3-4 provides a comparison of clinical problems in SGAs and premature infants. The major pulmonary difference is due to lack of organ development in prematures versus the affects of in utero stress for SGA infants. Apnea, hyperbilirubinemia, and

Table 3-3.

Decline in low birth weight rates per 1000 deliveries

	Weight	1971	1976	1981
United States	VLBW*	11	12	12
	MLBW†	65	61	56
California	VLBW	9	9	10
	MLBW	57	52	49
Massachusetts	VLBW	10	9	9
	MLBW	61	57	50
Michigan	VLBW	12	13	13
	MLBW	64	62	57
North Carolina	VLBW	14	14	15
	MLBW	74	69	65
Oregon	VLBW	8	8	9
	MLBW	49	46	41

From Behrman R E J Pediatr **107**:842 1985
*Very low birth weight = 1500 gm
†Moderately low birth weight 1 501 to 2 500 gm

Table 3-4.

COMPARISON OF PROBLEMS OF SMALL-FOR-GESTATIONAL-AGE AND IMMATURE INFANTS

	Small-for-Gestational-Age°	*Immature*
Birth weight of siblings	Low	Normal
Early weight change	0 to <5% loss then rapid gain	5 to 10% loss then slow gain
Pulmonary problems	Aspiration syndrome Pneumomediastinum Pneumothorax	Hyaline membrane disease
Apnea spells	±	+++
Infection (congenital)	++	±
Hyperbilirubinemia	+	++++
Hypoglycemia	+++	+
Hypocalcemia	+	+
Hematocrit	Normal or high	Normal or low
Congenital malformation	+++	±
Intracranial hemorrhage	+	+++
Persistent fetal circulation	++	+
Growth	Catch-up by 6 months or remain small	Normal

°Problems of small-for-gestational-age infants of very short gestation become less distinguishable from those of immature ones.

intracranial hemorrhage are problems seen more often in the premature infant. Congenital infection, hypoglycemia, and congenital malformations are more often observed in the SGA infant (152).

Maternal risk factors associated with delivery of a LBW infant without distinguishing SGA or premature infants has been outlined by Behrman (31) (Table 3-5).

Table 3-5.

Risk factors associated with low birth weight

I Demographic risks
- A Age (younger than 18, older than 35 years)
- B Race (black)
- C Low socioeconomic status
- D Unmarried
- E Low level of education

II Medical risks preceding pregnancy
- A Parity (0 or more than 4)
- B Low weight for height
- C Genitourinary anomalies surgery
- D Selected diseases such as diabetes, chronic hypertension
- E Nonimmune status for selected infections such as rubella
- F Poor obstetric history including previous LBW infant, multiple spontaneous abortions
- G Maternal genetic factors

III Behavioral and environmental risks
- A Smoking
- B Poor nutritional status
- C Alcohol and other substance abuse
- D Diethylstilbestrol and other toxic exposures including occupational hazards
- E High altitude

IV Health care risks
- A Absent or inadequate prenatal care
- B Iatrogenic prematurity

V Medical risks in current pregnancy
- A Multiple pregnancy
- B Poor weight gain
- C Short interpregnancy interval
- D Hypotension
- E Hypertension preeclampsia toxemia
- F Selected infections such as symptomatic bacteriuria, rubella, cytomegalovirus
- G First- or second-trimester bleeding
- H Placental problems such as placenta previa, abruptio placentae
- I Hyperemesis
- J Oligohydramnios polyhydramnios
- K Anemia abnormal hemoglobin
- L Isoimmunization
- M Fetal anomalies
- N Incompetent cervix
- O Spontaneous premature rupture of membranes

VI Evolving concepts of risk
- A Stress (physical and psychosocial)
- B Uterine irritability
- C Events triggering uterine contractions
- D Cervical changes detected before onset of labor
- E Selected infections such as mycoplasma and *Chlamydia trachomatis*
- F Inadequate plasma volume expansion
- G Progesterone deficiency

From Behrman, R.E. J. Pediatr. **107**:842, 1985

Maternal history, socioeconomic status, and a variety of medical complications contribute to the designation, high risk pregnancy. Ten to twenty percent of pregnant patients can be identified as high risk on the basis of medical history. Over half of the perinatal morbidity and mortality is associated with these pregnancies (138). There are obvious implications for preventative care, prenatal care, and early identification of mothers at risk. A decreased incidence of LBW is well correlated with adequate prenatal care in high risk socioeconomic group women (5). In addition to prevention, therapeutic treatment of certain conditions reduces the risk to the fetus. For example, treatment of maternal hypertension, diabetes, or endocrine disorders will reduce the risk of fetal morbidity and mortality (138). Table 3-6 outlines maternal factors that are associated with high risk pregnancy (30).

The major risk in premature birth is the development of Respiratory Distress Syndrome (RDS). Depending on the degree of prematurity lung maturation may be incomplete. Immature lung morphology and lack of surfactant lead to severe respiratory compromise. The problem is complicated by high morbidity associated with the treatment of RDS. This is a complex problem and so will be discussed in depth and be the focus of this work.

Table 3-6.

FACTORS ASSOCIATED WITH HIGH-RISK PREGNANCY

A. Demographic Factors
   1. Lower socioeconomic status
   2. Disadvantaged ethnic groups
   3. Marital status: unwed mothers
   4. Maternal age
      a. Gravida less than 16 years of age
      b. Primigravida 35 years of age or older
      c. Gravida 40 years of age or older
   5. Maternal weight: nonpregnant weight less than 100 pounds or more than 200 pounds
   6. Stature: height less than 62 inches (1.57 m)
   7. Malnutrition
   8. Poor physical fitness

B. Past Pregnancy History
   1. Grand multiparity: 6 previous pregnancies terminating beyond 20 weeks' gestation
   2. Antepartum bleeding after 12 weeks of gestation
   3. Premature rupture of membranes, premature onset of labor, premature delivery
   4. Previous cesarean section or mid- or high-forceps delivery
   5. Prolonged labor
   6. Infant with cerebral palsy, mental retardation, birth trauma, central nervous system disorder or congenital anomaly
   7. Reproductive failure: infertility, repetitive abortion, fetal loss, stillbirth, or neonatal death
   8. Delivery of preterm (less than 37 weeks) or postterm (more than 42 weeks) infant

C. Past or Present Medical History
   1. Hypertension or renal disease or both
   2. Diabetes mellitus (overt or gestational)
   3. Cardiovascular disease (rheumatic, congenital, or peripheral vascular)
   4. Pulmonary disease producing hypoxemia and hypercapnia
   5. Thyroid, parathyroid, and endocrine disorders
   6. Idiopathic thrombocytopenic purpura
   7. Neoplastic disease
   8. Hereditary disorders
   9. Collagen diseases
   10. Epilepsy

D. Additional Obstetric and Medical Conditions
   1. Toxemia
   2. Asymptomatic bacteriuria
   3. Anemia or hemoglobinopathy
   4. Rh sensitization
   5. Habitual smoking
   6. Drug addiction or habituation
   7. Chronic exposure to any pharmacologic or chemical agent
   8. Multiple pregnancy
   9. Rubella or other viral infection
   10. Intercurrent surgery and anesthesia
   11. Placental abnormalities and uterine bleeding
   12. Abnormal fetal lie or presentation, fetal anomalies, oligohydramnios, polyhydramnios
   13. Abnormalities of fetal or uterine growth or both
   14. Maternal trauma during pregnancy
   15. Maternal emotional crisis during pregnancy

IV

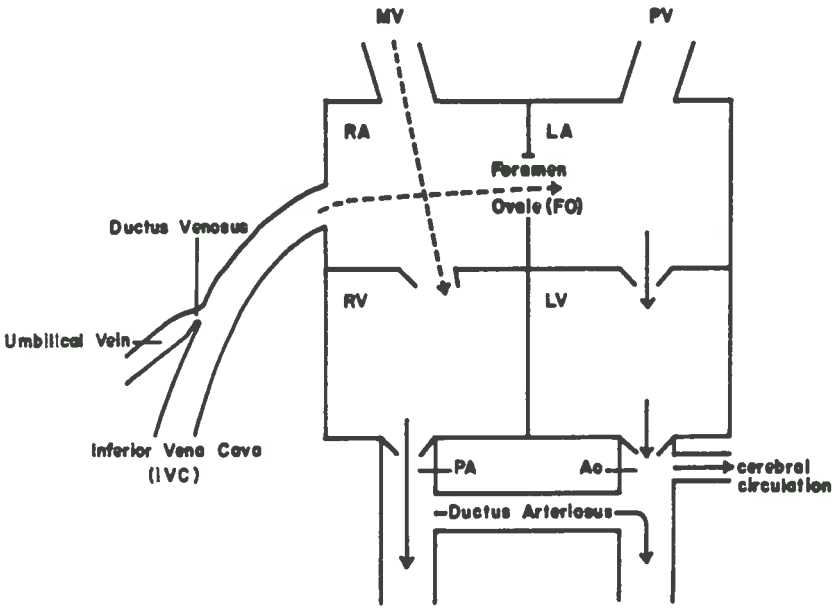
FETAL AND NEONATAL CIRCULATION

To understand conditions such as respiratory distress syndrome in which pulmonary hypoperfusion is an important factor, it is necessary to understand fetal circulation and the changes that occur in the hours following birth (193).

A. Change in Circulation at Birth

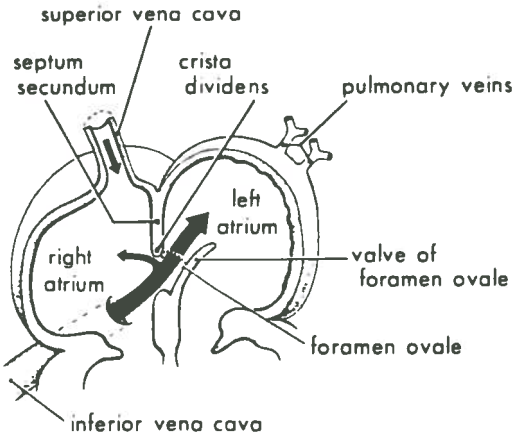
Three circulatory structures cease to exist in the change from fetal to postnatal circulation. These are: the foramen ovale, the ductus arteriosus, and the ductus venosum (Figure 4-1). These structures function to bypass the fetal lungs and liver in utero since the placenta serves the purpose for both organs prenatally.

Figure 4-1. (184)



Fetal circulation.

In the fetus oxygenated blood from the placenta enters via the umbilical vein bypasses the fetal liver through the ductus venosum to inferior vena cava. Blood enters the right atrium and passes right to left across the foramen ovale to the left atrium bypassing the pulmonary circuit. This oxygenated blood is pumped by the left ventricle mainly to the head and upper limbs (129). Figure 4-2. (184)



A schematic diagram illustrating how the crista dividens (lower edge of the septum secundum) separates the blood from the inferior vena cava into two streams. The larger stream passes through the foramen ovale into the left atrium, where it mixes with a small volume of deoxygenated blood from the pulmonary veins. The smaller stream remains in the right atrium and mixes with a large amount of deoxygenated blood from the superior vena cava and the coronary sinus.

Deoxygenated blood enters the right atrium from the superior vena cava and is directed across the tricuspid valve to the right ventricle where it exits via the pulmonary artery. This blood is diverted across the ductus arteriosus to the descending aorta and

returns to the placenta via two umbilical arteries to be oxygenated (129).

The changes that alter this circulatory pattern are the changes in pulmonary and vascular resistance produced by loss of placental blood flow at birth and increased negative pressure in the thorax created by respiration. Loss of placental blood flow almost doubles systemic vascular resistance which increases aortic, left ventricular and left atrial pressures. Pulmonary vascular resistance decreases as a result of lung expansion and opening of pulmonary blood vessels. Hypoxia induced vasoconstriction of pulmonary vessels is eliminated by oxygenation. The vasodilation produced decreases resistance and reduces pulmonary arterial pressure, right ventricular pressure, and right atrial pressure (109).

Decreased right atrial pressure countered by increased left atrial pressure causes the foramen ovale to functionally close. As long as pressures remain higher in the left atrium than the right atrium, the right-to-left shunt is occluded. Anatomic closure occurs in two-thirds of all infants by approximately the second year of life. In the remaining third, the 2-4 mmHg higher left atrial pressure keeps the valve closed although it may never become adherent (129).

Prenatally approximately one-half of placental blood bypassed the fetal liver and passed instead through a sphincter (either anatomic or physiologic) in the ductus venosum to the inferior

vena cava. The remaining blood flow circulates through the hepatic sinusoids (86). At birth blood flow from the umbilical vein ceases, the sphincter in the ductus venosum constricts, and all the blood flows into the hepatic sinusoids (184). As a result, portal venous pressure rises from about zero mmHg to 6-10 mmHg (129).

The ductus arteriosus closes in response to exposure to increased PO_2 levels coinciding with onset of respiration. As breathing is established there is increased systemic vascular resistance and decreased pulmonary vascular resistance. At first, blood flows backward from the aorta across the ductus arteriosus to the pulmonary artery but within a few hours the muscular wall of the vessel begins to constrict and functionally occlude flow. Closure of the ductus arteriosus may be mediated by bradykinin released from the lungs (182). Patency of the ductus arteriosus in the fetus is controlled by local prostaglandins which produce smooth muscle relaxation (193).

This phenomenon can be utilized to either preserve patency or induce closure after birth. Prostaglandin inhibitors, such as indomethacin, can pharmacologically cause constriction of the vessel walls in premature infants with patent ductus arteriosus (255). The opposite rationale may be used to preserve patency using exogenous prostaglandins (PGE_1) to prevent the ductus from closing. Certain cardiac anomalies in which outflow is restricted or nonexistent are ductal dependent for circulation of oxygenated

blood to the periphery.

B. Persistent Fetal Circulation

Persistent fetal circulation (PFC) is a syndrome consisting of pulmonary hypertension resulting in severe hypoxemia secondary to right-to-left shunting through persistent foramen ovale and ductus arteriosus in the absence of structural heart disease (152). The PFC may be idiopathic or secondary to hyperviscosity of blood, aspiration pneumonia (especially meconium aspiration), neonatal sepsis, hypoglycemia, congenital diaphragmatic hernia, or neonatal pulmonary disease (particularly RDS or pulmonary hypoplasia) (95, 110).

The end result is cyanosis, tachypnea, and acidemia that can resemble cyanotic congenital heart disease, neonatal pulmonary disease, or cardiomyopathy. The management of these infants is difficult. These infants are very sensitive to changes in environmental oxygen. Most require 100% oxygen and assisted positive pressure ventilation. Echocardiography is a useful diagnostic modality in identification of anomalous stunting in the absence of other defects. Tolazoline is frequently used to cause systemic and pulmonary vasodilation but hypotension is a serious side effect (152, 95).

V

FROM FETUS TO NEONATE

A. Fetal Lung Development

Lung development is generally divided into three or four stages:

1. The Pseudoglandular Period from the 5th to 17th fetal week. Lung tissue resembles a gland early in development but by week 17 all major elements are formed with the exception of those for gas exchange. Respiration is impossible at this stage.

2. The Canalicular Period from the 16th to the 25th week. This period slightly overlaps stage 1 since cranial lung segments mature faster than caudal segments. During this period lung lumina enlarge and become vascularized. Each terminal bronchiole gives rise to two or more respiratory bronchioles and there is early formation of terminal sacs. These latter are primitive alveoli and are highly vascularized and thin walled. Respiration is possible toward the end of this period.

3. The Terminal Sac Period from the 24th week to birth. There is further development of terminal sacs and thinning of the epithelial lining. The epithelial cells are of endodermal origin and form a flattened lining. These are known as type I alveolar epithelial cells. The capillary network in the mesenchyme around the developing alveoli proliferates and there is development of lymphatic capillaries.

At this stage there is sufficient alveolar surface area to provide adequate gas exchange to permit survival of a prematurely born infant. This alveolar epithelium together with adequate pulmonary vasculature is critical for survival of the preterm infant.

4. The Alveolar Period from late fetal life to approximately 8 years. The type I epithelial lining of the alveoli becomes extremely thin so that alveolar capillaries bulge into the sac space. Prior to birth terminal sacs represent the future alveolar ducts. Immature alveoli appear as bulges in the walls of terminal sacs and respiratory bronchioles (184, 34).

At birth, the primitive alveoli enlarge as the lungs expand. Lung development up to the age of 3 years consists primarily in an increase in the number of respiratory bronchioles and primary alveoli (68). One-eighth to one-sixth of the number of adult alveoli are present in a newborn infant (184). From the third to eighth year the number of immature alveoli increases. As these alveoli increase in size, they become mature. The lympahatic vessels of the term infant are relatively large and more numerous than in the adult (68). Lymph flow is high in the hours following birth serving to remove excess lung fluids.

Respiratory movements occur in the fetus causing aspiration of amniotic fluids. At birth the lungs are about half inflated with fluid from the tracheal glands, amniotic fluid, and fluid derived from the lungs themselves (184). Aeration at birth

requires replacement of intra-alveolar fluid by air rather than inflation of a collapsed organ (94).

At autopsy, the lungs of a stillborn infant are firm, fluid-filled, and sink when placed in water indicating inflation with air never occurred. This has medico-legal significance (184).

Adaptation to extrauterine life necessitates the transition of respiratory function from the placenta to the lungs. This transition is generally a smooth one but involves initial instability of various hormonal and neurogenic control sytstems (129). The instability is amplified when the neonate is immature.

B. Neonatal Physiology

Normal respiration in the newborn infant is approximately 40 breaths per minute with a tidal volume of about 16 ml with each breath (109). This results in a total minute respiratory volume of 640 ml per minute (40 X 16 = 640 ml), which is about two times greater, relative to body weight, than the adult. But, the functional residual capacity of the infant is only one-half that of the adult in relation to body weight (129). Therefore, cyclic changes in blood gases can occur when the respiratory rate is slowed.

At birth blood volume is approximately 300 ml with a cardiac output of about 550 ml/minute. The cardiac output is also almost two times greater than the adult relative to body weight. Blood pressure at birth averages 70/50 which increases over the first

months of life to childhood levels of 90/60. There is a gradual rise through adolecence to an adult blood pressure of 120/80 (95).

The blood composition is different in the newborn than in an adult. There are about 4 million red blood cells per cubic millimeter which may be higher if blood has been stripped from cord to infant at birth. Hematopoiesis is low in the first week and the red cell count drops to about 3.25 million per cubic millimeter at about 8 weeks of life. White blood cell count is much higher in the neonate than the adult at almost 45,000 per cubic millimeters (129, 95).

Bilirubin, the degradation product of red blood cells, is excreted poorly. The newborn liver cannot conjugate bilirubin with glucuronic acid for excretion with bile. Physiologic hyperbilirubinemia may result if plasma bilirubin concentrations rise too precipitously in the immediate newborn period. Normally values are less than 1 mg/100 ml but may average 5 mg/100 ml in the first three days of life and then declines as the liver begins to function.

The liver is deficient in forming plasma proteins and gluconeogenic function. The unfed infant must depend on fat stores for energy sources. Blood glucose levels may drop dangerously low. Coagulation factors formed in the liver (factors 2, 7, 9, and 10) may be low, vitamin K is routinely given to newborns to prevent hemorrhagic disease of the newborn (34). Fragile blood vessels may aggravate the tendency to bleed and lead

to intracranial or pulmonary hemorrhages.

Digestion, absorption, and metabolism are similar in neonates and older children except for decreased fat absorption, decreased starch utilization, and greater instability of blood glucose. Protein synthesis and nitrogen storage are better, however, than at later stages of life. With an adequate diet, the newborn can utilize almost 90% of ingested amino acids for formation of body proteins (129).

In the preterm infant stomach capacity is reduced and the cardiac sphincter is poorly developed, thus regurgitation of feedings is common and is a risk for aspiration. Suck, swallow, and gag reflexes may all be diminished or nonexistent in the premature infant and may prohibit nipple or breast feeding. Gavage feeding is often necessary. Both gavage and nipple feedings may provoke vagal stimulation and exacerbate apnea and bradycardia. These may be profound and are potentially dangerous causes of hypoxic insult often requiring intervention and pharmaceutical treatment. In addition to difficulties with the mechanics of feeding, the premature infant has an immature gut which often results in ineffective bowel peristalsis. Abdominal distension and constipation are common. Hypoxia at birth is associated with an increased incidence of necrotizing enterocolitis in prematures, which may be heralded by increasing abdominal girth, feeding intolerance, and the presence of occult blood in the stools (34).

Most prematures can digest milk readily but since there is a decreased capacity to digest fat, vitamins A and D must be supplemented (34). Calcium absorption is reduced in preterm infants and the vitamin D deficient infant can develop rickets in a matter of weeks (129).

Metabolic rate, like cardiac output and respiratory volume, is two times that of the adult relative to body weight. The infant has a large surface area to mass ratio and therefore greater heat loss. This results in drastic body temperature declines when exposed to room temperature. Regulatory mechanisms are unstable in the early newborn period. Regulatory instability combined with a higher metabolic rate can result in marked deviations in body temperature. A small or immature infant has both less body fat to insulate and immature neuroregulatory abilities that result in poor ability to control body temperature. Cold stress can be a dangerous problem which will be discussed later (95, 34).

Glomerular filtration rate and tubular excretory absorptive capacity is 20% to 50% adult levels relative to body weight. There is a decreased ability to concentrate and acidify urine. Preterm infants have even more immature renal function and excrete large volumes of dilute urine, thus are liable to dehydration and acidosis (34).

The term newborn inherits immunity from maternal antibodies which cross the placenta. Gamma globulin levels fall toward the

second month by about one half the newborn levels and there is a decrease in immunity. However, protective maternal antibody last to most major infectious diseases of childhood until about the sixth month. Gamma globulin concentration returns to normal between 12 to 20 months as the infant's own immune system begins to function (129). Since the preterm infant has less time to accumulate maternal antibody there is a greater tendency to develop infection (34).

VI

ONSET OF BREATHING

In addition to the alterations in fetal circulation necessary for adaptation to extrauterine existence, respiratory exchange of oxygen and carbon dioxide must be established since at birth the placenta no longer provides this function. Failure to initiate breathing and inadequate or ineffective respiration result in the most common causes of neonatal morbidity and mortality.

The fetal lung is fluid filled and receives only 10% to 15% of the cardiac output. High vascular resistance in the fetal lung is due to vasoconstriction of the pulmonary artery (152). The pulmonary arterial vasodilation occurring at delivery results from increased oxygen tension, decreased CO_2 tension and change in pH, and partially from the mechanical effect of inflation (77). Within the first minutes of life, a large portion of the fluid is absorbed, the lungs fill with air, and blood flow through the lungs increased 8- to 10-fold. The increased flow is secondary to a decrease in pulmonary arterial tone and circulatory conversion from a parallel to a series circuit (152).

Functional residual capacity (FRC), lung compliance, and vital capacity reach normal levels quickly. Chemical control of respiration is similar in the newborn infant and the adult. As inspired carbon dioxide increases, the percentage of ventilatory increase is similar in infants and adults. Ventilation is altered

when the inspired gas contains less than 20% oxygen which is considered evidence that aortic and carotid chemoreceptors are active at birth (77).

The promptness with which the neonate begins to breathe is affected by sudden exposure to the exterior world, probably resulting from a slightly asphyxiated state incident to the birth process and sensory impulses from sudden cooling of the skin (129). The neonate's response to hypoxia differs from that of the adult. Prior to birth the fetus was protected from hypoxia by differences in oxygen affinity and binding (to be discussed in later sections). Maternal anesthesia may suppress respiration depending on the drug, the route of administration, and the drug-delivery interval. An infant who doesn't breathe immediately becomes progressively more hypoxic and hypercapnic. This provides stimulus to the respiratory center to institute respiration (129). Marked hypoxia depresses the medullary respiratory center and negates the hypoxic stimulation of aortic and carotid chemoreceptors. The effects of pulmonary stretch receptor activity on respiration are greater in the newborn than the adult (152).

Drugs (analgesics, narcotics, tranquilizers, anesthetics), intrauterine hypoxia, nervous system trauma, immaturity, airway obstruction, and congenital respiratory malformation are influences which may inhibit the onset of respiration (34). Hypoxia frequently occurs during delivery because of; compression

of the umbilical cord, premature separation of the placenta, excessive uterine contaction compromising uterine blood flow, maternal hypoxia, and anesthesia (220).

Death or permanent brain damage occurs in an adult exposed to anoxic insult in approximately 3 to 5 minutes (according to the American Heart Association). An infant may withstand anoxia for slightly longer periods but neurolgoic damage can be expected if respiration is failed to be initiated in 8 to 10 minutes of birth (255).

The Apgar score was introduced to quantitate the initial evaluation of the infant. Five vital signs: heart rate, respiratory effort, muscle tone, reflex irritability, and color are evaluated at one and five minutes routinely. These five signs disappear in a predictable manner during asphyxiation of the neonate (9) (Table 6-1).

Table 6.1.

APGAR SCORE°

Sign	Score		
	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Weak, irregular	Good, crying
Muscle tone	Flaccid	Some flexion of extremities	Well flexed
Reflex irritability (Catheter in nose)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink Extremities blue	Completely pink

°Adapted from data of Apgar.

Scores of 0 (zero), 1 and 2 are given for each sign corresponding to absent or no response, present but abnormal response, and normal response respectively. The score, from zero to ten, provides a guide for the need to resuscitate. This system of scoring identifies infants at risk for mortality and morbidity. The mortality in low-score infants is nearly 15 times greater than high-score babies. Respiratory distress syndrome occurs at far greater frequency in low-score infants (95).

The Apgar scoring system is also useful for evaluating premature infants but scores for muscle tone must be corrected. Tone is normally reduced in very low birth weight (VLBW) infants (95).

Arterial blood gases reflect the pulmonary, cardiac, and metabolic status of the newborn in addition to providing indications of perinatal asphyxia. The partial pressure of carbon dioxide (PCO_2) reflects the ability of the lung to remove CO_2. Bicarbonate (HCO_3) is controlled by the kidney. When the pH and HCO_3 are measured the PCO_2 is calculated using the Henderson-Hasselbach equation: $pH = 6.1 + \log \frac{HCO_3}{PCO_2 \times Sol.}$ Metabolic versus respiratory factors are reflected in the HCO_3 and PCO_2 respectively. Pulmonary disease, apnea and hypoventilation cause the arterial PCO_2 ($PaCO_2$) to increase. The kidney attempts to compensate by conserving HCO_3 and excreting hydrogen ions (H^+). This causes the pH to drop resulting in respiratory acidosis. Metabolic acidosis is indicated by a decreased HCO_3 and pH.

Compensatory hyperventilation attempts to alleviate the acidosis by decreasing the $PaCO_2$ (152).

Regulation of acid-base balance implies regulation of the hydrogen ion concentration in body fluids. Slight changes result in marked alteration in the rates of cellular reactions, therefore acid-base regulation is an important aspect of homeostasis. To prevent acidosis or alkalosis three major control systems are available:

1. Bodily fluids contain buffering systems to prevent excessive changes in hydrogen ion concentration.

2. Changes in hydrogen ion concentration stimulate the respiratory center to alter the rate of breathing.

3. Changes in hydrogen ion concentration stimulate the kidneys to excrete either an acid or alkaline urine resulting in compensatory adjustment toward normal.

Buffer systems act almost instantaneously while the respiratory system responds in minutes and the kidneys take hours to days to readjust the hydrogen in concentration (131).

VII

ROLE OF SURFACTANT

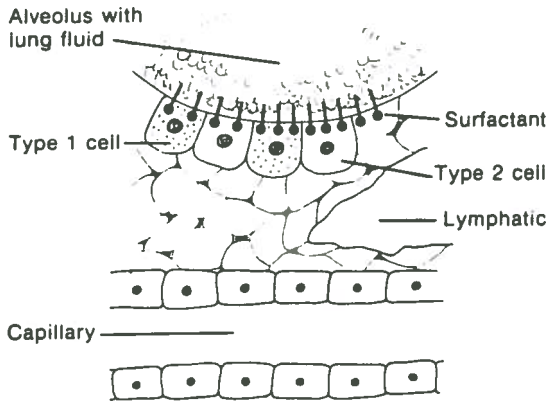
A. Cellular Differentiation

Cellular diversity of the lung is complex, about 40 cell types exist. Epithelium involved in gas exchange, however, is fortunately more simple, consisting of two major cell types.

Early in gestation (as discussed in the section on lung development), epithelial cells are simple, columnar, and contain few organelles. Type I epithelial cells line the terminal sacs and thin as gestation proceeds. In the final 10% to 20% of gestation certain epithelial cells undergo changes and become type II pneumonocytes. Type II cells have been identified at around the 24th week of gestation but are more prominent at 34 to 36 weeks. These are notable for cytoplasmic lamellar bodies (206).

Type II pneumonocytes have abundant mitochondria, endoplasmic reticulum, polyribosomes, and golgi apparatus indicating high rates of metabolism (95). The role of type II cells is synthesis, storage, and secretion of surfactant. Type I epithelial cells provide the sight for gas exchange (99) (Figure 7-1).

Figure 7-1. (184)



Structure of the fetal lung at term.

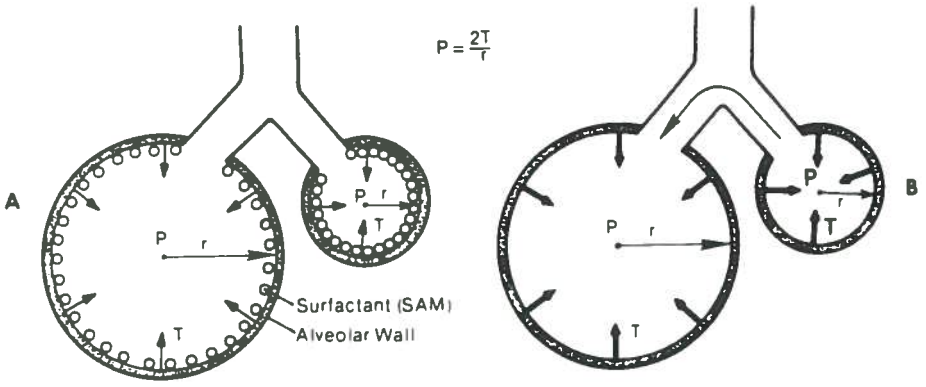
B. Mechanics: Laplace's Law $P = 2T/r$

In order to inflate the alveoli at birth fluid must be removed and replaced by air. The removal of fluid is partially accomplished by the compression of the chest during delivery, thus, infants delivered by cesarian section have notably increased respiratory secretions in the immediate newborn period. Remaining fluid is absorbed and removed by lymphatic vessels.

In order to inflate the lungs with air the surface tension of the film of fluid that lines the alveoli must be overcome. The combination of hypoxia, hypercapnia, and acidosis created by termination of oxygenated blood flow through the placenta at birth provide the stimulus for inspiration. Respiratory movements

create a slightly negative intrathoracic pressure which overcomes alveolar surface tension and inflates the alveoli with air (109). If the surface tension is not kept low during expiration, the alveoli would collapse as they become smaller. This follows the Laplace law, in which spherical structures like alveoli have a distending pressure equal to two times the tension divided by the radius (P = 2T/r). If tension (T) is not reduced as the radius (R) gets smaller, the tension overcomes the distending pressure and the alveoli collapse (Figure 7-2).

Figure 7-2.



Relationship of Laplace's law to alveolar stability in the normal and surfactant-deficient lung. Although schematically represented as spherical, terminal respiratory units tend to be polygonal in the mature lung. Laplace's law states that the pressure *(P)* within a sphere is directly proportional to surface tension *(T)* and inversely proportional to the radius of curvature *(r)*. **A,** Normal lung. As alveolar size diminishes, surface tension is reduced in the presence of SAM, thereby decreasing the collapsing pressure to be opposed. The pressure within the small and large interconnected alveoli is equal, negating the tendency for transfer of gas. **B,** Surfactant-deficient lung. Without the surface tension–lowering capacity of SAM, alveoli become unstable at low volume and tend to collapse. Some alveoli may empty into large ones to equalize pressure between the two in accordance with Boyle's law. (Modified from an original painting by Frank H. Netter, M.D., from THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS, copyright by CIBA Pharmaceutical Co., Division of CIBA-GEIGY Corporation.)

C. Surfactant: The Surface Active Material

Hundreds of papers on the properties of surfactant have been published since the physiologist von Neergaard first studied surface forces in 1929 (258). Surfactant is the substance responsible for lowering surface tension in alveoli as size decreases with expiration and prevents alveolar collapse. It is a phospholipid which is synthesized and secreted by type II pneumonocytes. The presence of surfactant at birth is vital for effective respiration and gas exchange.

Research has provided a biophysical view of pulmonary surfactant as an antiatelectasis factor located in the alveolar lining layer that provides a low and variable surface tension and imparts hysteresis to the air-tissue interface. Surfactant provides two functions: (1) decreasing the pressure required to distend the lungs, and (2) maintaining alveolar stability over a range of local volumes (95).

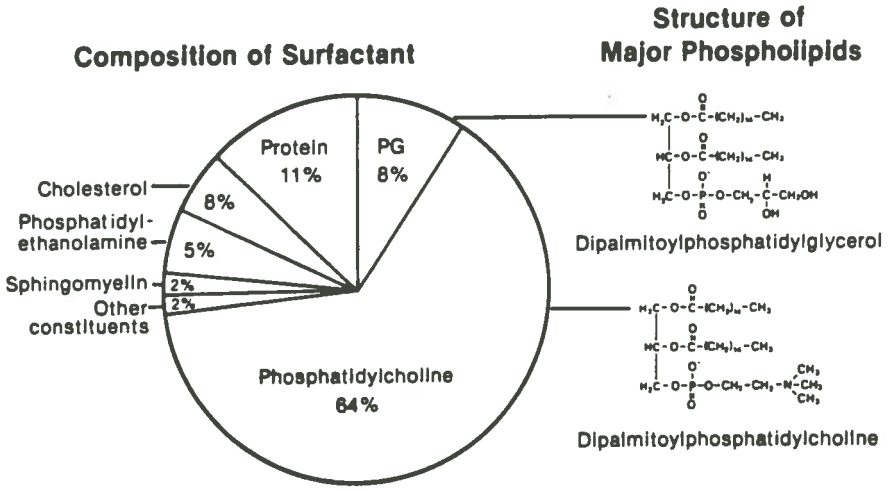
Surfactant is a lipoprotein mixture that contains dipalmitoyl phosphalidyl choline (DPPC) which is synthesized from fatty acids which are either extracted from the blood or synthesized in the lung (265). Surfactant is formed relatively late in fetal life and babies born prior to its presence commonly develop Respiratory Distress Syndrome (RDS) or what used to be known as Hyaline Membrane Disease. Pathophysiology of RDS will be discussed in a later section.

Surfactant acts by forming a monomolecular layer at the

interface between the fluid lining of the alveoli and the air in the alveoli which prevents the development of water-air interface (129). Surface tension of the fluid in the alveoli also tends to pull fluid into the alveoli from the alveoli wall. In the absence of surfactant there is massive filtration of fluid into the alveoli resulting in pulmonary edema (95).

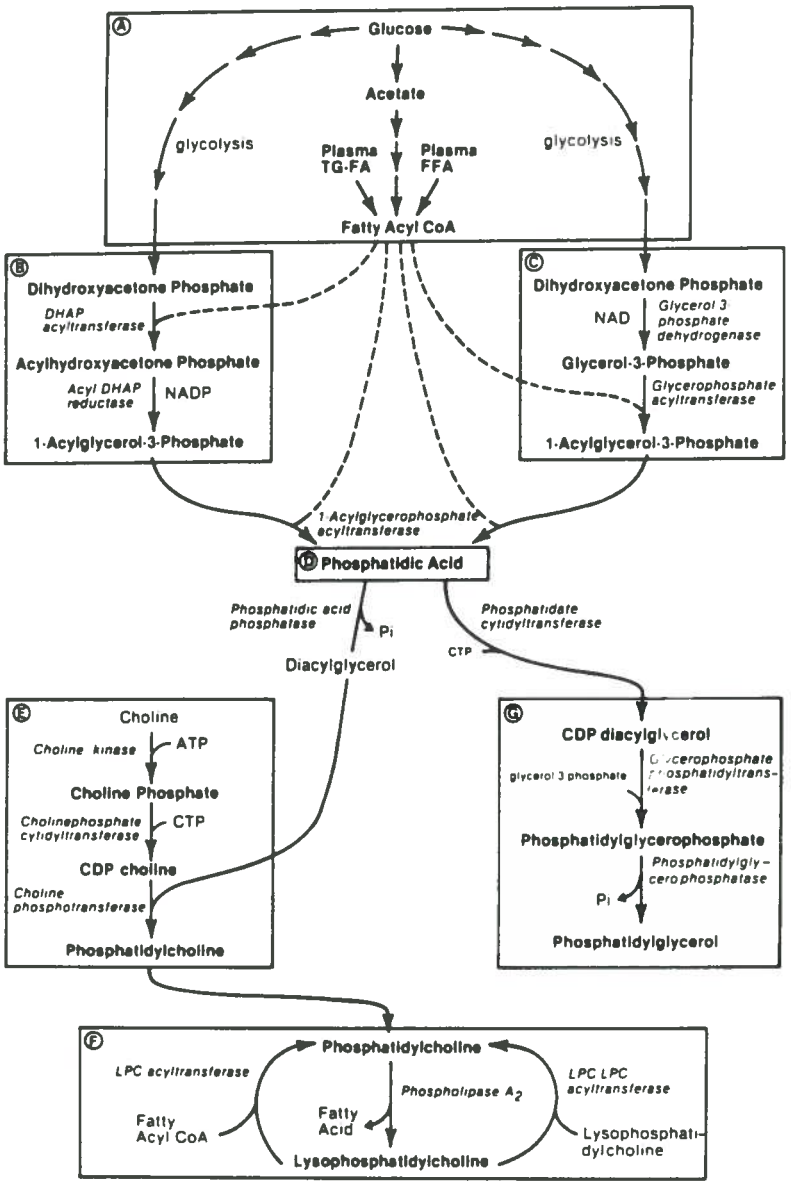
Studies have indicated that surfactant is composed largely of lipid, particularly phospholipid, and small amounts of protein. Pulmonary surfactant has been defined by Farrell and Avery (98) as a "unique lipoprotein, particularly rich in highly saturated lecithins (saturated phosphatidylcholine molecules) and containing lesser amounts of cholesterol, neural lipid, and other phospholipids." (Figure 7-3; Figure 7-4) (206).

Figure 7-3.



Composition of surface-active material, obtained by lung lavage, and the structure of major phospholipids present in pulmonary surfactant. (From Perelman, R., Engle, M.J., and Farrell, P.: Lung **159**:53, 1981.)

Figure 7-4.



Pathways of phosphatidylcholine and phosphatidylglycerol biosynthesis *TG-FA*, Triglyceride fatty acids; *FFA*, free fatty acids; *DHAP*, dihydroxyacetone phosphate; *LPC*, lysophosphatidylcholine. (From Perelman, R., Engle, M.J., and Farrell, P.: Lung **159**:53, 1981.)

There are two pathways for the synthesis of phosphatidylcholine. First, is the choline-incorporation mechanism also known as the cytidine diphosphocholine pathway. Second is the denovo mechanism, called the methylation pathway.

Fetal lung undergoes major biochemical changes late in pregnancy. Research in this area has shown a high degree of uniformity with regard to the stage at which these biochemical changes occur (99, 12, 207). It has been found that lung phosphatidylcholine production is demonstrable between 85% and 90% of gestation regardless of the total duration of a species' pregnancy. Much of this research has been conducted in lower animals and primates like rhesus monkeys. Phosphatidylcholine concentrations rise in amniotic fluid corresponding the attainment of fetal lung maturity (111). This has been utilized to provide a means of assessing fetal lung maturity clinically. The lecithin/sphingomyelin (L/S) ratio measured in amniotic fluid is used to determine adequacy of surfactant levels and thus lung maturation (34).

A major emphasis of research has been directed toward regulation of phosphatidylcholine and identification of agents that hasten fetal lung maturation and stimulate synthesis of surfactant. Certain hormones, including corticosteroids, influence the rate of phosphatidylcholine biosynthesis. Thyroid hormone, estrogens and theophylline have also been shown to have this effect (239). Other hormones such as insulin may inhibit

formation of surfactant. Cyclic AMP may have a role in stimulating lung metabolism (99).

Type II cells have receptors for hormones in their cytoplasm which exist throughout gestation. The concentration of binding sites is constant in fetal lungs studied from 12 to 20 weeks of gestation. Lower concentrations of steroid receptors were found between 27 and 40 weeks of gestation (162). The high concentration of corticosteroid receptors in type II pneumonocytes indicates that the lung is a target tissue for this class of hormone (95).

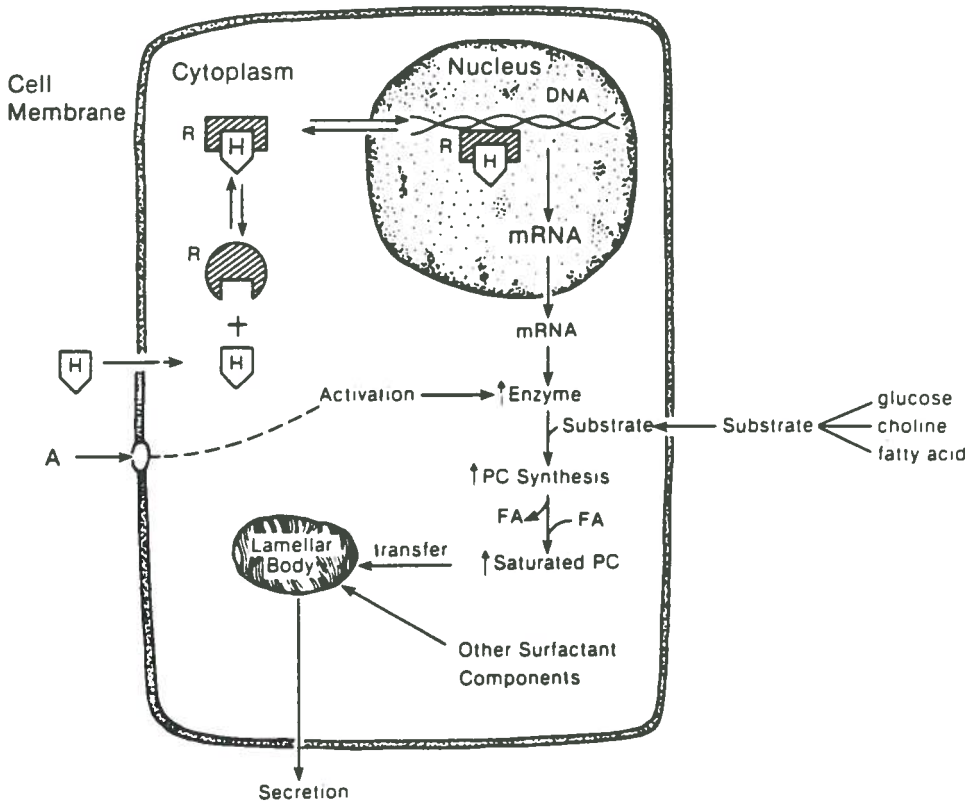
Animal studies by Liggins, Kotas, and Avery (169, 162, 14) confirmed the stimulatory effect of corticosteroids on fetal lung maturation. The exact mechanism of action is still argued by various researchers. It is believed, however, that glucocorticoids combine with the specific cytoplasmic receptors in type II cells and translocates to the nucleus. There the steroid-receptor complex initiates synthesis of specific messenger RNA which ultimately directs the synthesis of enzymes responsible for the production of phosphatidylcholine (126). Farrell, Zachman, and Ballard (100, 22) disagree which enzyme is responsible but it may be that there are specific differences in the specific enzyme (126).

In numerous controlled clinical trials (22, 44, 169, 248) antenatal administration of betamethasone or dexamethasone to women in premature labor, less than 34 weeks, the risk of

respiratory distress syndrome in the offspring was reduced. Since corticosteroids act through enzyme induction, at least 24 to 48 hours is needed between treatment and delivery to induce adequate levels of lung surfactant. Most studies showed a 60% to 70% reduction in RDS under these conditions.

Limitations of this therapy have been noted when premature labor occurs less than 27 to 28 weeks gestation. Induction of surfactant synthesis has been less successful when the fetus is less than 28 weeks gestation. This may be due to ineffective hormone receptor sites, failure of cellular apparatus in type II cells to induce enzyme production, lack of appropriate substrate levels, inability of the cell to secrete product, or presence of too few and too immature type II pneumonocytes to effectively produce sufficient quantitites of surfactant.

Figure 7-5.



Hypothetic scheme of the production and delivery of surfactant to the "alveolar lining layer" by a type II pneumonocyte. Various potential regulatory steps illustrate hormone-mediated control mechanisms, regulation by substrates, and the key role of enzymes in phospholipid production. *A*, Activator; *H*, hormone, particularly corticosteroid. *R*, receptor; *FA*, fatty acid. *DNA*, deoxyribonucleic acid molecule stimulated by hormone to increased "expression". *mRNA*, messenger ribonucleic acid molecules coding for increased synthesis of specific enzymes. (Reprinted from Ballard, P L. In Hodson, W A., editor: Development of the lung. New York, 1977, Marcel Dekker, Inc. By courtesy of Marcel Dekker, Inc.)

VIII

VENTILATION/PERFUSION

In order for effective respiration and gas exchange three components must be functional. They are:

1. pulmonary blood flow or perfusion;
2. breathing or ventilation;
3. exchange of gases at the alveolar-capillary interface.

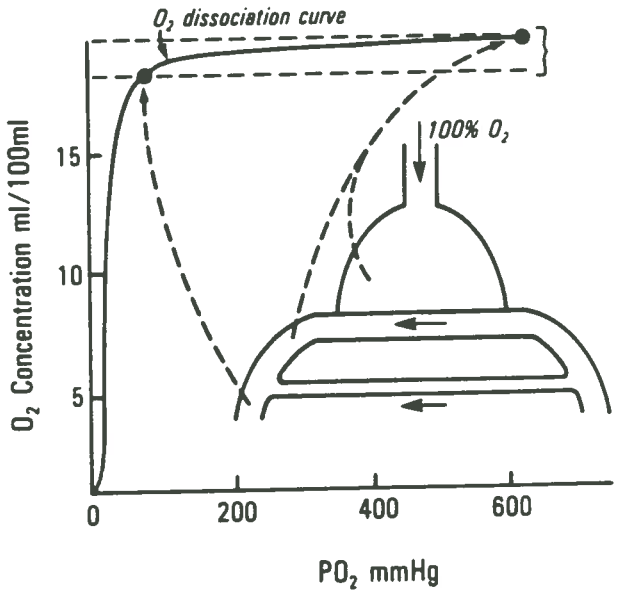
A mismatch in perfusion and ventilation is a common cause of defective gas exchange.

In the premature infant several factors affect the success of the components above. The role of surfactant and RDS have already been discussed to some degree. Deficient lung surfactant cause ventilation to be compromised due to hypoventilation. Blood cannot be oxygenated nor can carbon dioxide be effectively removed if alveoli fail to be inflated. Diffusion of gases is dependent on loading and unloading oxygen onto the blood. This will be discussed in chapter IX and factors affecting gas exchange in later sections.

In chapter IV, the change from fetal circulation was discussed. Besides persistent fetal circulation, transient shunting of pulmonary blood may occur and result in decreased perfusion of alveolar capillaries. This can be due to periodic shunts through the ductus arteriosus as it opens and closes in the days following birth. Premature infants have a higher incidence

of patent ductus arteriosus than do term infants. Shunts can be due to congenital intracardiac lesions in which blood bypasses pulmonary vessesl. In addition, intrapulmonary shunts occur in normal lungs as bronchial artery blood is collected by pulmonary veins and coronary vessels are drained by Thesbesian veins. This poorly oxygenated blood depresses the partial pressure of oxygen in arterial blood.

An important feature of a stunt is that the hypoxemia produced cannot be eliminated by giving 100% oxygen to breathe. The shunted blood is never exposed to the oxygen and so does not become saturated. Giving 100% oxygen to breathe is a sensitive measure of shunt because when the PO_2 is high, a small depression of the arterial O_2 concentration causes a relatively large fall in PO_2 since the slope of the O_2 dissociation curve in this region is practically flat (265) (Figure 8-1).



Depression of arterial P_{O_2} by shunt during 100% O_2 breathing. The addition of a small amount of shunted blood with its low O_2 concentration greatly reduces the P_{O_2} of arterial blood. This is because the O_2 dissociation curve is so flat when the P_{O_2} is very high.

Interestingly, shunts do not cause the PCO_2 of arterial blood to increase because chemoreceptors respond to any elevation in CO_2 by hyperventilation. This reduces the $PaCO_2$ of the unstunted blood (265).

Failure to adequately ventilate results in not only a depressed PaO_2 but an elevation in the $PaCO_2$. The level of alveolar PO_2 is determined by a balance between the rate of oxygen uptake by the blood, which is metabolically determined, and the rate of replenishment of oxygen by alveolar ventilation (265). Hypoventilation may be due to RDS, meconium aspiration, pneumothorax, or neurologic deficit caused by drugs or severe asphyxia which depress the central nervous system respiratory center. Damage to the chest wall at birth is also a possible cause of hypoventilation. The compliant immature chest wall is a disadvantage. As the infant attempts to increase negative intrathoracic pressure the chest wall collapses known as retraction (189).

Lung compliance depends on the elasticity of the tissues and the FRC (functional residual capacity). Compliance is low in normal newborns at first breath but increases with establishment of respiration. Compliance is low in RDS in which alveoli are stiff and resistant to ventilation. Placental transfusion with increased blood volume and transudation of fluid into the interstitial tissue of the lung results in low compliance and impedes ventilation (227).

The work of breathing is a measure of the energy utilized to inflate the lungs and move the chest (65). Pulmonary work in the normal infant has been assessed as 1440 gm-cm/min. and RDS inflates this figure as much as six times. There is an important implication of this in terms of the oxygen cost for breathing. Neonates have higher caloric requirements than adults normally. Infants with respiratory disease require even more calories for respiration and utilize greater amounts of oxygen for metabolic demands of labored respiration (227).

Gases move across the alveolar-capillary interface by passive diffusion (265). Diffusion through tissues is described by Fick's Law. That is, that the rate of diffusion across tissue is proportional to the tissue area and the difference between partial pressure of the gas on either side. The rate of transfer is proportional to a diffusion constant which reflects the properties of the tissue and the gas. The constant is proportional to the solubility of the gas and inversely proportional to the square root of its molecular weight: $D. \propto 501/\sqrt{m.w.}$
The Fick equation is: $\dot{V}_{gas} \propto A.D. (P_1 - P_2)/T$ (265, 129).
In severe prematurity, in which lung development is incomplete, the alveolar basement membrane may be thickened and present a diffusion limitation (95). Under conditions of exercise pulmonary blood flow is increased and thus the time the red blood cell is exposed to alveolar oxygen is reduced (265). Under normal circumstances there is no appreciable fall in PaO_2 due to

increased flow due to compensatory hyperventilation in exercise. In the premature infant, thrashing agitated behavior is akin to exercise. When the ventilation-perfusion balance is disturbed due to organ immaturity as in the premature, the PaO_2 may fall due to failure in compensatory mechanisms.

IX

GAS EXCHANGE

Human cellular metabolism is dependent on an adequate supply of oxygen. The oxygen transport system in humans is the erythrocyte and its primary function is to bring oxygen to the tissues.

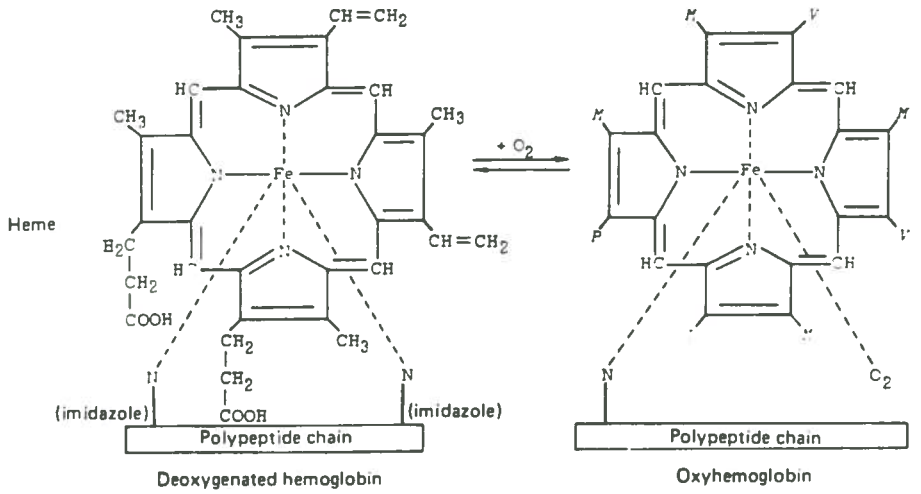
The oxygen-carrying pigment in the red blood cells of vertebrates is hemoglobin, a protein with a molecular weight of 64,458. The hemoglobin molecule is made up of four subunits. Each subunit contains a heme moiety which is conjugated to a polypeptide. The heme is a porphyrin derivative. The globulin portion of the molecule is composed of four large polypeptide chains, one pair of subunits contain one type of polypeptide and a second pair of subunits contain another type of polypeptide. The nature of the polypeptide chain determines the affinity of the hemoglobin molecule for oxygen (109, 129).

A. Transition To Hemoglobin A

In the normal adult human the hemoglobin, hemoglobin A, contains two alpha chains and two beta chains. Human fetal hemoglobin, hemoglobin F, contains two alpha chains and two gamma chains. Hemoglobin A begins to appear in fetal blood at approximately 20 weeks of gestation when the fetal bone marrow begins to function. At term, 38-42 weeks gestation, only 20% of circulating hemoglobin is hemoglobin A. Therefore, prematurely

born infants have less hemoglobin A than full term infants. The percentage of hemoglobin A depends on the degree of prematurity, the more premature infants will have the least hemoglobin A. However, no additional hemoglobin F is normally formed after birth and by the age of 4 months 90% of the circulating hemoglobin is hemoglobin A (109).

Since premature infants are commonly transfused at frequent intervals due to various clinical reasons, the percentage of hemoglobin A may increase more rapidly than in normal term infants. This is significant due to the difference in oxygen carrying capacity between hemoglobin A and hemoglobin F. Figure 9-1. (109)



Chemistry of heme. The hemoglobin molecule is made up of 4 of the units shown on the left. The abbreviations M, V, and P stand for the groups shown on the molecule on the left.

B. Oxygenation of Hemoglobin

Deoxyhemoglobin binds oxygen to form oxyhemoglobin by attaching to the ferrous ion (Fe^{2+}) in the heme molecule. This is a weak and reversible bond which allows oxygen to dissociate from the hemoglobin molecule when oxygen concentrations are low and bind oxygen when concentration is high. Thus, binding and release of oxygen is facilitated by the concentration gradient between the lungs, where PO_2 is high, and tissues, where PO_2 is depleted (109, 129).

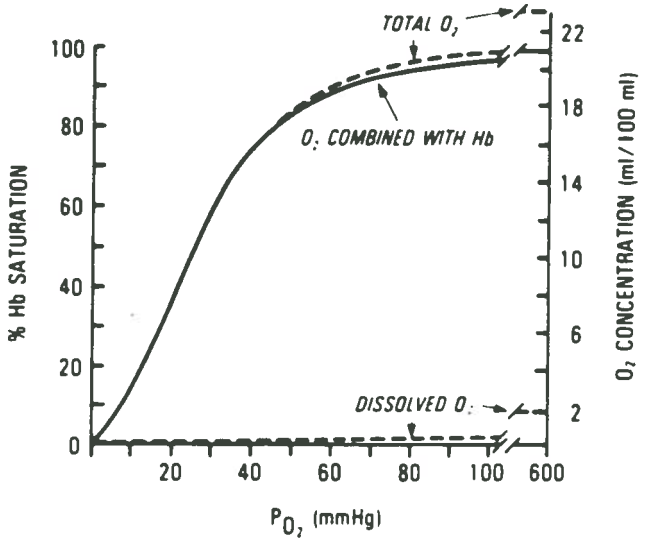
Certain drugs and chemicals, including nitrites, sulfonamides, and acetanid, can oxidize the ferrous of hemoglobin A to the ferric form (Fe^{3+}). This ferric form is known as methemoglobin. There is a congenital cause in which the enzyme methemoglobin reductase is deficient within red blood cells. Methemoglobin is not useful for oxygen carriage (265).

When hemoglobin A binds oxygen, its quaternary structure changes as the conformation of the molecule changes from the T (tense) to the R (relaxed) state (221). It is the quaternary structure of hemoglobin that determines the affinity for oxygen. Shifting the axis of its four component polypeptide chains fosters oxygen uptake or oxygen delivery (109). Hemoglobin is an allosteric protein and the change in structure that occurs with oxygen binding are both electronic and steric. The stoichiometry of oxygen binding is $Hb + 4O_2 \rightleftharpoons Hb(O_2)_4$.

The R state of hemoglobin favors oxygen binding while the T

state decreased oxygen binding. When hemoglobin takes up a small amount of oxygen, the R state is favored and additional oxygen uptake is facilitated (109). This explains the sigmoidal shape to the oxygen-hemoglobin dissociation curve.

Figure 9-2. (109)



O_2 dissociation curve (*solid line*) for pH 7.4, P_{CO_2} 40 mm Hg, and 37°C. The total blood O_2 concentration is also shown for a hemoglobin concentration of 15 g/100 ml of blood.

C. O_2 Dissociation

The oxygen-hemoglobin dissociation (or equilibrium) curve is a representation of the relationship between the percent saturation of hemoglobin (the oxygen carrying vehicle) and the PO_2 in millimeters of mercury.

Oxygen is carried in two forms in blood, bound to hemoglobin and dissolved. According to Henry's Law, the amount of oxygen

dissolved is proportional to the partial pressure. For each millimeter of mercury (mmHg) of PO_2, there is 0.003 ml O_2/100 ml of blood (0.003 vols %). Therefore, normal arterial blood with a PO_2 of 100 mmHg contains 0.3 ml O_2/100 ml dissolved (265).

When blood is equilibrated with 100% oxygen (PO_2 = 760 mmHg), the hemoglobin becomes 100% saturated. Completely saturated hemoglobin contains between 1.34 ml of O_2 and 1.39 ml of O_2 (depending on the source you read and the fact that some of the hemoglobin is in the form of methemoglobin (109, 129, 265). Pure hemoglobin contains 1.39 ml of O_2. When the hemoglobin concentration is 15 g/dl the oxygen capacity is 15 X 1.39 = 20.8 ml O_2/100 ml of blood. This is the amount of oxygen bound to hemoglobin when it is 100% saturated, the dissolved oxygen is a linear function of the PO_2 (0.003 ml/dl blood/mmHg PO_2) (109).

The O_2 saturation of hemoglobin is given by:

$$\frac{O_2 \text{ combined with HB}}{O_2 \text{ capacity}} \times 100$$

Normally as blood circulates in the lung arterial oxygen tension rises from 40 mmHg to approximately 110 mmHg producing at least 95% saturation of the hemoglobin. The oxygen tension falls as blood travels from the lungs to peripheral tissues and oxygen is released from the hemoglobin (109, 129, 265).

In vivo, hemoglobin is 97.5% saturated with oxygen (PO_2 = 97 mmHg) at the ends of the pulmonary capillaries. Due to physiologic shunting in which small amounts of venous blood

bypasses the lungs, the systemic arterial hemoglobin is 97% saturated. Venous blood (at rest) is 75% saturated (109).

The sigmoidal shape of the dissociation curve has physiologic advantages. The lower steep portion of the curve reflects the large incremental increases between PO_2 and percent saturation. This means that large amounts of oxygen can diffuse to peripheral tissues for a small drop in capillary PO_2. There is a maintenance of PO_2 which facilitates diffusion to the tissues. At the flat upper portion of the curve a fall in PO_2 affects the saturation minimally. In the pulmonary circuit a large partial pressure gradient continues to exist between alveolar gas and the blood even when most of the O_2 has been exchanged (265). Under normal conditions of binding and dissociation (to be elaborated upon in the following pages) when the oxygen tension is 27 mmHg, 50% of the oxygen bound to hemoglobin has been released. This point is defined as the P_{50}. The PO_2 at 50% saturation is 27 mmHg. This is a useful reference point in the coming discussion of factors affecting the affinity of hemoglobin for oxygen and conditions causing the normal curve to be shifted.

X

OXYGEN TRANSPORT

Delivery of oxygen to peripheral tissues is dependent on numerous factors all of which relate, either directly or indirectly, to one another. Several of these have already been discussed.

Adequate tissue oxygenation depends on:

A. The fraction of oxygen in the inspired air;

B. The partial pressure of oxygen in the inspired air;

C. Alveolar ventilation;

D. Pulmonary perfusion;

E. Peripheral perfusion;

F. Cardiac output;

G. Blood volume;

H. The type and concentration hemoglobin;

I. The affinity of hemoglobin for oxygen;

J. Arterial pH;

K. Temperature;

L. Metabolic status.

The mechanics of delivering oxygen from the air to the blood, circulation of oxygen and release to the tissues and the effect of hemoglobin have been discussed in previous sections. Factors that affect binding and release of oxygen to hemoglobin will be covered in some detail. Prematurity and RDS have significant impact on

the effective delivery of oxygen to vital organs. Where pathology is present there is a fine line between hypoxemia and damage due to oxygen toxicity. To best appreciate this delicate balance, it is vital to understand the different factors that play important roles in oxygenation.

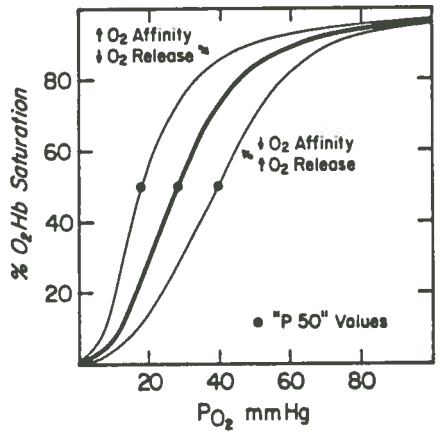
XI

FACTORS AFFECTING THE AFFINITY OF HEMOGLOBIN FOR OXYGEN

Affinity of hemoglobin reflects the degree to which binding occurs. Remember that oxygen binds loosely and reversibly to hemoglobin. $Hb + 4O_2 = Hb(O_2)_4$.

The P_{50} was described in chapter IX. That is, when 50% of the oxygen bound to oxygen has been released the oxygen tension is 27 mmHg at a pH of 7.4 and temperature of 37°C (190). When the affinity of hemoglobin is reduced, oxygen is more easily released at a give oxygen tension and the oxygen dissociation curve is shifted to the right. The P_{50} in this case is at a higher oxygen tension. Conversely, if oxygen affinity is increased, the oxygen tension is lower than normal before the hemoglobin releases an equivalent amount of oxygen (190). The P_{50} is at a lower oxygen tension and the curve is shifted to the left (Figure 11-1).

Figure 11-1. (82) *Oski and Delivoria-Papadopoulos*



The oxygen dissociation curve of normal adult blood. The P_{50}, the oxygen tension at 50 per cent oxygen saturation, is approximately 27 mm. Hg. As the curve shifts to the right, the oxygen affinity of hemoglobin decreases and more oxygen is released at a given oxygen tension. With a shift to the left, the opposite effects are observed. A decrease in pH or an increase in temperature decreases the affinity of hemoglobin for oxygen.

Six major factors affect the affinity of hemoglobin for oxygen. They are:

A. Type and concentration of hemoglobin;

B. 2,3-Diphosphoglycerate (2,3-DPG);

C. Adenosine triphosphate (ATP);

D. pH;

E. CO_2 tension;

F. Temperature

A. The Type and Concentration of Hemoglobin

In chapter IX the differences between fetal and adult type hemoglobin were described as well as the timing of the development

of adult-type hemoglobin (HbA). The presence of fetal hemoglobin in any significant concentration shifts the oxygen-hemoglobin dissociation curve to the left. This is due to the greater affinity of fetal hemoglobin (HbF) for oxygen. In utero this increased affinity facilitated the movement of oxygen from the mother across the placenta to the fetus (152).

The increased affinity of HbF to oxygen is due to the decrease in binding of the organic phospate 2,3 diphosphiglycerate (2,3-DPG). HbF binds 2,3-DPG less effectively than does HbA. This phenomenon is thought to make the fetus more tolerant to hypoxia. Anselmino and Hoffman (8) were the first to observe the greater affinity of fetal hemoglobin for oxygen in 1930. The P_{50} of HbF has an oxygen tension 6 to 8 mmHg lower than HbA (190). Several researchers showed that the discrepancy in affinity of HbF and HbA was due to the difference in 2,3-DPG (28, 85, 246).

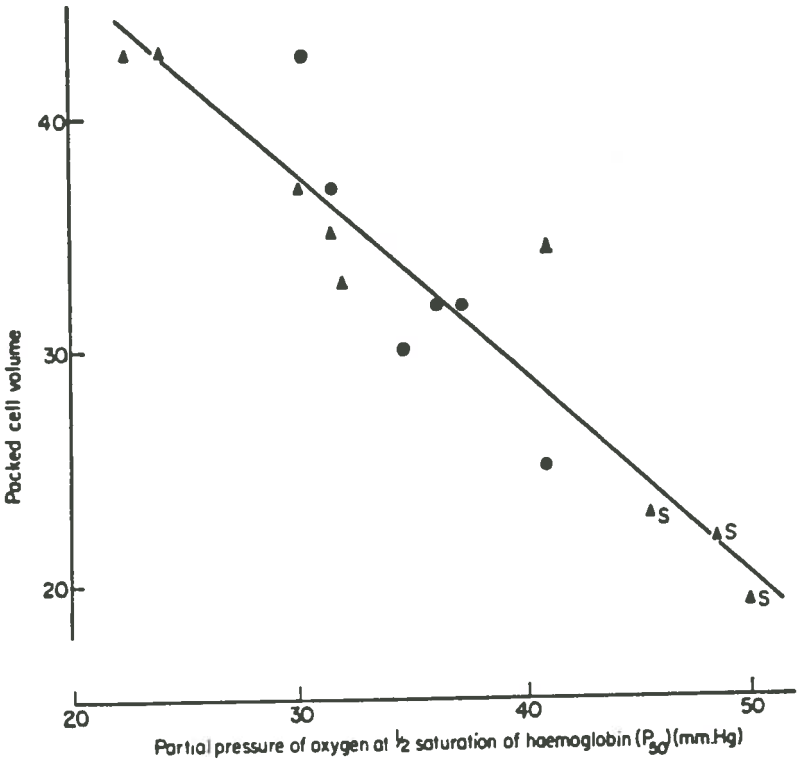
Bunn and Briehl (54) demonstrated the difference biochemically. Binding of 2,3-DPG occurs in the internal cavity of the hemoglobin molecule by salt bonds between the phosphate of 2,3-DPG and the imidazole group of the beta chain, B-H-21, histidine and the N terminal of the non-alpha chain. Fetal hemoglobin has two alpha and two gamma chains. The gamma chains lacks the histidine residue and instead have serine residues, therefore there is a decreased interaction with 2,3-DPG.

Another important affect of hemoglobin on oxygen binding is its concentration. Hematocrit, the percentage of red blood cells

per unit volume, can alter the total carrying capacity when concentrations are either too high or too low.

Torrance and associates (253) described the relationship between the degree of anemia and the 2,3-DPG and recorded the P_{50}s. Huehns and Bellingham (145) showed the relationship between the P_{50} and the packed cell volume (Figure 11-2).

Figure 11-2.



Correlation of the oxygen affinity of red cells with the packed cell volume of patients with chronic hemolytic anemias in the steady state due to abnormal hemoglobins (▲), sickle cell disease (▲S), and red cell enzyme deficiencies (●). From Huehns and Bellingham.

When the ratio of fetal to adult-tye hemoglobin is high the affect of anemia will be an increased affinity, a shift to the left and a lower P_{50}. HbA may be able to boost concentrations of 2,3-DPG to compensate and show less decrease in P_{50} in anemic conditions. Low affinity hemoglobins better tolerate anemias (1). Higher affinity hemoglobins are polycythemic (262).

The baby with a left-shifted curve has less exercise ability (190), and because of the inability to release oxygen from the hemoglobin an increase in cardiac output is necessary to provide adequate oxygen to meet metabolic demands. Failure to make this adjustment results in a decreased oxygen tension which may have disastrous results.

Iatrogenic anemia is a common problem in sick premature infants due to repeat laboratory exams. As blood volume is depleted oxygenation declines. Relatively high fetal hemoglobin concentration combined with anemia has been treated by many with transfusion of adult blood (190) to improve low oxygen tension. Banked blood has diminished 2,3-DPG levels with time. In order for oxygenation to improve and shift the dissociation curve to the right, fresh adult blood must be used. In more recent years blood banking techniques have improved and transfusion with adequate levels of 2,3-DPG causes a prompt right shift in the curve. This improvement is due to increase hemoglobin concentration, increased levels of hemoglobin A and increased levels of 2,3-DPG. Together these factors alleviate hypoxemia due to anemia and decreased red

blood cell mass. This can be seen if one compares HbF and HbA: Figure 11-3.

	HbF	HbA
concentration of 2,3-DPG	low	high
affinity for oxygen	high	low
oxygen release	low	high

Gestational age can be used to determine the amount of HbA and therefore provide an estimate of the oxygen affinity of fetal blood (190). Premature infants who have a low P_{50} and low "Effective DPG Fraction" are less capable of adapting effectively to severe hypoxia (192). Both Oski and Orzalesi concur that transfusion with fresh adult blood may be beneficial in preventing tissue hypoxia.

B. 2,3 DPG

Although 2,3-DPG has been discussed in terms of the differences in concentration between HbF and HbA and its role in oxygen affinity, it is important to understand the synthesis and metabolism of this organic phosphate to fully appreciate its role in oxygenation.

The affect of 2,3-DPG an oxygen affinity was clarified in the

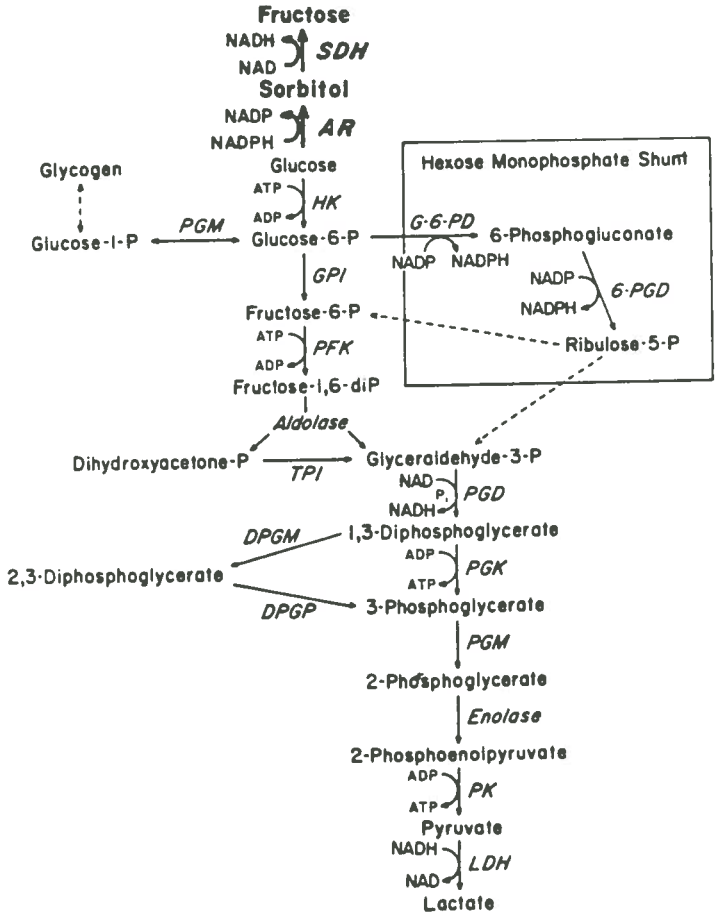
late 1960s and early 1970s by the work of such researchers as Oski, Delivoria-Papadopoulos, Orzalesi, Duc and Bauer (190, 83, 192, 91, 28). Until this time only pH, temperature and PCO_2 were thought to affect oxygen-hemoglobin dissociation. These researchers were the leaders in demonstrating the role of organic phosphates in the red blood cell.

The oxygen-hemoglobin dissociation curve is altered by the allosteric effector 2,3-DPG which binds the various legends in a sigmoidal manner (221). The affinity of 2,3-DPG for oxygenated states of hemoglobin is an order of magnitude lower than its affinity for deoxyhemoglobin and decreases in the order $Hb(O_2) > Hb(O_2)_2 > Hb(O_2)_3$. 2,3-DPG does not bind to fully oxygenated hemoglobin because the central cavity of oxyhemoglobin is too small to accommodate DPG (209).

2,3-DPG is a product of glycolysis via the Embden-Meyerhof pathway. The pathway to pyruvic acid through the trioses is the Embden-Meyerhof pathway, through gluconic acid and pentoses is the direct oxidative pathway (hexose monophosphate stunt) (109). In the red blood cell the step catalyzed by phosphoglycerate kinase (PGK) is bypassed and instead of forming 3-Phosphoglycerate and ATP, the enzyme diphosphoglycerate mutase (DPGM) catalyzes the formation of 2,3-DPG. This reaction effectively dissipates the heat of free energy associated with the high energy phosphate of 1,3-diphosphoglycerate. There is no net formation of ATP when glycolysis takes this route. 2,3-DPG

can be further converted to 3-phosphoglycerate by the enzyme diphosphoglycerate phosphatase (DPGP) (221, 179) (Figure 11-4).

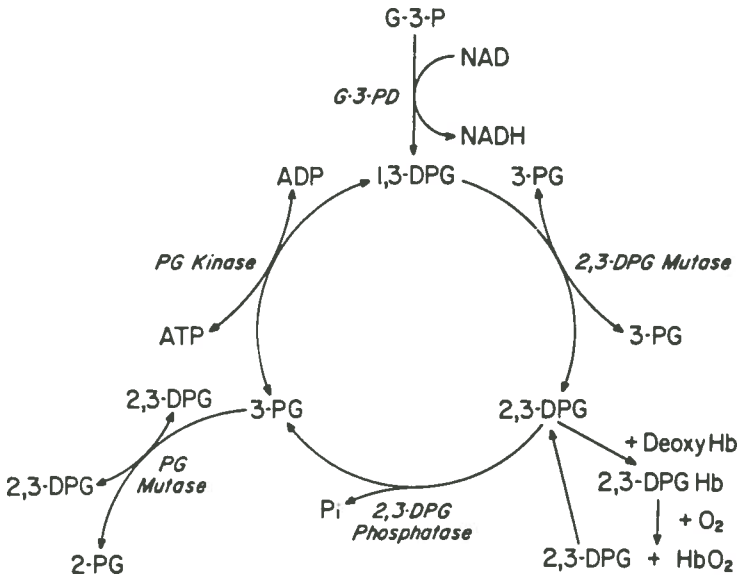
Figure 11-4.



The metabolism of the human erythrocyte. *HK* = hexokinase; *GPI* = phosphoglucose isomerase; *PFK* = phosphofructokinase; *TPI* = triosephosphate isomerase; *PGD* = phosphoglyceraldehyde dehydrogenase (glyceraldehyde phosphate dehydrogenase); *PGK* = phosphoglyceric acid kinase; *PGM* = phosphoglyceromutase; *DPGM* = diphosphoglyceratemutase; *DPGP* = diphosphoglycerate phosphatase; *PK* = pyruvate kinase; *LDH* = lactic dehydrogenase; *G-6-PD* = glucose-6-phosphate dehydrogenase; *6-PGD* = phosphogluconic dehydrogenase; *PGM* = phosphoglucomutase; *SDH* = sorbitol dehydrogenase; *AR* = aldose reductase.

The conversion of 1,3-DPG to either 2,3-DPG or 3-PGA is governed by the concentration of unbound 2,3-DPG, the level of 3-PGA, and the adenosine diphosphate (ADP), adenosine triphosphate (ATP) ratio (28, 190). Increased concentrations of ADP facilitate conversion of 1,3-DPG to 3-PGA. High levels of 3-PGA inhibit the phosphoglycerate kinase reaction and increase synthesis of 2,3-DPG (Figure 11-5).

Figure 11-5.



Hydrogen ion concentration influences the metabolism of 2,3-DPG (190) by regulating red blood cell glycolysis or by effects of pH on enzyme activity of 2,3-DPG Mutase and 2,3-DPG Phosphatase. Alkalosis stimulates red cell glycolysis and

formation of 2,3-DPG. Acidosis inhibits glycolysis and formation of 2,3-DPG.

A genetic defect in certain individuals leads to a deficiency of pyruvate kinase. In this case glycolytic intermediates, including 2,3-DPG, accumulate in the blood. Concentrations of 2,3-DPG become inordinately high, oxygen binding is inhibited and oxygen transport is diminished (221). When there is a hexokinase deficiency, too little 2,3-DPG is produced and causes inefficient transfer of oxygen from hemoglobin to myoglobin. A balance must be maintained for adequate oxygen transport.

Certain clinical conditions are associated with alteration in the level of 2,3-DPG and thus the oxygen affinity of blood. Conditions associated with increased levels of 2,3-DPG and an increased P_{50} with a right shifted curve are:

1. high altitude
2. hypoxemia
3. anemia
4. decreased red blood cell mass
5. chronic liver disease
6. hyperthyroidism
7. red cell pyruvate kinase deficiency

Conditions associated with decreased 2,3-DPG, decreased P_{50} and a left-shifted curve are:

1. septic shock
2. severe acidosis

3. transfusion of old, stored blood

4. neonatal respiratory distress syndrome

In addition, certain conditions are associated with an elevated P_{50} but without a consistent change in levels of 2,3-DPG. Certain abnormal hemoglobins and vigorous exercise can cause this. Hemoglobins E, Kansas, Seattle, Hammersmith and Tacoma have increased P_{50}s. While other abnormal hemoglobins (Kempsey, Philly, Chesapeake, J. Capetown, Yakima and Rainier) are associated with a decreased P_{50} without consistent change in 2,3-DPG (190).

C. ATP

Adenosine triphosphate (ATP) like 2,3-DPG is an organic phosphate and is also effective in lowering oxygen affinity (38, 57). Adenosine diphosphate, adenosine monophosphate, pyrophosphate, and inorganic phosphate have progressively decreasing degrees of effectiveness.

ATP binds in a manner similar to 2,3-DPG. The positively charged histidine residue located at the entrance to the central cavity of hemoglobin binds anions like ATP and 2,3-DPG to form electrostatic binds (85).

When ATP is utilized in the cell to produce energy it is converted to ADP (adenosine diphosphate). Recall the usual step in glycolysis from 1,4-DPG catalyzed by phosphoglycerate kinase (PGK) to form 3-phosphoglycerate (3-PGA), fig. 11-4. ATP is converted to ADP liberating energy (190). The increasing

concentrations of ADP increases the metabolic usage of both oxygen and the various nutrients that combine with oxygen to release energy (129). The energy is used to reform ATP. Therefore, under normal operating conditions the rate of oxygen consumption by cells is regulated by the rate of ATP expenditure.

D. pH

Normal blood pH is 7.4 and reflects the hydrogen ion concentration and functioning of normal blood buffering systems. As blood pH increases, alkalemia, the affect on the oxygen dissociation curve is a shift to the left, a lower P_{50}, increased oxygen affinity and decreased oxygen release (109, 190, 265). As blood pH falls, acidemia, there is a right shift to the curve, higher P_{50}, lower oxygen affinity and increased oxygen release.

Alkalemia may be due to metabolic or respiratory causes. Acidemia may also be due to metabolic or respiratory causes. The decreased oxygen affinity of hemoglobin due to a fall in pH is known as the BOHR effect (109, 28). The pH of blood falls as its CO_2 content rises, the curve shifts to the right and the P_{50} increases.

Respiratory distress syndrome in premature infants is commonly associated with respiratory acidosis. The normal response to low pH by a shift of the curve to the right and increased oxygen release is often compromised by presence of fetal hemoglobin, low amounts of 2,3-DPG and low body temperature (95, 152).

Acid-base balance is regulated by the kidneys and functional development of the kidneys is not complete until the end of the first month of life (129). Even the normal newborn can only concentrate urine one and one-half times that of plasma. The metabolic rate of the infant is two times that of an adult relative to body mass. It is even higher in premature infants. This leads to the tendency toward acidosis in infants (95, 19).

E. CO_2

An increase in CO_2 tension has the same effect as a decrease in pH (265). CO_2 and pH are related as the Bohr effect. As blood perfuses the lungs CO_2 diffuses out of the blood into the alveoli. This decreases the blood PCO_2 and increases the pH which shifts the curve to the left and upward. There is an increase in the oxygen that binds to hemoglobin and increased oxygen transport to the tissues. In the tissue capillaries the opposite effect occurs. CO_2 from the tissues replaces the oxygen on the hemoglobin, tissues receive the oxygen and the curve shifts to the right. The Bohr efect of CO_2 is to shift the curve to the right in the tissues facilitating oxygenation, and shift the curve to the left in the lungs facilitating CO_2 diffusion and oxygen binding to hemoglobin.

Respiratory abnormalities are common in premature infants. RDS, the most common, is due to immature pulmonary architecture and deficient levels of surfactant. Inadequate ventilation due to RDS causes $PaCO_2$ levels to be elevated. A $PaCO_2$ of 80 mmHg is

not unheard of and causes the oxygen dissociation curve to shift to the right. As mentioned previously, this shift may be relative to an already left shifted curve due to the presence of HbF and hypothermia, common problems in prematurity. Therefore, the attempt to increase oxygen release in response to hypercapnia may be limited.

F. Temperature

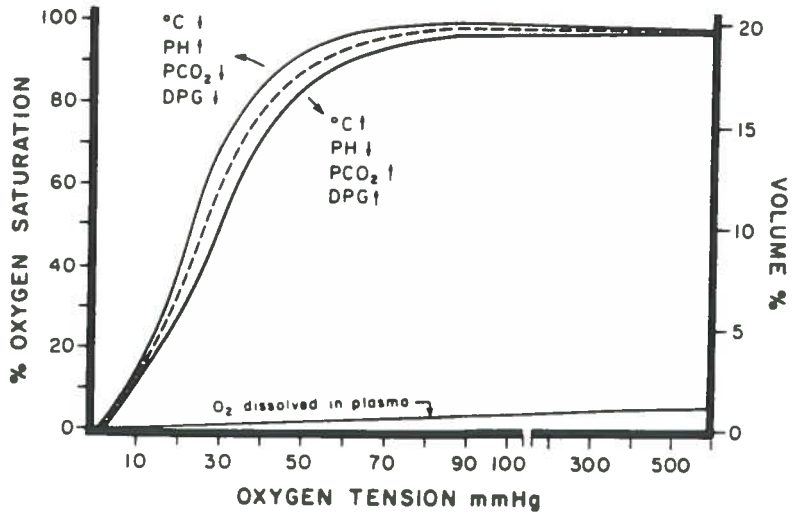
The oxygen dissociation curve is shifted to the right when temperature rises above a normal 37°C. This causes a decrease in oxygen affinity, an increased P_{50}, and increased oxygen release (109). Conversely, hypothermia causes the curve to shift to the left resulting in increased oxygen affinity, decreased P_{50}, and decreased oxygen release.

In a normal full term newborn body temperature falls in the first hours following birth but returns to normal by 6 to 8 hours (236). This is due to the increased metabolic rate of infants and large surface area relative to body mass (152). Body temperature falls easily in premature infants due to control system immaturity an lack of insulating adipose tissue. Thermal instability is common in premature infants. Temperature of the preterm infant tends to approach its surroundings. A body temperature maintained below 35°C is associated with a high incidence of death (236). Providing a neutral-thermal environment for temperature instability in premature infants has significantly reduced neonatal mortality. The first neonatologist, Pierre Budin (53)

was the first to advocate the need for temperature control.

Elevated temperature may be due to excessive environmental temperature, infection, dehydration, or alteration in the mechanisms of heat control associated with cerebral birth trauma or drugs (152).

Figure 11-6.



Factors shifting the oxygen dissociation curve of hemoglobin (fetal hemoglobin is shifted to the left). (From Martin, R.J., Klaus, M., and Fanaroff, A. Respiratory problems. In Klaus, M., and Fanaroff, A., editors: Care of the high risk neonate. Philadelphia, 1986, W.B. Saunders Co.)

XII

EFFECTS OF THE PHYSICAL ENVIRONMENT

From the turn of the century and Pierre Budin's (58) observations on the maintenance of adequate temperature in premature infants, numerous studies and all types of equipment have been devised to provide the ideal "external milieu." In the early days of neonatology, laundry baskets were padded, equipped with hot water bottles, and placed by the fireplace or stove to help keep the tiny baby warm. Even these efforts contributed to decreasing the astronomically high mortality rate of premature infants.

As technology advanced the birth rate was declining and so perhaps the impetus to save more premature infants directed technical efforts toward this end. Cone (66) details the development and history of infant incubators in the early 1900s. The understanding of thermal requirements for small premature infants has been very slow to develop. Other environmental factors such as light, noise, tactile stimulation, and the amount and type of handling have been examined only in more recent years and the effect of these is still being defined at this time.

A. The Thermal Environment

Protecting the premature infant against heat loss reduces mortality. There is significant published data to convince us that this is true (4, 79, 234).

Table 12-1.

Mortality of premature infants maintained in environments providing more or less protection against heat loss

	More		Less	
	Number	Died (%)	Number	Died (%)
Silverman and co-workers (1985)	91	16	91	32
Beutow and co-workers (1964)	89	42	69	54
Day and co-workers (1964)	60	23	65	37
Perlstein and co-workers (1976)	105	22	105	35
Totals	345	26	330	40

Blackfan and Yaglou (42) published a paper in 1933 which directed the routine of care for years to follow. They found that a high relative humidity with an air temperature of approximately 25°C was required to maintain body temperature in low birth weight (1360 to 2270 gram) infants. These authors concluded that "a subnormal temperature, particularly in lower weight groups, is a characteristic of prematurity."

Silverman (230) solved the issue of temperature versus humidity. In three studies he was able to show that control of environmental temperature was responsible for increasing survival. A 4°F increase in incubator temperature to 89°F caused a 15% increase in survival. Varying humidity under controlled temperatures had no effect on survival.

In the late 1950's, Cross and associates (71) showed a decreased oxygen consumption when environmental oxygen was reduced in normal term infants. They concluded that reduced oxygen consumption was a defense against asphyxia. These infants had

lower body temperatures when environmental oxygen was reduced however. Hill (137) found that in room air, oxygen consumption and rectal temperature varied with the environmental temperature. She noted "a set of thermal conditions at which heat production (measured as oxygen consumption) is minimal yet core temperature is within normal range (neutral thermal environment)."

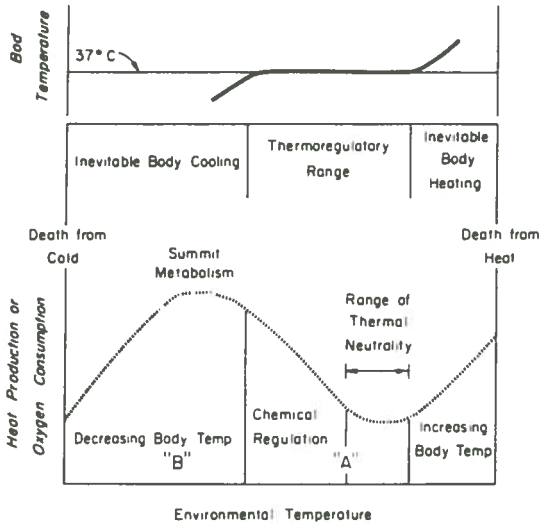
Infants are homeotherms not poikilotherms (48, 79, 93, 185). Turtles are poikilotherms and drops its body temperature if placed in a cold environment. Small premature infants are handicapped homeotherms who attempt to maintain body temperature by increasing oxygen and caloric consumption to generate heat. Infants respond to heat loss by generating heat through the conversion of substrates to metabolic acids often producing an oxygen debt.

Adults can produce heat by voluntary muscle activity, involuntary muscle activity (shivering), and nonshivering thermogenesis (152). Shivering is the most significant in the adult but nonshivering thermogenesis is most important in infants. This nonshivering thermogenesis is a cold induced increase in heat production and oxygen consumption. Brown fat is plentiful in term infants and provides triglyceride hydrolysis to free fatty acids and glycerol (221). Premature infants are less able than term infants to generate heat in this manner without depleting vital substrates and creating oxygen deficits since there is less available brown fat to provide the metabolic fuel.

Merenstein and Blackmon (152) studied the effect of

environmental temperature on oxygen consumption and body temperature. In figure 12-1, oxygen consumption is least in a neutral thermal environment and in severe hypothermia.

Figure 12-1.



Effect of environmental temperature on oxygen consumption and body temperature (Adapted from Merenstein and Blackmon.

Decreased oxygen consumption in hypothermic conditions has been responsible for survival after near drowning in freezing water. Cardiac surgeons make use of this fact too. Creation of a neutral thermal environment for infants attained credence in the 1960's (4, 108, 107). This type of thermal environment provides a reduced need for heat production by the infant and therefore minimizes metabolic demands. Neutral thermal conditions are considered most important for young immature infants whose ability

to increase metabolic rate is nampered by impaired gas exchange and lack of caloric intake (95).

Premature infants were once thought to have immature central regulatory structures resulting in increased instability of temperature. More recently though, instability was recognized to be "due to the discrepancy between efficiency of the effector systems and body size" (49). The regulatory center is intact but infants have a high surface area to mass ratio and a narrower control range than adults. This is even truer in premature infants.

Heat loss from body surface to the environment involves radiation, conduction, convection, and evaporation. The newest thermal regulation devices have advanced from Budin's early incubators. The two most common types of units used in today's intensive care units are isolette-type incubators and open radiantly heated beds. There are advantages and disadvantages to each and neither controls all four sources of heat loss.

Radiant heat loss is rapid and involves heat loss from a warmer object to a cooler one although there is no actual contact. Conduction heat loss involves a heat transfer directly from a warmer object to a cooler one in which there is contact (204). The infant can lose heat conductivity to a cold bed or blankets. There is radiant loss from the infant to the walls of the isolette if it is not insulated even if the air temperature inside is warm. This has been observed when isolettes are placed

against cold walls or windows in the nursery. Heat can be transferred in the opposite directions, from isolette walls to the body, if the surface is allowed to heat excessively. Hyperthermia has been observed in infants under phototherapy or when isolettes are exposed to sunlight.

Convection is heat loss from a warmer object to a less dense material such as air (204). This type of heat loss can occur not only on exposure to cooler air but also in adequate temperature air with drafting. Circulating air fans inside isolettes may cause drafts as well as air currents across open radiant warming units.

Every milliliter of water that evaporates produces about 0.58 calories lost body heat (202). Evaporative heat loss involves not only the skin but also insensible losses through respiration and sweating. Premature infants with respiratory distress are ventilated with warmed humidified air to reduce insensible water loss and cooling. The standard of care at delivery is to quickly dry the newborn and provide a heat source to reduce cooling by evaporation.

Convectively heated incubators like the isolette-type consist of a clear plastic box that is either one or two layers, a heating unit that is thermostatically controlled, an insulated mattress, fans to circulate filtered and warmed air and portals through which the infant can be accessed. Heating can be controlled in one of two ways. First, heating by control of a thermostat

referenced to the internal air or second, control by a servo-loop that references the heater-on or heater-off decision to a narrow range of infant skin temperatures.

Disrupting the internal environment repeatedly, as is often necessary for care of the sick infant, causes the temperature to fall abruptly. This fact has led to the use of radiantly heated units for unimpeded access to infants requiring abundant care. Most radiant warmers utilize skin servocontrol to provide consistent temperature. There is a risk of hyperthermia if there should be; mechanical failure and malfunction in heat output, the alarm fails to sound, or the skin sensor becomes dislodged. Diligent supervision is necessary.

Although radiant warmers provide greater convenience to caregivers there is a greater insensible water loss (268). The metabolic costs of this are uncertain but there are known fluid and electrolyte disturbances associated. Depending on air flow, traffic pattern and nursery air temperature, air currents and drafts may create a wind chill effect. It is common to protect the exposed infant with acrylic plastic air/heat shields to reduce drafting and insensible water loss. Plastic bubble packing paper is used as an alternative to the shield.

Though both types of units attempt to provide the infant a neutral thermal environment disruption to provide intensive care breeches the seal. Diligent care must be used to minimize deviation from optimal thermal ranges least the already compromised

premature infant will have to create heat using metabolic reserves and oxygen needed to support life. The small sick perterm infant is least able to tolerate this demand.

B. Nursery Activity

Several studies (160, 41, 26) have examined the problem of caregiver disruptions on sleep patterns in premature infants. Nurses are responsible for the majority of disruptions, as could be expected, since they provide the bulk of intensive care. Infants who are most ill are disturbed most frequently. In Korones' study disruptions averaged 5.5 per hour while Duxbury's group averaged 2 disruptions per hour. This results in decreased amounts and quality of sleep and loss of normal diurnal rhythms.

The premature infant is less able than a mature newborn to control and decrease response to noxious stimuli (115). The immature infants' usual response to overstimulation (noxious or otherwise) is compromised physiologic function. Social interaction, not just painful stimuli, provoke behavioral and physiologic distress according to Gorski (119). He described such signs of distress as cyanosis, bradycadia, apnea, decreased perfusion, vomiting, gasping, and hyperexcitability states of arousal and activity.

In his 1982 paper, Gorski (121) noted increased physiologic distress coincided with peak caregiving activity. Episodes of apneas tended to occur in clusters associated with nursery rounds (115). Other researchers have also suggested that rather than

premature infants having too little interactive stimulation, there is overstimulation by the very nature of the intensive care nursery (165). These units have expanded over recent years into highly technical intensive care units. Physical space is usually minimal, equipment is noisy, the number of caregivers high, 24 hour bright lights, and high levels of activity contribute to making the environment full of noxious stimuli.

There has been an attempt to modulate the degree of this source of overstimulation and provide caregiving activities in a manner that minimizes the duration and quality of noxious interventions. Several nurse researchers advocate "minimal handling" as philosophy of organizing nursing care to decrease provocation of physiologic compromise (26, 41).

At the same time Solkoff (243) and others (67, 132, 103, 244, 266) suggested that appropriate types of stimulation were missing in the intensive care setting. The premature infant, had he not been born, would normally be provided auditory, vestibular, and proprioceptive stimulation in utero. Many believed these same kinds of stimuli would contribute to growth and development which had been interrupted by precipitous entrance of extrauterine life.

Barnard (26) and Blackburn (41) showed that the ability of the infant to organize behavioral states was associated with gestational age. Infants had increased proportions of quiet sleep with repetitive kinesthetic and auditory stimuli during the 32nd to 35th week of gestation. Korner (157) studied preterm

infants using an oscillating waterbed to provide proprioceptive-vestibular stimulation and found reduced incidence of apnea.

Obviously there is a balance between excessive and deficient amounts of stimulation and types of stimulation which promote physical and neurologic growth and development. It appears that critically ill premature infants are least able to regulate incoming stimulation. These babies are certainly overstimulated with primarily noxious forms of tactile and auditory input. At the same time holding, rocking, and positive forms of tactile and auditory stimulation are either prohibited by the medical state or replaced with noxious forms of stimuli.

Korner (157) and others have demonstrated that positive forms of proprioceptive-vestibular stimulation reduce the incidence of physiologic compromise and promotes growth and development. Further research into positive forms of stimulation, and modification of light and noise levels and caregiver activity in intensive care settings is a necessary goal for the future.

XIII

RESPIRATORY DISTRESS SYNDROME

A. Definition

Respiratory distress syndrome, otherwise known as hyaline membrane disease, is the most common serious problem associated with premature birth. The name hyaline membrane disease was derived from the postmortem finding of acid-staining hyaline-like membranes in the lungs of newborns with the disease (139, 80). Hyaline membranes have also been pathologic findings of other diseases so this name has given way to the more generic term of respiratory distress syndrome (RDS).

Although the pathophysiology is not completely understood, a primary feature of the disease is a deficiency in the surface pressure lowering phospholipid, surfactant. This was described most brilliantly by the work of Avery and Mead in their landmark paper (15). Lack of surfactant results in decreased lung compliance and an increased work of breathing.

Infants with RDS develop signs of respiratory distress either immediately at birth or within a few hours. Signs and symptoms of RDS include tachypnea, nasal flaring, intercostal and subcostal retractions, cyanosis and expiratory grunting (95). Severity varies, often depending on the degree of prematurity, presence of pulmonary surfactant, and failure of pulmonary gas exchange (131). Complications of a patent ductus arteriosus (PDA), air leaks,

pulmonary hypoperfusion and sepsis contribute to a poor prognosis (112). Uncomplicated clinical course is characterized by worsening symptoms from birth to two or three days then onset of recovery (95). The greatest risk factor appears to be premature birth, but other factors include maternal diabetes, delivery by cesarean section, and perinatal fetal distress and asphyxia (66, 95).

B. Incidence

Quotes of incidence vary in the literature but all agree that RDS produces the highest rates of neonatal morbidity and mortality. According to Hodson and Guthrie (140), about 15% of premature infants develop RDS in inverse proportion to gestational age (Table 13-1).

Table 13.1

Incidence of Hyaline Membrane Disease Related to Gestational Age

Gestation (weeks)	Incidence (%)
40	0.05
36	0.70
34	20.00
32	37.00
28	66.00

Source: W. A. Hodson and R. D. Guthrie. Hyaline Membrane Disease. In V. C. Kelley (ed.), *Practice of Pediatrics*, Vol. 2. Philadelphia: Harper & Row, 1984.

Fanaroff cites incidence figure for RDS of greater than 70% of newborns at 28 to 30 weeks gestation (95). RDS is rare in

newborns 37 weeks gestation or more and there is a slight predominance of disease in males.

Morbidity and mortality rates are staggering. Ten to fifteen thousand infants died out of 40,000 with RDS when Avery and Farrell published in 1975 (12). In 1983 Hodson and Guthrie (143) gave an overall mortality figure of 25% with figures up to 50% in babies weighing less than 1250 grams. Mortality rates have improved very slightly with advancing therapeutic ability but as a result, morbidity has increased with the sequelae of treatment.

C. Pathogenesis

The lungs of infants with RDS are diffusely atelectatic. This produces the characteristic x-ray findings of reticulo-granular infiltrate throughout the lung fields (255). This has been described as a "ground glass" appearance in which the lungs appear white and hazy. The tracheal-bronchial tree is air-filled and is seen as an air bronchogram against the opaque perihilar region (87). Macroscopically, the lung tissue is purplish and resembles liver in texture (95, 32).

The most important factor in the pathogenesis of RDS is prematurity and is directly proportional to the degree of prematurity unless efforts are made to stimulate maturation of the lungs prior to delivery. Immature lungs that fail to secrete surfactant have increased alveolar surface tension which require higher opening pressures and collapse without a maintained positive airway pressure (124). This causes atelectasis which

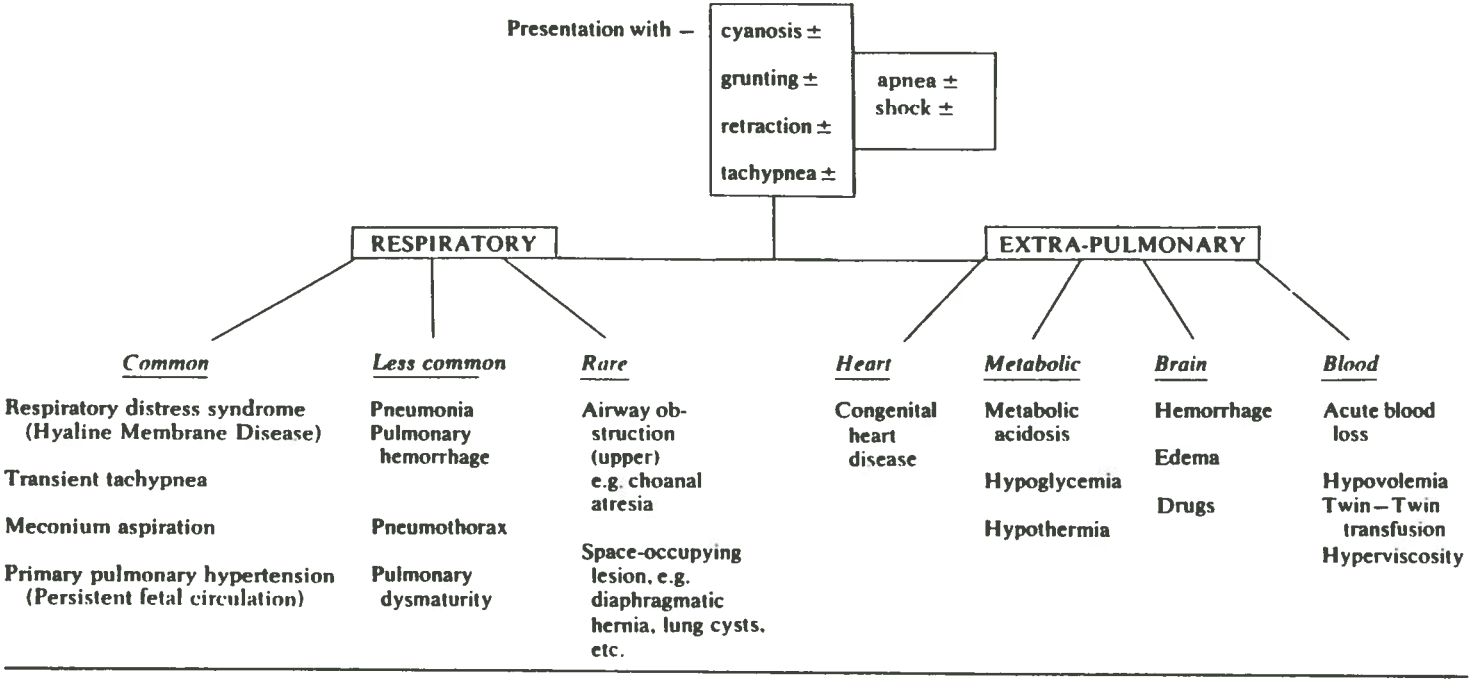
Surfactant synthesis and function was discussed in chapter VII. To summarize, surfactant is a phospholipid that is produced by type II alveolar cells and binds to the internal surface of the alveoli reducing its surface tension at the air-water interphase. This results in reduced alveolar pressure and prevents collapse at the end of inspiration. Surfactant is not produced in significant quantities prior to 34 to 36 weeks gestation although type II cells may be pharmaceutically stimulated to produce the phospholipid as early as the 27th or 28th week of gestation.

RDS is not the only cause of tachypnea, grunting, flaring, retractions and cyanosis, although it is by far the most common in premature infants. A differential diagnosis of respiratory distress includes such other entitites as meconium aspiration, transient tachypnea of the newborn (TTN), persistent fetal circulation (PFC), and extra-pulmonary causes such as congenital heart defects (152) (Figure 13-2).

D. Treatment

Treatment of RDS is primarily supportive according to Hodson and Guthrie (140). Once the infant presents clinical signs and symptoms, prevention is lost. But, recent studies have shown some success with administrative of surfactant into the lungs of infants with RDS (92, 105). Surfactant therapy has been complicated by development of left to right shunting through a PDA (62) (Figure 13-3).

Figure 13-2.



Differential diagnosis of respiratory distress in the newborn period.

Figure 13-3.

Surfactant therapy for RDS

KNOWN

Improvement in arterial oxygenation and ventilation
Major ingredient Dipalmitoyl phosphatidylcholine—Dose of 50 to 100 mg/kg
Administration of fluid suspension by means of endotracheal tube
Natural surfactant more efficacious than synthetics
Instillation before first breath optimal

UNKNOWN

Optimum preparation: natural/synthetic, combination and stability
Duration of effect and need for retreatment
Risk of infection
Pharmacokinetics metabolism of surfactant preparation
Timing and proper administration for established RDS
Effects on ductus arteriosus
Interaction with endogenous surfactant
Immunologic effects

Modified from Taeusch H W Clements J and Benson B Am Rev Respir Dis **128**:791 1983 Adaptation by M S Kwong

The newest and most highly technological treatment is called ECMO (extracorporeal membrane oxygenation). This technique involves perfusion and gas exchange via cardiopulmonary bypass through a membrane lung (27). ECMO is an extraordinarily invasive technique used rarely and only in specially equipped centers under dire circumstances of respiratory failure.

Usual treatment for RDS is, as Hodson and Guthrie (140) suggested, supportive. Invasive techniques are avoided until absolutely necessary due to the association of these treatment

modalities with increased incidence of morbidity. Treatment is aimed at providing thermoregulation, maintaining fluid and electrolyte balance, maintaining acid-base balance and thus ventilatory function, and preventing the complications of infection and anemia (152, 95, 131).

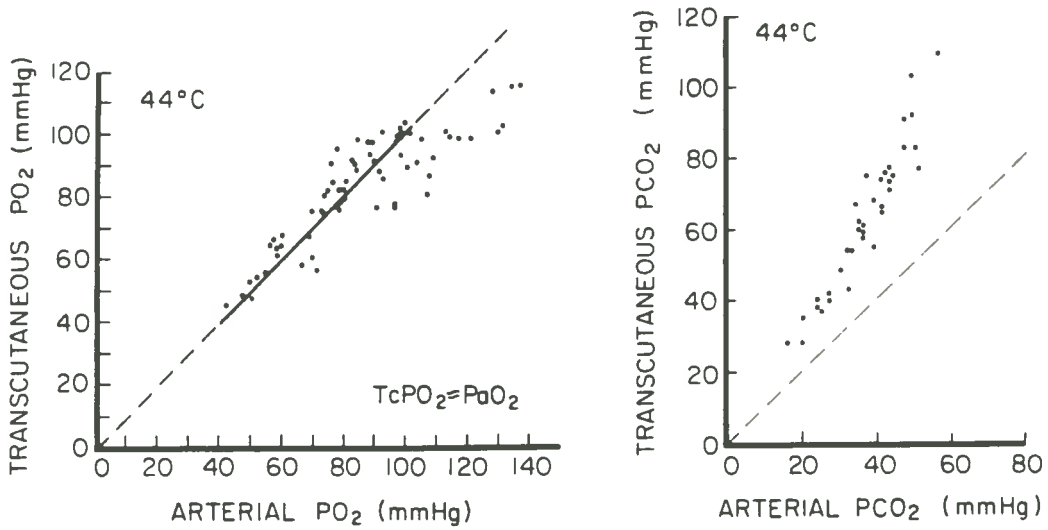
Thermoregulation minimizes oxygen consumption and oxygen requirements as previously discussed. Infants who are hypoxic lose the ability to increase metabolic rate when allowed to become cold stressed (202). Maintenance of fluid and electrolytes as well as providing at least minimal nutrition is most often accomplished via intravenous routes. Nutrition is provided by administration of glucose, amino acids, and lipids supplemented with vitamins and minerals. Parenteral nutrition is usually well tolerated but is not totally without untoward effects. Oral feedings are usually prohibited due to tachypnea and risk of aspiration as well as decreased bowel motility.

Maintenance of acid-base balance is directed toward correcting hypoxemia, acidosis, and hypercapnia. Repeated blood gas sampling is necessary and when stability is poor the placement of an arterial line provides access without repeated arterial punctures. Umbilical artery catheters are often used when RDS is severe. These can provide a means to infuse fluids, medications, obtain blood samples, monitor arterial blood pressure, and certain models have an oxygen sensor to provide continuous PaO_2 monitoring. Placement of these lines can be difficult if the

umbilical artery spasms and an untoward affect of indwelling umbilical artery lines is vasospasm, which can compromise perfusion to extremities. Vasospasm may be so profound that amputations of necrotic fingers, toes or worse, a whole limb has been required.

Transcutaneous measurement of PO_2 ($TcPO_2$) has been shown to be a reliable, well correlated way to monitor the PaO_2 in a noninvasive and continuous manner (144). Arterial blood gas samples are still necessary at periodic intervals but in mild RDS $TcPO_2$ monitoring may negate the necessity for umbilical artery catheters. $TcPCO_2$ does not correlate as well to $PaCO_2$ when the PCO_2 is high (144).

Figure 13-4.



Left, Correlation between transcutaneous and arterial Po_2 in preterm infants with RDS. *Right*, Correlation between transcutaneous and arterial Pco_2 in preterm and term infants with cardiopulmonary disease

$TcPO_2$ monitoring provides a minute to minute update of oxygenation and allows caregivers to make adjustments in the amount of supplemental oxygen. This has helped reduce some of the affects of oxygen toxicity on one end and hypoxia on the other (171). This form of monitoring lets caregivers know when the infant is not tolerating a particular procedure. Subtle changes in $TcPO_2$ gives clues to the caregiver to modify activities. An example is in handling or suctioning activities.

Oxygen saturation monitors are gaining popularity in recent years as an alternative or adjunct to $TcPO_2$ monitors. Solimano and associates (242) show good correlation between $TcPO_2$, SaO_2, and PaO_2. This application has best been applied to the care of older infants with bronchopulmonary dysplasia (BPD), a sequelae of RDS.

Although PaO_2 and $PaCO_2$ can be monitored indirectly, pH must be measured, therefore arterial blood gases remain an important part of the management of RDS and prevention of acidosis.

Hypoventilation can be treated in mild RDS by provision of supplemental humidified oxygen. Respiratory acidosis may require transient or prolonged ventilation therapy. The most serious derangements of acid-base metabolism and oxygenation are associated with the most severe forms of RDS in which there is failure in gas exchange (164). Assisted ventilation is used to treat respiratory failure whether due to apnea or severe RDS with hypoxemia, hypercapnia and respiratory acidosis. Alkali therapy

in addition to assisted ventilation to decrease $PaCO_2$ may be necessary to correct severe acidosis.

Continuous positive airway pressure devices were developed by Gregory (124) and helped reduce the airway collapse between breaths that was inherent to RDS. Severe disease requires ventilation with a pressure ventilator via an endotracheal tube. These machines provide intermittent mandatory ventilation (IMV), positive end expiratory pressure (PEEP), positive inspiratory pressure (PIP), and ability to set the timing of both inspiratory and expiratory phases as well as the concentration of oxygen in the inspired air (F_iO_2). Carlo, Martin and Fanaroff recommend initiation of assisted ventilation if any of the following are present:

1. Respiratory acidosis with a pH less than 7.20 to 7.25;
2. Severe hypoxemia (PaO_2 less than 50 to 60 mmHg) despite a high F_iO_2 (70% to 100%);
3. Apnea complicating the clinical course of RDS.

An adjunct to assisted ventilation is the use of pharmaceutical sedation or paralysis to decrease risk of pneumothorax with asynchronous respirations (164). Narcotics, muscle relaxants, and the paralytic Pancuronium bromide (Pavulon) have been used to suppress or inhibit the baby's own respiratory efforts. Finer and Tomney (101), Crone and Favorito (70) studied the effects of Pavulon on infants with RDS. Both studies showed improved gas exchange, reduced periods of nonoptimal oxygenation,

and reduced periods of elevated intracranial pressure. The use of paralytic drugs is of limited duration and has a high associated risk. Accidental extubation of a paralyzed infant is a serious emergency. Care of the infant who is mechanically ventilated and paralyzed requires a high level of expertise.

E. Complications and Sequelae of RDS

Most complications of RDS are due to treatment (152, 95, 66, 34, 255). The major sources of complications are results of umbilical artery catheters, long term use of endotracheal tubes, oxygen therapy, and mechanical ventilation.

Fanaroff, Martin, and Carlo (95) identify the following complications of mechanical ventilation:

1. Pulmonary air leaks: pneumothorax, pneumomediastimum, pulmonary interstitial emphysema;

2. Endotracheal tube complications: displacement, occlusion atelectasis following extubation, palatal grooves;

3. Tracheal lesions: eriosion, granuloma, subglottic stenosis, necrotizing tracheobronchitis;

4. Infection: pneumonia, septicemia;

5. Impaired cardiac function;

6. Chronic lung disease: bronchopulmonary dysplasia;

7. Miscellaneous: intracranial hemorrhage, PDA, retrolental fibroplasia (RLF).

Hypoxia for any duration leads to brain damage. Transient severe hypoxic events may be sufficient to cause intracranial

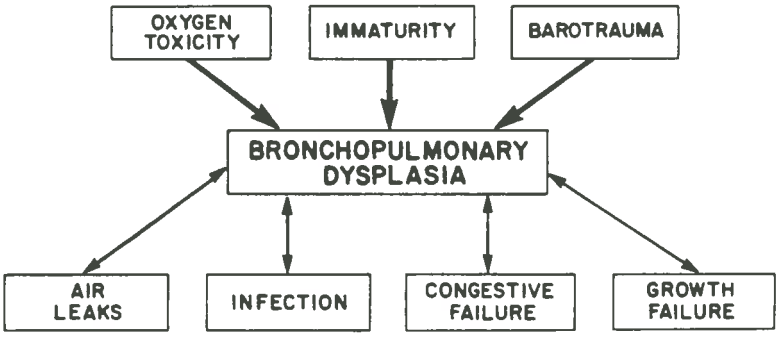
hemorrhage (95). Both hypoxia and hypercapnia cause a marked increase in cerebral blood flow. Subependymal germinal matrix hemorrhage and intraventricular hemorrhage (SEH/IVH) are the most common neuropathologic findings in preterm neonates and second only to RDS as a major cause of neonatal death. The etiology of SEH/IVH is not completely understood but one hypothesis is that hypoxia causes increased cranial blood pressure, ischemic injury to the endothelium of germinal matrix capillaries, and hemorrhage occurs (197).

Oxygen toxicity is responsible for causing retrolental fibroplasia (RLF) and contributes to development of bronchopulmonary dysplasia (BPD). Although supplemental oxygen is essential to prevent the hypoxia caused by hypoventilation in RDS, too much of a good thing is harmful. Administration of high concentrations of oxygen for long periods exposes sensitive immature tissues, such as the retina and lung, to toxic byproducts of oxygen, oxygen free radicals. RLF results in damaged retinal vessels which proliferate and extend into the aqueous humor dragging down the retina and causing separation. This results in blindness. Stevie Wonder is a product of zealous oxygen therapy for respiratory distress as a premature newborn as were many others born in the early 1950s. RLF continues to be a tenacious problem in modern care of RDS.

BPD is the result of the combined effects of mechanical ventilation. Oxygen toxicity together with barotrauma secondary

to high pressure ventilation are thought to be culprits (188, 222). The treatment is supportive. BPD may require oxygen therapy and management of the repeated respiratory infections and complications associated. The incidence of BPD secondary to RDS varies from 5% to 30% depending on gestational age with a mortality rate as high as 38% (177) (Figure 13-5).

Figure 13-5.

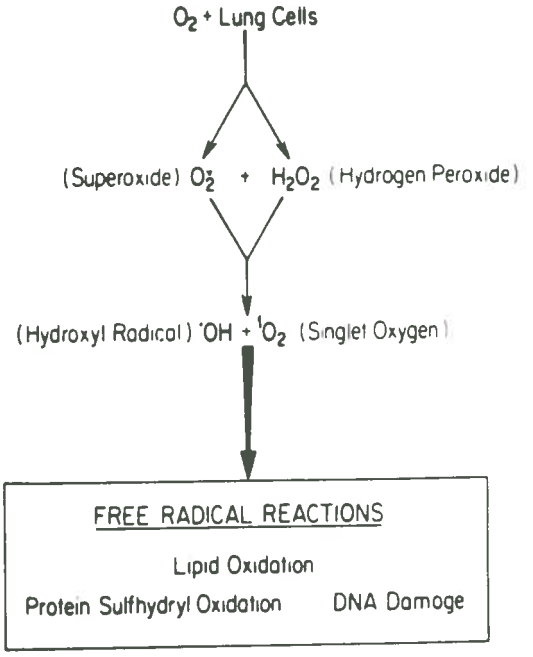


Schematic representation of the pathophysiologic events that contribute to the progressive development of chronic lung injury.

A safe level of supplemental oxygen is not known. Concentrations of oxygen of 50% administered over days is known to increase risk of toxicity (45). The pathogenesis of oxygen toxicity is nonspecific and includes endothelial damage, inflammation, edema, hemorrhage, fibrin deposition and thickening of membranes in the lungs. The mechanisms involve univalent reduction of molecular oxygen and formation of free radical intermediates (84). These free radicals react with membrane lipids provoking chain reactions which cause tissue damage.

Possible other agents of hyperoxia damage include hydrogen peroxide, superoxide radical, hydroxyl radical in addition to the single excited oxygen. All have been implicated in lipid peroxide formation and free-radical chain reactions.

Figure 13-6.



Chemical mechanisms of oxygen toxicity (From Deneke, S.M., and Fanburg, B.L. N Engl J Med **303**:76 1980. Reprinted by permission of the *New England Journal of Medicine*.)

The body normally resists the effects of oxygen toxicity with endogenous antioxidant enzymes. Vitamin E has been shown to have some protective effect on free-radical toxicity due to its antioxidant effect (147).

F. Prevention

The best cure for RDS is the prevention of premature birth but sadly significant reduction in the incidence of prematurity has not occurred. There has been some reduction in the incidence of RDS which can be attributed to advances in the obstetrical management of premature labor (7). The statistics are clouded by an increased survival at very low birth weights and lower gestational age. A short time ago these infants would have died before a diagnosis of RDS could be made.

An estimate of 10% to 20% of cases of RDS resulted from iatrogenic causes (113). Induced delivery or elective cesarean section often resulted in an unanticipated premature neonate since gestational age cannot be accurately determined by obstetrical dates. Advances in evaluation of fetal maturity have helped reduce this problem. Gluck and associates (112) have developed analysis techniques to identify the presence of adequate levels of surfactant, indicating fetal lung maturation, in amniotic fluid samples. The lecithin/sphingomyelin (L/S) ratio is still an accurate index of fetal lung maturity. Two other procedures were required to measure lung maturity by this technique, fetal ultrasonography and amniocentesis. In the last decade these techniques have evolved to help provide the means to assess gestational age with accuracy.

Pharmacological acceleration of fetal lung maturation and therefore adequate levels of pulmonary surfactant has been a focus

of research. The corticosteroid hormones have been shown to increase surfactant synthesis in fetal lung when administered to the pregnant woman between the 28th and 34th week of gestation (170). Successful inhibition of labor with the use of betamemetic agents has provided the time necessary to induce fetal lung maturation pharmacologically.

With these tools in our armamentarium, one would think it a simple task to assess lung maturity and inhibit premature labor until lungs can be induced to mature, then once maturation is accomplished permit delivery. Theory and actuality are often at odds. Not all institutions are equipped to perform these procedures. Not all labors can be inhibited, and sometimes the intrauterine environment is too hostile and life threatening, in which case delivery must be expedited. Diabetes falsely influences our ability to accurately predict maturation since insulin inhibits the formation of surfactant (99). Inhibition of preterm labor with potent pharmacologic agents has associated risks and side effects which prohibit their use in some instances. All these factors sum to a less than perfect success rate. There is significant room for improvement in perinatal management.

Prevention of the sequelae of RDS is a complex problem involving a balance of therapeutic factors if there is to be reduction in the incidence of neurodevelopmental deficits, RLF and blindness, BPD and chronic lung disease, impaired growth, hearing damage, and intracranial hemorrhage with varying degrees of

neurologic outcome. Hypoxia and oxygen toxicity are major culprits.

Surveillance techniques for oxygenation have contributed to some improvement in the incidence of hypoxia and oxygen toxicity. Accurate blood gas determination, techniques to access arterial blood for sampling, indirect monitoring techniques such as transcutaneous PO_2 and PCO_2 and pulse oximetry permit better management of oxygenation at the bedside. But the sick neonate with RDS is not a static organism and a variety of factors continually alter the balance between oxygen availability and oxygen demand.

I have examined several factors that influence oxygenation. Together the internal and external environment influence the balance between demand and supply, and hypoxia and hyperoxic toxicity. Hypoxia is often an immediate problem at birth. Improved obstetric management and resuscitation techniques have been successful in reducing this insult. Hypoxia also occurs in the longer term care of the mechanically ventilated neonate with RDS. Sudden and intermittent increase in oxygen demand without increased O_2 supply results in hypoxia. Some infants are known to have very labile fluctuations in oxygenation. Ventilation-perfusion mismatch, temperature instability, decreased availability of metabolic substrates, anemia, high concentrations of fetal hemoglobin, and agitated activity contribute to the unequal demand/supply. As the caregiver responds to increasing

oxygen demand by increasing oxygen flow, the rate of ventilation or the pressure at which the oxygen is delivered, the balance swings to the other extreme and the infant is exposed to potentially toxic concentrations of oxygen which have predictable sequelae.

This problem has led to the use of pharmacologic agents which decrease oxygen demand by reducing activity and permit unimpeded ventilation. The side effects of these drugs often limit the extent and duration of their use. Other techniques are needed that modify the environmental effects on oxygen demand. Strategies of critical care have been devised to reduce the types and amounts of noxious stimuli. These include noise abatement and minimal handling of small labile sick prematures. Modification of the intensive care nursery environment as a whole is a difficult and expensive undertaking. I propose to modify the microenvironment of the infant's isolette to reduce noxious stimuli, provide positive proprioceptive stimulation, reduce thermal lability, reduce nonpurposeful gross motor activity, conserve heat and energy, and therefore reduce oxygen demand. The technique I propose will therefore contribute to reducing the incidence and sequelae of hypoxia and hyperoxic toxicity.

XIV

RESEARCH PLAN

A. Specific Aims

Respiratory Distress Syndrome (RDS) is a major consequence of prematurity. Treatment with high concentrations of oxygen and assisted ventilation at high pressures for long periods are known to cause serious sequelae (131). The new mattress design proposed in this pilot study provides passive containment of body movement and autostimulation which are expected to reduce the incidence and duration of nonoptimal oxygenation and reduce episodes of agitation in premature infants. Reduced gross motor activity will reduce oxygen consumption for muscle metabolism, decrease caloric waste, and conserve heat and energy.

The mattress to be used in this study is an original design which combines the concepts of passive containment, to reduce gross motor activity, and vestibular stimulation, to increase state control. Both of these concepts have been previously shown to be safe and effective in reducing neonatal morbidity due to RDS (70, 101, 157, 158, 159).

Hypothesis: The Nesting Mattress will increase the stability of $TcPO_2$ in premature infants with RDS as compared to a conventional type isolette mattress. Additionally, the Nesting Mattress will have no adverse effects on vital signs when compared to the standard isolette mattress.

B. Significance

The premature infant is even less able than a mature newborn to control and decrease response to noxious stimuli (47). Uncontrolled nonpurposeful gross motor activity increases oxygen demand and the agitated infant experiences increased oxygen need, decreased perfusion to peripheral tissues, and increased lability of the $TcPO_2$ (115).

Several techniques have been used to decrease the occurrence and duration of hypoxia and hyperoxia. Two studies were done that specifically examined the effects of Pancuronium Bromide (Pavulon) induced muscle relaxation on RDS. Crone and Favorito studied 20 premature infants with severe RDS requiring mechanical ventilation (70). They were able to show significant improvement in blood gas values after treatment with Pavulon without changes in heart rate or blood pressure. Similarly, Finer and Tomney studied 10 mechanically ventilated premies and compared the occurrence and duration of hypoxia ($PO_2 < 50$), hyperoxia ($PO_2 > 70$), and intercranial pressure (ICP) with the use of Pavulon (101). This study also assessed the association of hypoxia, hyperoxia, and ICP to handling during study and control periods. Finer and Tomney note that handling, which is a source of noxious stimuli to tiny immature babies, was reduced during periods of Pavulon induced paralysis. This reduction in noxious stimulation reduces provocation of agitated motor activity and thus decreases oxygen consumption for muscle metabolism, decreases caloric waste, and

conserves heat and energy (101).

Korner et al. carried out several studies looking at the clinical response to premature infants to compensatory vestibular-proprioceptive stimulation using an oscillating water bed (157, 158, 159). In her pilot study, Korner demonstrated the safety of the water bed. Vital signs including temperature were unaffected by the use of the water bed. It was also found to reduce pressure induced skin lesion development and assymetrical shaping of the premature head. Specifically, the oscillating water bed reduced the incidence of apneic episodes (157). These researchers examined the variabilty of state control with the water bed in a study published in 1978 (158). These data replicated those of the pilot study with regard to significant reduction in apneas while infants were on the water bed. The most significant reduction occurred in apneas associated with severe bradycardia. There was an average of 30% reduction in all types of apneas during study periods compared to controls. The effect of the water bed on state control was polygraphically recorded but, unfortunately, periods of thrashing body movements could not be recorded in this manner. Infants in this study were shown to have less awake time on the water bed and greater indeterminate sleep states as compared to controls.

In a third study by Korner, the effects of the water bed on state control was looked at again. In this study subjects were receiving theophylline treatment for apneas. Importantly, all but

Figure 14-1

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THE PERMANENTE MEDICAL GROUP
San Francisco, California

Consent to Participate in Medical Research Study -
Effects of the Nesting Mattress on Transcutaneous Partial Pressure of Oxygen in Premature Infants with Respiratory Distress Syndrome:
A Pilot Study

A medical research study involving premature infants with respiratory distress syndrome is being conducted by Joan Ertel-Howley, RN who is also a third year medical student in the UCB/UCSF Joint Medical Program. The objective of this study is to determine what effects, if any, a new mattress design may have on the level of blood oxygenation in premature newborns. The level of oxygenation is measured by attaching a sensing device with an adhesive patch to the baby's skin. This device is called a Transcutaneous Oxygen Monitor and is commonly used to measure blood oxygen levels in babies with respiratory difficulties.

The new mattress, called the Nesting Mattress, is slightly thicker than the usual mattress and contains a silicone gel flotation pad in a recessed area in the middle. These features are thought to reduce periods of agitation and excess body movements by cushioning the baby's body. Decreasing fussy periods and movements reduces extreme fluctuation in the baby's blood oxygen levels.

Since your infant was born prematurely and has respiratory distress syndrome you have been invited to permit your infant to participate in this study.

The study will involve infants of less than 37 weeks gestation, who are less than 60 days old, and who require the use of an oxygenation monitoring device for their medical management. Each infant will be continuously monitored for three - 24 hour periods. The first 24 hours will be a control period during which the infant is monitored on the usual isolette or warmer mattress. Next, the baby will be transferred to a pre-warmed nesting mattress at the time the nurses move the baby to weigh him/her. This way the baby is not moved unnecessarily. During this 24 hour study period the baby is monitored for heart rate, respiratory rate, blood pressure, temperature, and oxygen levels, just as in the control period. Finally, the baby is moved back to his/her own bed when the nurses do the morning weight and monitored for a second 24 hour control period.

During this study the infant will continue to be provided usual intensive care by hospital personnel without interference. Participating infants will not be disturbed unnecessarily. Transfer to and from the Nesting Mattress will be done at the time the nurses weigh the infant so that there is no unnecessary movement. There will be no additional monitoring devices used except for those required for the infant's care and ordered by his/her physicians.

No direct hazzard is expected with the use of the Nesting Mattress. The safety of the Nesting Mattress will be assessed by monitoring the infant's heart rate, respiratory rate, blood pressure and temperature. Any negative change from the infant's usual vital signs will warrant discontinuation of the study. There may be no direct benefit of the study to the infant. There is a benefit to knowledge of environmental influences on oxygenation. In addition, there may be benefits to future patients if it becomes known that certain kinds of care affect oxygen levels of premature newborn infants.

Participation in a research study is completely voluntary. The infant may be withdrawn from this study at any time without prejudice to receit of future care. There will be no payment or compensation for participating in the medical research study. Care for illness or injury will be provided to members of Kaiser Foundation Health Plan, Inc., in accordance with the terms of Health Plan coverage.

Confidentiality will be maintained throughout the study. The infant's name or other identifying information will not be used in reporting results of the study.

Any questions or concerns may be addressed to the baby's attending physician or the investigator. For further information concerning the study, please contact:

_____at_____.

I have read the foregoing and am satisfied with my understanding of it. I have had an opportunity to have my questions answered. I hereby consent to the participation of my infant in the above-described medical research study.

_____ _____

(Name of Child) Date

_____ _____

Parent Witness

JEH

12/09/87

Figure 14-2

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THE PERMENENTE MEDICAL GROUP

Information About Rights of Medical Research Participant

California law (Health and Safety Code sections 24170-24178) requires that a potential participant in a medical research study or investigation (the "subject") be presented with an "experimental subject's bill of rights ". The following list of rights and privileges is intended to satisfy the statutory requirement.

Persons who participate in medical research, investigation, or experimentation are entitled to certain rights, which include (but are not necessarily limited to) the right to be:

1. Informed of the nature and purpose of the study, investigation, or experiment.
2. Given an explanation of the procedures to be followed in the medical study, investigation or experiment, and a description of any drug or device to be used.
3. Informed of any related discomforts and risks reasonably to be expected from participation in the study, investigation or experiment.
4. Told of any benefits to the subject, reasonably to be expected, if any.
5. Advised of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and the relative risks and benefits of these alternatives.
6. Informed of the availability of medical treatment, if any, to the subject, after the experiment, should complications arise.
7. Given the opportunity to ask any questions concerning the study, investigation or experiment, or about the procedures involved.
8. Instructed that consent to participate may be withdrawn at any time and that the subject may discontinue participation in the medical study, investigation or experiment without prejudice.
9. Given a copy of the written consent to participation as a research subject, as signed and dated.
10. Allowed to decide to consent or not to consent to participate in a medical study, investigation or experiment, without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

Received by

_____
Date

_____
Subject (or guardian, conservator personal representative)

_____
(Relationship to Subject)

Figure 14-3

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

1) To be told what the study is trying to find out,

2) To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice,

3) To be told about the frequent and/or important risks, side effects or discomforts of the things that will happen to me for research purposes,

4) To be told if I can expect any benefit from participating and, if so, what the benefit might be,

5) To be told the other choices I have and how they may be better or worse than being in the study,

6) To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study,

7) To be told what sort of medical treatment is available if any complications arise,

8) To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study.

9) To receive a copy of the signed and dated consent form,

10) To be free of pressure when considering whether I wish to agree to be in the study.

If I have other questions I should ask the researcher or the research assistant. In addition, I may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. I may reach the committee office by calling (415) 666 1814 from 8:00 AM to 5:00 PM, Monday to Friday, or by writing to the Committee on Human Research, University of California, San Francisco, CA 94143.

Call X1814 for information on translations.

No invasive procedures or treatments are involved in this study. Study infants are monitored with equipment necessary for their medical management; no additional monitoring devices are utilized. At the onset of the study period (the second of three 24 hour data collection periods), the infant is transfered to the prewarmed Nesting Mattress. This transfer takes place at the time the infant is routinely weighed and so he/she is not unnecessarily moved. At the end of the study period, the infant is transfered back to his/her usual mattress at the conclusion of the morning weight recording. Transfer to and from the Nesting Mattress will be supervised by the Primary Investigator or a Co-Investigator. There will be no interruption or interference with normal delivery of intensive care and any sudden deterioration in the infant's condition will warrant immediate discontinuation of the study. Participation is voluntary; a parent may withdraw their infant from the study at any time, for any reason, without jeopardizing the infant's subsequent care. Confidentiality will be maintained throughout the study. Study subjects will be assigned numbers upon recruitment and will be referred to only by number in reporting of results and in any papers which may arise as a result of this work.

2. Procedures

Each of the 10 study subjects will serve as his/her own control to eliminate the bias of nonidentical age, weight, sex, maturity, and extent of RDS. Once the infant has been recruited

and appropriate consents have been obtained, the infant will be assigned a study number and a series of codes for data collection. This will ensure patient confidentiality and allow blind interpretation of the data. A log book will be kept identifying patient study numbers and data codes. $TcPO_2$ will be recorded throughout the study using a SensorMedics Transend Cutaneous Gas System. This system has the capacity to collect $TcPO_2$ and $TcPCO_2$ via computerized memory and produce hard copy printouts of trend recordings including cumulative histographic representations of the number of minutes at each 10 mmHg increment of $TcPO_2$.

Each infant will be studied for three consecutive 24 hour periods. The first 24 hours is a control period during which $TcPO_2$ is recorded while the infant is on the conventional isolette mattress. At the beginning of the second 24 hour period the infant will be transfered to the prewarmed Nesting Mattress. This transfer will take place when the infant is moved for his/her daily weight. This procedure is normally done early in the morning on the day shift. At least one investigator will be present during the transfer to the Nesting Mattress at the conclusion of weighing. Again, $TcPO_2$ will be collected in the manner previously described. At the beginning of the third 24 hour period the infant will be returned to his/her usual isolette mattress under the supervision of at least one investigator at the conclusion of the morning weighing procedure. $TcPO_2$ will be recorded for an additional control period.

To ensure the safety of the Nesting Mattress, heart rate, respiratory rate, blood pressure, temperature and the incidence of bradycardic episodes will be monitored. Any significant deviation from the infant's norm will warrant discontinuation of the study. All data to be collected is readily available through electronic monitoring equipment routinely used in the ICN for patient care. No additional or invasive procedures will be performed on study subjects. Infants will not be disturbed in any way other than for providing clinically relevant care by the infant's own nurse or respiratory therapist (RT). Data collection will not infringe upon usual intensive care.

3. Measurements

Safety will be assessed by comparing vital signs in both study and control conditions. Vital signs include: heart rate (HR), respiratory rate (RR), blood pressure (BP), and temperature (T). In addition, the number of bradycardic events will be compared. Any untoward effects on vital signs or increased number of bradycardic events will warrant discontinuation of the study period.

Periods of nonoptimal oxygenation will be assessed by continuous recording of $TcPO_2$ during two 24 hour control periods separated by a 24 hour study period during which the infant is monitored while on the Nesting Mattress. A SensorMedics Transend Cutaneous Gas System will be used to collect $TcPO_2$. This monitor is routinely used in the ICN for monitoring oxygen status in

ventilated infants. No additional or unnecessary equipment will be employed.

Background information on participating infants including pertinent prenatal and delivery histories will be obtained by reviewing the infant and maternal hospital records. This information will be crucial in determining the suitability of the infant for participation. The opinion of the nurse caregiver will be sought in the form of a questionnaire. This will assess the convenience of the Nesting Mattress as compared to a conventional mattress for delivery of usual intensive care.

Samples of data collection forms are Figure 14-4 and 14-5.

Figure 14-4

INTAKE DATA RECORD

BABY:

Name:_____
Birth date and time:_____
Birth weight:_____length:_____head circumference:_____
Gestational Age:_____AGA/SGA/LGA
Apgars:_____Type of delivery:_____
Type of resuscitation:
Mec below?_____
Oxygen:_____
Intubation:_____
CPR_____
Drugs_____
Date of RDS Dx:_____

MOTHER:

Name:_____
Age:_____Parity: G_____P_____Ab_____
Hx of previous premature birth:_____
Complications of pregnancy:
1st Trimester:_____
2nd Trimester:_____
3rd Trimester:_____

EDC:_____Anesthesia:_____
Labor Complications:_____
_____
Tx of preterm labor:_____
Date(s) of Betamethasone_____
Hx of maternal drugs / EtOH / Caffeine / Smoking ?_____
_____

Figure 14-5

INFANT PHYSIOLOGIC DATA RECORD

Name _____ Date _____

Age (number of days) _____

Ventilator settings: Time FIO2 IMV P.I.P./PEEP

Blood gas: Time Ph PCO2 PO2 HCO3 Base

IV Fluids (Type/Route/Rate): _____

Medications: _____

Hct: _____ BloodOut: _____ D/S: _____

VITAL SIGNS:

Time	HR	RR/IMV	Temp	BP(S/D+M)	TcPO2	*Bradys

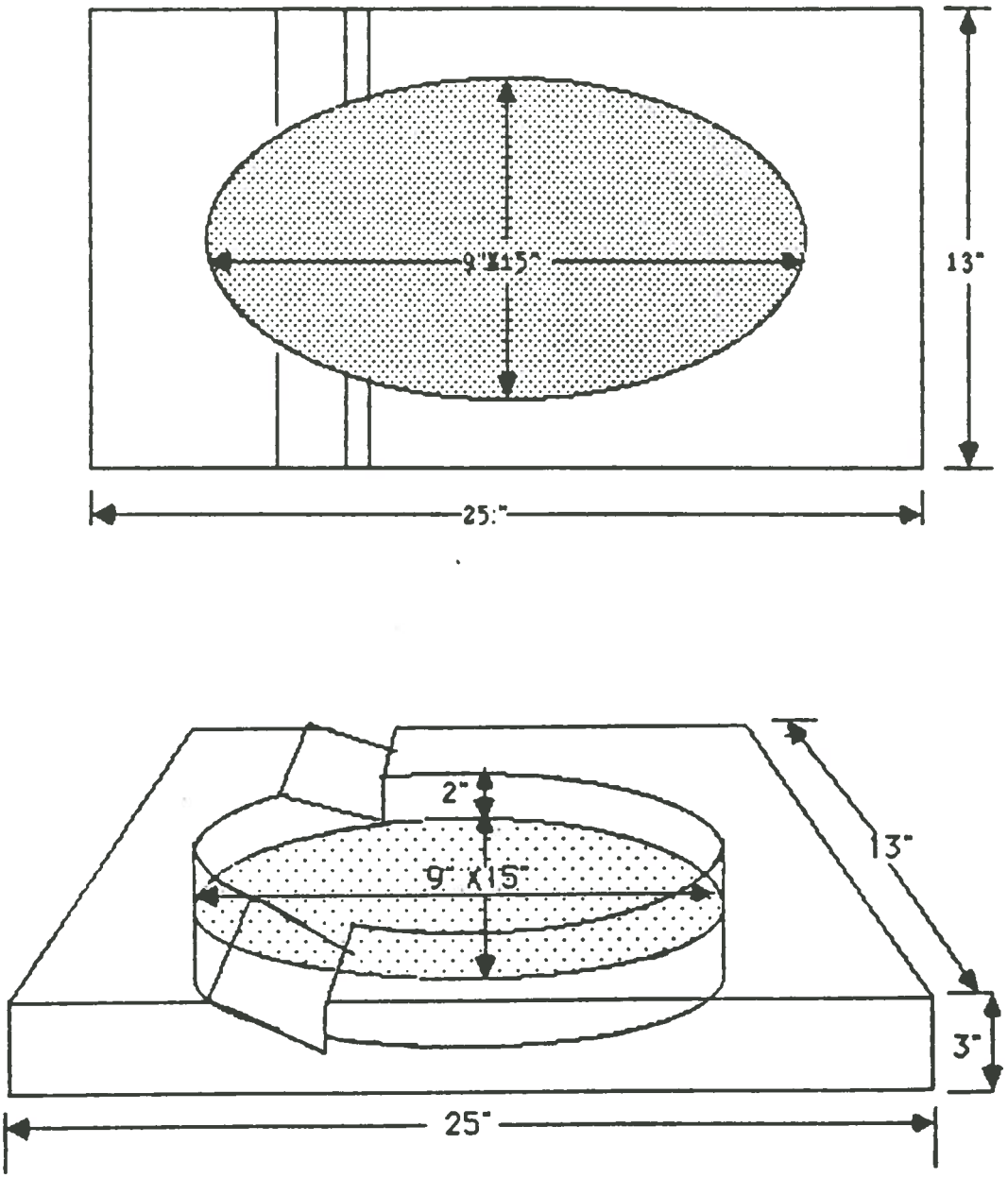
4. Equipment

The Nesting Mattress is an original design which includes a silicone gel flotation pad, a foam mattress with cut-outs for ventilator tubing and the gel pad, a cotton crib sheet and a k-pad heat source. A diagram, figure 14-6, is included.

The silicone gel was obtained by purchasing large silicone gel breast prostheses from the Jobst Company. The gel is contained in custom made waterbed bags provided by New World Manufacturers in Cloverdale, California. These were donated. A moderately dense synthetic fire retardant foam pad was cut to the overall dimensions of a standard isolette mattress except that this pad is 1" higher. A central oval was cut and removed. The measurements are given in figure 14-6. Toward the head-end of the mattress are two wedge-shapd cuts to accommodate ventilator tubing at the level of the infant's mouth. This feature secures tubing without kinking. The foam pad is covered with a cotton backed washable plastic material. The entire unit may be washed and cleaned in the usual manner that infant beds are sanitized. The k-pad is a water circulated heating pad that is routinely used as a heat source in the Kaiser ICN.

The Nesting Mattress may be used inside an isolette or on a radiant warming table so that the study infant's usual environment is unaltered during the study.

Figure 14-6



Nesting Mattress Design

5. Data Analysis

Three sets of $TcPO_2$ trend data will be collected, two 24 hour control periods separated by the 24 hour study period. These 24 hour data sets include histographic representations of minutes spent as 10 mmHg increments of PO_2. Comparisons will be made between the two control periods to determine if there is a difference in the variability of $TcPO_2$ in the control conditions and to rule out the effect of study order. Comparison will also be made of variability between the study period and each of the control periods. Student's T test will be used to compare the number of hyperoxic and hypoxic episodes, lability of the $TcPO_2$, and to compare the mean $TcPO_2$ between study and control conditions.

Safety of the Nesting Mattress will be determined by comparing vital signs (HR, RR, BP, and T) and the number of bradycardic episodes between study and control conditions. No untoward effects are anticipated. The convenience of using the Nesting Mattress will be assessed for each baby by his/her nurse caregiver using a five point scale.

6. Benefits

The major benefit anticipated with the use of the Nesting Mattress is the reduction in periods of agitation and excess gross motor activity with increased stability of temperature control which results in increased stability of oxygenation. Lesser benefits include amelioration of skin problems, reduction of head

molding, and reduction of noxious environmental noise and drafts.

The expected decreased incidence of nonoptimal oxygenation is of benefit in reducing the risk of neonatal morbidity secondary to the effects of the treatment of RDS. A benefit may be gained by reducing this risk. There is a benefit to knowledge of the impact and effects on neonatal environmental controls. Previous studies of this type have not directly examined the effects of the environment on ventilated infants.

7. Risks

The Nesting Mattress is not anticipated to pose a direct hazard to the infant. Previous studies have demonstrated compensatory vestibular-proprioceptive stimulation to be safe (157, 158, 159). The safety of recessing the infant by 2 inches has yet to be determined but access and visualization are not anticipated to be inhibited in any way. Thermoregulation is thought to be facilitated by heat conduction from the K-Pad (water circulated heating pad) through the silicone gel flotation pad. K-Pads are routinely used as a heat source and provided good thermoregulation even in ambient temperature isolettes. In addition, conducted heat causes less insensible water loss than does radiant heat. A firm chest board will be readily available at the bedside in the case of emergency need to perform cardiopulmonary resuscitation (CPR).

8. Results

Data were collected on three infants in August of 1985 during the initial study development as part of the Mellon Foundation summer fellowship program in epidemiology. At this time an observational component was included to examine possible effects of the Nesting Mattress on state control. This involved one hour observation periods which were very labor intensive.

There were two unavoidable problems with the observational component which resulted in its ultimate exclusion from the design. First, it was impossible to blind the observer as to study condition (control versus experiment) because the presence of the mattress was clearly visible. Second, there does not exist a behavioral state scale for ventilated infants. Usual scales of state control utilize respiratory patterns and thus a standardized tool for state assignment was not available.

Since study periods in the original study were so short (one hour each in study and control conditions), analysis of these data was determined nonproductive. Graphic representations of the results of $TcPO_2$ on and off the Mattress are provided to stimulate curiosity rather than to make statements on effect. $TcPO_2$ printouts are provided in Figures 14-7, 14-8, and 14-9 of study babies A, B, and C respectively. In the case of infant A, the trend recording is also provided (the irregular time line across the graph). In this case (A), the trend was smoother in the study condition, on the Nesting Mattress, than in the control

state. Histogram summaries are given in study and control conditions for all three infants. In all cases the $TcPO_2$ was in a narrower range while on the Nesting Mattress compared to control conditions.

Figure 14-7

Example $TcPO_2$ Histogram

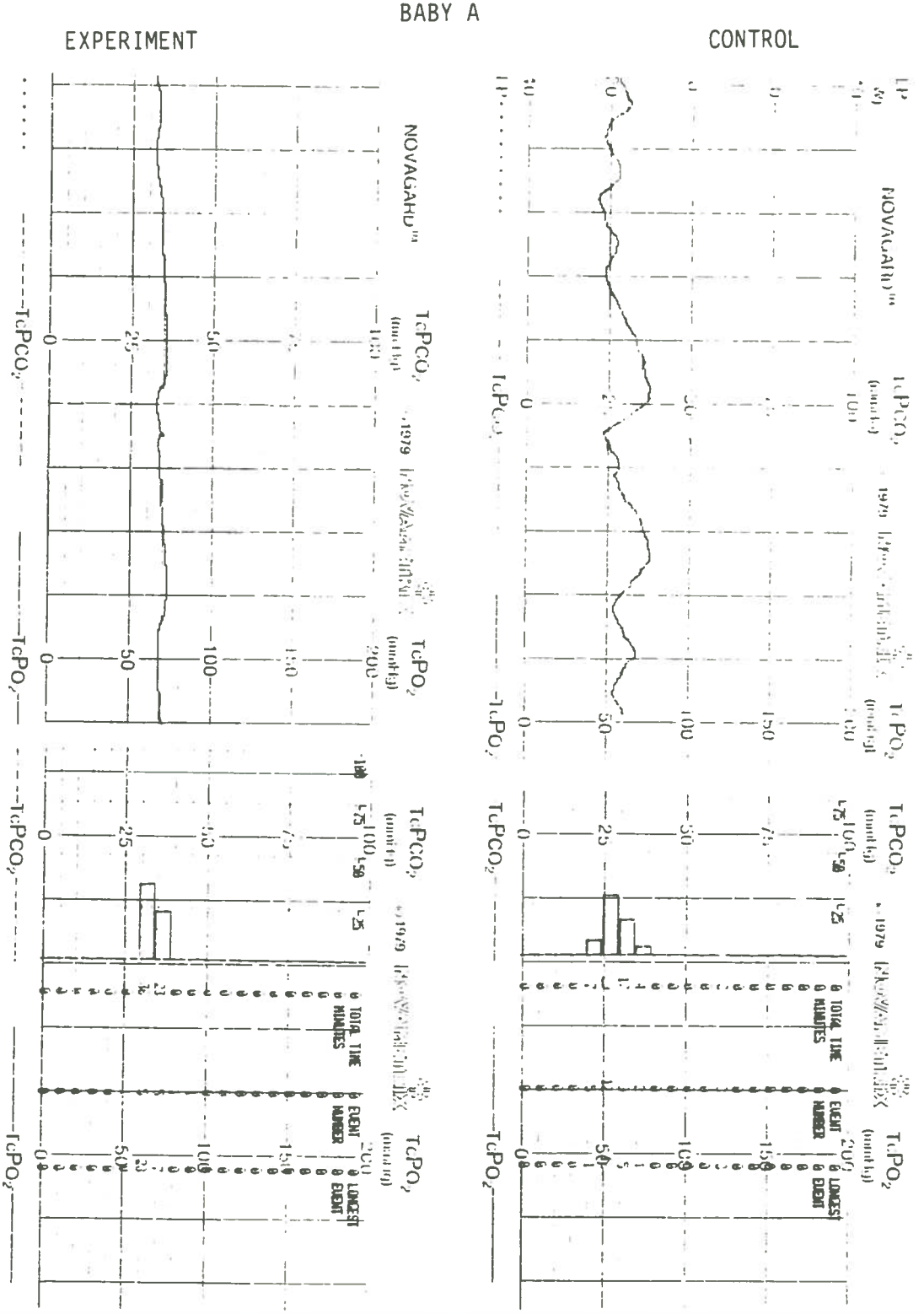


Figure 14-8

Example $TcPO_2$ Histogram

BABY B

EXPERIMENT

CONTROL

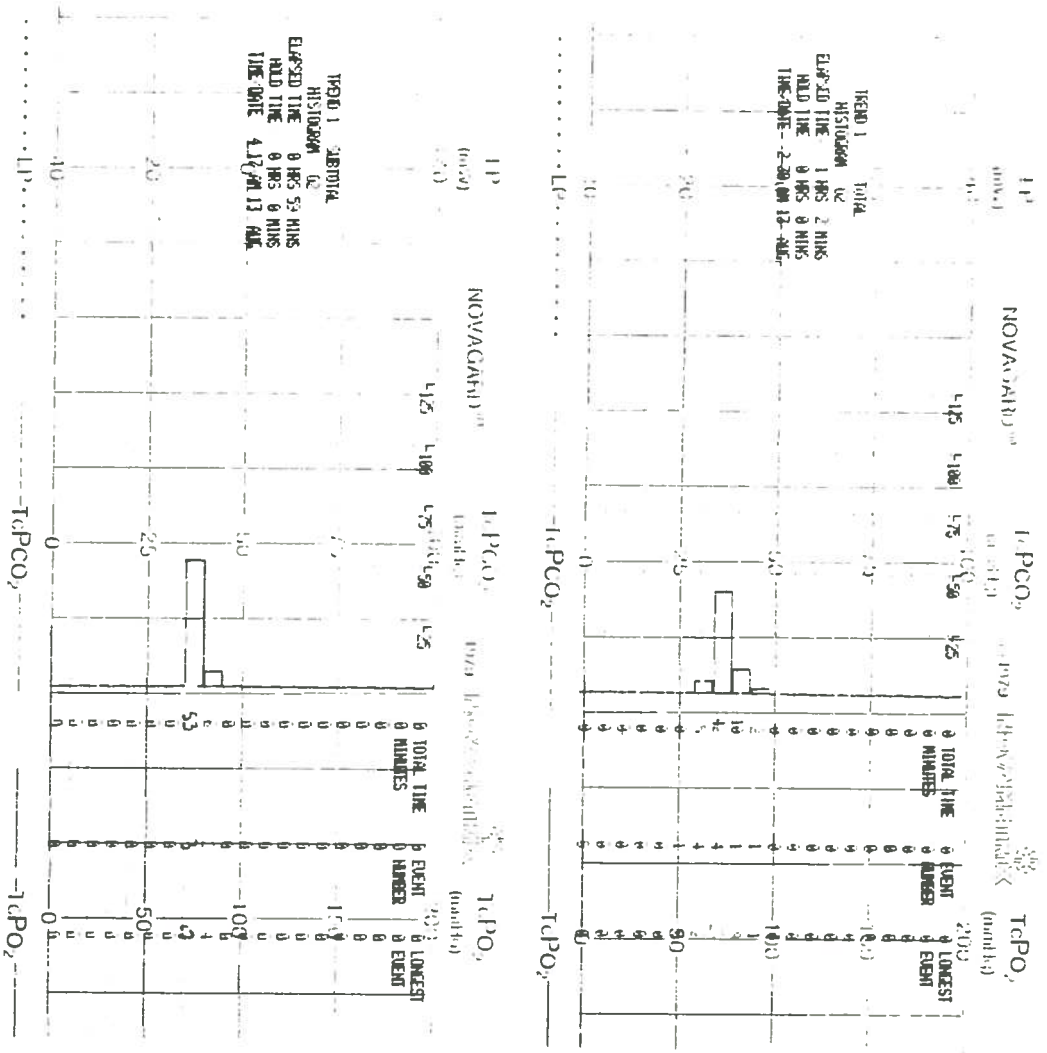


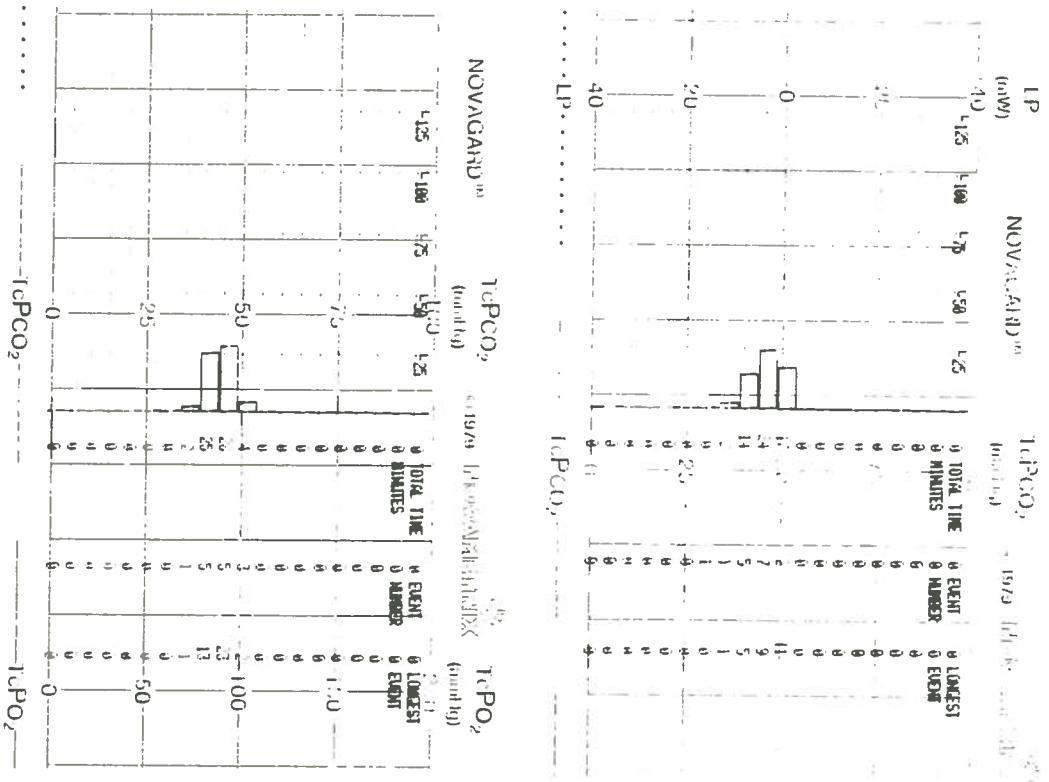
Figure 14-9

Example $TcPO_2$ Histogram

BABY C

EXPERIMENT

CONTROL



In Tables 14-1 and 14-2 $TcPO_2$ data are given for babies A, B, and C. Figure 14-10 provides a histogram of the composite data. Although no statistical relevance can be drawn from such a small sample, there does appear to be reduction in $TcPO_2$ variability in the study condition as compared to the control. It is interesting to note that the mean $TcPO_2$ is very similar in both study and control data but both range and standard deviation are smaller in the experimental phase. This was exactly the result I had hoped to see. In Table 14-3, there was less time spent in nonoptimal $TcPO_2$ ranges, <60 and >90, when babies were on the Nesting Mattress.

Table 14-1.

$TcPO_2$ Data from 1985 Pretest

Study Subject	On Mattress		Control	
	# of minutes	$TcPO_2$ Range	# of minutes	$TcPO_2$ Range
A	23	70-80	4	70-80
	36	60-70	17	60-70
			29	50-60
			7	40-50
B	6	80-90	2	90-100
	53	70-80	10	80-90
			42	70-80
			5	60-70
C	4	90-100	17	90-100
	28	80-90	24	80-90
	25	70-80	14	70-80
	2	60-70	2	60-70
Summation of Data From All Three Infants	4	90-100	19	90-100
	34	80-90	34	80-90
	101	70-80	60	70-80
	38	60-70	24	60-70
			29	50-60
			7	40-50

Table 14-2

Study Subject	On Mattress		Total # Minutes	Control		Total # Minutes
	Mean $TcPO_2$	Range		Mean $TcPO_2$	Range	
A	68.9	60-80	59	58.2	40-80	57
B	76.0	70-90	59	76.5	60-100	59
C	80.8	60-100	59	84.8	60-100	57
A+B+C Composite	75.2	60-100	177	73.2	40-100	173

Figure 14-10. Composite of subjects A+B+C, 1985

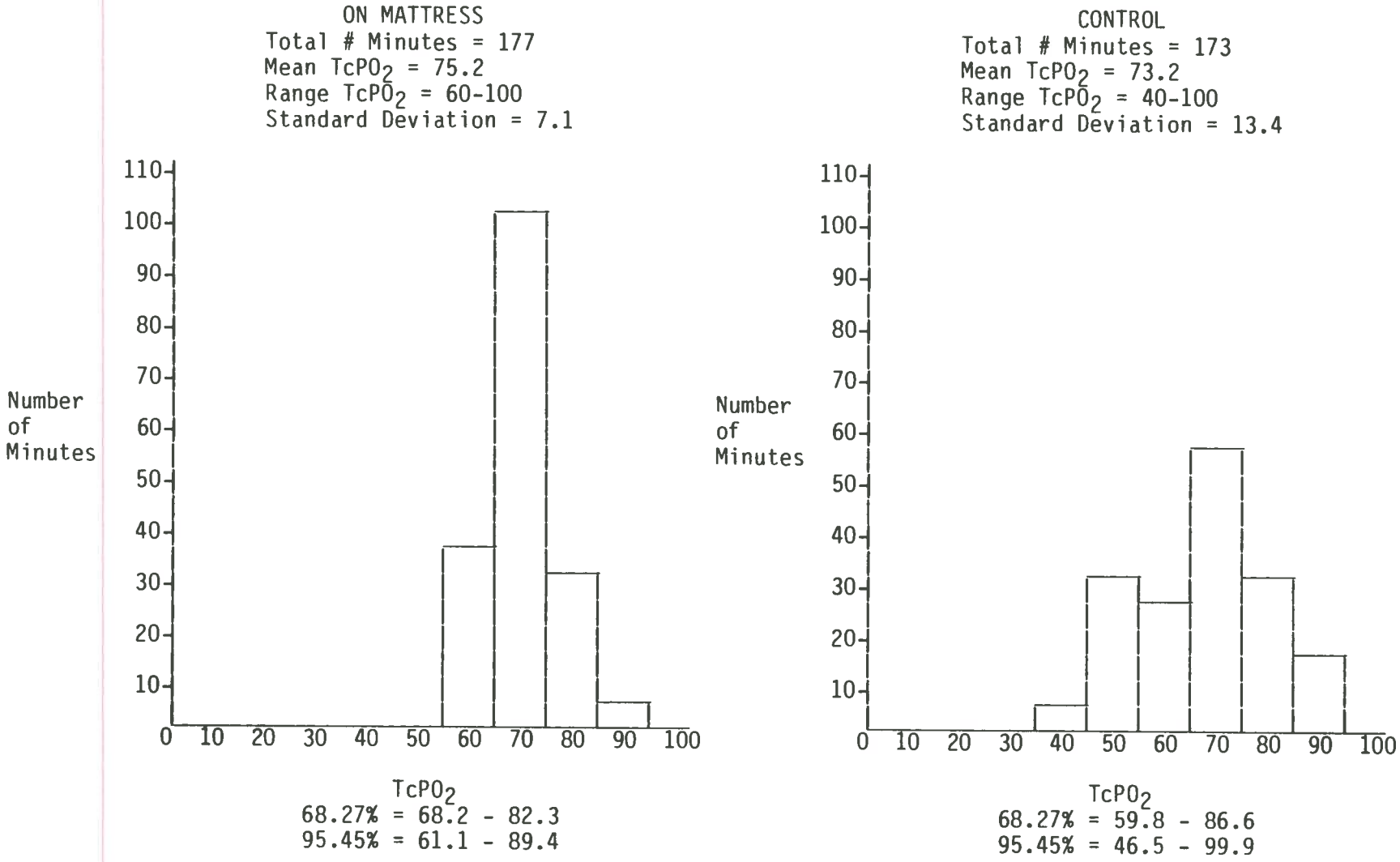


Table 14-3

Number of Minutes in Nonoptimal Range

Study Subject	ON MATTRESS <60	ON MATTRESS >90	CONTROL <60	CONTROL >90
A	0	0	36	0
B	0	0	0	2
C	0	4	0	17

The study design was revised in 1986 eliminating observation periods and increasing the amount of $TcPO_2$ data per study infant. In addition, increased data collection periods provided an increase in vital signs data. Heart rate, respiratory rate, temperature, and the number of bradycardic episodes were collected in both study and control conditions to monitor and assess adverse effects of the mattress. These vital signs data wee collected from the bedside nursing record and usually provided 8 to 12 data measurements for each parameter per 24 hour period.

Complete vital signs data were collected on four infants, 3 females and 1 male. A description of the four 1988 babies and the three 1985 babies is given in Table 14-4. One infant was dropped from the 1988 study because his medical condition was unstable in the initial control period. The infant's physician ordered pharmacologic paralysis with Pavulon (Pancuronjun bromide) which prohibited inclusion in the study. This infant was subsequently found to have beta strep pneumonia.

Table 14-4

Description of Study Subjects

Infant #	Sex	G.A.	Birth Weight	Postnatal Age in Weeks	Adjusted Age	Weight at Study	FIO_2 Average	Assisted Ventilation
A	M	29	1060	7	36	2060	28%	yes
B	M	33	1195	4	37	1585	21%	yes
C	F	34	1140	2	36	1330	23%	yes
1	F	28	850	5	33	1195	31%	yes
2	F	32	1440	4	36	1830	21%	yes
3	M	30	1080	3	33	1200	40%	yes
4	F	27	980	7	34	1260	32%	yes

Vital signs data on the four 1988 babies is summarized in Table 14-5. Due to the extremely small sample size, elaborate statistical analysis was not undertaken. Instead, for each parameter, the mean, range and standard deviation is given. There is very little if any difference in the means for heart rate, respiratory rate, or temperature when the infant is compared to himself in study or control conditons. In addition, study order appeared to have no effect since control periods a versus b, before and after the study period, were consistent. There were slightly lower ranges and standard deviations in the study condition for both heart rate and temperature.

Table 14-5

Vital Signs Data

HEART RATE

	ON MATTRESS				CONTROLS			
Study Subject	Mean	Range	S.D.	# Bradys	Mean	Range	S.D.	# Bradys
1	155	148-160	4.7	0	a 155 b 153	146-162 148-160	5.9 4.2	1 0
2	142	138-146	2.9	0	a 144 b 149	136-154 138-162	6.9 11.1	0 0
3	140	136-146	4.6	0	a 145 b 146	135-158 146-156	8.6 9.8	0 0
4	155	152-158	2	0	a 148 b 151	138-160 138-161	7.6 9.1	0 1
Combined Sample	148	138-160	7.8	0	a 148 b 150	136-162 136-161	8.1 8.9	1 1

Table 14-5

Vital Signs Data

RESPIRATORY RATE

Study Subject	ON MATTRESS Mean	Range	S.D.	CONTROLS Mean	Range	S.D.
1	56	48-66	7.1	a 57 b 55	50-64 51-62	5.3 4.8
2	54	50-60	3.7	a 51 b 51	36-60 40-60	8.4 6.5
3	41	36-44	3.1	a 42 b 40	39-44 32-46	2.1 4.7
4	38	24-44	7.0	a 43 b 42	36-50 39-50	5.0 4.4
Combined Sample	47	24-66	9.8	a 48 b 47	36-64 32-62	8.2 7.8

Table 14-5

Vital Signs Data

TEMPERATURE

Study Subject	ON MATTRESS Mean	Range	S.D.	CONTROLS Mean	Range	S.D.
1	36.83	36.6-37.0	0.137	a 36.83 b 36.85	36.6-37.1 36.7-37.0	0.197 0.138
2	36.97	36.8-37.1	0.121	a 36.93 b 36.97	36.6-37.2 36.7-37.1	0.223 0.197
3	36.77	36.7-36.9	0.082	a 36.72 b 36.73	36.6-36.9 36.5-36.9	0.117 0.225
4	36.87	36.8-36.9	0.052	a 36.75 b 36.78	36.5-37.0 36.7-37.0	0.207 0.171
Combined Sample	36.85	36.6-37.1	0.114	a 36.80 b 36.83	36.5-37.2 36.5-37.1	0.190 0.171

9. Discussion

Data collection presented several unanticipated obstacles in addition to the many anticipated problems encountered in this research endeavor. First, the current study was finally initiated in the late fall of 1987 after a prolonged interval of application revisions and consent form rewrites. Although Kaiser San Francisco presented the optimal research opportunity due to my long working relationship with the ICN attending staff and ideal patient population, it is not generally research oriented. This fact made the process of research application and human subjects approval lengthy and arduous. At several stages I considered abandoning Kaiser and pursuing another facility, however, Children's Hospital Oakland was resistant and UCSF had an unsuitable patient population. Kaiser clearly was the best source of uncomplicated prematures with RDS.

Second, after finally gaining approval to begin the revised study, Kaiser faced a strike of nursing personnel and was forced to keep the ICN census at a minimum and transport to other Bay Area hospitals most of the small ventilated premature infants to avoid compromising their care. The census remained low well into January of 1988. Between January and April 1988 five infants were recruited. One infant was dropped from the study when he proved to be medically unsuitable. At this writing (May, 1988), the census is again extremely low, only six infants are ICN patients today and none is ventilated. It appears that obtaining an

adequate sample size will take much longer than originally anticipated, at least beyond the termination of this phase of my education.

Third, although I believe the study design requires a minimum of intricacies, one investigator cannot directly supervise data collection for 72 consecutive hours. A variety of nurses and respiratory therapists assisted in the data collection on a purely voluntary basis. Unfortunately, diligence is improved when there is more reward than my heartfelt thanks.

To avoid becoming visually familiarized with the $TcPO_2$ data, the records were coded and not examined until all the data were to be analyzed. This was an attempt to blind the interpretation. However, when the $TcPO_2$ tracings were finally examined, the data on all four infants were found to be contaminated by intermittant failure in turning "off" the monitor memory prior to removing the skin electrode. When the memory is "on" and the electrode is exposed to room air, it records the PO_2 of room air. This was seen as a sudden drop in $TcPO_2$ from the infant's recorded blood level to the partial pressure of oxygen in room air. Since the memory was continuing to record, this value was added into the final histogram rendering the data useless.

Another error involved failing to turn "off" the monitor memory during calibration procedures which also resulted in contaminated and useless data. Since the electrode is heated to increase skin perfusion at the site it is necesary to relocate the

probe every 2 to 3 hours to prevent burning the infant's skin. This fact generated 8 to 12 potential episodes for error in data collection each 24 hour study period. In addition, the monitor is generally calibrated once every 8 hour shift to ensure accuracy in the recording.

In the absence of $TcPO_2$ data from the current study series, no conclusions can be drawn regarding the effect of the Nesting Mattress on the variability of $TcPO_2$. The mattress appeared to have a visual effect on $TcPO_2$ variability in the three 1985 study babies but in both groups sample size was too small to generate statistically significant conclusions.

The data provided on vital signs in the 1988 series are also deficient for statistical purposes. The null hypothesis--the nesting mattress has no effect on vital signs compared to a standard isolette mattress--can neither be rejected or upheld due to the small sample size. The initial appearance of this small data set would support the thesis that no deviation from the infant's usual vital signs occurs when the infant is on the nesting mattress. There was no increase in the incidence of bradycardic events in experiment periods. Temperature control was improved slightly compared to controls. Temperature range was narrower while infants were on the Nesting Mattress. Reduced fluctuation in temperature is facilitated by conductive heating through the silicone gel which acts like an insulating layer of fat. Reduced drafting due to the recessed position of the infant

in the nesting mattress may also faciltiate temperature control.

XV

CONCLUSION

The treatment and prevention of Respiratory Distress Syndrome is a most important goal in perinatal medicine. Reduction in the incidence of premature birth, however, has been minimal. As technology and knowledge have advanced, there has emerged a morbidity more associated with treatment techniques than to RDS itself. These serious sequelae of treatment have led researchers to seek alternatives and modifications in therapeutic practices.

In order to change treatment methods to cause less harm, it has been necessary to investigate the pathophysiology of RDS and its major sequelae. I have completed an exhaustive review of the relevant literature in respiratory physiology, anatomy, embriology, biochemistry, epidemiology, and current practices in perinatal-neonatal medicine. I have reviewed the pharmocologic and biotechnological techniques most frequently employed in the management of RDS. I submit this review as support for a technique which modifies the infant's noxious environment as a source which fosters rather than prohibits the harmful effects of the treatment of RDS.

I have proposed a noninvasive technique for reducing excess movement, agitation, and heat loss as a method for conserving oxygen and metabolic substrates. This technique is supported by the scientific principles of oxygen metabolism, and utilization

which I have discussed at length. In addition, research data from pharmacologic and behavioral studies support a technique which reduces activity and conserves heat and energy. Reduction in the lability of blood oxygen facilitates increased control of aberrant blood oxygen levels, either high or low. Since severe deviation from an optimal oxygen range has associated poor clinical outcome, reduced lability will help decrease the sequelae of RDS.

Preliminary results of a study to test this noninvasive intervention are encouraging but still as yet not conclusive. The pilot study of the effects of the Nesting Mattress on the variability of $TcPO_2$ in premature infants with RDS will continue into the summer and will help to provide information necessary for a larger study of this technique in the future.

The impetus for the invention of this technique came originally from my professional experience as an ICN nurse. For years I have observed creative nurses attempt to decrease noxious stimuli to fragile premies by patching their eyes and ears, swaddling flailing arms and legs, shielding from drafts with plastic wrap or bubble packing paper, and providing confinement with blanket rolls. I have simply applied some science to these techniques to incorporate as many of their features as possible.

In 1885, Stephane Tarnier said, "All the world knows that premature infants die in great numbers ... to give them any chance to live they need special care" (250). My medical training has provided an arena to study the problem of RDS in some depth. My

experience thus far has confirmed my belief that the more one learns about any given subject, the more there is to learn about that subject and the many sub-subjects one discovers within. So it is for special care of premature infants.

I have devised a relatively simple intervention to alter noxious aspects of the infant's environment to reduce its influence on respiratory stability in vulnerable patients. I hope in the future to be able to research this subject to a positive conclusion. This is a vast field with enormous potential for change. Far more research is needed to reduce the hazardous effects of the treatment of RDS. It is well to preserve life but "first, do no harm" (From the Hippocratic Oath).

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