

Dunham's

PREMATURE INFANTS

Third Edition

Dunham's
**PREMATURE
INFANTS**

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DUNHAM'S PREMATURE INFANTS

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*This volume is affectionately dedicated to Ruth
who helped and to Danny, Jenny, and David
who waited*

. . . our path is . . . cumbered with guesses, presumptions and conjectures, the untimely and sterile fruitage of minds which cannot bear to wait for the facts, and are ready to forget that the use of hypothesis lies not in the display of ingenuity but in the labour of verification.

—SIR CLIFFORD ALLBUTT

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Preface to the Third Edition

In the first two editions of *Premature Infants* Dr. Ethel C. Dunham declared her intention that the book should "serve as a source of information in regard to prematurity and as a guide for the general care of the premature infant." The success of her endeavors is a matter of international record. Mindful of the many people who have looked to this book for information and guidance, I approached the task of preparing the third edition with a grave sense of responsibility.

That this third edition has increased in size is evident. Since publication in 1955 of the second edition, a large number of studies on premature infants have been published, the most momentous being those of research resulting in the conquest of retrolental fibroplasia. The completely unexpected effects that therapeutic agents could produce in immature subjects was emphasized by further experiences in which drugs proved harmful when administered to premature infants during the neonatal period. These tragic clinical experiences led to studies that increased knowledge of metabolic deficiencies in newborn infants. It also became evident that the pharmacologic action of drugs is not necessarily the same in infants as in adults and that investigation must be made in fetal and neonatal animals before drugs are used in human infants. As established treatments and practices have come under critical scrutiny, the "hands-off" policy that discouraged all clinical investigation among premature infants appears now to be at an end.

The basic organization of the book in previous editions has been retained: Part I deals with general, Part II with clinical, and Part III with public-health considerations. However, Part II now has been divided into two sections. Section A includes seven chapters dealing with the care of premature infants beginning with perinatal aspects and ending with a discussion of problems encountered after discharge from the hospital. Section B comprises eleven chapters describing the abnormal conditions (including diagnosis and treatment) that occur most frequently in premature infants during the first months of life.

Since many aspects of the management of premature infants are highly controversial, it was not always possible to make unequivocal recommendations. In these instances I have reported the practices in the premature nursery of the

Babies Hospital to indicate to the reader that "we" have made tentative judgments while awaiting further evidence.

The amount of published material dealing with prematurity is now so vast that the compilation of a complete bibliography would be a formidable task and one which is unrelated to the primary intentions of this book. Wherever possible, however, I have attempted to include references to reviews of specific subjects for the reader who would like access to a comprehensive bibliography of the existing medical literature.

In the preparation of this edition of *Premature Infants* I was particularly fortunate to have the wise counsel of Dr Dunham. She reviewed an early draft of the entire manuscript and made many valuable suggestions which were responsible for corrections and improvements in the text. I appreciate the considerable amount of time and effort which she gave so generously to the task and I am deeply grateful to her.

Dr. Rustin McIntosh read a later draft of the complete manuscript; his keen editorial eye was invaluable to me. I wish also to acknowledge my indebtedness to many colleagues who allowed me to borrow freely from their published and unpublished works, and to numerous publishers for permission to reproduce valuable tables and figures which appear throughout the book. Priscilla C. Parke, R.N., and Drs. Frederic J. Agate, Murray Davidson, Richard L. Day, Louis Gluck, Donald Gribetz, L. Stanley James, Charles D. May, Frank Moya, Herbert Rackow, Ernest Salnitre, Thomas V. Santulli, Irving Schulman, and Harold Speert reviewed parts of the manuscript and made important criticisms for which I am grateful.

Mr. Bernard R. Friedman made all of the original drawings which appear in this edition; he interpreted my crude directions with exceptional artistic skill. The labor of tracking references and the proofreading of the manuscript were made easier with the help of Miss Eva Eckert, Mr. A. D. Hirsch, Mrs. Ellen Hirsch, Miss Cecile E. Kramer, and Mrs. Thelma Phelan; Mrs. Barbara Ann Dabrowski typed the manuscript. I am deeply appreciative of their faithful assistance.

Finally, I wish to record the contribution of my wife, who was my collaborator at every stage in the preparation of this book and who was responsible for the maintenance of high morale in a household that was essentially fatherless for a protracted period of time.

W.A.S.

New York

Preface to the Second Edition

Premature birth is now recognized as a world health problem and efforts to decrease the mortality rates from this important cause of neonatal death are being made on an ever-increasing scale. In addition newer knowledge is leading to a clearer understanding of the causes of premature labor which should result in lowering the incidence of premature birth.

In spite of a steadily increasing volume of research into these aspects of prematurity, *premature birth continues to play the major role as a cause of neonatal death.*

Some idea of the magnitude of the problem can be gained from recent findings for the United States on birth weights of live born infants. A sample survey indicated that, in 1950, about 7.4 per cent of live born infants, an estimated 270,000, weighed 2500 Gm. or less. The neonatal mortality rate was 173.7 per 1000 live births, a rate that was twenty-two times greater than that for infants who weighed more than 2500 Gm. In addition about two thirds of the infants who died during the first 4 weeks of life were premature on the basis of their birth weight.

It is obvious that, in spite of the efforts that have been made and are being made to reduce neonatal mortality from premature birth, there is need for greater efforts to improve premature infant care and to prevent premature termination of pregnancy.

This book has been prepared to serve as a source of information in regard to prematurity and as a guide for the general care of the premature infant.

Part I deals with general considerations—definitions of and criteria for prematurity; incidence, causes, and prevention of premature birth; and the growth and development of premature infants. Material from a wide variety of sources, with references for the convenience of those interested in more detailed study, has been brought together in compact form with a view to orienting the reader and providing a background for the clinical material.

Part II deals with the physiologic handicaps of premature infants; the general

problems of their care; and the congenital and acquired conditions that tend to affect them adversely.

It is obvious that many problems of the medical and nursing care and the diagnosis and treatment of pathologic conditions of premature infants are similar to those of mature infants and of children in general. This book therefore attempts, in general, to deal only with conditions that are distinctly applicable to the premature infant in the first few weeks or months of life, or until the period is reached when the premature infant may be handled in the same way as the mature infant

Part III outlines some of the public aspects of prematurity including death rates and causes of death and cites examples of organized programs for care and for prevention of premature birth

The first edition appeared in 1948 under the same title as Publication Number 325 of the Children's Bureau. The author again expresses gratitude to those members of the professional staff of the Children's Bureau who assisted in the preparation of this manuscript and to all others who contributed with their advice or by permitting me to quote from their publications.

E.C.D.

Washington, D.C.

Part One

GENERAL CONSIDERATIONS

Definitions and Criteria of Prematurity

DEFINITIONS

Prematurity

Prematurity needs to be clearly defined for three reasons: (1) for statistical purposes, so that comparable data in regard to all aspects of premature infant births and deaths may be obtained, (2) for legal purposes, for example, in the determination of legitimacy, and (3) for clinical purposes, in order to recognize the infants needing special types of care and to evaluate methods for care and treatment in relation to the degree of prematurity.

In 1948 the World Health Assembly recommended the adoption by all countries, for purposes of vital statistics, of the following definition:

For the purpose of this classification an immature infant is a live-born infant with a birth weight of 5 lb 8 oz (2500 Gm) or less, or specified as immature. In some countries, however, this criterion will not be applicable. If weight is not specified, a live-born infant with a period of gestation of less than 37 weeks or specified as "premature" may be considered as the equivalent of an immature infant for purposes of this classification.³⁵

This definition is now used in official national vital statistics for the United States of America.

Related Terms

Statistics in regard to births and deaths of premature infants are useful in measuring the results of the care afforded these infants and their progress from year to year. To obtain accurate vital statistics within individual countries and to make them comparable with those of other countries, uniformity of reporting and the use of standard definitions of certain terms are prerequisites.

The following definitions (with the exception of Perinatal Period) have been

recommended for international use by the World Health Organization (WHO).^{34, 37}

Live Birth

Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.³⁴

Death

Death is the permanent disappearance of all evidence of life at any time after live birth has taken place (post-natal cessation of vital functions without capability of resuscitation). This definition therefore excludes fetal deaths.³⁴

Fetal Death

Fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation, the foetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.³⁷

There is still little agreement among countries on the definition of the terms "stillbirth" and "abortion." By accepting the above definition of fetal death and by reporting fetal death and period of gestation at the time of its occurrence, international uniformity may be more easily obtained than by attempting conformity in definitions of stillbirth and abortion.

Period of Gestation

Period of gestation is the number of completed weeks of pregnancy which have elapsed between the first day of the last menstrual period and the date of delivery, irrespective of whether the product of conception was live-born or born without evidence of life.³⁵

For clarity this period should always be reported in completed weeks rather than in lunar or calendar months.

Perinatal Period

Peller regarded the first week of life as subject to influences which are distinct from those operating in the second to the fourth weeks of life. He coined the term "perinatal" to mean ante-, intra-, and postpartum, the period around and including the time of birth. There is some agreement that the perinatal period extends from 20 completed weeks of gestation up to the end of the first

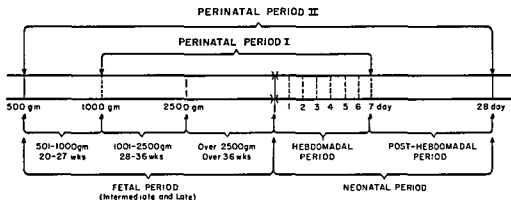


FIG. 1-1. Two definitions of the perinatal period in relationship to other perinatal terms. When perinatal period II or other combinations of end points are used it has been recommended that the data be collected and tabulated in such a manner that perinatal period I can be extracted. (Redrawn from *A Guide for the Study of Perinatal Mortality and Morbidity*; Chicago, Ill., Committee on Maternal and Child Care, Council on Medical Service of the American Medical Association, 1959.)

week of life (0 through 6 days)²⁸ However, until an international definition has been accepted it will be necessary to specify the range whenever it is used³⁵ (Fig. 1-1)

Neonatal Period

The term "neonate" means, literally, newborn; the term "neonatal period" is usually used to include the first month, but for statistical purposes this "month" has been limited to the first 28 days of life (0 through 27 days).³⁵ Reported data on neonatal mortality in the past have often been difficult to compare because of differences in the definition of the neonatal period.¹⁹ As Peller pointed out, the first month of life, biologically speaking, is not a unit. There is much to commend his advice that the events of the first week of life (hebdomadal period) be considered separately from those in the next three weeks.

CRITERIA OF PREMATURITY

The diagnosis of prematurity is sometimes based on the physician's interpretation of certain clinical signs. This interpretation reflects the individual physician's training and experience and may therefore vary rather widely. The estimate of conceptional age is dependent upon the mother's memory and menstrual regularity.

It is obvious that criteria are needed for the diagnosis of prematurity that are entirely objective. The only satisfactory ones that can be used at present are those of physical size of the fetus. Although fetal size, age, and function are

related, there are often wide discrepancies. It is hoped that chemical definitions¹⁴ or other criteria that are related more closely to function will be established. Until that time we must rely on estimates of age and measurement of size.

BODY SIZE

Certain measurements of body size are used singly or in combination as criteria of prematurity; these include birth weight, crown-heel or crown-rump length, and measurements of the head and thorax.

Birth Weight

As already pointed out, a birth weight of 2500 Gm. (5 lb. 8 oz.) or less, regardless of estimated period of gestation and other criteria, has been recommended as the definition of prematurity. Such a weight is generally recognized as the most practical clinical criterion of prematurity and consequently, as evidence of need for special care, in spite of the fact that some infants of this weight, especially twins, may have reached ten lunar months of gestation age.

It is essential that birth weight be obtained immediately after delivery and reported as accurately as possible for all newborn infants, including those that die soon after birth. Allowance should be made for coverings or for a clamp on the cord. The birth weight should be noted to the nearest ounce or 10 Gm.²² The weight should be expressed to a degree of significance which will allow a classification by at least 500-Gm. groups.³⁴ The following class intervals are recommended

500 Gm. or less	= 1 lb. 1 oz. or less
501-1000 Gm.	= 1 lb. 2 oz.-2 lb. 3 oz.
1001-1500 Gm.	= 2 lb. 4 oz.-3 lb. 4 oz.
1501-2000 Gm.	= 3 lb. 5 oz.-4 lb. 6 oz.
2001-2500 Gm.	= 4 lb. 7 oz.-5 lb. 8 oz.
(2501-3000 Gm. and 1000 Gm. intervals thereafter, i.e., "mature")	
Specified as premature (immature) but weight not stated	

There are certain disadvantages, however, in using birth weight as a criterion of prematurity. One of these is that the average birth weight of term infants from different countries and from areas within certain countries shows wide variations. Average weights of live births throughout the world, collected from UN, WHO, and other reports, ranged from 2760 to 3500 Gm.³⁶ Caucasians showed the highest birth weights regardless of geographic location. On the basis of a weight of 2500 Gm. or less as the criterion, a high incidence of prematurity will be found if the average birth weight at term is low.*

*A discussion of factors influencing birth weight of premature infants will be found in Chap. 2

Another disadvantage of this criterion is that at birth, for one reason or another, the birth weight of many infants is either not taken or not recorded. Entry of birth weight on birth certificates, if required, would be impracticable for large areas of certain countries, since scales are not available.

The question often arises as to the lower limit of birth weight that might be used, since it has been customary in some reports to regard the birth of a live infant whose birth weight is below a given amount as an abortion. The World Health Organization Expert Group on Prematurity made the following statement in their report (1950):

*The group considered the question of setting a weight limit below which a premature birth should be considered an abortion. The majority of the group agreed that no such limit should be set, for two reasons: (a) the exact lower weight limit cannot be defined on the basis of present knowledge, and (b) such a delimitation would not be in line with recommendations of the above-mentioned subcommittee to define 'foetal death' rather than 'stillbirth' and 'abortion'.*³⁸

Finally it should be pointed out that low birth weight, although not an exact criterion of prematurity, has a practical use in the selection of infants needing a special type of care and, as a statistical standard, has the acknowledged advantages mentioned.

External Dimensions

Other external birth measurements have also been proposed as criteria of prematurity. As with birth weight, individual variations are found at every level of development. However, there are two principal disadvantages to the use of various external measurements as criteria of prematurity: (1) the difficulty in standardizing the techniques of measurement and (2) the fact that no fiducial values have been universally adopted.

Length Although there is not complete agreement,⁷ a crown-heel length below 47 cm. is often used as a criterion of prematurity.

Crown-rump length was found by Ellis and Lawley to have distinct advantages over crown-heel length in measuring premature infants, and was suggested for routine measurement. On the basis of studies of 119 premature infants and 452 term infants they suggested that a crown-rump length of less than 32 cm. might be used in combination with other measurements as a criterion of prematurity.

In this study each infant was measured while in the supine position on a measuring board fitted with a stationary footpiece. The ischial tuberosity was placed against the footpiece, which was curved to allow flexion of the knee to

a right angle, and a sliding headboard was adjusted to the position of the crown of the head.

Head. Measurement of the head of newborn infants presents a number of problems. In addition to the expected biologic variation, other factors which produce discrepancies are the effects of molding during birth, edema, and hemorrhage into soft tissues. Further difficulties are introduced because there is no precise definition of the anatomic points from which measurements are taken.

Among measurements of the head, the occipitofrontal diameter and circumference are those most often used. The data obtained from both dead and living infants indicate that an occipitofrontal diameter of 11.5 cm. or less²⁵ and an occipitofrontal circumference (the largest horizontal circumference) of less than 33 cm probably indicate prematurity.^{7, 18, 25, 39}

Thorax. An infant is probably premature if at birth the circumference of the thorax at the nipple line measures less than 30 cm^{23, 33, 39}. It has been generally held that children with a chest circumference of less than 21 or 22 cm. are not able to survive.²³ Rossier has observed exceptions to this rule.

Relation of Thoracic to Head Circumference. Disproportion between the circumference of the head and that of the thorax is generally recognized as a more reliable sign of prematurity than either measurement alone. Zeltner found that the average difference between the head and thorax circumferences was 2.1 cm. in term infants and 3.5 to 4.1 cm. in premature infants, varying with the birth weight of the infant. From these observations and the results of earlier studies^{23, 33, 40} it can be stated that in normally formed newborn infants an excess of head circumference over thorax circumference of more than 3 cm., or a ratio of thorax to head circumference of less than 0.92, probably indicates prematurity.

GESTATIONAL AGE

Errors in determination of gestational age are usually due either to error by the pregnant woman in giving the date of the first day of the last menstrual period or to menstrual irregularities.⁵ Nevertheless, in the absence of information regarding birth weight the gestational age must be accepted as a criterion of prematurity. An alternative definition of prematurity adopted by the World Health Organization³⁸ states that "if weight is not specified, a live-born infant with a period of gestation of less than 37 weeks or specified as 'premature' may be considered as the equivalent of an immature infant for purposes of [this] classification." The class intervals recommended for a standard classification are³⁴

Less than 20 completed weeks
 20-27 completed weeks
 28-36 completed weeks
 (37 completed weeks and over—"mature")
 Not stated

The period of gestation will very likely continue to be reported in terms of months despite these recommendations. If gestation is reported in lunar months there is no difficulty in converting to weeks by using a factor of four. If *calendar* months are reported the following classification is suggested:³⁵

Less than 5 completed calendar months (less than 20 completed weeks)
 5 and 6 completed calendar months (20 completed weeks to less than 28 completed weeks)
 7 and 8 completed calendar months (28 completed weeks to less than 37 completed weeks)
 (9 and more completed calendar months—"mature")

COMBINATIONS OF CRITERIA

When weight, length, and gestational age combined are used to determine prematurity, the proportion of live-born infants classified as premature differs widely from the proportions found by using any one or two of these criteria. **Gestational Age and Birth Weight.** Most studies using the combination of gestational age and birth weight as a criterion of prematurity^{15, 29, 32} have shown a wide distribution of birth weights among infants born at specific gestational ages and conversely a wide distribution of gestational ages at given birth weights. Despite the considerable variations both criteria are important since mortality varies with one characteristic at any level of the other.²⁶ Although birth weight is the most satisfactory single criterion of prematurity the potential usefulness of the gestational age criterion should not be overlooked (see Appendix 5).

Weight, Length, and Gestational Age. Potter and Adair devised an arbitrary classification of all products of conception into five developmental classes (abortion, previable, viable, term, and postmature). For each class they assigned mutually exclusive ranges of weight, length, and gestational age. To use this scheme the values for weight, length, and gestational age of a given infant are compared with the ranges given in the table. The infant is assigned to the group in which at least two of his values fall

The influence of refinements of a definition of prematurity upon the calculation of the incidence of prematurity in a community is shown in Table 1-1. As has been pointed out repeatedly,^{17, 31} there is considerable variation in the size of fetuses and newborns. When the number of size criteria which the in-

TABLE 1-1 PERCENTAGE OF WHITE, SINGLE LIVE BIRTHS CLASSIFIED AS PREMATURE BY GESTATIONAL AGE, BIRTH LENGTH, AND BIRTH WEIGHT
San Diego County, California, 1955

	<i>Incidence (%) of prematurity</i>		
	<i>Male</i> (9,438)	<i>Female</i> (8,649)	<i>Total</i> (17,997)
One criterion			
Gestation ^a	84	72	78
Length ^b	55	73	64
Weight ^c	54	66	60
Two criteria			
Weight and length	35	44	40
Weight and gestation	35	33	34
Length and gestation	29	30	30
Three criteria			
Weight, length, and gestation	25	26	26

Courtesy of Leslie Corsa, Jr., M.D., Chief, Bureau of Maternal and Child Health, State of California Department of Public Health.

^a 36 completed weeks of gestation or less ^b Crown heel length less than 47 cm (18½ inches)

^c Birth weight 2500 Gm or less

dividual infant must satisfy to be considered premature are increased, the total number of individuals who are so classified decreases. The purposes for which the classification is being made must be considered before the degree of restriction in the definition is decided. When confronted with an individual infant the physician would be well advised to use combined criteria (make a restricted definition of prematurity) for the purpose of improving his estimate of the immediate prognosis for life.

ANTENATAL CRITERIA

The maturity of the fetus is an important consideration whenever the obstetrician is called upon to make the difficult decision of terminating pregnancy artificially. Since the accuracy of this estimate exerts a pronounced effect upon neonatal mortality, there is considerable interest in improving methods of intrauterine diagnosis of the maturity of the fetus.

Antenatal Radiography

Apprehension concerning the possible effects of antenatal radiography on the fetus³⁰ has not extinguished interest in this method of estimating matu-

ity.⁶ However, a review of the available evidence leads one to the conclusion that fetal roentgenography should be reserved for specific antenatal indications.

Centers of Ossification. According to Hartley, the centers for the lower femoral epiphyses begin to appear on antenatal radiograms with considerable regularity at the end of the thirty-sixth week of intrauterine life, and the centers for the upper epiphyses of the tibia at 38 weeks.⁸ From a study of the knee and the size and degree of ossification of the remainder of the skeleton he concluded that the estimation of fetal maturity from 36 weeks to term was quite accurate. In a carefully controlled study of 200 pregnancies Berridge and Eton noted that in some instances both centers for the epiphyses of the knee were present as early as 32 weeks; in others they were absent as late as 39 weeks. The radiologic diagnosis of "prematurity" (less than 37 weeks) was in error on 12 occasions and the diagnosis of "mature infant" (37 weeks or more) was erroneous 16 times. Approximately this degree of accuracy had been observed by Christie *et al.*³ in a study in which they judged the maturity of 100 fetuses in utero solely by the presence or absence of the centers for the distal femur and the proximal tibia, their predictions of fetal weight were within 500 Gm. of actual birth weight in 76 per cent of the pregnancies and within 750 Gm. in 92 per cent of the cases studied.

In an extensive study of the presence of ossification centers in newborn infants on the ward service of Johns Hopkins Hospital, using roentgenograms made within 72 hours after birth, race and sex differences were found to be significant (Table 1-2).² These results confirmed the findings of Hess and Weinstock earlier.

The diameters of the distal femoral and proximal tibial epiphyses in roentgenograms of the knees of 300 newborn Negro infants weighing 2268 Gm. (5 lb.) or more were larger in girls than in boys of the same weight or length.¹³ No relation was found to the economic status or the maternal milk intake.

It should also be pointed out that placental blood supply influences the development of the ossification centers. Twins not of the same birth weight show differences in the appearance of the ossification centers, the smaller twin having less advanced osseous development.²⁷

The wide variation in development of osseous centers, not only between race and sex groups but also among individual infants, implies that a roentgenographic estimate probably does not allow any closer approximation to gestational age than do most of the postnatal criteria.

Cephalometry. There are conflicting opinions upon the predictive value of cephalometry from antenatal roentgenograms.^{4, 11, 12} Hodges presented a method of evaluating fetal age from multiple stereoroentgenograms. The dimensions

TABLE 1-2. PRESENCE OF EACH OF SIX CENTERS OF OSSIFICATION (RIGHT SIDE) IN ROENTGENOGRAMS OF NEWBORN INFANTS, BY BIRTH WEIGHT, COLOR, AND SEX

Race	Sex	Birth weight (Gm)		
		Under 2000	2000-2499	2500-2999
Distribution of Infants				
No White	Male	11	15	33
	Female	6	23	45
No Negro	Male	11	26	75
	Female	14	31	100
TOTAL		42	95	253
Per cent of infants with centers of ossification present				
Distal femoral epiphysis				
White	Male	9%	75%	85%
	Female	50	92	98
Negro	Male	18	89	91
	Female	50	94	99
Proximal tibial epiphysis				
White	Male	0	19	53
	Female	0	54	76
Negro	Male	0	39	63
	Female	14	41	77
Cuboid				
White	Male	0	6	15
	Female	0	38	57
Negro	Male	0	23	44
	Female	21	38	68
Head of humerus				
White	Male	0	8	14
	Female	0	6	26
Negro	Male	0	0	15
	Female	0	11	23
Capitate				
White	Male	0	0	0
	Female	0	0	15
Negro	Male	0	8	16
	Female	0	13	20
Hamate				
White	Male	0	7	6
	Female	0	0	11
Negro	Male	0	16	16
	Female	0	9	23

From Christie ²

of the skull and extremities exhibited variations which in Hodges' opinion were no greater than would be expected in any biologic problem. He suggested that fetometry in some cases gives a more dependable estimate of fetal age than does the menstrual history

External Measurements of the Mother

McSweeney reviewed the methods of estimation of fetal weight on the basis of external measurements of the mother and presented data compiled from 500 vaginal deliveries and 100 elective cesarean sections. From the dimensions of the uterus as measured externally and the occipitofrontal diameter of the fetal skull determined through the abdominal wall he was able to predict fetal maturity with a high degree of accuracy.

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Incidence of Prematurity

Information about the incidence of premature births in different countries^{52, 62} is meager and, to a large extent, limited to data from areas within individual countries or from local hospitals. The data available are, moreover, not always comparable because of the use of varying definitions of "live birth" and "premature birth."

United States. For the United States, adequate data for estimating the incidence of premature births have not been available until comparatively recently. Prior to 1939, the Standard Certificate of Live Birth did not call for information either on duration of gestation or on birth weight. While an item on "number of months of pregnancy" was carried on the revised Standard Certificate for 1939, the data obtained were not satisfactory for tabulation by the National Office of Vital Statistics.

On the 1949 revision of the Standard Certificate of Live Birth the items "Length of pregnancy—weeks" (item 22a) and "Weight at birth" (item 22b) were added. Tabulations of the data for these two items, based on reported births in all states except Massachusetts,* have been available in special reports by the National Office of Vital Statistics published at intervals since 1949.^{41, 53-56, 59, 60} In 1956, 7.6 per cent of 4,163,090 live-born infants in the United States weighed 2500 Gm or less; for white infants the percentage was 6.8; for nonwhite 12.1⁶¹ (see Appendix 3). Information regarding birth weight and length of pregnancy is expected to be available on a continuing basis for births in the United States.⁵⁸

Other Countries. For Great Britain, 6.4 per cent of births were reported to be premature (birth weight 5 lb. 8 oz. or less) in 1948;²⁷ for Finland, 5.97 per cent of hospital births and 4.93 per cent of home births were reported to be premature (birth weight less than 2500 Gm.) in the period 1939-1944.³⁴

INCIDENCES REPORTED BY HOSPITALS

Many hospitals have reported their incidence of premature births, but the data are often not comparable⁵⁷ because the definition of prematurity has varied,

* Until recently Massachusetts did not collect information on the birth certificate for birth weight or length of pregnancy, at present (1959) birth weight is recorded

some reports are based on gestational age and some on birth weight, or infants below a specified weight have been excluded. Moreover, the analyses of the data have not, in some instances, been made in relation to certain factors influencing premature birth, such as race, plurality of birth, and other factors.

TABLE 2-1 INCIDENCE OF PREMATURE BIRTHS IN NINE HOSPITALS

<i>Hospital</i>	<i>Years included</i>	<i>Total live births</i>	<i>Premature births</i>	
			<i>No</i>	<i>% of total</i>
Charity, of Louisiana New Orleans ¹	1951	11,228 ^a	1,174	10.5
Los Angeles County Calif. ⁵	1949 and 1950	15,728	1,723	11.0
Vanderbilt University Nashville, Tenn. ²²	1948-52	7,973 ^b	567	7.1
Johns Hopkins Baltimore, Md. ¹⁸	1926-49	38,111 ^c	4,459	11.7
Long Island College Brooklyn, N.Y. ²⁹	1940-45	9,084	637	7.0
St. Francis Wichita, Kan. ²²	1949 and 1950	4,596 ^d	312	6.8
Freedmen's Washington, D.C. ⁴⁰	1939-47	11,818 ^c	1,126	9.5
Colorado General Denver, Colo. ⁵⁰	1946-52	5,142	650	12.6
Denver General Denver, Colo. ⁵⁰	1948-52	3,586	597	16.0

^a About 85 per cent "colored." ^b All white ^c Half of the patients are "colored" ^d 2.9 per cent "Negro" ^e All "Negro"

The following data on incidence are restricted to reports from maternity hospitals based on all live births and on those using as the criterion of prematurity a birth weight of 2500 Gm. or less. Data from pediatric services have not been included since the infants admitted to these services are usually a heterogeneous group composed of infants sent in from other hospitals or a combination of these with infants born in the same hospital and transferred from the obstetric to the pediatric service routinely or for special reasons such as low birth weight or illness.

United States. At nine hospitals the incidence of premature births varied from 6.8 per cent to 16.0 per cent (Table 2-1). In 193 hospitals in five regions in the United States a composite rate of 6.1 per cent of 18,895 births was reported.³

An analysis of the various factors influencing these variations in rates would be valuable but data are unavailable for many of them. In regard to the racial factor, the hospital reporting all-Negro births had one of the lowest rates of incidence of prematurity (see Table 2-1)

The incidence of premature births in hospitals on a statewide basis (Massachusetts) in 1951, according to the annual hospital reports, was 6491 in 97,134 live births, 6.7 per cent.³⁷ In the eight Health Districts the incidence varied from 6.0 to 7.3 per cent. Ninety-eight per cent of the births in Massachusetts occur in hospitals.

TABLE 2-2 INCIDENCE OF PREMATURE BIRTHS IN HOSPITALS IN FOREIGN COUNTRIES

Country	Hospital	Period of study	Total no live births	Premature births	
				No	%
Rumania	Obstetric Clinic ⁶⁴	1915-42	24,000		12.6
Scotland	Aberdeen Maternity ³⁹	1941-42	3,156		11.1
Sweden	Maternity Hospital Stockholm ⁷¹	1936-38	9,393	579	6.2
Sweden (northern)	Maternity Department of the General Hospital, town of Umea ⁷⁸	1938-47	8,284	466	5.6
France	Baudelocque Maternity Paris ³⁰	1949-50	3,427	247	7.2
The Netherlands	University Maternity Utrecht ⁴⁸	Nov 1, 1939-May, 1, 1940	1,024	41	4.0
		Nov 1, 1944-May 1, 1945	628	54	8.6
Canada (British Columbia)	Hospital "A" Vancouver ⁴⁵	1937-48	39,540	2736	6.8
Finland	Several hospitals ³⁴	1940-43	32,283	1609	5.0
England	Sorrento Maternity Birmingham ¹²	1947-50		426	6.6
Ireland	Coombs Lying-In Dublin ²⁰	1950-51	3,627	313	8.7
Japan	Tohoku University Hospital, Sendai ¹⁰	1950-52	1,951	192	9.9
	Keio University Hospital Tokyo ¹⁰	1947-52	1,301	149	11.5

Other Countries. The incidence of premature births in women hospitalized for delivery varies widely in different countries, as does the proportion of women hospitalized for delivery. In maternity hospitals in eleven countries the reported

incidence of premature births varied from 4.0 to 12.6 per cent (Table 2-2). The criteria for including a birth as premature were not stated in all of these reports, however.

FACTORS INFLUENCING INCIDENCE

BIRTH WEIGHT

Since a birth weight of 2500 Gm. or less is the generally accepted definition of prematurity, it is obvious that the incidence of prematurity is influenced by most of the factors that exert a decremental influence on birth weight.

The average birth weight in some countries is so low that if a birth weight of 2500 Gm. or less is used as the criterion of prematurity the proportion of

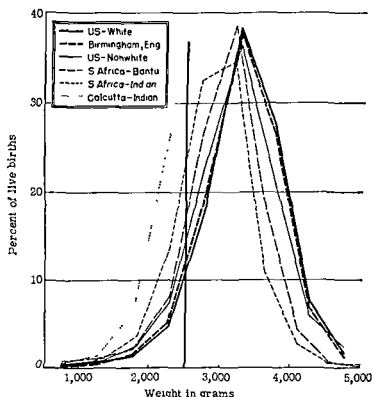


FIG. 2-1. Percentage distribution of live births by weight in grams for six areas or groups. The 2500-Gm. criterion of prematurity may not be appropriate for all populations throughout the world. (From Verhoestraete, L. J., and Puffer, R. R. Challenge of fetal loss, prematurity, and infant mortality—a world view. *J.A.M.A.* 167:950, 1958.)

premature infants will necessarily be high (Fig. 2-1) Verhoestraete and Puffer note that the proportions of live-born infants weighing 2500 Gm. or less range from 3.5 per cent for the Netherlands and 5.4 per cent for Oslo, Norway, to 11.6 per cent for the Bantu in South Africa, 18.3 per cent for East Indians in South Africa, and 34.7 per cent for Indians in Calcutta (For a discussion of birth weight as a criterion of prematurity see Chap. 1).

RACE, SEX, AND PLURALITY OF BIRTH

The influence of race, sex, and plurality of birth on birth weight has been repeatedly reported. Several studies showed that the percentage of live-born infants with a birth weight of 2500 Gm. and less varied with race and sex.^{15, 16} These variations in 1956 in the continental United States ranged from 6.3 and 7.4 per cent for white males and females to 11.0 and 13.2 per cent for nonwhite males and females, respectively (see Appendix 3). There was a preponderance of live-born females among infants with birth weights between 1501 and 2500 Gm.; below 1501 Gm. the distribution of birth weights was essentially the same in both sexes.

The incidence of prematurity among single-born and plural-born infants by race in the United States early in 1950 is shown in Table 2-3. Live-born infants

TABLE 2-3 PERCENTAGE DISTRIBUTION OF LIVE BIRTHS BY BIRTH WEIGHT
ACCORDING TO RACE AND PLURALITY OF BIRTHS
United States, January 1 to March 31, 1950

Race and plurality	Birth Weight (Gm)						Total	Total no live births
	1000 or less	1001- 1500	1501- 2000	2001- 2500	2500 or less	2501 or more		
United States	0.5	0.6	1.4	4.9	7.4	92.6	100.0	837,786
White	0.4	0.6	1.3	4.7	7.0	93.0	100.0	717,133
Nonwhite	0.6	0.8	1.8	6.4	9.7	90.3	100.0	120,653
Single births	0.4	0.5	1.1	4.4	6.4	93.6	100.0	820,618
White	0.4	0.5	1.0	4.2	6.0	94.0	100.0	702,966
Nonwhite	0.5	0.7	1.5	5.9	8.6	91.4	100.0	117,652
Births in plural sets	4.0	5.6	14.2	29.2	53.0	47.0	100.0	17,168
White	3.9	5.4	14.2	29.2	52.8	47.2	100.0	14,167
Nonwhite	4.2	6.1	14.5	29.2	54.0	46.0	100.0	3,001

in plural sets represented only 2.0 per cent of all live births in this period, but they accounted for 14.8 per cent of the infants weighing 2500 Gm. or less at birth.

The difference in the proportions of white and Negro infants weighing less than 2500 Gm. may or may not be racial. Difference in economic status, with accompanying differences in nutrition and complications of pregnancy, may account, at least in part, for the lower average birth weight of Negro infants. Anderson *et al.*, however, suggested that the gestation period for the Negro infant may actually be shorter than for the white infant and that race and sex should be considered in the definition of prematurity. In a later study by Brown and co-workers, data were presented that were considered justification for lowering, from 2500 to 2350 Gm., the upper limit of birth weight for prematurity among Negro infants in order "to make their stage of maturity more comparable to that of the white infants." When this was done the differences in the incidence of prematurity between white and Negro mothers disappeared, both for

TABLE 2-4 INCIDENCE OF PREMATURE BIRTHS ACCORDING TO TYPE OF MATERNAL HISTORY

Maternal history	Live-born premature infants					
	White		Negro			
	Birth weight less than 2500 Gm.		Birth weight less than 2500 Gm.		Birth weight less than 2350 Gm.	
	No	%	No	%	No	%
Normal	201	5	244	9	145	5
Illness or abnormality	379	12	435	14	314	10
TOTALS	580	8	679	12	459	8

From Brown *et al.*⁶

well mothers and for those who had some complications of pregnancy (Table 2-4). This study was based on 1259 live-born premature infants (580 white and 679 Negro infants weighing less than 2500 Gm.) in a series of 13,526 consecutive single births.

The published results of this study do not demonstrate conclusively that the difference in average birth weight between white and Negro infants is of racial origin. Though almost all the mothers included in the study were "unable to afford the services of a private physician at delivery," the Negro mothers may still have been of a generally lower economic group than the white mothers.

Furthermore, no information is given in regard to employment during pregnancy; and even if most of each group of mothers were employed, the Negro mothers may have worked longer hours and for a greater number of months and they are much more likely to have done heavy physical work. Until comparative environmental conditions have been studied in much more detail in relation to the birth weight of white and Negro infants, the difference in birth weight cannot be definitely attributed to inherent racial differences. Similar uncertainties exist with respect to the factors which influence the birth weight of Negro infants in Africa.²²

From these data it appears that the incidence of prematurity is higher among Negro than white infants, among females than among males, and among plural-born than among single-born infants. ✓

MATERNAL FACTORS

A number of essentially nonobstetric maternal factors which are associated with an increased incidence of prematurity will be reviewed in the section which follows. *For a discussion of the influence of the various complications of pregnancy on the incidence of premature birth, see Chapter 3.*

Age and Parity

In 1925 Woodbury pointed out that the mother's age and the order of birth influenced the incidence of prematurity. His findings were confirmed in a recent study by the National Office of Vital Statistics of 837,786 live births which occurred in the United States early in 1950.⁶⁰ The incidence of prematurity was highest among very young mothers (9.0 per cent at 15-19 years), was minimal at 25-29 years (6.7 per cent), and then rose (Fig. 2-2). Births of premature infants occurred most frequently in the first and the fifth (and over) pregnancies (7.7 per cent each) (Fig. 2-3). The similarity between the variations in incidence of prematurity by the age of the mother and variations by birth order was due in part to the close correlation between these two factors. However, a cross-tabulation indicated that the pattern of incidence of prematurity was not consistent for all age-of-mother groups (Fig. 2-4). This suggests the effect of an additional factor or factors related to a composite of age of mother and birth order. ✓

Socioeconomic Factors

Economic Status. Obviously there is a close relationship between the birth weight of the infant and race, economic status, and related factors. In an unpublished Children's Bureau study of infants born over a period of several years

PERCENT

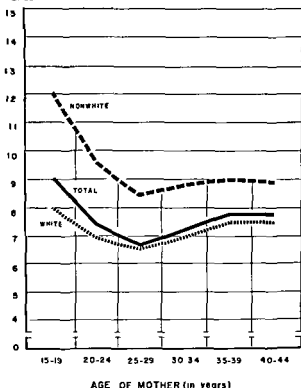


FIG. 2-2. Percentage of live births at weights of 2500 Gm. or less by age of mother and color, United States, January 1 to March 31, 1950. (From U.S. National Office of Vital Statistics: Weight at birth and survival of newborn, by age of mother and total-birth order: United States, early 1950. *Vital Statistics—Special Reports 47: (No. 2), 1958.*)

PERCENT

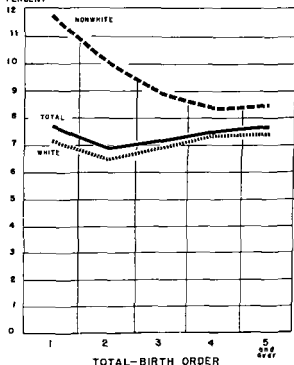


FIG. 2-3. Percentage of live births at weights of 2500 Gm. or less by total-birth order and color, United States, January 1 to March 31, 1950. (From U.S. National Office of Vital Statistics: Weight at birth and survival of newborn, by age of mother and total-birth order: United States, early 1950. *Vital Statistics—Special Reports 47: (No. 2), 1958.*)

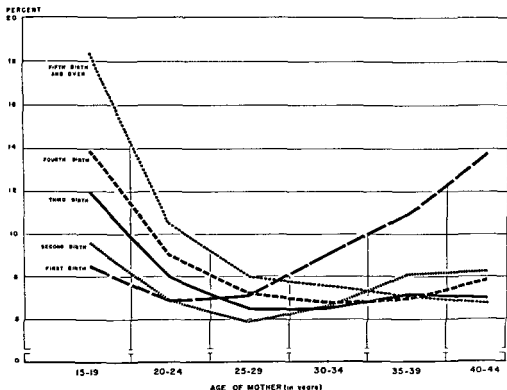


FIG. 2-4. Percentage of live births at weights of 2500 Gm. or less, by total-birth order for each age-of-mother group: United States, January 1 to March 31, 1950. (From U.S. National Office of Vital Statistics: *Weight at birth and survival of newborn, by age of mother and total-birth order: United States, early 1950. Vital Statistics—Special Reports 47: (No. 2), 1958.*)

in two hospitals, the hospital service on which the mother's delivery took place was taken as a measure of her economic status. The series comprised 4704 white single-born infants, of whom 258 weighed less than 2500 Gm. The incidence of prematurity was higher among the 2192 ward patients (6.8 per cent) than among the 2512 private and semiprivate patients (4.3 per cent).

Confirmation of the probable role of economic factors in the incidence of premature birth is found in a study by Eastman,¹⁷ who found an incidence of prematurity of 4.7 per cent among private patients (3979 single pregnancies with no demonstrable cause of prematurity), an incidence of 7.1 per cent among 6491 white clinic patients, and 11.7 per cent among 6135 Negro clinic mothers. Similar differences between the incidence in private and clinic patients in Aberdeen, Scotland, were reported by Baird.

Gibson and McKeown presented evidence which indicated an association between low birth weight and poor economic circumstances of the parents as judged by the quality of their housing. This association could not be accounted

for by the differences in the birth order of the individuals in each group and was more conspicuous when first births were compared. When duration of pregnancy was used as a criteria of prematurity no significant associations with economic circumstances could be demonstrated.

Bundesen and his co-workers, reporting the incidence of premature births in five socioeconomic classes (areas) and by race in Chicago (1950),* showed that "as the socioeconomic area of the city improved, the incidence of prematurity decreased." The incidence varied from a rate of 9.7 per cent live births in the lowest economic area to 7.3 in the highest. The same relation of incidence to economic area was found when the data were analyzed by race, the incidence of prematurity being, in each socioeconomic class, higher among the Negroes.

Nørregaard found, in a study of 1125 premature births and 1000 term controls in Copenhagen, that 18 per cent of mothers of premature infants were from the indigent class, compared with 10 per cent of the control series; the well-to-do class was represented by 3 per cent of the premature infants, and 6 per cent of the control series. Absence of antenatal care (examination by a physician) was reported in 19 per cent of the former group and in 7 per cent of the control series.

Social Class. The incidence of prematurity in Great Britain was found to be 4.3 per cent among infants born to wives of professional and of salaried workers and 6.5 per cent among those of "black-coated" wage earners.²⁷

Drillien conducted a detailed inquiry into the social and economic factors affecting the incidence of premature birth in two Edinburgh maternity hospitals during the period 1953 to 1955. A random sample of maturely born infants was selected as controls. Among prematurely born infants having no complications of pregnancy she observed that the social class of the husband had only a slight influence upon the risk of premature birth as compared with the class in which the mother was born and raised. The efficiency of the maternal grandmother as a homemaker (arbitrarily graded by an interviewer) was found to be inversely related to the liability to premature birth in the next generation. Drillien classified one group of premature infants as "early" (gestation period under 38 weeks) and another group with a gestation time of 38 weeks or longer as "small." She observed that the mothers of "small" babies were significantly shorter than those with "early" babies. When social class and maternal stature were considered together it was found that the likelihood of "early" delivery was dependent upon the social class of upbringing and not on maternal stature. However, the likelihood of producing a "small" baby was affected about equally by social class and maternal stature.

* Incidence is not given for highest economic class since there were less than 100 Negroes in this class.

Illegitimacy. The associations between premature birth and age of mother and birth order noted above may be influenced to some extent by an interdependent relationship to illegitimacy which is commonest at the lower birth orders and among younger mothers.⁶⁰

A relatively high incidence of prematurity among unmarried mothers has been reported by a number of observers.^{27, 36} In Nørregaard's study 20 per cent of the mothers of premature infants were unmarried, compared with 15 per cent of the mothers of the term control series. Stevenson found a high incidence of illegitimacy among Negro premature births as compared with white premature and Negro term births.

Employment During Pregnancy. In some reports it has been concluded that employment outside the home, particularly if continued too long into pregnancy, tends to bring about its earlier termination, and, in this way, is conducive to prematurity. Among the earliest studies is that by Sarraute-Lourié, who observed that the duration of pregnancy depended to a considerable degree upon the general care received by women in the last several weeks of pregnancy. She found that pregnancy was at least 20 days longer in 1550 women who lived comfortably during the last several weeks of pregnancy in a maternity home than in another group of 1550 women who entered a hospital shortly before the onset of labor. Both institutions were serving mostly low-paid working women. Sarraute-Lourié concluded that a rest in the last several weeks of pregnancy is important for the normal development of the fetus, and consequently also for the prevention of prematurity.

Since this report there have been many observations on the association between paid work and the incidence of prematurity.^{13, 32, 36} Drillien was unable to demonstrate an effect on the duration of pregnancy among women who held paid employment during pregnancy. Illsley and others observed that, although primiparas who worked until a late stage in pregnancy were more likely to have premature babies, they found no evidence that increased length of work, by itself, predisposed to prematurity.

Nutritional Factors

A number of studies have been made of premature birth in relation to diet during pregnancy. The incidence of premature birth was found by Ebbs *et al.* and by Burke *et al.*⁹ to be higher among mothers who had poor diets than among those who had good diets. Burke and her co-workers⁸ subsequently reported that among the 216 women whose diets were studied during the fourth through the ninth months of pregnancy, only 10 per cent consumed the daily amount of pro-

tein (85 Gm. or more) recommended by the National Research Council as desirable in the latter part of pregnancy. They found a significant relationship between the protein content of the mother's diet during pregnancy and the birth weight and birth length of the infant; increase in birth weight and birth length was found with each increment of protein. No infants weighing less than 5 pounds at birth were included in this analysis.

A group of 750 expectant mothers on a controlled diet reported by Tyson had no premature infants, whereas 37 premature (including stillborn) infants were born to a similar group of mothers not on the special diet. The controlled diet contained "large amounts of proteins, vitamins, and minerals with definite limitation of fluids and water-embracing fruits. Adequate supervision was secured by having one physician examine all patients, one nurse make all home visits, and the hospital issue all dietary instructions." A correlation between types of maternal diet during pregnancy and varying birth weight and length of the infants was also noted.

In certain countries during the war years conditions arose which made it possible to study these factors and to contrast them with those in prewar years. R  ih   reported that in Helsinki, Finland, the percentage of premature deliveries was relatively constant—about 10 to 12 per cent—in the period 1917–41. In 1942 it dropped to about 6 per cent, without significant change in the number of deliveries, and it remained almost unaltered until 1946. This decrease, the author considers, must have been due in part to the greatly lowered incidence of toxemia of pregnancy. It is puzzling that the decrease occurred as living conditions worsened and female labor was mobilized as a result of the war.

The decrease in premature births in maternity hospitals in Finland during most of the Second World War (1939–45) was substantially confirmed by Parviainen. After an increase in 1940, the first full year of the war, to 7.6 from 6.3 per cent in the previous year, the incidence continued to fall to 5.6 per cent in 1944, the last full year of the war.

On the contrary, an increase in premature births under wartime starvation conditions has been reported by Smith. In a pre-hunger year—October, 1943, to May, 1944—in Rotterdam, The Netherlands, 5.0 per cent of the infants born weighed less than 2250 Gm., while for those conceived in the "hunger period" (October, 1945, to December 31, 1945) the percentage was 8.4. In The Hague the incidence was 8.2 per cent for those born in a pre-hunger year and 11.0 per cent for those conceived in a hunger year.

Studies made in the United States and Canada in which the mother's diet during pregnancy was graded showed that the incidence of prematurity is highest among the women with the poorest diets. Speert and co-workers reviewed this

evidence and judged that it failed to prove conclusively that premature labor results from inadequate maternal nutrition. They studied the dietary histories of 70 mothers of live-born premature infants and 67 control mothers of term infants. There were no significant differences in calculated intake of the various food essentials in the two groups. Hematologic and blood-chemistry determinations in the early puerperium also failed to reveal any significant differences between the mothers of premature infants and the controls. The authors concluded that their study offered no support to the theory that nutritional deficiency is a common cause of premature labor.

Stearns has suggested that the nutritional state of the mother prior to conception may influence the outcome of the pregnancy. She found that young mothers illegitimately pregnant were more poorly nourished than older and *more emotionally stable pregnant women. In this connection, Drillien observed* that there was a tendency for an inadequate diet of the pregnant woman to be associated with domestic inefficiency of her own mother (the prospective grandmother).

For recommended dietary allowances during pregnancy see Appendix 6.

OTHER FACTORS

Geographic Area. Among a total of 4,163,090 live births in the United States in 1956, the proportion of white infants weighing 2500 Gm. or less at birth was highest (8.3 per cent) in the Mountain Division (see Appendix 3). However, for the nonwhite group premature births occurred most frequently (18.0 per cent) in the New England area.

Altitude. Lichty and co-workers examined the distributions of birth weights in the counties of Colorado and found an association between altitude and high incidence of infants of low birth weight. During a five-year period (1949-53) 30.8 per cent of live-born infants in Lake County (altitude 10,000-11,000 feet) weighed 2500 Gm. or less as compared with 10.4 per cent for the state average. Although the Lake County newborns also exhibited reduced body measurements (length and head size), the distribution of gestational ages was comparable with a series of pregnancies at sea level.²⁴ During the period studied the over-all neonatal death rate for this county was 4.2 per cent as compared with 2.3 per cent for the state.

The arterial-oxygen saturations and hematocrit values of infants born in Lake County were similar to values found in a control series of infants born in Denver (5280 feet).²⁵ The high incidence of low birth weight could not be explained on the basis of race or maternal diet.

Urban and Rural Areas. A study of live births early in 1950 revealed a higher

incidence of prematurity in urban (7.8 per cent) than in rural areas (6.7 per cent).⁵⁸ The difference was greater in the nonwhite than in the white groups.

Blood Group. In an effort to find a mechanism which would explain the relative infrequency of blood group B in the western world, Plotkin compared the blood types of 100 prematures and 1033 term infants. He found a significantly higher incidence of group B in the premature (31.0 per cent) than in the control group (22.5 per cent). Plotkin urged that these studies be repeated in a larger series.

Cigarette Smoking. Simpson found prematurity to be approximately twice as frequent among 2371 cigarette smokers than in 5128 nonsmokers. A disparity was observed at all maternal ages; an analysis by birth order was not presented. The author stated that these preliminary observations will be followed by further study.

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Causes and Prevention of Prematurity

The causes of prematurity must be clarified if there is to be any reduction in the incidence of premature births. Although the problem of prolonging pregnancy is primarily the concern of the obstetrician, it is also of considerable interest to all who have the responsibility for caring for premature infants after birth.

INCIDENCE OF CONDITIONS ASSOCIATED WITH PREMATURE BIRTH

The earlier North American literature dealing with causes of prematurity was reviewed by Anderson and Lyon in 1939. Table 3-1 shows the lowest and highest incidence for each condition, as reported by thirteen American authors.

In a later report Anderson *et al*³ found that, although these conditions may be associated with delivery at term, they appear with greater frequency among women who give birth to infants weighing less than 2500 Gm. In neither of these reports was information included as to the severity of each condition or as to whether labor was spontaneous or induced. Obviously, the association of some abnormal condition with premature labor does not mean that it was necessarily the causal factor.

✓ Eastman¹⁶ contributed to a clearer understanding of the relation of complications of pregnancy to premature labor by classifying the circumstances of prematurity into three major categories: (1) multiple pregnancy, with either spontaneous or induced termination, (2) induced termination (including cesarean section) of single pregnancy, (3) spontaneous termination of single pregnancy.

✓ In a study of 4459 premature live births (11.7 per cent of the total live births) in Johns Hopkins Hospital, 1926 to 1949, he observed that plural births accounted for 12.2 per cent, induced termination for 13.3 per cent, and spontaneous termination for 74.5 per cent of the premature infants. Considering

TABLE 3-1 INCIDENCE OF CONDITIONS ASSOCIATED WITH PREMATURE BIRTH ✓

	% of premature births	
	<i>Lowest</i>	<i>Highest</i>
No associated conditions	18.8	92.8
Multiple birth	6.3	22.9
Toxemia	1.4	29.9
Bleeding		
Placenta previa	1.3	9.0
Premature separation of placenta	0.2	5.1
Unstated	1.2	18.2
Premature rupture of membranes	0.4	20.9
Syphilis	1.4	19.0
Serious illness of mother		
Heart disease	0.1	8.3
Tuberculosis	0.2	5.5
Other acute and chronic conditions	1.4	16.3
Abnormalities of genital tract		
Pelvic deformities	0.3	7.8
Myoma uteri	0.1	1.6
Hydramnios	0.1	2.9
Trauma to mother	0.1	5.2
Other conditions	1.1	9.8

From Anderson and Lyon,² based on reports of thirteen American authors

the largest category (spontaneous termination of single pregnancy) apart from the others, he then compared the percentage frequency of each of the conditions associated with premature labor in the "general clinic population" with the "expected incidence." The data are shown in Table 3-2.

There appears to be agreement, in general, in regard to the relative frequency of the major conditions reported to be associated with premature birth, although there is considerable variation in their reported incidence.

PRINCIPAL CONDITIONS ASSOCIATED WITH PREMATURE BIRTH

The various factors that may influence premature labor will now be discussed broadly; for the details of prevention and obstetric treatment of these conditions an obstetrics-gynecology textbook should be consulted.

TABLE 3-2 ROLE OF VARIOUS DISEASES IN INITIATING SPONTANEOUS PREMATURE LABOR (SINGLE PREGNANCY)

<i>Disease</i>	(1)	(2)	(3) <i>Prematures found</i>		(3 minus 2)
	<i>Total no. cases</i>	<i>No prematures expected^a</i>	<i>No</i>	<i>%</i>	<i>No. prematures due to disease^a</i>
Placenta previa	107	11	52	48.6	41
Abruptio placentae	174	17	106	60.1	89
Preeclampsia	3,126	315	496	15.9	181
Eclampsia	115	12	29	25.2	17
Chronic hypertension	666	67	145	21.8	78
Syphilis					
Negro patients	2,927	395	470	16.1	75
White patients	354	25	39	10.7	14
Heart disease	614	61	96	15.6	35
Congenital abnormalities	240	24	60	25.0	36
TOTALS	8,323	927	1,493	17.9	566

From Eastman.⁴⁴

^a Eastman explains the method used to obtain the figures in columns (2) and (3 minus 2) as follows: "The table shows 107 cases of placenta previa. If the placenta previa had nothing whatsoever to do with the cause of premature birth we would expect about the same incidence of prematurity as in the general clinic population or, in other words, we would expect about 10 per cent or 11 prematures in this group. But we found 52, or 48 per cent of the 107. I have subtracted the prematures expected from the prematures found, and have concluded that these 41 cases must be due to the disease process, because that is the figure by which the number of prematures found exceeds those expected."

TABLE 3-3 PERCENTAGE DISTRIBUTION OF SINGLE LIVE BIRTHS ACCORDING TO COLOR AND OUTCOME OF PREVIOUS DELIVERIES, BY BIRTH WEIGHT
United States, January 1 to March 31, 1950

<i>Color and outcome of previous pregnancies</i>	<i>Birth weight (Gm.)</i>						<i>Total</i>
	<i>1000 or less</i>	<i>1001-1500</i>	<i>1501-2000</i>	<i>2001-2500</i>	<i>2500 or less</i>	<i>2501 or more</i>	
White							
No previous fetal death	0.3	0.4	1.0	4.1	5.9	94.1	100.0
Previous fetal death	1.1	1.1	1.9	5.9	10.0	90.0	100.0
Nonwhite							
No previous fetal death	0.5	0.7	1.5	5.8	8.4	91.6	100.0
Previous fetal death	0.9	1.0	1.8	6.3	10.1	89.9	100.0

From U.S. National Office of Vital Statistics.⁴⁵

Cases in which no cause for prematurity is determined comprise the largest number of premature births. Stevenson and co-workers indicated that the pregnancies which resulted in large premature infants (2001-2500 Gm.) were associated with "no reported (maternal) abnormalities" more frequently than the pregnancies which produced smaller infants. The wide range of estimates of the size of the "no associated condition" category (see Table 3-1) is, for the most part, the result of diverse classifications of the conditions associated with premature birth.

Eastman¹⁷ observed that the woman whose pregnancy terminates prematurely may give birth repeatedly to premature infants. This is supported by many observations in the past² and more recently by evidence obtained in local^{9 45} and national⁴⁹ surveys. For single births in the United States early in 1950, the delivery of a premature infant occurred more frequently among women who had previously had one or more fetal losses than among other women (Table 3-3)

MULTIPLE BIRTH

Eastman^{16, 18} pointed out that, although twin pregnancies cannot be prevented, attempts should be made to forestall the onset of premature labor in these pregnancies. He made the following suggestions:

1 Toxemia occurs four to five times more frequently in twin than in single pregnancies. As soon as the diagnosis of multiple pregnancy is made the patient should be placed on a salt-poor diet. The frequency of antepartal visits should also be increased to detect preeclampsia. If it appears, and treatment at home does not cause a rapid response, the patient should be hospitalized promptly.

2 The second preventive step in twin pregnancies is rest. There are several mechanical factors that predispose to prematurity—the presence of hydramnios, the larger intrauterine mass, and the earlier effacement and dilatation of the cervix. These women should have more rest at home after the twenty-fourth week and some should be admitted to the hospital for the last few weeks of pregnancy.

Others have also advised that mothers bearing twins should remain in bed during the latter stage of pregnancy.^{7, 15}

TOXEMIAS OF PREGNANCY

Toxemias of pregnancy were associated with a very wide range (1.4-29.9 per cent) of the premature births reported in earlier studies. This variation may be the result of differences in the incidence of toxemia or in classification and diagnosis.

In Eastman's series of 8323 single pregnancies (spontaneous termination)

there were 666 cases of chronic hypertension, 3126 cases of preeclampsia, and 115 of eclampsia. The incidence of prematurity in each of these three groups was 21.8, 15.9, and 25.2 per cent, respectively. In each group the incidence of prematurity was higher than that for the general clinic population.

Prevention

There appears to be considerable evidence that progress in the prevention of the toxemias of pregnancy has been made in recent years and that the incidence of the more severe forms has been reduced. For example, Hamlin reported the development of an intensified program for improving antenatal care aimed specifically toward reducing the incidence of eclampsia in the Women's Hospital, Sydney, Australia. The annual rate for "booked" patients was between 1.2 and 2.5 per 1000 patients in 1945 to 1947, whereas for the period 1935 to 1947 the average was 2.9. Following the introduction of new standards for antenatal care in 1948 there was a rapid reduction in the number of cases of eclampsia, and, for the year March, 1950, to March, 1951, not a single case occurred among the 5000 "booked" patients. In contrast, the incidence of eclampsia in two other women's hospitals in Australia was 2.0 per 1000 patients in 1949 and an average of 4.0 for the period 1930 to 1946, respectively. The preventive measures developed in this intensified antenatal program are outlined in Programs for Premature Infant Care.

- ✓ It is well recognized that toxemia of pregnancy cannot be wholly prevented, since the cause is not known. It has been found, however, that when early and adequate antenatal care is given, with proper regard to the mother's diet and rest, severe toxemia and eclampsia, with which premature birth is frequently associated, rarely occur. When toxemia does occur, the welfare of both mother and infant must be carefully considered in deciding whether or not to attempt to prolong pregnancy until the infant attains a weight compatible with a good chance of survival (more than 1500 Gm.).

✓ *Diethylstilbestrol Therapy* Although it had been suggested that the administration of diethylstilbestrol during pregnancy decreased the incidence of toxemias of pregnancy and that premature infants born after this treatment were unusually large for their gestational age,⁴² these claims were not confirmed by a well-controlled clinical trial conducted by Dieckmann and co-workers.

ANTEPARTUM HEMORRHAGE

Antepartum hemorrhage is frequently associated with premature birth. Stevenson *et al.* observed that both a history of unexplained bleeding early in

pregnancy and a history of bleeding resulting from placentation difficulties are more frequent in premature deliveries than among term pregnancies.

Abortion

In a series of 700 pregnant women studied by Speert and Guttmacher,⁴⁴ approximately 28 per cent reported gross vaginal bleeding or staining at some time between the twenty-fifth and one hundred and ninety-sixth days of pregnancy. Abortion occurred in about one-third of those who stained or bled. These authors noted that *physiologic bleeding of early pregnancy is usually scant in contrast to the bleeding of abortion, which is usually associated with a greater flow of blood, a brown-black color of the initial vaginal discharge of blood, uterine cramps, and the absence of nausea.*

Threatened abortion, according to Hertig and Livingstone, occurs in at least 16 per cent of all pregnancies. There are conflicting estimates of the frequency of "habitual" abortion.^{24, 43}

Speert⁴³ reviewed the evidence on pregnancy prognosis following repeated abortion and reported the outcome of 121 pregnancies among women with a succession of 3 or more spontaneous abortions of a fetus weighing less than 1000 Gm. He found that 81 per cent of the patients carried to viability in a fourth pregnancy. Women with a viable pregnancy antedating the abortion sequence appeared to have a better prognosis than women whose abortions began with the first pregnancy.

There is no agreement concerning the role of developmental abnormalities of the fetus in the production of abortion.^{25, 39} It is difficult to interpret the available evidence because only a small proportion of the fetuses recovered after spontaneous abortion are subjected to postmortem study.³³

Placenta Previa and Abruptio Placentae

In Eastman's series¹⁶ (*spontaneous termination of single pregnancy*) 49 per cent of 107 cases of placenta previa and 60 per cent of 174 cases of abruptio placentae were associated with premature birth, an incidence of prematurity much higher than that in the general clinic population (10 per cent) (see Table 3-3).

Parks recommends that when the diagnosis of placenta previa is made between the twenty-eighth and thirty-sixth weeks the pregnant woman should be hospitalized and treated conservatively. He believes that this is justified as long as maternal and fetal life are not jeopardized by continuous blood loss, since the likelihood of survival of the fetus increases with each week that the pregnancy can be carried closer to term.

Nilsen reviewed the topic of premature separation of the normally implanted

placenta (abruptio placentae) and reported observations on 357 patients. These women gave birth to 359 infants (2 sets of twins); more than half (207 infants) weighed 2500 Gm. or less at birth.

PREMATURE RUPTURE OF THE MEMBRANES

Cron and Brown reported the incidence of spontaneous rupture of the membranes as 9 per cent in 2982 deliveries and of surgical rupture of the membranes as 5.8 per cent in 6050 deliveries. The incidence of prematurity for the total number of deliveries was 4.1 per cent, for cases in which spontaneous rupture occurred, 9.4 per cent; for those surgically induced, 3.2 per cent.

Flowers *et al.* observed an over-all incidence of 15.8 per cent of spontaneous premature rupture of membranes among 7511 deliveries in three teaching hospitals in North Carolina. It occurred more frequently among nonwhite and less educated mothers. This complication occurred in 32.9 per cent of infants that weighed 400 to 2000 Gm. and 18.7 per cent of those that weighed 2001 Gm. and over. A high incidence of major obstetric complications (prolapse of the cord, maternal fever, antepartum bleeding, etc.) was observed in association with premature rupture of membranes. Infection was the major lethal factor in the infant deaths which were thought to be related primarily to premature rupture of the membranes.

The management of this complication, notably with respect to the use of antibacterial agents, is in dispute (see Chap. 19). The North Carolina group proposed that premature rupture of the membranes is a major obstetric complication worthy of additional study particularly as it relates to the problem of mothers in poor socioeconomic circumstances who do not avail themselves of antenatal care even when it is offered.

NONOBSTETRIC CONDITIONS

The influence of socioeconomic, nutritional, and other factors on the outcome of pregnancy has been discussed (see Chap. 2). For a discussion of diabetes see Chapter 22.

Syphilis

The incidence of syphilis in pregnant women varies widely in different countries and within areas of the same country. In the past, syphilis was an important cause of premature birth (see Table 3-1). In the series reported by Stevenson and co-workers, syphilis was not important in the etiology of prematurity among white mothers in a Pittsburgh hospital. Among Negro mothers

the incidence of positive serologic tests was 18 per cent in premature births, and 10 per cent in term controls.

Antenatal Treatment. Penicillin should be administered to the infected mother when the diagnosis is established, and as early in pregnancy as possible.⁴¹ Moreover, treated women must be followed closely, so that retreatment may be given to those who failed to respond and to those who develop an infectious relapse or a reinfection late in pregnancy. It is never too late to start treatment, and success has been reported even when treatment has been completed during labor.²¹

The amount of penicillin to be given during pregnancy depends on the stage of maternal infection. In primary and secondary syphilis, Slatkin and Nelson recommended 900,000 units of procaine penicillin G in oil containing 2 per cent aluminum monostearate intramuscularly twice weekly for 4 weeks (total dose 7.2 million units). In latent syphilis, these authors advised 5 to 8 weeks of treatment (total doses 9.0 to 14.4 million units). Longer periods were recommended for late syphilis. These schedules provide higher total doses of penicillin than were advocated in earlier years.^{21, 29, 30}

Thomson reported the results of treating 83 pregnant women in Hong Kong who were unable to attend antenatal clinics regularly. A single injection of 2.4 million units of long-acting (dibenzylethylenediamine) penicillin was administered whenever the diagnosis of syphilis was made; on the average this was at the *thirty-second week*. *Eighty-five infants (2 sets of twins) delivered by these mothers were examined at 4 months of age; 2 had serologic evidence but no clinical signs of congenital syphilis and were given penicillin; 83 children were seronegative.*

Slatkin and Nelson noted that it is not necessary to give penicillin during each pregnancy. One adequate course of penicillin treatment suffices during the life of the syphilitic patient unless subsequent relapse or reinfection occurs. They advised that women previously treated for syphilis should have regular clinical examinations and quantitative serologic tests for syphilis at monthly intervals during pregnancy. If there is any question concerning the adequacy of the previous treatment or the possibility of an active syphilitic infection, retreatment should be started at once.

Tuberculosis

Ratner and his co-workers studied the relation of the severity of tuberculosis in the pregnant woman to the incidence of prematurity. They concluded that the incidence of prematurity was high (22 per cent) in 260 pregnant

women with arrested or chronic tuberculosis and appeared to be even higher (64 per cent) in a small group of mothers (39) who had advanced tuberculosis and died soon after delivery.

Early and adequate antenatal examination of pregnant women for evidences of tuberculosis, and proper care if the disease is found, is essential not only for the welfare of the mother but for the welfare of her infant. Schaefer and others found that the incidence of tuberculosis complicating pregnancy in a New York hospital remained essentially the same (1.5–2.0 per cent) between 1933 and 1956. These authors found no apparent deleterious effects of antimicrobial therapy (streptomycin, para-aminosalicylic acid and isoniazid) in newborn infants whose mothers were treated during pregnancy.

Malaria

A study made in Nigeria showed that in 362 births, 30 per cent of the placentas were infected with malarial parasites.¹¹ The mean birth weight of the infants whose mothers had infected placentas was significantly lower than that of infants whose mothers had noninfected placentas. The incidence of prematurity (birth weight 2500 Gm or less) was 33 per cent in the group with infected placentas and 12 per cent in the group with noninfected placentas. No examples of congenital malaria were found in 117 of the infants investigated within 25 hours after birth. (See also Cytomegalic Inclusion Disease and Toxoplasmosis in Chap. 19.)

Acute Infectious Diseases

The pregnant woman should as far as possible avoid exposure to acute infectious diseases. If exposed to measles, she should be given passive immunization with immune serum globulin (gamma globulin) with a view to preventing the disease or at least modifying it. To prevent measles in those exposed, gamma globulin in doses of 0.25 ml. per kg. body weight should be injected intramuscularly prior to the sixth day after exposure. Thereafter, larger doses may be used, but prevention is not likely to be successful.¹

Avoidance of exposure to virus diseases, especially rubella, in the early months of pregnancy is important (see Chap. 17).

The use of antibacterial drugs in the treatment of acute infections occurring in the course of pregnancy is discussed in Chapter 19.

Cardiac Disease

In 1941 Beck suggested that women with severe cardiac disease should have careful examinations before conception and that many should be advised not to

risk a pregnancy. In 1958 Burwell and Metcalfe took a more liberal stand and suggested that most cardiac patients are entitled to a trial of pregnancy. They believed that with developing medical and surgical techniques the immediate and long-term maternal risks will be reduced.

Although there are conflicting estimates of fetal and neonatal mortality among women with mild heart disease,^{22, 46} there is general agreement that in women with severe heart disease perinatal mortality is high in both interrupted pregnancies and those which terminate spontaneously. Premature termination of pregnancy is now only rarely recommended, owing to a recent trend of increasing confidence in the conservative management of heart disease in pregnant women.¹⁰

Thyroid Disease

Hyperthyroidism. In 1951 Astwood reviewed the literature dealing with the concurrence of hyperthyroidism and pregnancy. These reports indicated that the high incidence of miscarriage and stillbirth in thyrotoxic mothers had been reduced as the result of treatment with Lugol's solution during pregnancy but that the rate of fetal loss still remained higher than in normal mothers.

Astwood used antithyroid drugs (principally propylthiourcil) during or shortly before pregnancy in 22 hyperthyroid women. Twenty-two living children were delivered, none showing evidence of thyroid disturbance or goiter. Three of the offspring were born prematurely, they survived and developed normally.

Thiouracil derivatives pass across the placenta and may produce a goiter in the fetus.¹⁹ In order to minimize this possibility Bongiovanni *et al* advised that thyrotoxicosis be only partially corrected with the thiouracil drugs and, if the hyperthyroidism has been reasonably well controlled, the drug should be withdrawn two or three weeks before delivery.

Hypothyroidism. Most women with myxedema are sterile. Hodges and co-workers reported an interesting exception—a woman who had been myxedematous for 15 years conceived and delivered six children. During this time she received no thyroid substance. Two of the children died in the neonatal period and 3 of her 4 living children had multiple congenital defects. (See Chaps. 6 and 17.)

Exogenous thyroid is commonly administered to women with habitual abortion. Conninos presented evidence which indicated that this was of questionable value in euthyroid mothers.

Abnormalities of the Genital Tract

Congenital malformations of the uterus, uterine tumors, and hydramnios may give rise to uterine irritability resulting in premature onset of labor. Previous cervical amputation is also a cause of premature labor.

There has been considerable interest in the subject of incompetence of the internal os of the cervix as a cause of habitual abortion, and suggestions for the surgical correction of this condition have been made.^{27, 31, 32} The frequency of occurrence of this condition has not been established and the influence of therapy on reducing the over-all incidence of premature delivery has not been evaluated.

Trauma and Overexertion

The onset of premature labor is often ascribed by the patient to a fall or a blow. Physicians, however, tend to minimize the significance of this association, though a few premature births are attributed to this cause (see Table 3-1). Traumatic intercourse is considered to be a cause of prematurity.³⁵

Raihä observed that the incidence of prematurity was significantly increased among a group of pregnant women who were found to have small heart volumes (determined radiographically) and low concentrations of hemoglobin. These observations led him to attempt to prevent prematurity in these mothers by asking them to decrease the amount of manual work and to rest daily. Two premature infants were delivered in 91 pregnancies under this regimen, in contrast to 43 per cent premature deliveries in 631 pregnancies in the previous three years. A clinical trial of this program with concurrent controls has not been reported.

In this connection, the results of a study referred to in the last chapter should be mentioned. Illsley *et al.* conducted an investigation into the association between paid work during pregnancy and premature delivery. Preliminary results indicated that the prematurity rate increased with the length of time worked during pregnancy. They analyzed the relationship in more detail among single births to married women pregnant for the first time, abnormalities of pregnancy were excluded. It was found that the duration of work was similar in the group whose pregnancies terminated prematurely and in a control group whose pregnancies went to term. The two groups were matched for social class, height, age, timing of marriage, and type of work done during or before pregnancy.

The authors stressed that the study did not show that the amount of physical strain experienced by the individual mother during pregnancy was unimportant; nor did it show whether type or duration of work had any influence on the production of abnormalities of pregnancy which in turn might give rise to prematurity. However, the results suggested that further social measures designed to reduce the duration of paid work undertaken by primigravidas would do little to lower the incidence of prematurity.

PREVENTION OF PREMATUREITY

In 1948 the report of a committee which investigated the medical aspects of the decline in the birth rate in Canberra, Australia, outlined methods to prevent prematureity as follows:

Much could be done to lower the incidence of prematureity with all its attendant loading effect on the infant mortality, merely by instituting those measures recommended by the Scottish Committee (in 1946). Measures referable to overcrowding, poor housing and poverty, would alleviate many of the hardships of the "working class" groups. Education of the public and more specialized education of the medical profession, together with provision of more adequate hospital and clinical facilities, would ensure an improvement in the prenatal care, thereby enabling such complication as toxæmias, malpresentation and antepartum hæmorrhage to be more adequately treated than at present.⁴⁰

The first item in the recommendation of this committee was that more vigorous methods be instituted to combat the incidence of prematureity by (1) improved antenatal supervision; (2) dietary and general hygienic education of the expectant mother; and (3) introduction of more comprehensive socio-economic measures to alleviate the harmful effects of overcrowding, poor housing, and inadequate hospital and clinic facilities for the pregnant woman ✓

In the United States, although much attention has been paid to the high mortality rate from premature birth, reports of attempts to reduce the number of these births have been very few. There have, however, been numerous studies of the causes of premature labor which have been reviewed briefly in the foregoing pages. Methods are known for preventing or ameliorating some of the antenatal causes but are still unknown or in the experimental stage for others.

Whether or not dietary deficiency is a cause of premature labor, advice as to diet is an important part of antenatal care. Standards set by different authors for dietary requirements in pregnancy vary considerably. The standards that we follow are those of the Food and Nutrition Board of the National Research Council (U.S.A.), first issued in 1941 and most recently revised in 1958 (see Appendix 6).

Taylor, in the course of a discussion of prevention of deaths from prematureity, said: "We do not suggest that we have a formula for preventing premature labor. We do, however, in our teaching and practice of obstetrics, try to emphasize prolongation of gestation in certain patients where the maternal complication might otherwise lead to early interruption of pregnancy." The education of physicians in this regard is an important aspect of the problem.

Antenatal care throughout pregnancy is essential, and special efforts should be

TABLE 3-4 INCIDENCE OF PREMATUREITY BY MONTH OF FIRST VISIT FOR ANTENATAL CARE IN NEW YORK CITY, 1957

<i>Month of first visit (calendar months)</i>	<i>Total no live-born infants</i>	<i>Live-born premature infants (2500 Gm or less)</i>	
		<i>No.</i>	<i>%</i>
1-3	70,952	5,506	7.8
4-6	62,939	5,475	8.7
7-9	24,403	2,496	10.2
No antenatal care	8,683	1,760	20.3
TOTALS	166,977	15,237	9.1

Courtesy of Jean Pakter, M.D., Maternity and Newborn Division, The City of New York Department of Health

TABLE 3-5 DISTRIBUTION OF LIVE BORN INFANTS* IN PRIVATE SERVICE AND GENERAL SERVICE BY MONTH OF FIRST VISIT FOR ANTENATAL CARE, NEW YORK CITY, 1957

<i>Month of first visit (calendar months)</i>	<i>Live-born infants (all weights)</i>			
	<i>Private service</i>		<i>General service</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
1-3	62,231	61.5	5,733	10.0
4-6	31,933	31.5	28,088	48.8
7-9	4,726	4.7	18,369	31.9
No antenatal care	2,297	2.3	5,349	9.3
TOTALS	101,187	100.0	57,539	100.0

Courtesy of Jean Pakter, M.D., Maternity and Newborn Division, The City of New York Department of Health

* Excludes 8,251 infants for whom information concerning antenatal care and hospital service was incomplete

made to provide such care particularly for mothers who have had previous premature deliveries. Although other factors undoubtedly play a role, the evidence presented in Table 3-4 suggests that perhaps the earlier in pregnancy antenatal care is received, the lower will be the proportion of premature births. The results of a survey conducted in New York City (Table 3-5) indicated that mothers must be educated to avail themselves of existing facilities for antenatal care earlier in their pregnancies.

Programs for prevention of premature birth need to be organized with coordination of antenatal, labor, and delivery care. In these efforts, medical, nursing, and welfare organizations should cooperate with public-health and welfare pro-

CAUSES AND PREVENTION OF PREMATURITY

grams. The California State Health Department has pioneered in this field and has proposed a plan (see Chap. 25).

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Fetal and Postnatal Development and Growth

Knowledge of some aspects of the growth of premature infants is of practical value to the clinician. As has been said earlier, standards for weight and length at birth are used as indices of maturity. Expected rates of extrauterine growth are also useful as standards by which to evaluate the progress of individual infants. An attempt will be made here to present some of the available growth data. Mere attainment of size, however, does not enable the fetus to exist outside the uterus. The infant must be able to breathe, to use his muscles, to digest, and to excrete, all of which activities are dependent upon the development of bodily organs and the integrity of the nervous system and the circulation. A brief review of development of the embryo and fetus will therefore precede consideration of growth in weight, height, and other over-all physical measurements.

ANTENATAL DEVELOPMENT

ANTENATAL PERIODS

The changes from the embryonic to the fetal period and from the fetal to the postnatal period are not sharply differentiated. In certain structures development *is proceeding even after term birth*. These variations in the antenatal growth of different organs have been described by Ballantyne as follows:

It will probably have already struck the reader that the division of antenatal existence . . . into germinal, embryonic, and fetal periods is not free from error. It is quite evident, for instance, that all the setting up of scaffoldings is not ended at the end of the sixth week, nor yet indeed at the end of the thirteenth; all organogenesis does not take place in the embryonic period, some of it is still going on in the fetal. One part of the organism may be in the embryonic stage while the others are in the fetal phase . . . the skeleton and the limbs are good examples of parts of the body whose embryology, so to speak, does not end with the embryonic epoch, the uterus and teeth are

instances of the projection of the embryonic still further onward, i.e., into postnatal life. Probably no two parts of the developing organism pass out of the embryonic into the fetal condition at just the same time . . . the progress of the growth of a city is not equal throughout; one part, e.g., the suburbs, may be little more than planned when another, e.g., the center, is already built; so in the body, the evolution of the limbs is slower than the development of the head and trunk. Again, the germinal period does not abruptly stop at the end of the first week of pregnancy. the character of abundant, luxurious cell formation which so specially belongs to it is projected through the embryonic and fetal periods, and is seen in postnatal life normally in one organ, the reproductive gland, testicle or ovary.

BODY FORM AND INDIVIDUAL ORGANS

During the first two months of intrauterine life the following developmental changes take place, according to Arcey:

1. Changes in the flexures of the body; the dorsal convexity is lost, the head becomes erect, and the body straight.
2. The face develops.
3. The external structures of the eye, ear, and nose appear.
4. The limbs organize as such, with digits demarcated.
5. The prominent tail of the fifth week becomes inconspicuous both through actual regression and concealment by the growing buttocks.
6. The umbilical cord becomes a definite entity, its embryonic end occupying a relatively diminishing area on the belly wall.
7. The heart, which was the chief ventral prominence in earlier embryos, now shares this distinction with the rapidly growing liver; the two organs determine the shape of the ventral body until the eighth week, when the gut dominates the belly cavity and the contour of the abdomen is more evenly rotund.
8. The neck becomes recognizable, due chiefly to the settling of the heart caudad and the effacement of the branchial arches.
9. The external genitalia appear in their "sexless" condition.
10. The neuromuscular mechanism attains sufficient perfection so that spontaneous movements are possible.

Almost all the internal organs are well laid down at two months; henceforth, until the end of gestation, the chief changes are those of growth and further tissue differentiation.

Arcey states that "after the second month the developing young is commonly called a *fetus*." The fetal development is described by Arcey as follows:

During the *third month* (lunar) the fetus definitely resembles a human being, but the head is still disproportionately large [Figs. 4-1 and 4-5]; the umbilical herniation

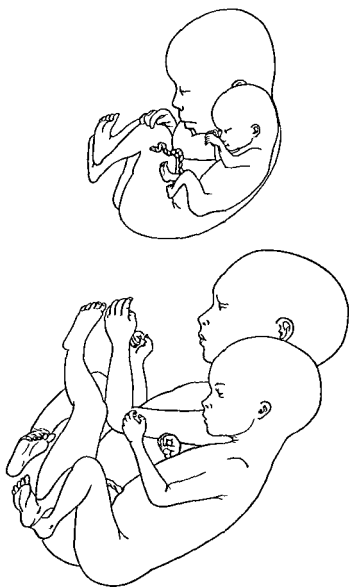


FIG. 4-1. Human embryos and fetuses, 12 weeks, 16 weeks, 5 months, and 6 months old, approximately one-third actual size. [From Patten, B. M.: *Human Embryology*. Philadelphia, The Blakiston Company, 1946.]

is reduced by the return of the intestine into the abdomen; the eyelids fuse, nails begin forming, and sex can now be distinguished readily. At 4 months fetal movements begin to be felt by the mother; the face has a truly "human" appearance. At 5 months hair is present on the head and body. During the sixth month the eyebrows and lashes grow; the body is lean but in better proportion. At 7 months the fetus looks like a dried-up, old person with red, wrinkled skin, the eyelids reopen. In the eighth month subcutaneous fat is depositing; the testes are invading the scrotum. In the ninth month the dull redness of the skin fades, wrinkles smooth out, the limbs become rounded, and the nails project at the finger tips. During the tenth month the body continues to round out, due to the progressive accumulation of fat; the provisional downy hair coat begins to shed, the fetus is now at "full term," ready for birth.

The changes of the various structural components of the human body in antenatal development are depicted in Figure 4-2 in volumetric histograms based upon data collected from the literature by Wilmer.

Changes in growth of organs and tissue differentiation taking place after the second month of fetal age are shown in the following list. Items have been se-

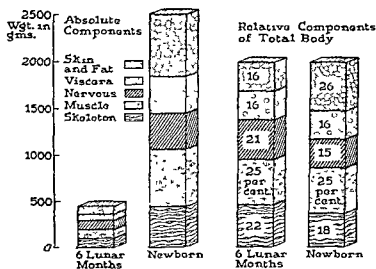


FIG. 4-2. Antenatal growth of human body components. The relative changes in the distribution of structural components between the sixth month of gestation and term are as follows: skin and subcutaneous fat from one-sixth to over one-fourth of body mass; visceral (including heart) and voluntary-muscle components essentially unchanged; nervous tissue and skeletal components a relative decrease. During this interval the net weight of the body increases approximately fivefold, from 500 to 2500 Gm. (From Wilmer, H. A.: Changes in Structural components of human body from six lunar months to maturity. *Proc. Soc. Exper. Biol. & Med.* 43:545, 1940.)

lected from Arcy's table which might be helpful to the physician who wishes to judge the gestational age of a newborn infant and also the changes which have significance from the point of view of function. Since the end of the seventh

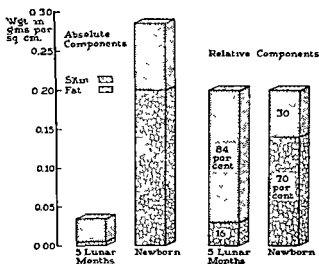


FIG. 4-3. Antenatal growth of human skin and subcutaneous fat. Between the fifth fetal month and term the skin increases about $17\frac{1}{2}$ times in absolute weight, while the subcutaneous fat increases about 196 times. Surface area increases so rapidly during this time interval that in terms of grams per square centimeter of surface the subcutaneous fat increases only about 35 times. (From Wilmer, H. A.: Quantitative growth of skin and subcutaneous tissue in relation to human surface area. *Proc. Soc. Exper. Biol. & Med.* 43:386, 1940.)

month (twenty-eighth week) is the period often considered the earliest at which extrauterine existence is possible, data are given for development up to this time. Numbers in parentheses refer to fetal age in lunar months.

INTEGUMENTARY SYSTEM [Fig 4-3]

- Epidermis three-layered (3)
- Body hair starts developing (4)
- Sweat glands appear (4)
- First sebaceous glands differentiating (4)
- Nail plate begins (5)
- Vernix caseosa seen (5)
- Hairs emerge (6)

MOUTH

- Palate fusion complete (3)

- Enamel and dentine depositing (5)
- Lingual tonsil forming (5)
- Permanent tooth primordia indicated (6-8)

PHARYNX AND DERIVATIVES

- Thyroid attains typical structure (3)
- Thymus forming medulla and becoming increasingly lymphoid (3)
- Tonsil structurally typical (5)

DIGESTIVE TUBE AND GLANDS

- Bile secreted (3)
- Pancreatic islands appearing (3)
- Meconium collecting (4)
- Duodenum and colon affixing to body wall (4)
- Lymph nodules and muscularis mucosae of gut present (5)
- Ascending colon becomes recognizable (6)

RESPIRATORY SYSTEM

- Lungs acquire definitive shape (3)
- Accessory nasal sinuses developing (4)
- Tracheal glands appear (4)
- Elastic fibers appearing in lungs (4)
- Cuboidal pulmonary epithelium disappearing from alveoli (6)
- Pulmonary branching incomplete (7) (only two-thirds completed at term)

UROGENITAL SYSTEM

- Kidney able to secrete (2½)
- Female urogenital sinus becoming a shallow vestibule (5)
- Vagina regains lumen (5)
- Uterine glands appear (7)
- Scrotum solid until sacs and testes descend (7-9)
- Kidney tubules still forming (7) (cease at term)

VASCULAR SYSTEM

- Heart acquires its general definite form (1½)
- Main blood vessels assume final plan (2)
- Enucleated red cells predominate in blood (2½)
- Blood formation in bone marrow beginning (3)
- Heart musculature much condensed (4)
- Blood formation increasing in bone marrow and decreasing in liver (5-10)
- Spleen acquires typical structure (7)

NERVOUS SYSTEM

- Commissures (of brain) completed (5)
- Myelination of cord begins (5)
- Cerebral cortex layered typically (6)
- Cerebral fissures and convolutions appearing rapidly (7)

SENSE ORGANS

- Nasal septum and palate fusions completed (3)
- Nose and ear ossify (5)
- Retinal layers completed and light-perceptive (7)
- Vascular tunic of lens at height (7)
- Eyelids reopen (7-8)
- (See also Chap 16)

FETAL LENGTH AND WEIGHT

The clinician, in assessing the postnatal growth rate of premature infants, wishes to know the rate of antenatal growth at each month of gestation and whether the same rate of growth is to be expected postnatally

Data from numerous studies of antenatal growth are available but they provide a somewhat unsatisfactory foundation for a standard growth curve because of disagreements in observed values and in their interpretation, the small numbers on which some of the studies are based, and fundamental differences in methods of analysis of the data.

Studies of antenatal growth are based largely on measurements of dead fetuses and sometimes, for the later months, on measurements of both dead fetuses and living premature infants. In the earlier studies especially, allowance was not always made for the effects of preservatives on the weight and length of the fetuses. In addition, measurements of fetuses are difficult to make, and techniques of measurement have varied in different studies and with different observers. A drawback inherent in the use of measurements of dead fetuses for establishing growth standards is the fact that normal growth may have been retarded by the conditions that caused fetal death. It therefore seems unnecessary to repeat here all of the data on antenatal growth in weight and length from the earlier studies, but reference will be made to some of those most frequently quoted.

The formation of composite averages of the data of several investigators, although a procedure that has the advantage of large numbers, is a synthesis of measurements obtained by varying techniques which yields dubious results. Among the earlier European studies frequently quoted are those of Daffner, Zangemeister, and Friedenthal. Daffner gave upper and lower limits of weight and length for each month instead of single averages, and the wide limits of his groups provide an interesting indication of the extent of individual variations. His data are comparable with those of Zangemeister, who prepared growth curves for "practical use," showing the average and the upper and lower zones of growth in weight and length for each lunar month of antenatal life, together with the average weight and length of 11,181 term infants (tenth month).

TABLE 4-1. ANTENATAL GROWTH IN LENGTH

Conceptional age (lunar month)	Average crown-heel length (cm)			% increase over previous month ^a		
	Mall ¹²	Scammon & Calkins ¹⁹	Ylppö ¹⁸	Mall ¹²	Scammon & Calkins ¹⁹	Ylppö ¹⁸
1	0.3		0.7			
2	3.0		2.8	1100		300
3	9.8	8.0	8.0	227		186
4	18.0	15.9	13.7	84	99	71
5	25.0	22.9	21.5	39	44	57
6	31.5	29.2	30.1	26	28	40
7	37.1	35.1	35.6	18	20	18
8	42.5	40.6	40.2	15	16	13
9	47.0	45.7	45.0	11	13	21
10		50.5	50.0		11	11

^a Calculated by the Children's Bureau.

Zangemeister's averages were based on the combined numerical data of earlier investigators. Friedenthal also combined measurements from various studies in presenting monthly averages for antenatal weight and length. Ylppö's growth data likewise are based on the research of previous investigators, and are shown in Tables 4-1 and 4-2.

In the United States the chief sources of information on antenatal growth in length and weight are the data presented by Mall,¹² Streeter, and Scammon and Calkins.¹⁹

Length at Given Fetal Ages

For the length of the fetus some investigators have used crown-rump and others, crown-heel measurements, and formulas have been devised to convert numerical values from one to the other.

Mall¹¹ stated that obstetricians and embryologists give as standard measurement the crown-heel length after the fetus has been straightened out more or less. But, in his opinion, the crown-rump measurement should be used "for the present" as the standard. Mall's data¹² for length of the embryo and fetus were based on more than 1000 measurements, about half from his own collection and the remainder from published sources and from correspondence.

However, Scammon and Calkins,¹⁹ after experimental and statistical studies^{17,18} of actual measurements of "preserved, fresh-dead, and living material,"

concluded that the "error in determination of crown-heel length . . . seems somewhat less, relatively, than that of crown-rump length." They calculated the crown-heel length by measuring 2202 dead embryos and fetuses.^{17,18}

Data from these investigations and those by Ylppö are given in Table 4-1. It can be seen that there is considerable variation in the values which were obtained by the different observers

Weight at Given Fetal Ages

Data on weight gathered by Streeter, Scammon and Calkins, and Ylppö are presented in Table 4-2. As with length, there is considerable variation in the reported mean values for body weight.

TABLE 4-2 ANTENATAL GROWTH IN WEIGHT

Conceptional age (lunar month)	Average weight (Gm)			% increase over previous month ^a		
	Streeter	Scammon & Calkins ¹⁸	Ylppö ¹⁷	Streeter	Scammon & Calkins ¹⁸	Ylppö ¹⁷
1			1			
2	1		3			240
3	14	12	30	1191	231	779
4	108	73	92	661	508	209
5	316	256	254	193	251	176
6	630	561	633	99	119	149
7	1045	988	1150	66	76	82
8	1680	1537	1645	61	56	43
9	2478	2208	2281	48	44	39
10	3405	3001	3066	37	36	34

^a Calculated by the Children's Bureau

Relationship between Length, Weight, Surface Area, and Fetal Age

Streeter presented data on antenatal weight and crown-rump length based on a study of 704 fetuses with a menstrual age of 2 to 7 lunar months and on figures adapted from Zangemeister for the last 3 months of antenatal life. He did not present sex-specific data because he considered that the total number of fetuses available was too small to warrant conclusions. In regard to race, since by far the greater number (493) were white, he concluded that other races "were not sufficiently represented to alter appreciably the general results." The weight recorded

was the "Formalin weight," that is, weight of the fetus after fixation with Formalin. This was estimated as approximately 5 per cent greater than fresh weight, and for this reason 5 per cent was added to the values taken from Zangemeister.

On the basis of their own measurements and the data of Mall, Scammon and Calkins presented formulas for calculating the lineal growth of the human fetus for certain age periods,¹⁶ the relation between body length and body weight,¹⁷ and the relation between body weight and age.¹⁸ The authors considered their formulas accurate from the fetal age of 2½ months. Their data are based on measurements of 2202 dead embryos and fetuses and, for the purpose of comparison, on 5674 computations on an unspecified number of "living fetuses and

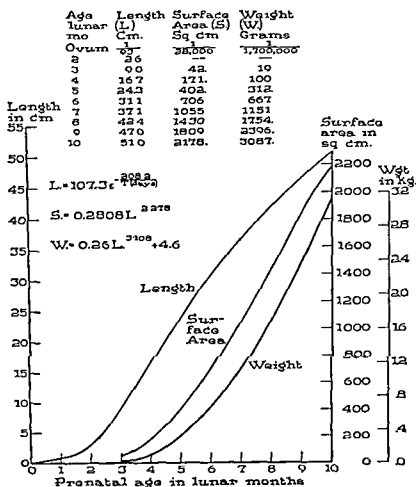


FIG 4-4. Calculated trends of three major dimensions in the antenatal period. (Calculated from Scammon and Calkin's formulas, from Boyd, E.: *Outline of Physical Growth and Development*. Minneapolis, Minn., Burgess Publishing Co., 1941.)

newborn children." They found that the weights of live-born and stillborn fetuses of the same length were different; the live-born being heavier. They did not give data for the sexes separately, but they stated that "no consistent sex difference in the relation of body weight to body length was noted in either the living or the dead material"

The trends of antenatal growth in weight, length, and surface area calculated from Scammon and Calkins' formulas are shown graphically in Figure 4-4.

GROWTH OF THE FETAL HEAD

In fetal life growth of the head proceeds at a very rapid rate, which is greater in the earlier months of pregnancy. The head comprises about half the body length at the second fetal month, about one-third in the fifth month, and about one-fourth at term (Fig 4-5) The measurements of the head that are particularly useful clinically are the occipitofrontal diameter and circumference.

Occipitofrontal Diameter. Scammon and Calkins¹⁹ have reported the rela-

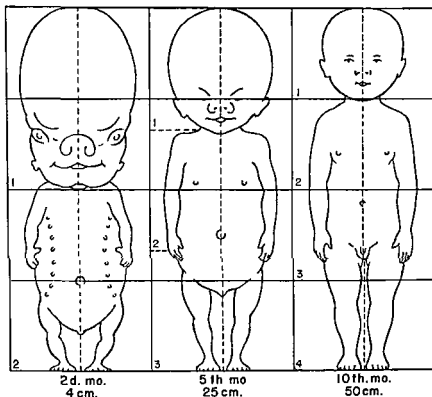


FIG. 4-5. The changes in body proportions in fetal life. (From Stratz, C. H.: *Wachstum und Proportionen des Fötus. Ztschr. Geburtsh u Gynak.* 65:36, 1910.)

tion of the occipitofrontal diameters of the heads (glabella to inion) to the body length in 369 dead fetuses and infants. The observed and the calculated diameter—to allow for the effect of birth molding and of preservation—are shown in Table 4-3.

TABLE 4-3. OCCIPITOFONTAL DIAMETER OF THE HEAD BY CROWN-HEEL LENGTH
369 Dead Fetuses and Infants

Mean crown-heel length (cm.)	No. cases	Occipitofrontal diameter (cm.)			
		Observed range		Observed mean	Calculated mean
		Max	Min		
3.7	17	1.8	1.0	1.4	1.3
7.5	29	2.7	1.4	2.2	2.2
12.4	45	3.9	2.6	3.3	3.3
17.3	28	5.1	3.8	4.5	4.5
22.5	52	6.8	4.8	5.8	5.7
27.2	46	7.8	6.0	6.9	6.9
32.4	36	9.0	7.1	8.0	8.0
37.1	36	10.1	7.9	8.9	9.1
42.4	29	11.5	8.7	10.0	10.4
47.1	24	12.3	9.9	10.9	11.5
52.3	27	12.9	10.5	11.7	12.7

From Scammon and Calkins¹⁹

The differences between the observed means and the calculated means are slight except in the more mature infants, in whom the differences are attributed by the authors to birth molding. For an average body length at birth of 50.2 cm (not shown in Table 4-2), Scammon and Calkins¹⁹ reported a head diameter of 11.2 cm. for "fresh dead" infants, 12.1 cm. for infants with unmolded heads, and 12.2 cm. as calculated to allow for molding.

Occipitofrontal Circumference. The data of Scammon and Calkins¹⁹ for observed and calculated head circumference of 367 dead fetuses and infants of specified mean crown-heel lengths are shown in Table 4-4.

FETAL ORGAN WEIGHTS

Potter and Adair presented the mean weights of individual organs by birth weight, as determined at the time of postmortem examination, of more than 1000 fetuses and infants who showed no evidence of malformation, infection, or maceration at the time of death. Infants more than two days of age were

TABLE 4-4. OCCIPITOFRONTAL CIRCUMFERENCE OF THE HEAD BY CROWN-HEEL LENGTH
367 Dead Fetuses and Infants

Mean crown-heel length (cm)	No cases	Occipitofrontal circumference (cm)			
		Observed range		Observed mean	Calculated mean
		Max	Min		
3.7	16	4.9	2.6	3.8	3.8
7.5	29	7.6	4.2	6.2	6.4
12.4	45	11.3	7.6	9.6	9.7
17.3	28	14.6	10.7	13.2	13.0
22.5	52	19.4	14.2	16.7	16.5
27.2	46	22.5	17.3	20.0	19.7
32.4	36	26.1	20.4	23.3	23.2
37.1	35	29.3	23.4	26.0	26.3
42.4	29	31.2	25.5	29.1	29.9
47.1	24	36.4	28.8	32.3	33.1
52.3	27	37.3	32.0	34.9	36.6

From Scammon and Calkins¹⁹

excluded from this series. However, the variability around the mean values was not presented. Data obtained more recently are given in Appendix 13.

POSTNATAL GROWTH

Interpretation of Growth Data

Adequate data for postnatal growth in weight and length are available for term infants, but for premature infants the information is less satisfactory. Since premature infants are born at varying periods before term, it has been customary to compare their postnatal growth with antenatal growth curves. The only procedure that is completely satisfactory for establishing standards for growth rate is measurement of the same infants repeated at stated intervals. This is obviously impossible in the antenatal period; and repeated measurements of live-born premature infants in the neonatal period have been made by few investigators, whose results are sometimes not comparable because of differing techniques. Moreover, only the average values are presented in many of the studies. Investigators have found wide variation among individual infants, which must be taken into consideration in judging the gain to be expected in a given case.

The postnatal growth of premature infants can be measured most conveniently

by serial determinations of weight, head circumference and length. Other methods^{3, 7} of measuring changes in body size may also be employed but they are not convenient for routine use.

Much of the information on postnatal growth of the premature infant found in English-language textbooks is taken from the earlier European studies. A few studies are reported of measurements of North American premature infants. The data from both sources are somewhat unsatisfactory in coverage and methods. The obviously important factors influencing size (length and weight) of infants, which have not all been considered in any one study reported, are:

1. *The parents:* race, height and weight, and economic status; mother's age, parity, and general health and nutrition (especially during the antenatal period).

2. *The infant:* sex, single or plural birth, health and nutrition, birth weight, maturity, feeding, and environmental conditions.

3. *Conditions of the study:* regularity of measurements, qualifications of observers, number of cases adequate for separate study of race, sex, and birth-weight groups, comparable control material (for a discussion of the choice of appropriate controls in studies of premature infants see Chap. 5).

Factors Influencing Growth

The growth of the premature infant in the neonatal period is influenced by some of the factors that influence birth weight—race, the state of health, feeding, the environment of the infant, and certain maternal factors (see Chap. 2).

Atmospheric Conditions. Blackfan and Yaglou studied the gain in body weight of premature infants under controlled atmospheric conditions (Fig. 4-6). They observed that when small infants (under 2.0 kg.) were exposed to 50-75 per cent relative humidity for more than one week, weight gain was more rapid and digestive upsets occurred less frequently than among controls in 25-49 per cent relative humidity. The importance of increased humidity was less with a higher body weight and appeared reversed in large infants. There have been no controlled studies of the influence of higher humidities than those used in the trials of Blackfan and Yaglou.

Hormone Preparations. From time to time interest is expressed in the use of hormones (principally testosterone and thyroid substances) to stimulate the growth of premature infants. Despite favorable clinical impressions that have been reported, there is no convincing evidence of a significant growth-promoting effect of any available hormone preparation.

Testosterone. Agerty and Seitchik conducted a controlled trial of the influence

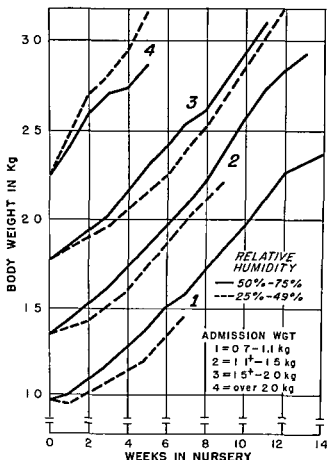


FIG. 4-6. Comparative weight gain of premature infants by birth-weight groups under two conditions of atmospheric humidity. Infants who weighed less than 2.0 kg. gained more rapidly in 50-75 per cent relative humidity than in atmospheres of lower humidity; the reverse was true of the infants whose weight on admission was 2.0 kg. or over. (Redrawn from Blackfan, K. D., and Yaglou, C. P.: The premature infant: A study of the effects of atmospheric conditions on growth and on development. *Am. J. Dis. Child.* 46:1175, 1933.)

of methyltestosterone and testosterone on the growth of premature infants, using a population of 100 children who weighed 1.8 to 2.3 kg at birth. No significant influence on weight gain was observed.

Thyroid Hormone Stevenson and others reported the results of a double-blind controlled study of the effects of thyroid hormone on premature infants. Forty-eight subjects whose weights approximated 1500 Gm were enrolled in the study at one week of age, the controls received lactose and the treated infants received desiccated thyroid (60-180 mg per day) or thyroxine (0.2 mg per day). Daily doses of 60 to 120 mg of desiccated thyroid produced no significant effect upon the infants' clinical condition. However, desiccated thyroid 180 mg per day or thyroxine 0.2 mg per day resulted in less weight gain, increased pulse rate, and a higher incidence of diarrhea as compared with controls. The authors concluded that the administration of thyroid hormone to premature infants was without recognizable benefit and was sometimes harmful.

Adrenocorticotropin. We observed that a group of premature infants virtually stopped growing when they received adrenocorticotropin (ACTH) in daily doses greater than 5 mg. per kg.²⁰ Increased caloric intake failed to alter the growth-inhibiting effect of ACTH. Marked increase in growth ("rebound") took place when ACTH was discontinued.

Growth Hormone. Grumbach and Ducharme administered growth hormone prepared from human pituitary glands to five premature infants. Although the blood sugar was significantly elevated following the injections of growth hormone, there was no appreciable influence upon growth. In one infant whose growth was arrested by ACTH, growth hormone had no demonstrable counter-acting effect.

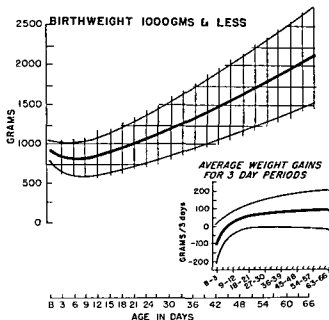
POSTNATAL WEIGHT AND LENGTH

From the point of view of clinical use of the available material comparing antenatal with postnatal growth, a fundamental question is whether the healthy premature newborn infant tends to gain at approximately the same rate as the fetus of the corresponding conceptional age (see Tables 4-1 and 4-2). Within the limitations already discussed, the results of many earlier studies indicated such a growth tendency, though some retardation was demonstrated for varying periods.

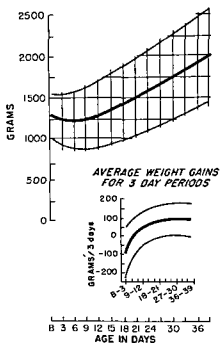
Scammon compared monthly weight-increment rates of 78 premature infants with his calculated norms for fetal growth. He concluded:

These results indicate that premature children, after a short period of retarded growth incident to the adjustment to the extrauterine environment, tend to regain the fetal rate of growth and to follow this course of growth until some time in the latter part of the first year, when the rates of fetal and postnatal growth approximate one another. In other words, the growth tendency of prematures is in general that of fetuses of the same size and age rather than that of full-term children.¹⁵

Ylppö²⁴ studied the growth of 700 premature infants, nearly half of whom died before the end of the first year of life. He compared the growth of the premature infant with an intrauterine-growth curve and with figures for growth of the term infant. Almost all of Ylppö's group of premature infants showed disturbances of growth in both weight and length. At three months after birth the most premature infants (birth weight less than 1000 Gm.) weighed 1600-2000 Gm., compared with the 3000 Gm. that Ylppö took as the average weight of an infant 9 months in conceptional age. Though the smallest infants showed the greatest retardation, all the premature infants studied, except a few in the higher weight groups, showed a retardation in growth that was not overcome for



BIRTHWEIGHT 1001-1500GMS



BIRTHWEIGHT 1501-2000GMS

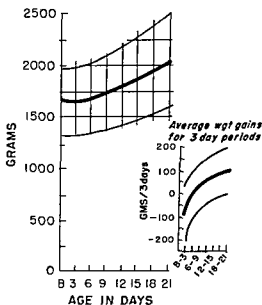


FIG. 4-7. Body weights at given ages and increments of weight gain for three-day periods for 235 apparently healthy surviving infants in the premature nursery of Babies Hospital, New York City (see Appendix 9). Arithmetic means and two standard deviation limits are depicted (graphic smoothing) for three birth-weight classes. All received cow's-milk formulas (see Chap. 10). No significant sex and color differences were observed.

a considerable period. For a discussion of the growth of exprematures beyond the first three months of life see Chapter 5.

Weight Gain During Nursery Stay. Weight gain of premature infants during their stay in the premature nursery of Babies Hospital, New York City, is shown in Figure 4-7. More detailed growth data are given in Appendix 9.

POSTNATAL GROWTH OF THE HEAD

As has been noted (see Chap. 1), the head of the premature infant at birth has a considerably greater circumference than the thorax. Average ratios between the chest circumference and head circumference of infants of different birth weights were determined by Ylppö²⁴ and these are given in Table 4-5

TABLE 4-5. AVERAGE HEAD AND THORAX CIRCUMFERENCES AND RATIO OF THORAX TO HEAD CIRCUMFERENCE AT BIRTH, BY BIRTH WEIGHT GROUPS
243 Premature and 100 Term Infants

<i>Birth weight group (Gm.)</i>	<i>No infants</i>	<i>Average circumference of head (cm.)</i>	<i>Average circumference of thorax (cm)</i>	<i>Ratio of thorax to head</i>
1000 or less	16	25.0	20.8	.83
1001-1500	78	31.8	24.5	.77
1501-2000	75	30.0	26.3	.88
2001-2500	74	32.3	29.5	.91
3000-3500	100	33.5	31.0	.93

From Ylppö.²⁴

The disproportion between the rate of growth of the premature infant's head and that of the rest of his body after birth is responsible for the megacephalus²⁵ (or so-called pseudohydrocephalus) of prematurity. In the first weeks of life it is a matter of some importance to distinguish between rapid normal growth of the head, particularly in small premature infants, and an abnormally rapid rate of increase as the result of intracranial abnormality. In an attempt to establish the extent of normal variations in the first month of life among small subjects, Parke obtained serial measurements of the circumference of the head of 208 apparently normal surviving premature infants weighing 2.0 kg. or less at birth (Tables 4-6 and 4-7). No significant sex and color differences were observed in this study. Appendix 9 contains further data on the growth of the head.

TABLE 4-6 OCCIPITOFRONTAL HEAD CIRCUMFERENCE^a AT BIRTH AND AT WEEKLY INTERVALS IN THE FIRST MONTH OF LIFE

Age	Birth weight groups								
	1000 Gm. and less			1001-1500 Gm.			1501-2000 Gm		
	N ^b	Mean (cm)	S D. ^c	N	Mean (cm)	S D.	N	Mean (cm)	S D
Birth	17	24.6	±1.1	86	27.7	±1.3	105	30.0	±1.1
7 days	17	24.4	±1.4	86	27.7	±1.6	105	30.1	±1.3
14 days	17	24.8	±1.5	86	28.5	±1.7	105	30.9	±1.4
21 days	17	25.8	±1.6	86	29.5	±1.8	99	31.7	±1.3
28 days	16	26.7	±1.7	72	30.5	±1.8	62	32.3	±1.2

Obtained by Priscilla C. Parke, R.N., Babies Hospital, N.Y., in "normal" infants who survived the first month of life.

^a Largest horizontal circumference. ^b N = number of infants. ^c S D = standard deviation.

TABLE 4-7 WEEKLY INCREMENTS OF INCREASE OF THE OCCIPITOFRONTAL HEAD CIRCUMFERENCE^a IN THE FIRST MONTH OF LIFE

Age interval	Birth weight groups								
	1000 Gm. and less			1001-1500 Gm			1501-2000 Gm		
	N ^b	Mean (cm)	S D. ^c	N	Mean (cm.)	S D.	N	Mean (cm.)	S D
Birth-1 week	17	-0.3	±0.5	86	0.1	±0.6	105	0.1	±0.7
1-2 weeks	17	0.4	±0.3	86	0.7	±0.4	105	0.8	±0.4
2-3 weeks	17	0.9	±0.4	86	1.1	±0.4	99	1.0	±0.3
3-4 weeks	16	0.9	±0.4	72	1.0	±0.3	62	0.9	±0.4

Obtained by Priscilla C. Parke, R.N., Babies Hospital, N.Y., in "normal" infants who survived the first month of life.

^a Largest horizontal circumference. ^b N = number of infants. ^c S D = standard deviation.

OTHER INDICES OF POSTNATAL DEVELOPMENT

There is increasing interest in other indices of development that may be of at least equal importance with increase in size of these infants during the postnatal period. The rate of neurologic maturation is receiving considerable attention, and the technique of its measurement is being developed (see Chap. 8).

As Kretchmer has indicated, measurements of the activities of critical enzymes in premature infants will very likely serve to establish important new indices of postnatal development.

Time of Eruption of Deciduous Teeth. The time of eruption of deciduous teeth in ex-premature children has not been extensively investigated. In the Fetal Life Study at Columbia University it was found that the mean age at the time of eruption of the first tooth was greater for premature than for term infants (Table 4-8). These data were obtained by anamnesis and corroborated by evidence from examinations at 6 and 12 months of age; as compared with term infants the ex-premature group had fewer erupted teeth present (Fig. 4-8).

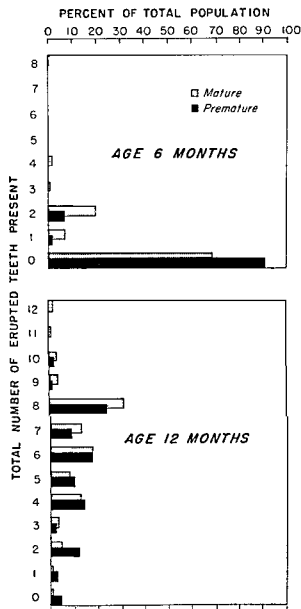


FIG. 4-8. Percentage distribution of ex-premature children and term controls at 6 months of age (219 ex-prematures, 2541 controls) and 12 months of age (222 ex-prematures, 2591 controls) by number of erupted teeth present. (From unpublished data of Mellin, G. W., Rosenstein, S. N., Merritt, K. K., and Downs, E. F.: Fetal Life Study, Columbia University, College of Physicians and Surgeons, New York.)

TABLE 4.8 TIME OF ERUPTION OF FIRST TOOTH, BY BIRTH WEIGHT

Birth weight (Gm)	No. children	Mean age ^a (mo)	S D
Term (2501 or more)	2505	7.2	±1.9
Premature			
2001-2500	145	7.9	±1.8
1501-2000	58	8.2	±2.1
1001-1500	11	10.3	±1.8
1000 or less	2	12.0	..

From unpublished data of G. W. Mellin, S. N. Rosenstein, K. K. Merritt, and E. F. Downs
Fetal life study, Columbia University, College of Physicians and Surgeons, New York, N.Y.

^a Mean chronologic age (in calendar months) at time of eruption of first tooth, as reported by mother

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Prognosis of Prematurity

SURVIVAL

In general terms, the prognosis for infants in the higher birth-weight groups (above 1500 Gm.) is excellent, for the group of infants weighing 1001-1500 Gm. the prognosis is good, for those weighing 1000 Gm. or less the prognosis for life is unfavorable. This subject is discussed in detail in Chapter 24.

Karn and Penrose reviewed the records of nearly 14,000 newborn infants and analyzed the combined effects of birth weight and gestation time on survival to 28 days of age. On the basis of their calculations, diagrams were prepared for estimating the survival rate for any given birth weight and gestational age. These are shown for males in Figure 5-1 and for females in Figure 5-2.

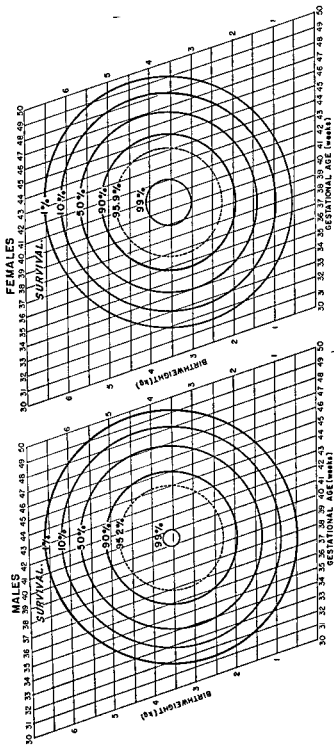
There is a general impression that survival rates of premature infants have improved in recent years. Data to support this impression are available (see Chap. 24), they indicate that the greatest improvement has occurred among the larger babies.

LATER PHYSICAL DEVELOPMENT

Interpretation of Available Data

There are two methods of approach to studies of growth in size: longitudinal studies, or serial measurements of the weight and length of individual infants made at intervals over a period of time; and cross-sectional studies based on averages of the weights and lengths of infants at different ages. In most cross-sectional studies the averages at each age level are not based on measurements of the same infants.

Criteria of Optimal Growth. Before discussing the results of growth studies it must be admitted that no entirely satisfactory norms for growth of premature infants have been established. A definition of the optimal rate of growth of premature infants has not yet been established, and it is by no means certain that change in body size furnishes the best clue to the state of nutrition of these



Figs. 5-1 (left) and 5-2 (right). Percentage survival to age 28 days of male and female infants of given birth weight and gestational age. The ring of dashes denotes the boundary on which the mortality of males is, on the average, 4.83 per cent, and of females, 4.09 per cent. (Adapted from Karn, M. N., and Penrose, L. S.: Birth weight and gestation time in relation to maternal age, parity and infant survival. *Ann. Eugenics* 16: 147, 1951.)

children (see Chap. 10). However, for the present we shall have to be content with measurements of the bodily dimensions.

Criticism of Earlier Studies. Many long-term studies of the physical growth of expremature children have been conducted during the past forty years. For a critical survey of the publications on this subject between 1913 and 1952 the reader is referred to the monograph by Alm. The results of the studies are conflicting, and there is still considerable controversy concerning the physical prognosis of prematurity.

Douglas and Mogford¹⁰ offered possible explanations for the confusion. They noted that few investigators were able to trace more than half the survivors of premature birth after a lapse of years. As a result there can be no assurance that those who were traced constituted a representative sample.

A major difficulty has been the choice of a control population. As Douglas and Mogford¹⁰ pointed out, premature children tend to be female, to be first born, to come from poorer classes, and to have mothers whose age is different from the average age for child bearing. Unless they are compared with mature children chosen to conform to this pattern, it is difficult to interpret the results. Often the expremature child is compared with a sibling, who obviously cannot be of the same age or birth order, and often is not even of the same sex. Since there has been considerable variation in the composition of the control populations in published studies, it is not surprising that the conclusions from follow-up studies have not been uniform.

GROWTH IN INFANCY AND CHILDHOOD

Weight and Height

One of the first studies of growth of premature infants was published in 1919 by Ylppo, who reported the results of repeated weights and measurements of 700 premature infants in four birth-weight groups. He found that in the first three to five years of life the weight and length of nearly all the premature infants remained lower than the weight and length that he accepted as normal for children of equal conceptional age who were mature at birth. The delay in growth among the premature children was inversely proportional to the weight and length at birth.

Mohr and Bartelme obtained serial measurements of 250 expremature white children who were born between 1922 and 1933. The study group was selected for the most part at random as they came through the nursery and clinic. The growth of these survivors was compared with that of 150 of their siblings. The

authors concluded that there was very little difference in weight and height after 3 years of age. Persistent though slight differences suggested that the group weighing 1500 Gm. or less at birth tended to remain smaller and lighter than their siblings.

Drillien¹⁵ in 1948 reported the first of a series of follow-up studies of the growth in height and weight of 103 premature infants born in England; 174 concurrent controls were selected in modified random order from the full-term population. She found that at any given age in the preschool period, follow-up weights continued higher among the infants with the higher birth weights. A similar trend was observed for follow-up height. Illingworth and co-workers also observed a correlation between birth weight and the body dimensions of 238 children aged 5 to 8 years.

Douglas and Mogford¹¹ conducted a study of the growth of legitimate, single-born, premature children from birth to 4 years. These children were born in England, Wales, and Scotland during the first week in March, 1946. Each premature child was paired with a full-term singleton born (in wedlock) during the survey week, of the same sex and place in the family, living in the same locality, with its mother of the same age and from a family in the same social group. Twenty-one children weighed 1500 Gm. or less at birth. The children were measured at birth, when they were 2 years old and again when they were 4 years and 3 months. Of 676 pairs (premature and control) enrolled in the study, measurements for both members of the pair were available in 350 to 375 sets in the follow-up surveys. The degree to which the expremature children lagged behind their controls in either weight or height at 4½ years did not differ in the two sexes. As a group, at the final follow-up age the prematurely born children were lighter and shorter than the controls. Expremature children whose weight had been low at birth appeared to be no more stunted than were those who were heavier at birth. However, the number of surviving children of very low birth weight was too small to permit a firm conclusion on this point.

The proportions of expremature children in Douglas and Mogford's¹¹ study who caught up with their controls at age 2 and age 4½ years are given (by birth weight) in Table 5-1. The children who weighed 1.8 kg. or less at birth appeared to be the least successful in overtaking the controls at 2 years, but at 4½ years they were the most successful in achieving this.

Studies of the growth of infants of low birth weight (1500 Gm. or less)^{8, 16, 22, 27} are difficult to interpret because relatively few individuals are available for follow-up and because there is considerable uncertainty about the choice of appropriate controls for these highly selected groups of survivors.

Other Measurements

Speirs presented the results of a cross-sectional anthropometric study of 217 prematurely born and 222 full-term Glasgow children aged 5 years. Fourteen of the children weighed 1500 Gm. or less at birth. The expremature children represented 69 per cent of survivors born in one hospital in 1949; the controls were obtained by tracing every fifth mature child dismissed from the hospital during

TABLE 5-1 PERCENTAGE OF EXPREATURE CHILDREN WHO OVERCAME
WEIGHT OR HEIGHT HANDICAPS BY 2 AND 4½ YEARS

Birth weight of premature (kg)	Weight handicap overcome		Height handicap overcome	
	By age	By age	By age	By age
	2 yrs	4½ yrs	2 yrs	4½ yrs
1.8 or less	21 ^a	42	32	47
1.8-2.0	34	41	57	45
2.0-2.3	34	32	42	42
2.3-2.5	31	36	45	44
All prematures	31	36	44	44

Adapted from Douglas and Mogford ¹¹

^a Percentage of expremature children who caught up with their matched maturely born controls

the same period. There was a slight bias toward poor social class in the prematurely born group. The mean values of height, weight, sitting height (in girls), biacromial diameter, and bi-iliac diameter were all significantly smaller in the expremature children. Subcutaneous-fold thickness in both sexes and sitting height in boys were not significantly different in the expremature and mature groups.

The results of a series of measurements of weight, length, and head circumference from birth to one year in a group of Negro premature infants are summarized in Appendix 9.

Associated Factors

Douglas and Mogford ¹¹ found that the mothers of premature children were on the average shorter and lighter than the mothers of the controls. However, the mothers of those expremature children who at 4½ years had caught up in height and weight were as large as the mothers of the controls. They concluded that the height of the mother gave a better indication of the likely

growth pattern of her premature baby than birth weight, medical history of the pregnancy, or the length of gestation.

Drillien^{17, 18} conducted an extensive investigation of the growth in height and weight of 595 premature and maturely born children delivered in Edinburgh in the years 1953 to 1955. Fifty-four weighed 1500 Gm. or less at birth. The children were measured at birth and at 6, 12, 18, and 24 months of age. Throughout the two-year period mean weights were closely related to birth weight. Drillien evaluated the relative influences of parental stature and environmental factors (diet, illness, social class, and maternal efficiency) on growth. She concluded that genetic and environmental factors were intercorrelated to a high degree and that these factors were of approximately equal importance in their influence on the rate of growth in the first two years of life after premature birth.

SIZE AS ADULTS

Alm obtained the measurements of 999 adult males in Stockholm who had been born prematurely between 1902 and 1921. Relatively few of these men had been small premature infants (21 had a birth weight of 1500 Gm. or less). A control series was obtained by selecting from maternity-hospital records the male whose term birth in the same maternity hospital followed each premature birth chosen for study. Only those born in wedlock were included. The distribution of children with respect to the social group of the father was essentially the same in the prematurely born and control groups. Measurements obtained at the time of enrollment in military service revealed that 407 expremature men were slightly but significantly smaller and lighter than 645 controls (Table 5-2). Adult size

TABLE 5-2 MEAN HEIGHT AND WEIGHT OF EXPREMATURES AT 20 YEARS OF AGE^a

Birth weight (Gm.)	Height (cm.)			Weight (kg.)		
	No	Mean	S.D.	No	Mean	S.D.
Premature						
1010-2000	44	171	±9	35	61	±7
2010-2250	117	173	±6	99	64	±7
2260-2500	246	173	±7	206	65	±8
Term						
2760-3250	219	174	±6	183	66	±7
3260-3750	426	176	±6	357	67	±7

From Alm.¹

^aAt enrollment in military service, in almost every case at the age of 20 years, single births only.

(height and weight) was related to birth weight in both the prematurely born and term groups

MENTAL DEVELOPMENT

In the care of premature infants the physician needs a basis for giving a prognosis for mental and emotional development and he needs to know the factors that may influence the prognosis for the individual infants under his care (Fig. 5-3)



FIG. 5-3. Two exprematures. Child at left weighed 1247 Gm. at birth, she had numerous bouts of apnea and cyanosis during the first few weeks of life. At $2\frac{1}{2}$ years of age (shown here) she exhibited severe mental retardation; no specific abnormal neurologic signs were present. Child at right weighed 1000 Gm. at birth, her neonatal course was practically the same as that of A. At $2\frac{1}{2}$ years of age (shown here) she was bright and active, neurologic examination was normal

A large number of studies to determine the mental development of premature infants have been made. In 1940 Benton published a critical review of American and European studies since 1911, reporting marked divergence of opinion in the published literature. He suggested that the discrepancies were the result of (1) use of "clinical impression" and other subjective criteria instead of standardized tests, (2) little attention paid to the socioeconomic character of the children under study, (3) inadequate numbers and unsatisfactory controls, (4) selective nature of the sample

Preschool Children

Some of the large-scale investigations conducted since 1940 will be reviewed. In Drillien's¹⁹ longitudinal study of 595 prematurely and maturely born children described a little earlier in this chapter, mental development was assessed at six-month intervals to the age of 2 years. The observed developmental level was related to birth weight at all ages. Twins had consistently lower scores than did single-born children. At 2 years there was a markedly high proportion of dull, retarded, and grossly defective children in the birth-weight groups of 2.0 kg. and less.

Prematurely born children in the Edinburgh study¹⁹ were slower in learning to walk and talk. These assessments, made on the basis of observations of the children at 12, 18, and 24 months, confirmed earlier findings which were based on mothers' reports^{13, 15}. In this connection Drillien¹⁹ found that mothers of premature and retarded infants were particularly likely to be inaccurate in timing the milestones of development.

Knobloch and co-workers gave Gesell developmental tests to 992 infants at 40 weeks of age. Five hundred prematurely born singletons and 492 term controls were matched on the basis of race, season of birth, parity of mother, hospital of birth, and socioeconomic status. Fifty-six children weighed 1500 Gm. or less at birth. This study revealed a relationship between prematurity and lowered intellectual potential at 40 weeks of age. These conclusions were confirmed in repeat examinations of 900 of these children at 3 to 4 years of age (Table 5-3). The proportion of prematurely born children in the dull normal, borderline defective, and defective categories was greater than in the full-term group. The children whose birth weights had been lowest (1500 Gm. or less) were disproportionately represented in all the below-average categories.

School-age Children

Asher and Roberts tried to find a relationship between birth weight and intelligence of school children. They obtained the birth weights and the IQs of 4800

TABLE 5-3 INTELLECTUAL POTENTIAL OF EXPREATURE AND TERM CHILDREN AT 3 TO 4 YEARS

Birth weight (Gm.)	No subjects	% in each diagnostic category								Total
		Superior	High average	Average	Low average	Dull normal	Border- line defective	Defec- tive	Indeter- minate, Indeter- not defec- tive	
Premature										
1500 or less	54	1.9	3.7	24.1	20.4	16.7	7.4	13.0	9.3	100.2
1501-2500	406	5.2	11.6	29.8	16.0	15.0	4.9	2.0	12.6	100.1
SUBTOTAL*	460	5.0	11.2	29.5	16.2	15.1	5.0	2.6	12.4	100.0
Term										
2501 and over	440	6.1	19.3	35.7	16.4	9.1	2.0	0.9	8.2	100.0
TOTAL	900									

Courtesy of Paul A. Harper, M.D., and Rowland V. Rider, Sc.D. Study of Prematures, The Johns Hopkins University, Maternal and Child Health Division.

* Adjusted for birth weight distribution

children attending regular schools and 877 children in special schools for the educationally subnormal, and the birth weights of 343 "certified" mental defectives. They found that the children attending special schools for the educationally subnormal and the certified mental defectives had lower mean birth weights than the normal children. This was attributed by them to an excess of very low birth weights among the subnormal and defectives. This excess increased steadily with the fall of the birth weight. For example, there were four times as many low birth weights (i.e., below 1247 Gm. for girls, and 1474 Gm. for boys) among the children who were mentally below normal as there were among the mentally normal.

Blegen examined the scholastic records of 150 expremature children who had completed their primary schooling and the records of a corresponding number of term controls. In practical subjects (sewing, woodworking, and metalworking) achievement was similar in the two groups. However, in the scholastic subjects the students who had been prematurely born appeared to be at a disadvantage.

Eames investigated the speed of seeing and recognizing objects and words in 25 school children whose birth weight had been 2500 Gm. or less and in an equal number of term controls. Words and objects were projected on a screen for varying time periods, the speed was gradually reduced until the child was just able to recognize the test subject. As compared with the controls, children in the premature group recognized objects and words slowly. The results of these

studies suggested to the author that prematurity was an important handicap in learning

Douglas¹² reported the results of tests given to the children in the British National Survey¹¹ (described earlier) when they reached eight years of age. Reading, word comprehension (vocabulary), and the ability to appreciate relationships (picture intelligence) were evaluated in tests specifically designed for this inquiry. Eight pairs of children could not be tested because of educational subnormality; the expremature child was the affected member of the pair in six of the eight pairs. The prematurely born children also predominated among those not tested due to illness or physical handicap. In the tested group, expremature

TABLE 5-4 INTELLIGENCE TEST SCORES^a OF EXPREATURE CHILDREN AND CONTROLS AT 8 YEARS OF AGE

	<i>Mechanical reading (407 pairs)</i>	<i>Vocabulary (407 pairs)</i>	<i>Picture intelligence (406 pairs)</i>
Exprematures	13.65	14.47	36.82
Matched controls	16.55	15.47	39.83
Difference	-2.90	-1.00	-3.01
S.E. of difference	±0.48	±0.38	±0.67
Handicap of expremature child ^b	-17.5%	-6.5%	-7.6%

From Douglas¹²

^a Tests specially designed by the National Foundation for Educational Research in England and Wales

^b Difference in mean scores expressed as a percentage of the mean score of the controls, for each test

children scored lower than their controls in each of the tests and were proportionately more handicapped in reading (Table 5-4). Douglas¹² noted that there was a small group who made outstandingly poor scores in all tests. Prematurity (low birth weight) in these individuals was unexplained by obstetric abnormality (toxemia, antepartum hemorrhage, induction of labor, etc.) or by the small size of their parents. However, even after this group was excluded the exprematures still showed a slight but significant handicap in reading and picture intelligence, though not in vocabulary.

In a subsequent investigation of the mental ability and primary-school progress of these children, Douglas¹⁴ found handicaps in the expremature group which appeared to be of environmental origin rather than the result of low birth weight per se. At each social level the standards of care and educational interest

were lower among the expremature children than among their controls. These findings caused Douglas to question the utility of the method of controlled comparisons in sociomedical studies of expremature children.

The size of the intellectual handicap was not related to the degree of immaturity in the studies reported by Blegen and by Douglas.¹² However, it should be noted that children with gross defects were excluded and that there were relatively few children whose weights were 1.5 kg. or less at birth in both of these surveys. Studies of the intellectual development of children from the lowest birth weight categories present the same problems of interpretation as do those of growth.

Adults

The results of Alm's comprehensive, long-term follow-up of prematurely born males and comparable full-term controls are given in Table 5-5. Only a small number of individuals of very low birth weight are represented. Alm concluded that in this group of Swedish male adults, whose initial social status was not markedly poor, the prematurely born constituted no greater burden on the community than did the controls and, in the majority of aspects related to social adaptation, had done as well as the controls. As compared with the individuals in Alm's study, the more recent survivors of premature birth include a larger proportion of very small newborns and overrepresentation of those in poor socioeconomic circumstances. It remains to be seen whether Alm's conclusions can be applied to this latter-day group.

NEUROLOGIC SEQUELAE

The incidence of neurologic sequelae after premature birth has been difficult to estimate because of all the problems connected with follow-up studies of survivors which have been discussed above. It is not unreasonable to suggest that most estimates are too low, because children with brain damage who are institutionalized or die after leaving the hospital are more likely to appear in the "lost to follow-up" than in the "neurologic sequelae" category.

The classification of the neurologic manifestations has also presented problems because examinations in the newborn period cannot as yet be interpreted with complete confidence and precise examinations are difficult in uncooperative young children. On the other hand, surveys of older subjects are not completely representative, because a large proportion of the severely damaged individuals have died or have been institutionalized.

Despite these obstacles, the importance of neurologic follow-up studies cannot

TABLE 5-5 FOLLOW-UP IN 1948 OF PREMATURE MALES AND CONCURRENT FULL-TERM CONTROLS BORN IN STOCKHOLM IN 1902-21

	% of exprematures ^a		Controls ^b
	Single-born (N = 759)	Plural-born (N = 240)	Single-born (N = 981)
<i>Mental-development disturbances^c</i>			
Pupils in special classes	3	6	2
Institutional care	5 ^d	2	1 ^d
Spastic paralysis, epilepsy, mental deficiency	4 ^d	3	1 ^d
<i>Fitness for military service</i>			
Fully fit for active service	56	63	64
Unfit for active service	17	15	13
Military promotion of those fully fit	15	5	12
<i>Social and economic progress</i>			
Social group I (higher officials, directors, professionals, etc.)	10	11	12
Social group II (foremen, office workers, proprietors, craftsmen, etc.)	46	50	44
<i>Public relief</i>			
Unemployment relief	17	21	15
Poor relief	20	22	22
Sickness relief	10	11	12
Other relief	17	23	18
Median net income (Swedish crowns)	6080 cr	5900 cr	6270 cr
Convictions for crime	6	4	9
Convictions for drunkenness	11	15	11

From Alm ¹

	1010-1250	5	1760-2000	116
* Distribution of exprematures by birth weight (Gm)	1260 1500	16	2010-2250	300
	1510-1750	59	2260-2500	503

^b Birth weight 2760-3750 Gm^c The same individual is frequently recorded under more than one of the three classes^d Statistically significant difference between single-born expremature infants and controls

be overestimated. Much of the present-day controversy concerning the management of intracranial hemorrhage and of hyperbilirubinemia in the neonatal period will be resolved only by carefully conducted studies that include an evaluation of the late neurologic status of prematurely born children. The results of studies in progress at the present time are awaited with much anticipation.

Survivors of Premature Birth

Although there have been many retrospective surveys of the incidence of brain damage among survivors of premature birth, most such studies have suffered from the limitations discussed above. The Johns Hopkins University study of prematures, a longitudinal evaluation of a group of premature infants and term controls born in Maryland in 1952, represents a notable effort to obtain accurate data on the incidence of neurologic abnormalities in these children.²⁶ The first report of the Johns Hopkins study dealt with the status of children who survived to 40 weeks of age. The final group of babies who were completely examined (992 individuals) represented 85 per cent of the original study population. An estimate of the integrity of the nervous system was made on the basis of the presence or absence of impairment in neuromotor function and deviations in muscle tonus and control. The pediatrician who performed the examinations was not told the infants' birth weights. Following examination the infants were classified in various categories ranging from "normal" to "overt neurological defect." In the prematurely born group there was a lower proportion of normal infants and a higher incidence of neurologic defects than among the term controls. These findings were substantiated by the findings in 900 of the children who were available for re-examination when they were three to four years of age (Table 5-6). The most premature group (birth weight 1500 Gm. or less)

TABLE 5-6 NEUROLOGIC STATUS IN 900 PREMATURELY BORN AT 3 TO 4 YEARS

Birth weight (Gm.)	No children	% in each diagnostic category					Total
		Normal	Indeterminate	Questionable signs of minimal damage	Signs of minimal damage	Overt abnormality	
Premature							
1500 or less	54	51.9	3.7	24.1	7.4	13.0	100.1
1501-2500	406	80.0	4.4	12.3	2.2	1.0	99.9
SUBTOTAL ^a	460	78.6	4.4	12.9	2.5	1.6	100.0
Term							
2501 or more	440	87.3	3.4	7.0	1.6	0.7	100.0
TOTAL	900						

Courtesy of Paul A. Harper, M.D., and Rowland V. Rider, Sc.D. Study of Prematures, The Johns Hopkins University, Maternal and Child Health Division.

^a Adjusted for birth weight distribution.

included the highest proportion of children with all degrees of neurologic abnormality. A third round of examinations of children in the study who survived to six to seven years of age is now in progress.

We recently made detailed examinations of 66 two-year-old children who had been born prematurely.³⁰ Nineteen of the children had received penicillin and sulfisoxazole in the neonatal period, 47 received oxytetracycline prophylactically. The incidence of kernicterus among infants who died in the first week of life had been significantly higher in the sulfisoxazole group. However, no significant differences in neurologic status were found among the survivors in these two groups

Fourteen of the 66 had either definite or suspicious evidence of a neurologic deficit. The manifestations included hemiparesis and monoparesis, spastic quadriplegia and hemiplegia, gait disturbances, nystagmus, abnormal reflexes, etc. Perceptive deafness was found in one child. None of the children were thought to exhibit clear-cut choreoathetosis suggestive of kernicterus.

Brain-damaged Individuals

Many investigators have been aware of the frequent association between cerebral palsy and premature birth. Churchill reviewed this evidence and made additional observations on 76 brain-damaged persons whose ages ranged from 2 to 20 years. Thirty-four had neurologic signs which indicated pyramidal-tract damage only (simple spastic diplegia); 42 individuals had evidence of pyramidal-tract damage and in addition had signs referable to other regions of the brain (complex diplegia). Low birth weight was a prominent feature in the histories of those in the simple-spastic-diplegia group (mean birth weight 1662 Gm.); a relatively small proportion of persons in the complex-diplegia group weighed 2500 Gm. or less at birth (mean birth weight 2983 Gm.).

EMOTIONAL DEVELOPMENT

Much has been written concerning the behavior patterns of expremature children.^{3, 15, 21, 23, 29} It is widely held that these children are often emotionally immature (dependent, withdrawn, frequent tantrums, etc.) in childhood. The evidence which has been presented in support of this view is not conclusive. Properly controlled studies have not been reported.

There is much interest in the effects of the long period of separation of the mother and the prematurely born infant upon the course of emotional development. Parental anxieties during the infant's stay in the hospital and after dis-

charge are also a matter of real concern.^{9, 32} These problems deserve more extensive and critical study than they have received in the past.

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Part Two

CLINICAL CONSIDERATIONS

Section A • **Care**

Perinatal Care

ANTENATAL MEASURES

The care of the premature infant begins long before he is delivered. It is important that the physician who is responsible for the care of the pregnant woman be aware of the influence of her illnesses and his treatment upon the fetus. Certain of the therapeutic aspects of specific maternal complications are discussed elsewhere, e.g., Causes and Prevention of Prematurity, Infants of Diabetic Mothers, Infection, and others. Several other factors in antenatal care which may influence the infant's postnatal course will be considered in this section.

Treatment of Habitual or Threatened Abortion

Androgenic Steroids. Habitual abortion and threatened abortion are commonly managed by the administration of hormones to the mother during gestation. Several reports have indicated that masculinization of the female fetus may follow the administration of various progestins (Fig. 6-1), testosterone or other androgenic steroids.^{22, 25, 45, 56} However, as Greenblatt and Reifensstein have noted, such genital malformations are rare in view of the extensive use of exogenous progesterone in the treatment of habitual abortion.

Wilkins *et al.* and Moncrieff speculated about the possible influence of the dose and time of administration on the production of genital changes in the fetus. Grumbach *et al.*²¹ found labioscrotal fusion with a urogenital sinus only in those instances in which the female fetus had been exposed to the androgen prior to the thirteenth week of pregnancy.

Thyroid. Desiccated thyroid is often given to mothers with a history of habitual abortion or sterility. The influence of such treatment, the role of various antithyroid substances upon thyroid function in the newborn, and the management of the mother with thyroid disease are the subjects of two recent critical reviews.^{10, 43} Man and co-workers suggested that existing evidence favors the view that the developing fetus may be seriously affected by mater-



FIG. 6-1. The appearance of the external genitalia in 15-week-old female premature infant whose mother had received a semisynthetic oral progestin, 17 α -ethynyl-19-nortestosterone (Norlutin), 15 mg. per day from the eighth to the eighteenth week of pregnancy, followed by 5 mg. per day from the eighteenth to the twenty-ninth week. The infant weighed 1230 Gm. at birth. Note the enlarged clitoris, the fleshy, wrinkled labia majora, and the fusion of the labioscrotal folds which formed the slitlike orifice of the urogenital sinus. The sex chromatin pattern was female. The excretion of urinary 17-ketosteroids was normal; no pregnanetriol was detected in the urine. (Courtesy of Melvin M. Grumbach, M.D., Babies Hospital, New York.)

nal hypothyroidism (see Chap. 17). The offspring are usually normal in maternal hyperthyroidism or after the administration of desiccated thyroid during pregnancy (see also Chap. 3). This suggests that excessive transfer of hormone from mother to fetus may be interfered with by the relative impermeability of the placenta to thyroxine.²⁰ Carr *et al.* have advised that mothers who have given birth to cretins be treated with large doses of desiccated thyroid in subsequent pregnancies to increase the transplacental passage of the hormone and promote normal brain growth of the athyrotic infant in utero.

Other Substances. The effects on the fetus of other substances which have been advocated for the prevention and treatment of premature labor are unknown^{17, 51} (See also p 288).

Adrenal Steroid Therapy

Adrenal steroid therapy, even when administered to the mother for a considerable period during pregnancy and in large doses (e.g., in leukemia or rheumatoid arthritis), has been followed by few examples of adrenocortical failure in the neonate.⁵⁷ However, this possibility should be considered and a rapidly acting preparation of free hydrocortisone and corticotropin should both

be available following the delivery of infants whose mothers have received adrenal steroid therapy.

Vitamin K

There is considerable disagreement concerning the efficacy of antenatal and postnatal vitamin K administration (see Chap. 20). It has been demonstrated that vitamin K administered orally to mothers prevented a fall in the prothrombin level in the blood of their premature infants²⁸ and was associated with a reduced incidence of intracranial and other hemorrhages in these subjects.¹³ Westin observed that there was no significant difference in the incidence of hemorrhages when 5 mg. of synthetic vitamin K was given to the newborn premature infant alone and when both mother and infant were treated. Lucey and Dolan have suggested that the parenteral administration of large doses of synthetic vitamin K (72 mg.) may result in hyperbilirubinemia in the premature infant.

In the present state of our knowledge one can seriously question the advisability of administering vitamin K analogues to mothers who are about to give birth to premature infants.

INTRAPARTUM ANESTHESIA AND ANALGESIA

Preanesthetic Medication

Barbiturates. An accumulation of barbiturate was found in the liver and brain (especially the fourth ventricle) of 4- to 7-month fetuses obtained by legal abortion in 35 Swedish women who had been given ordinary sedative doses preoperatively.⁴⁷

Jondorf and others found that the duration of action of hexobarbital was considerably longer in newborn than in older experimental animals. Larger doses of this drug were highly toxic to 1-day-old animals, as compared to the effect obtained in older animals. It was found that the increased effect of hexobarbital in the newborn resulted from inability of the animals to inactivate the drug;^{18, 33} the possibility of greater sensitivity to the drug was also considered.³³ Controlled observations of the susceptibility of the human fetus to the respiratory depressant effect of barbiturates are not available.

Opiates. The use of opiates in premature labor is generally decried.²⁴ Despite this advice many premature infants are delivered from mothers who have received these drugs in an attempt to stop premature labor or for pain relief. As

a result, the problem of severe respiratory depression is frequently met among newly born premature infants

Analgesic and Anesthetic Agents

It is difficult to interpret studies of the effects on the fetus of various analgesic and anesthetic agents currently used for the relief of pain during premature labor. In most clinical evaluations the decision to administer a specific drug or combination of drugs to a mother in premature labor depends upon the judgment of the physician instead of on chance, as would be the case in a planned trial. Under these circumstances the opportunity for bias to influence the results is so great that the conclusions cannot be accepted without some reservations.

Effect on the Condition of the Infant at Birth. Although there is not complete agreement, most observations and formal studies of the effects of regional and general anesthesia have indicated that drowsiness and initial apnea last relatively longer in premature infants of mothers given general anesthesia.²⁹

Effect on Neonatal Mortality. Some observers reported a lower mortality rate among premature infants delivered from mothers who received regional anesthesia as compared with either general anesthesia or no anesthesia.^{8, 29, 44} However, controlled clinical trials have generally failed to demonstrate significant differences in neonatal mortality among premature infants whose mothers received different anesthetic agents.^{2, 28, 29}

Hingson and Hellman²⁹ considered that failure in their study to demonstrate a relatively high neonatal mortality with general anesthesia could be explained, in part, by the fact that an organized team of anesthesiologists maintained a 24-hour vigil for possible difficulty

✓ MANAGEMENT DURING AND AFTER DELIVERY

Whenever possible, the premature infant should be permitted to deliver spontaneously.²⁴ The use of episiotomy is controversial.^{3, 24} Forceps should be either avoided or, if unavoidable, applied with extreme caution. Many premature infants are born from the breech position and a successful, atraumatic delivery may require particular care on the part of the operator.⁴⁸

CLAMPING OF THE UMBILICAL CORD

From the first moment after delivery the premature infant's proper care is a controversial matter. Until recently there was general agreement that immediately postpartum the premature infant should be placed at a level lower than the placenta and that the cord should remain unclamped for several minutes to

allow the infant to receive a transfusion of placental blood in an amount estimated to range between 0.8 and 4.7 per cent of body weight.²³ DeMarsh and co-workers demonstrated that the average blood volume, hemoglobin concentration, and number of erythrocytes was greater in the first week of life among a group of term infants whose umbilical cords were clamped late as compared with controls whose cords were clamped early.

Landau and co-workers postulated that infants born by cesarean section and premature infants were often deprived of their placental blood. They advised that efforts should be made to provide these infants with more placental blood by suspending and draining the placenta or stripping the umbilical cord before it is clamped.

The ratio of placental to fetal blood volume is greatest in the most immature infants.⁵⁰ Thus in a small premature infant a placental transfusion may result in a relatively large expansion of the recipient's blood volume. This has led to the suggestion that the umbilical cord of premature infants be clamped early to prevent hypervolemia and the development of pulmonary edema (see Chap. 14).

Taylor and others conducted a controlled trial of the relative effects of early cord clamping (within 15 seconds) and late clamping (1-3 minutes) among 340 prematurely born infants. The time of clamping had no significant influence on mortality rates in the first week of life, but the late-clamped premature infants had an appreciably higher incidence of tachypnea and chest retractions. Further trials will undoubtedly be necessary to resolve the conflicting opinions concerning the recommended time of clamping the cord¹¹ in premature deliveries.

Generous lengths of umbilical cord are often left attached to premature infants on the presumption that umbilical catheterization may be necessary. On the other hand a short stump does not preclude the use of the umbilical vein and results in less trouble from superficial omphalitis.

ESTABLISHING SPONTANEOUS RESPIRATION

Role of Brief Asphyxia. The studies of James and others³² suggest that all newborn infants undergo some degree of asphyxia (simultaneous decrease in both the intake of oxygen and the elimination of carbon dioxide) in the process of being delivered. Furthermore, the biochemical response of these infants to asphyxia is identical to that of adults. In most infants, blood-oxygen saturation is reduced, carbon-dioxide tension is increased, and pH is low. The total available buffer (bicarbonate, protein, and hemoglobin) is usually normal, indicating that the duration of asphyxia has been brief and the derangement may be classified as respiratory acidosis. These chemical changes in the blood acting through chemoreceptors, together with sensory impulses from the periphery acting on the

respiratory center, probably constitute the most important stimuli to the initiation of respiration.

Weisbrot and co-workers demonstrated that vigorous infants recover rapidly from these effects of brief asphyxia, very much as would be expected in adults.

Other Factors. Karlberg analyzed the mechanics of the onset of respiration from recordings which he obtained of newborn infants' first breaths. From these studies and from the work of others he has reviewed the evidence which bears on the question of the relative roles of the elastic recoil of the chest cage, pulmonary capillary distention and inspiratory effort in overcoming the initial elastic resistance of the lungs and the surface tension in the respiratory tract. Needless to say, knowledge in this area is far from complete, and delineation of the premature infant's particular difficulty in this regard has only begun.

✓ Routine Measures

Immediately after delivery the premature infant should be held by his heels so that the first spontaneous breath will occur in the head-down position. Inhalation of vaginal mucus, blood, meconium, vernix, or other débris in the oropharynx will thus be minimized.

The next step is to clear the upper respiratory passages of fluid and débris. The infant should be placed in the supine position on a plane inclined about 30 degrees with the head down (Trendelenburg position). The head should be rotated into extension and the upper airway should then be gently aspirated with a soft, sterile catheter * There is general agreement that these maneuvers when performed gently and quickly probably provide safe and effective sensory stimulation followed by spontaneous respiratory movements in most premature infants. Evidence has been obtained from cinerentgenograms of full-term and premature infants³⁴ suggesting that these spontaneous first few breaths may result in rather complete expansion of the lungs. These observations challenge previously held opinion that expansion is usually gradual during the first few days of life.

Apgar¹ devised a scoring system to describe the condition of the infant at 60 seconds of age on the basis of objective signs (Table 6-1)

INITIAL RESUSCITATION

Some newly born premature infants either make no spontaneous respiratory movements or gasp irregularly. There is considerable disagreement about what steps, if any, the physician should take when he is confronted with this problem.

* Two-holed Rausch rubber catheter (size 12) and DeLee glass trap

James³¹ has obtained evidence which indicates that the problem of expanding the lungs of subjects who have never breathed may be mechanically different from that seen in others whose respirations have failed after the establishment of rhythmic ventilation. For this reason initial resuscitation will be considered separately from resuscitation in secondary respiratory failure (see Chap 14).

TABLE 6-1 EVALUATION OF THE NEWBORN INFANT AT 60 SECONDS OF AGE BY AN ARBITRARY SCORING SYSTEM (APGAR SCORE)

Sign	Score ^a		
	0	1	2
Heart rate	Absent	Slow (below 100)	Over 100
Respiratory effort	Absent	Slow Irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability (response to catheter in nose)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

From Apgar¹

^a Each of the five signs has a maximum 2-point score, a total of 10, therefore, indicates an infant in the best possible condition

Effects of Prolonged Asphyxia. James' group³² studied the acid-base status of depressed newborn premature and term infants who were cyanotic and limp and failed to establish respiration by one minute of age. The biochemical changes indicated that asphyxia in these infants had been prolonged. Blood obtained from these infants revealed low oxygen saturation, elevated carbon-dioxide tension, low pH, and a marked reduction in the total available buffer, indicating that a metabolic acidosis had been superimposed on respiratory acidosis. These findings have been interpreted to indicate that under conditions of prolonged asphyxia the chemoreceptors in the respiratory center are no longer able to respond to the elevated carbon-dioxide tension and low pH. This is in contrast to the situation in brief asphyxia, in which these stimuli are adequate to initiate gasps that promote oxygenation and spontaneous correction of the derangement. According to these views failure to breathe at birth may be the result of damage to the central nervous system, drugs which depress the respiratory center, obstruction of the airway, or severe respiratory and metabolic acidosis resulting from prolonged intrauterine asphyxia.

Indications

There is no agreement concerning the duration of asphyxia that the newborn infant can withstand without harm.³¹ Estimates of the period of time that may safely elapse between delivery and the onset of respiration vary widely. Thus both the time of intervention as well as the need for resuscitation²⁷ have been subjects of continuing debate. Methods which have been advocated for initial resuscitation are the same as those which have been proposed for vivification after secondary respiratory failure (see Chap. 14). There have been no acceptable well-controlled clinical trials of the effectiveness of any of the methods advocated for the resuscitation of newborn premature infants, including the method which is advocated below. Until such evidence is available this subject will continue to be a controversial one.

We have considered that if spontaneous respiration does not occur before one minute of age following clearing of the upper respiratory passages, resuscitation is indicated.

Methods

Mouth-to-Tube Insufflation. Direct laryngoscopy, tracheal aspiration, intubation, and mouth-to-tube insufflation have been used in all newborn infants requiring resuscitation in our hospital for several years (Fig. 6-2). Efficient clearing of the airway of meconium, vernix, or blood under direct vision has usually been followed by spontaneous, effective respirations. In flaccid infants the tongue may lie against the pharyngeal wall and obstruct the airway. Extension of the head and placement of a small size pharyngeal airway* often corrects this type of obstruction. If these measures are not promptly followed by spontaneous respirations, the lungs are inflated. Administration of antibiotics may be advisable after mouth-to-tube inflation of the lungs (see Chap. 19).

This active method of resuscitation has necessitated the maintenance of a special training program for the staff so that infants will not be injured by inexperienced operators. This program includes education and mandatory practice sessions on infant cadavers.

Care must be exercised to prevent injury of small premature infants during resuscitation. Squeezing the chest and abdomen may result in multiple rib fractures or subcapsular hemorrhage of the liver (see Chap. 18).

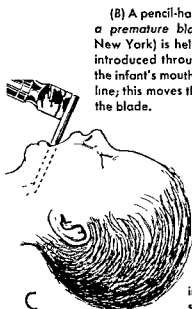
Opiate Antagonists. Respiratory depression in the newborn infant may be caused by the administration of opiates to the mother. Eckenhoff and co-workers conducted a controlled trial of the effectiveness of N-allylnormorphine as an

* Berman plastic pharyngeal airway

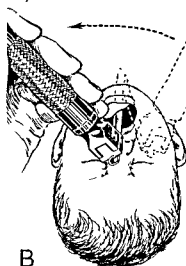
FIG. 6-2. Technique of mouth-to-tube resuscitation.



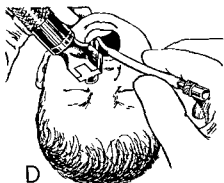
(A) A folded towel is placed under the shoulders. With the right hand the head is first lifted anteriorly and then rotated into partial extension ("sniffing position").



(B) A pencil-handle laryngoscope with a premature blade (Foregger & Co., New York) is held in the left hand and introduced through the right corner of the infant's mouth and swung to the mid-line; this moves the tongue to the left of the blade.



(C) Under direct vision through the slot in the right half of the blade the laryngoscope is dipped slightly and advanced so that the posterior surface of the epiglottis lies on the beak of the speculum. The tongue and epiglottis are lifted vertically, bringing the larynx into view.



(D) The right hand can now be released, and the infant's jaw is supported with the fifth finger of the left hand. An endotracheal catheter (Cole, size 10) is introduced at the right corner of the mouth and passed into the glottis through the vocal cords. The laryngoscope is then removed.



(E) A tube supplying oxygen is held in the operator's mouth. Inflation of the lungs is accomplished with short sharp

opiate antagonist. When this agent was given to mothers who received opiates before delivery there was a significant reduction in the time required to establish respiration and in the need for resuscitation in the offspring. Although N-allylnormorphine was shown by these authors to have a respiratory depressant effect in normal adults, no depression was shown in the infants except for suggestive evidence that the efficacy as an opiate antagonist was reduced when the mothers received nitrous-oxide anesthesia.

Eckenhoff and co-workers suggested that 0.2 mg. N-allylnormorphine* in 2 ml. of isotonic saline should be injected into the umbilical vein of depressed infants whose mothers have received excessive amounts of opiates (morphine, Dilaudid, Pantopon, meperidine (Demerol), and methadone). They warned however that the depression might be deepened if this agent is used in infants apneic from other causes. If inhalation anesthetics and opiates are administered to the mother, Eckenhoff's group advised that N-allylnormorphine be considered after artificial ventilation has removed most of the anesthetic from the infant's blood stream.

Further experiences^{4, 30, 46} with opiate antagonists have supported the initial favorable impressions of the specific effect of treatment on the initiation of respiration. However, Roberts *et al.* were unable to demonstrate that the antidote given to the mother had any influence on diminished respiratory activity which these infants exhibited beyond the first moments of life.

Respiratory Stimulants. Various drugs (including nikethamide, alpha-lobeline, picrotoxin, pentylene tetrazole, and epinephrine) have been thoroughly discredited as respiratory stimulants for apneic newborn infants. Reliance on these agents often delays the application of effective methods of ventilation, and overdosage may produce convulsions.

Caffeine sodium benzoate (3 mg. intramuscularly) is generally excluded from the list of useless drugs, despite the fact that there is virtually no evidence of its effectiveness. Fifty per cent glucose given intravenously has also not been critically evaluated as a resuscitative agent.

INITIAL FALL OF BODY TEMPERATURE

The body temperature of the premature infant falls rapidly during the first few moments of life, if the surrounding air temperature is between 70 and 80° F. (21.1–26.7° C), a range frequently encountered in delivery rooms. McClure⁴² recorded the rectal temperature of several premature infants continuously from the moment of birth and found that the fall in temperature was more profound in premature than in term infants.

*Nalline (Merck Sharp & Dohme) is supplied in 0.2 mg./1.0 cc. ampuls, Lofan (Roche) is supplied in 0.05 mg./1 cc. ampuls.

Heat loss by evaporation from the moist skin and from the lungs at the onset of respiration is probably considerable. In this connection, McClure^{41, 42} noted that the downward trend of rectal temperature in newborn premature and term infants was delayed or momentarily reversed during periods of apnea.

Burnard and Cross observed that body temperature during the first day in term infants who failed to establish respirations within three minutes after birth was lower than in a group of normal infants. A marked fall in body temperature was observed in infants born to mothers who received an opiate, however, in this group the magnitude of the fall was the same in infants who breathed spontaneously as in others whose respirations were delayed. The relative roles of heat production and heat loss could not be assessed.

The physiologic significance of this initial fall in body temperature in premature infants needs to be carefully studied.

It is generally, but not universally, advocated that attempts should be made to prevent the initial fall of body temperature. However, delivery-room personnel are often unable to give their attention to this detail of care, particularly if the attendants are preoccupied with efforts to establish respirations. Improved methods are needed to control body temperature of premature infants in the first moments of life (see Chap. 7).

FIRST APPRAISAL IN THE DELIVERY ROOM

Every effort should be made to have a qualified pediatrician and an experienced nurse present at the time of delivery of a premature infant. Following the initial efforts to insure the establishment of respiration, a rapid appraisal of the infant should be made. Obvious congenital anomalies that are amenable to early correction should be noted or ruled out before the infant leaves the delivery room. A detailed physical examination should be delayed until the infant has been transferred to the nursery. The initial evaluation can be performed without exaggerating heat loss if the infant is either in a warmed incubator or is placed under warming lamps during the examination.

Credé prophylaxis is usually performed before the infant leaves the delivery room (see Chap. 19).

Specific Maneuvers

- ✓ **Use of a Rubber Catheter.** A sterile two-holed Rausch rubber catheter, size 12, should be passed into the stomach and the contents of the stomach aspirated and measured. Esophageal atresia is effectively ruled out if passage is successful. A large volume of gastric fluid (more than 30 ml.)¹⁴ should raise the suspicion of high intestinal obstruction.

Blanc suggested that the gastric fluid be smeared and stained with methylene blue to search for increased numbers of leukocytes. This finding would suggest that the infant has been exposed to amnionitis.

The same catheter can be used to rule out choanal atresia and imperforate anus by successful passage into the appropriate orifices.

Auscultation. Auscultation of the chest may give an early clue to the presence of the most common type of diaphragmatic hernia—left-sided—when the heart sounds are loudest in the right chest.



FIG 6-3. Cut end of an umbilical cord, demonstrating a single umbilical artery (arrow) and the umbilical vein. (Courtesy of William A. Little, M.D., Sloane Hospital for Women, Columbia-Presbyterian Medical Center, New York.)

Inspection of Cut Ends of Umbilical Cord. The freshly cut ends of the umbilical cord should be inspected to see whether two umbilical arteries are present. The absence of one umbilical artery (Fig 6-3) has been associated with a high incidence of congenital anomalies^{5, 37}. Some of these anomalies (diaphragmatic hernia and malformation of the gastrointestinal tract) require prompt attention.

Abnormal Signs

The presence of other gross anomalies and abnormal signs (jaundice, generalized cyanosis, pallor, grunting respirations, hematemesis, melenas, etc.) are important and should be looked for in the initial appraisal. These examinations

should be made as quickly as possible so that the infant can be dispatched to the nursery without undue delay. In the nursery the measurement of vital signs can be made by the personnel who will use the early observations to provide a baseline for evaluation of events which follow

Inspection of the Placenta

The physician who is responsible for the care of the premature infant may obtain potentially useful evidence from inspecting the placenta before leaving the delivery-room suite⁴⁰

Landing called attention to the association between malformations of the infant's urinary tract and amnion nodosum (multiple, firm, rounded, raised yellow spots on the amnion of the fetal surface of the placenta).

Several methods of examination of the fetal adnexa to establish the diagnosis of amnionitis are discussed in Chapter 19

TRANSPORTATION

The distance between the delivery room and the nursery for premature infants is of little importance when these infants are cared for in the hospital of birth. In many cities infants are transferred, after a short stay in the delivery room or intramural nursery, to a center for the care of premature infants which is often a considerable distance away. Some consideration must be given to the principles of care during transportation, since death during or soon after transfer is not rare.

Time of Transfer

There is no agreement on the ideal time when transfer should take place. It is sometimes argued that transfer should be delayed for several hours until the vital signs have stabilized. Since the mortality rate of young premature infants is considerably higher than the rate of old premature infants (see Appendix 5), it is clear that, quite apart from any influence of transportation, an early-transfer policy can be expected to be accompanied by a large number of deaths during or immediately after transfer, and a late-transfer policy with fewer such incidents. Under the latter conditions only the most hearty remain to undertake this risk.

Accompanying Data

Sufficient information concerning the family, the pregnancy, and neonatal events should accompany the premature infant into the nursery. We have used the form of the Premature Transportation Service of the New York City Depart-

ment of Health (see Appendix 11) as a convenient method of collecting this historical information not only for infants born in other hospitals but also for those who come to the nursery from the intramural obstetric service. In addition, information concerning the duration of ruptured membranes and antibacterial drugs administered to the mother should be obtained.

For several years we have also asked that a tube of the mother's blood accompany each infant. Serologic tests and blood grouping and cross-matching may be performed on this sample as indicated.

Care During Transfer

Nursing Care. The nurse who accompanies the infant should be trained in resuscitative techniques. For this purpose the technique illustrated in Figure 6-2 can be used. It requires very little equipment, all of which is conveniently portable. The method may be used to attempt to resuscitate infants whose respirations fail during transfer. The efficacy of stimulants is, at best, doubtful.

Portable Incubators. Portable incubators are available (see Chap. 25) which provide heat from covered hot-water bottles and oxygen in small cylinders. If oxygen is administered the concentration can be controlled by attaching oxygen-limiting valves to the system (see Chap. 7).

The advantages of these incubators are light weight and simplicity of design. The principal disadvantage lies in the fact that in many types the infant cannot be adequately observed during transfer. The heating arrangement is usually too inefficient to permit the infant to lie unwrapped in the box and he must be swaddled to reduce heat loss. This hides all but his face from view. Underheating is common and overheating is not rare.

As our knowledge becomes more exact concerning the physical conditions of the environment best suited for the survival of premature infants it is hoped that there will be some improvement in the design of these incubators.^{38, 53}

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General Aspects of Nursery Care

The three major concerns in the care of premature infants have always been (1) keeping the infant warm, (2) feeding him properly, and (3) preventing infection. Even now, completely satisfactory solutions to these problems are not available. For historical details of the earliest records of clinical experience and research which became the basis for present-day methods of care, the reader is referred to Dunham's review.

NURSERY

The physical facilities for the care of premature infants should conform to those recommended by the American Academy of Pediatrics (Appendix 8).

Air Conditioning and Room Temperature. Although the A.A.P. standards do not require room air conditioning of nurseries for premature infants, we have found that without it a stable year-round air temperature (80° F., 26.7° C) in New York City cannot be maintained. As will be discussed, stability of the room temperature has become more important since the introduction of incubators with walls which provide very little insulation, in order to regularize heat exchange between incubator and room air.

CONTROL OF CROSS INFECTION

Isolation

Extensive studies have made it clear that when newborn infants are housed in common-nursery units, effective barriers are necessary to prevent the occurrence of epidemics of intramural infections^{3, 32, 33, 46, 51, 60, 61}. Premature infants who must remain under these high-risk conditions for long periods of time must have special protection. Effective methods of isolation designed to control cross-infec-

tion in colonies of experimental animals^{31, 48, 63} are particularly applicable to premature infants, since in both cases the individuals to be protected can be confined to a limited space.

Chapple¹² designed a barrier system in which each premature infant is enclosed in a unit which is individually ventilated with fresh outdoor air (Fig 7-1). The intake of air is adjusted to maintain a slightly greater pressure in the incubator than in the room. Whenever the partition barrier is broken (e.g., by opening a porthole) the sweep of air is away from the isolated infant. In this way a ventilation barrier is substituted for the broken partition barrier.

The effectiveness of mechanical and ventilation barriers in controlling cross-contamination was established in tests by Chapple and Kenney and by Reyniers.⁴⁷ Studies conducted in our nursery by Beckmann and Spencer⁵ indicated that the individually ventilated Chapple-type incubator was efficient in preventing the entry of airborne bacteria from the room. The development of effective air filters¹⁵ has made it possible to use intramural air for ventilating each incubator.

Other Measures

To prevent cross-contamination, scrupulous handwashing technique must be observed by all personnel¹⁹ (see Appendix 8).

In Babies Hospital an oil-in-water emulsion* is used in the daily wet mopping of the floor. Louvered ultraviolet fixtures are also utilized in an attempt to control airborne bacteria in the nursery suite.

REGULATION OF BODY TEMPERATURE

It is reasonable to assume that the body temperature of the human fetus before delivery is very close to that of the mother. As has already been noted, immediately after delivery the body temperature of the infant plummets. This initial phenomenon and thermoregulation during the next hours of life are quite dependent upon the thermal environment in which the infant finds himself. This dependence is more marked and more prolonged in the case of the prematurely born infant than in the term infant, and in general is inversely related to birth weight.

Measurement of Body Temperature. Something should be said about the concept of "body temperature." As DuBois emphasized, there is no uniformity

* Oil in water emulsion stock solution: mineral oil USP, 95 ml., water, 12 ml., Triton X-100, 3 ml. Mix in blender. For use on floors, 3 ounces of stock solution to 2½ gallons of warm mop water.*

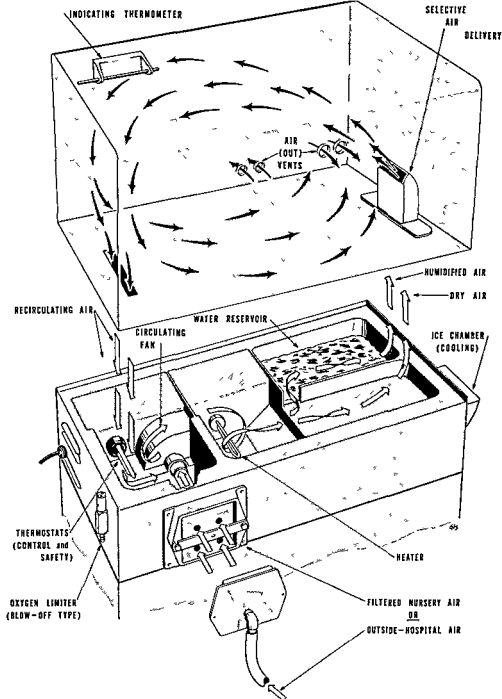


FIG. 7-1. An individually ventilated Chapple-type incubator. Outdoor air (or filtered nursery air) is drawn into the incubator at the rate of 10 liters per minute to prevent the accumulation of carbon dioxide; this assures an outflow of air which bars the entrance of nursery air through the access ports. Heating and humidification of the air in the incubator can be adjusted by means of individual controls. If the air temperature of the nursery exceeds 90°F. (32.2°C.) the unit can be kept cool by placing ice in the ice chamber. [Courtesy of Air-Shields, Inc., Hatboro, Pa.]

of temperature within the human body. The entire body is a mass of temperature gradients, and ordinary measurement gives only spot temperatures.

In premature infants a "spot" axillary temperature, obtained by holding the thermometer with the bulb enclosed between the arm and the chest wall for 1½ minutes, gives a satisfactory estimate of the "body temperature." Continuous recordings of axillary, rectal, and esophageal temperatures in our nursery revealed satisfactory correlations. It was not unusual, moreover, to obtain axillary readings that were higher than rectal values in very small infants.

Regulation at Different Environmental Temperatures

Zone of Circulatory Control. Thermal stability of the body is the net result of the balance between heat production and heat loss. Hardy and Soderstrom demonstrated that, by means of vascular reactions alone, an unclothed, motionless, adult human can keep his body temperature constant only within a narrow range of air temperature—between 82.4 and 86° F. (28–30° C.). Below this zone of circulatory control the body cools like an inert physical object until heat production is increased by muscular activity. Day *et al.* demonstrated that the circulatory responses of thriving premature infants at various air temperatures are similar to those of adults. Brück and co-workers⁹ found that infants weighing as little as 830 Gm. are capable of making these responses beginning from birth. **Cool Air.** However, vasoconstriction even if complete could be expected to provide only a limited defense against cold in both adults and premature infants. Gordon's group²⁶ reported that under conditions of normal wakeful activity—in environments of 72–77° F. (22.2–25° C.)—premature infants showed a relatively small rise in heat production above the "resting" level. This limitation has been attributed to the feeble skeletal musculature of the small infants.¹⁴

Even if the heat loss per unit of surface area were the same in the premature infant and the adult, the smaller subject would still be handicapped because of his proportionately larger surface area in relation to body weight.^{57, 58}

Day *et al.* demonstrated that this inherent defect in size is further exaggerated, since the heat loss per unit area of skin is greater in infants than in adults. An inadequate insulating blanket of fatty tissues and skin permits high conductance of heat from the warm inner core of the body to the cooler skin surface and is responsible in part for the enhanced loss.

Warm Air. Day and co-workers and Brück *et al.*⁹ demonstrated that in warm air, vasodilation in premature infants is quantitatively similar to that in adults.

Evaporative regulation constitutes the principal mechanism by which body temperature is controlled at high environmental temperatures.²⁹ Active sweat-

ing occurs in motionless adults at air temperatures above the zone of circulatory control, 86°F. (30°C.).

Inadequate sweat production prevents the premature infant from defending his body temperature against heat.^{7, 14} Kuno found that after the twenty-eighth fetal week the sweat glands of premature infants were completely formed and capable of producing sweat when stimulated with pilocarpine. He reviewed the observations of Uchino,³⁵ who studied the advent of thermal sweating in nine premature infants. No sweating was observed for 21 to 33 days after birth. Kuno concluded that hypohidrosis in newborn infants is the result of incomplete neural development and that the advent of sweating may be used as a sign of maturity in these subjects

Homeothermism

The thermoregulatory capability of an individual is expressed in terms of the range of environmental temperature that he can withstand without a significant deviation in the temperature of the inner core of the body. As just discussed, premature infants have a limited regulatory capacity. Under usual clinical conditions they cannot maintain their body temperature at 98.6°F. (37°C.) unless they are supplied with a source of heat

There is considerable controversy concerning the amount of warmth that should be provided for these infants. Although the limits have not been carefully defined, it is reasonable to assume that oxygen consumption increases when the body temperature of the premature infant rises significantly above 98.6°F. (37°C.). Examples of extreme hyperthermia accompanied by convulsions and followed by death have been observed following accidental overheating of premature infants. These accidents have led to the general recommendation that it is safer to keep the infant's body temperature below 98.6°F. (37°C.) As a result, there have been more studies of hypothermia than of the euthermic state in these subjects

Considerable difference of opinion has been expressed on the question of whether premature infants are temporary poikilotherms^{1, 21} in the first days of life (i.e., making no metabolic response to a fall in body temperature) or inefficient homeotherms who increase their metabolism feebly in response to this fall. The observations of Day *et al.* and of Mordhorst on thriving premature infants who were for the most part older than one week indicated that they were homeotherms. Brück¹⁰ studied several small premature infants from the period immediately after birth (0-6 hours) to 14 days of age. He found that when infants

were exposed to an air temperature of 73.4°F. (23°C) heat production was greater than at 95°F. (35°C.).

The results of these studies tend to confirm the suspicion that the optimum body temperature for premature infants is afforded by an environment that provides an ample supply of heat and thus makes the smallest metabolic demand. The range of environmental temperature within which the metabolic rate of an individual is lowest is usually referred to as the neutral or critical temperature. The metabolic rate increases in environmental temperatures above and below this neutral range. The critical temperature is expected to be inversely related to body size; however exact measurements in premature infants of different sizes have not been made.

Extraneous Factors Contributing to Instability of Temperature

Evaporative heat loss in premature infants can be reduced by raising the relative humidity of the surrounding air.^{7, 53} Day *et al.* estimated that loss by vaporization contributes approximately 25 per cent of total heat loss in contrast to loss by radiation and conduction, which forms about 65 to 70 per cent of the total.

A subtle increased loss of heat by radiation occurs in infants who are placed unclothed in incubators with uninsulated walls. The air temperature of the nursery influences the temperature of the wall of the incubator. As a consequence the net heat exchange between the infant and the wall of the incubator may fluctuate with changes in nursery temperature despite an unvarying incubator air temperature.²⁴

The level and stability of body temperature are influenced by many factors, including the amount of clothing, the precision of the thermostat in the incubator, the physical characteristics of the incubator, etc. The number of influences is so large that it is impossible to prescribe a specific air temperature to achieve a given body temperature in a given premature infant. It is more logical to propose that the body temperature should be prescribed and the physical conditions of the environment adjusted to accomplish this safely. At present the optimum body temperature is unknown.

To keep all premature infants at the same level of body temperature it would be necessary to supply the largest amount of supplemental heat to the smallest subjects. With present-day incubators this cannot be accomplished safely if the level of body temperature chosen is 98.6°F. (37°C.). The dilemma reflects the limitations of available methods of keeping infants warm rather than

the inherent defects in premature infants, since it is very likely that a single stable level of body temperature is achieved in utero.

Thermal Influences on the Well-being of Premature Infants

Studies in our nursery^{53, 54} have supported the long held view^{23, 52} that survival rates of newly born premature infants can be improved by reducing their heat loss. Future studies may provide answers to these questions: (1) How rapidly should cool premature infants be warmed?⁴⁰ (2) Must glucose be administered before warming?^{25, 38, 44} (3) What level of body temperature is associated with the highest rate of survival and the lowest rate of brain damage in these infants? (4) What is the influence of body temperature upon neural²² and chemical maturation?

Hypothermia

Lowering of the body temperature has been advocated in the management of asphyxia in newborn infants^{36, 42} (see Chap. 14). Brodie and others demonstrated that when the oxygen intake of term infants was reduced body-heat production dropped significantly. Burnard and Cross observed low body temperature in the first day of life in infants with asphyxia. They suggested that the marked ability of the newborn to survive anoxia may be explained by this phenomenon.

The metabolic demands of an infant can be sharply reduced through the use of drugs or anesthetics which interfere with homeothermic reflexes. However, it is not known whether ventilation diminishes proportionately at the same rate as metabolism when premature infants are cooled. If, as in anesthetized adults, ventilation decreases relatively more during cooling than does metabolism, hypoxia and respiratory acidosis may be expected to supervene. Since it has been shown that the newborn human infant is not a true poikilotherm,¹⁰ such artificial hibernation represents a special application of hypothermia with known risks^{40, 59}. This technique requires careful control of respiration and chemical changes^{39, 50} in the blood.

ATMOSPHERIC HUMIDITY

In studies reported in 1933, Blackfan and Yaglou observed that at a relative humidity of about 65 per cent, an air temperature of 77° F. (25° C.) was required to maintain equilibrium of body temperature in a group of premature infants. When the relative humidity was reduced to approximately 30 per cent it was

necessary to increase the air temperature to 80° F. (26.7° C.) to attain the same level of body temperature. Alternate exposures to each of these two air conditions for a week at a time resulted in no significant difference in the stabilization of body temperature, but in more prolonged exposures to low humidity marked differences developed. When low humidity prevailed for two weeks or longer, the incidence of diarrhea was found to increase, fluctuations of body temperature became more marked, gains in weight were generally reduced, and fatalities increased.

High Humidity

In recent years premature infants have been placed in environments of considerably higher moisture content than 65 per cent relative humidity, which was recommended in 1933. When high concentrations of oxygen were commonly used in the management of premature infants, high humidity was introduced in an attempt to minimize the desiccating and irritant effect of dry oxygen upon the respiratory tract⁵⁶ (see Chap. 14). Although prolonged high concentrations of oxygen are now never used in the routine management of premature infants, the routine use of high humidity has persisted. There have been no satisfactory studies of the influence of prolonged exposures to humidity above 80 per cent relative humidity.

Effect on Growth. Blackfan and Yaglou studied the influence of 65 per cent and 30 per cent relative humidity on growth in weight and length. The rates of gain were greater in 65 per cent relative humidity only for infants under 2000 Gm. in weight. In those who weighed more than 2000 Gm., faster rates were observed among the infants who were exposed to low humidity (see Chap. 4).

Effect on Insensible Water Loss. Reduced insensible water loss from the lungs was reported by O'Brien and others in ten thirsted premature infants who were in mist-filled atmospheres for the first 3 days of life. Hemoconcentration, as reflected by changes in the concentrations of chloride in serum, was less in supersaturated atmospheres. However, the economy in body water was not sufficient to provide any additional urine volume. We observed similar trends, as judged by weight loss, only among infants who were thirsted.⁵² No beneficial effect on survival rate or respiratory performance was observed that could be credited to mist therapy in the first three days of life.

Effect on Rate of Infection. Hoffman and Finberg reported that with the increased use of mist atmospheres for premature infants they observed the occurrence of an unusual number of infections caused by *Pseudomonas aeruginosa*. We

were unable to demonstrate a significant difference in the incidence of infections in the first three days of life between infants who succumbed in mist environments and those who died in 80 to 90 per cent relative humidity.⁵²

The results of studies by Dunklin and Puck, and by Lester indicated that relative humidity of 40 to 55 per cent is the least favorable to growth of bacteria and viruses. Beckmann and Spencer⁶ did not observe such an effect in open wards over a range of 12 to 73 per cent relative humidity. The effect of relative humidity on the growth of microorganisms within the confines of incubators and at their relatively high temperatures should be studied.

The elaborately designed barriers to provide air isolation for premature infants (see Fig. 7-1) are bypassed by mist-nebulizing devices which aspirate nursery room air. At the present time there appears to be no satisfactory reason for placing premature infants in mist-filled environments, there is no convincing evidence that they derive any practical benefit from such exposures.

RECOMMENDED CONDITIONS FOR INCUBATORS

In general the body temperature of larger naked premature infants (birth weight over 1500 Gm.) can be kept between 97° and 98° F. (36.1–36.7°C.) with air temperatures between 84° and 90° F. (28.9–32.2°C.) when the relative humidity is 50 to 60 per cent.* Smaller naked infants can be maintained at this level of body temperature only if the air temperature or the relative humidity is raised. The likelihood of overheating these small subjects is less if the humidity is elevated and air temperatures are kept between 88° and 90° F (31.1–32.2°C.).

If it is demonstrated that body temperatures more closely approximating 98.6° F (37°C) favorably influence survival, more efficient devices for supplying warmth will be indicated. Present-day warm air-humidity systems are not precise enough to accomplish this safely for unclothed, small premature infants.

SUPPLEMENTAL OXYGEN

Arguments Against Routine Administration

It is not known whether the survival of premature infants can be influenced by the routine administration of supplemental oxygen for the first day of life, as has been recommended. Further, there is no satisfactory evidence that the adminis-

* Relative humidity within incubators may be measured with a Psychron, Friez Instrument Division, Bendix Aviation Corp., Baltimore, Md.

tration of supplemental oxygen for such a short period can influence the incidence of retrolental fibroplasia^{27, 28} (see Chap. 16). In the absence of evidence from critical studies only an arbitrary judgment is possible. We believe that unless it can be shown that the survival rate or incidence of neurologic deficit is influenced by the use of supplemental oxygen, this gas should not be given routinely to premature infants.

Recommendations for Oxygen Therapy

Recommendations for the administration of oxygen to premature infants must be influenced principally by considerations of the retinal effects of hyperoxia. At the present time the influence of supplemental oxygen upon immature retinal vessels is the only untoward effect that has been well established. Other possible harmful influences in human infants are entirely speculative

Treatment of Cyanosis

Supplemental oxygen should be administered when it is evident that a premature infant has cyanosis which persists in the presence of a clear airway.

Oxygen Concentration. The lowest concentration of oxygen necessary to relieve cyanosis should be determined by trial. When this is determined the physician's order should specify the oxygen concentration to be maintained in the incubator instead of the rate of gas flow. In our nursery it has rarely been necessary to exceed 40 per cent oxygen concentration in even the smallest premature infants

The concentration should be monitored by frequent measurements (recorded at least every eight hours) with a reliable oxygen analyzer (Fig. 7-2). To guard against the occurrence of mechanical and human errors this precaution should be taken even if oxygen-limiting valves (Figs 7-3 and 7-4) or fixed-concentration tanks are used to supply the oxygen.

Duration of Therapy. The duration of oxygen therapy can be decided only by careful observation of the infant. When cyanosis has been relieved all efforts should be made to maintain the infant in a condition which permits the flow of oxygen into the incubator to be reduced and then stopped. Continuous administration of oxygen may be unavoidable because of persistent cyanosis. We have urged that at least one effort be made to stop supplemental oxygen every 24 hours. This advice is based on evidence from experimental animals that if the vaso-obliterative effect of hyperoxia is not too prolonged the retinal vessels will reopen when the animal is returned to air (see Chap. 16).

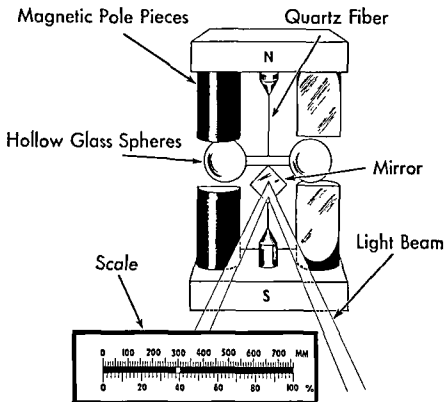


FIG. 7-2. Principle of operation of Beckman oxygen analyzer. Oxygen is attracted into a magnetic field (paramagnetic), while most other gases are slightly repelled (diamagnetic). The magnetic susceptibility of the gas sample, which is primarily due to oxygen, is measured by the displacement of a dumbbell-shaped test body (hollow glass spheres) suspended in a strong magnetic field. As the oxygen content of the sample gas changes the test body rotates until the magnetic force on the test body is balanced by the torsional restoring force of the quartz fiber. A mirror mounted on the test body reflects a beam of light onto a graduated scale. The oxygen content of the gas sample is read from the position of the light spot on the scale. (Courtesy Beckman Instruments, Inc., Fullerton, Calif.)

Cessation of Supplemental Oxygen. Although there is some disagreement concerning the rate of withdrawal of supplemental oxygen, we have recommended that when cyanosis is relieved the flow of gas should be stopped as quickly as possible. Gradual weaning (several days) from oxygen-enriched environments,²⁰ a practice previously adhered to rigidly, is no longer advised.

Low-Oxygen Environment

Sjöstedt and Rooth's suggestion that premature infants be maintained in an atmosphere of 15 per cent oxygen has not been subjected to a controlled trial.

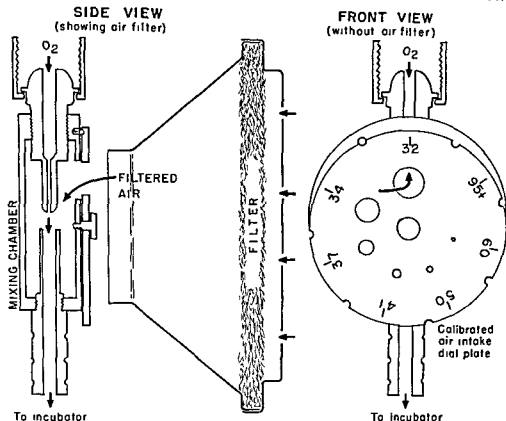


FIG. 7-3. Oxygen-limiting meter. Oxygen enters the meter and passes through a fine jet. In accord with the Venturi principle, oxygen leaving the jet at high velocity creates a negative pressure within the mixing chamber. An opening on the face of the meter allows air to be drawn into the mixing chamber, and the mixed gases leave by a distal secondary jet to enter the incubator through a connecting tube. The air intake of the meter is covered with a dial plate which has a series of calibrated openings. The size of these apertures controls the intake of air and determines the percentage mixtures of oxygen as indicated on the dial plate. It is essential that only the tubing supplied with the meter be used. A tube of different length or bore will make the delivery percentages of oxygen inaccurate. Recent models of this meter are provided with a spun-glass filter (shown in the side view) to prevent the entry of microorganisms from nursery air. (Courtesy of Respiration Aids, New York, N. Y.)

POSITION OF THE INFANT

The traditional recommendation that premature infants should not be permitted to lie in the same position too long may or may not be important. Barcroft's suggestion that afferent impulses from the skin, muscles, and joints act as potent stimuli to the respiratory center may be pertinent. However, there is no evidence that the survival of premature infants can be influenced by positioning. **Head-Down Versus Head-Up.** Newborn infants, including those born prematurely, are often placed supine and tilted head down to promote the drain-

age of fluid from the respiratory tract. There have been few studies of the effects of this practice.⁴¹

Observations that the recumbent position has an aggravating effect on periodic breathing² in adults with cardiac decompensation may stimulate studies in premature infants.

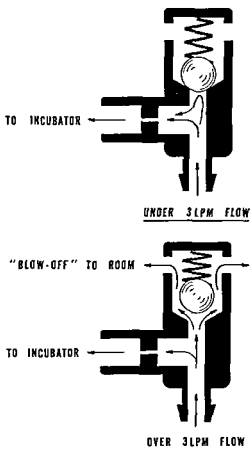


FIG. 7-4. "Blow-off" type oxygen limiting valve. When the flow of oxygen exceeds 3 liters per minute the excess escapes into the room. (Courtesy Air-Shields, Inc. Hatboro, Pa.)

Prone Versus Supine. Kravitz and co-workers demonstrated that the respiratory rate of premature infants was more rapid in the prone than in the supine position and that the difference was greatest in the smallest and youngest infants (see Chap. 14).

✓ Rossier recommended that premature infants be placed in a supine position with the shoulders elevated so that the abdomen is at a lower level than the thorax (Fig. 7-5). He demonstrated in dissections of fetuses that the very short falciform and coronary ligaments virtually unite the liver with the inferior aspect of the diaphragm and the sternum. He postulated that in the horizontal position



FIG. 7-5. The position for premature infants recommended by Rossier. With the infant supine, a folded towel is placed under the back so that the abdomen is at a lower level than the thorax. In this position the neck is in slight hyperextension. (Redrawn from Rossier, A.: "Clinical Study of Respiration in Premature Infants." In *Anoxia of the Newborn Infant*. Oxford, England, Blackwell Scientific Publications, 1953.)

the voluminous liver is forced back toward the dome of the diaphragm, reducing the respiratory capacity. Rossier considered that the funnel-chest deformity so commonly seen in very small premature infants may be due to the pull of the liver on the sternum.

We have adopted Rossier's suggestions in our nursery but have not made any critical studies.

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The Examination of the Newborn Premature Infant

The most neglected aspect of the management of premature infants is that of physical examination. This has been the result of a widespread belief that too much handling of the infant is harmful. There is no reason to accept this taboo, provided gentleness and reasonable dispatch are applied in the examination. Since disease occurs more frequently and the clinical signs are more subtle in these babies than in term infants, the need for careful physical examination is greater. There can be no argument that the examination should be performed cautiously with full appreciation of the fragility of skin, mucous membranes, bones, and viscera.

It is reasonable to delay physical examination after the infant is admitted to the nursery to allow body temperature to stabilize. However, this examination should not be postponed for more than one or two hours.

GENERAL PHYSICAL OBSERVATION

Color

The color of the infant is usually pink or red except for the hands and feet, which may have a dusky bluish tinge (acrocyanosis).

Cyanosis. When oxygenation is imperfect, cyanosis becomes generalized. An odd feature of color change in these infants is the delayed shading from pink to blue, even after apparent complete respiratory arrest (see Chap. 23).

Ecchymoses. Extensive ecchymoses of the skin, especially after delivery from the breech position, are often confused with cyanosis. Arajärvi studied the responsiveness of the premature infant's capillaries and suggested that the unusual extent of hemorrhages after slight trauma may be due to failure of capillary contraction around the damaged vessel.

A striking condition characterized by diffuse ecchymoses of the face, neck, and upper thorax is occasionally seen in premature infants. A similar appearance seen in adults after crush injuries of the chest is called "traumatic asphyxia." This extravasation of blood is attributed to a sudden rise of intrapleural pressure causing a forcible ejection of blood out of the thorax into the valveless veins of the head and neck.⁹ Although a similar mechanism is conceivable in infants there is no evidence on this point. Despite their alarming appearance these infants usually are not distressed.

- ✓ **Harlequin Color Change.** Neligan and Strang called attention to bizarre attacks of color change occurring in some premature infants during the neonatal period. This phenomenon, termed the "harlequin color change,"^{7, 11, 20, 39} is precipitated by placing the infant on his side. The upper half of the body is pale and the lowermost half remains pink or by contrast red. A clear line of demarcation (vividly shown in a color photograph by Birdsong and Edmunds) running exactly in the midline divides the two colors. When the infant is turned to the opposite side, after an interval of one-half to one minute the now-upper half blanches and the dependent half becomes suffused. Each attack terminates spontaneously after several minutes or when the infant stirs or cries. The significance of this vasomotor phenomenon is unknown. In our nursery it has been observed in otherwise asymptomatic infants.

Pallor. Generalized pallor should raise the possibility of fetomaternal transfusion or postnatal hemorrhage (see Chap. 20). In a study of 17 examples of fetomaternal transfusion O'Connor *et al.* observed that 7 of the infants were prematurely born.

Jaundice. Allen suggested that early jaundice in newborn infants (see Chap. 13) can be detected more accurately with the aid of bright illumination from fluorescent lamps than in incandescent light.

Activity and Posture

- ✓ **Levels of Consciousness.** Newborn premature infants are usually somnolent. However, St. Anne Dargassies⁴² distinguished between three levels of consciousness in these infants—sleep, torpor, and wakefulness. In sleep the infant makes no spontaneous movements and no response to touch; the extremities can be manipulated without eliciting a reaction. Torpor is distinct from sleep since in this state the infant can be roused by light cutaneous stimulation.
- ✓ **Posture.** During the first few hours after birth the position of the infant is the same as that in utero.⁴² The term infant assumes a posture of generalized hypertonic flexion of all four extremities. In contrast to this the premature in-

fant of six months' gestational age lies on his side with the upper extremities flexed, trunk slightly curved inward, and the lower extremities semiflexed at the knee (Fig. 8-1). The thighs are abducted and only slightly flexed on the abdomen. After several hours the infant begins to change his position and gradually uncurls. After several days the small infant (birth weight under 1500 Gm.) lies on his back, the upper extremities extended somewhat, and later may even lie fully extended along the trunk. When the premature infant is awake his lower extremities are rarely extended. Marked flexion and abduction of the thighs produces the familiar froglike position of the lower extremities

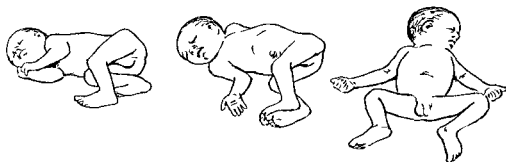


FIG. 8-1. Posture of premature infant: (Left) Immediately after birth, (center) several hours later, and (right) after several days. (Redrawn from St. Anne Dargassies, S.: *La maturation neurologique du prématuré* [The neurologic maturation of the premature infant]. *Neonatal Studies* 4:71, 1955.)

Spontaneous Activity. Contractions of isolated muscles of the face and extremities are often observed in infants as they lie quietly in a state of semiconsciousness (torpor). Slow, prolonged contraction of the facial muscles, quivering movements, or transient smiles are characteristic. There may be fine movements (flexion and extension) of the fingers and fanlike movements of the toes.

Repeated stereotyped movements of the upper extremities which resemble catatonia are described in these infants.⁴² An arm may suddenly extend, contract, and then rise slowly to the vertical position where it remains immobilized for a few seconds. Periods of generalized activity ("tempest of movements") are characteristic of very small premature infants and are unlike those of more mature babies. The movements may be spontaneous or provoked by the slightest stimulus; often they occur without crying.

Neuromuscular Excitability. Nieminen studied the nerve-muscle excitability of premature infants in response to galvanic stimulation. He found considerably lowered electric excitability as compared with term infants.

EXAMINATION OF SPECIFIC PARTS AND SYSTEMS

SKIN AND APPENDAGES

The skin of very small infants has a gelatinous appearance. On palpation the semblance to gelatin is even more striking

Vernix Caseosa. The skin is usually covered by only a scant amount of vernix caseosa, which rapidly disappears except in the skin folds. Saunders suggested that this material, which is rich in estrogen,²⁷ may influence heat control in premature infants.

Edema. Pitting edema is rarely present at birth. However, by twenty-four hours of age some pitting can be demonstrated in almost all infants whose birth weight is less than 2 kg. In these infants the distribution of edema, on the dorsum of the feet and the lower legs and hands, is the same as in newborn infants with gonadal dysgenesis.¹⁹

Desmond and Sweet noted that the concentration of protein in the plasma of premature infants was low. However, the protein values in edematous and non-edematous infants were not significantly different.

Subcutaneous Fat. One of the outstanding characteristics of premature infants is the small amount of subcutaneous fat. Since the fat is deposited rapidly in the weeks just before term, even the infant who is only slightly premature may have a relatively small amount of subcutaneous fat (see Chap. 4).

Skin Turgor. After the turgor imparted to the skin by subcutaneous fluid is lost, the dearth of subcutaneous fat makes the thin skin of these infants loose and wrinkled. Laron described a method of measuring skin turgor quantitatively, but standards for premature infants have not been established.

Petechiae and Hemangiomas. Petechiae should not be confused with ecchymoses, which, as noted, are commonly seen. Petechiae should suggest the presence of a thrombocytopenia (see Chaps. 19 and 20). Superficial hemangiomas of the skin are rarely seen at birth (see Chap. 12).

Appendages

Hair. Lanugo may be present on the forehead, the sides of the face, and the extremities. The hair of the head is scanty, and eyebrows are usually absent.

Nails. The length of the fingernails at birth was used in the past as an index of the degree of prematurity. Ylppo⁵² expressed considerable doubt concerning the validity of this criterion.

Breasts. The nipples and areolae of the breasts are inconspicuous. Parmelee observed, and we agree, that breast engorgement and lactation rarely if ever occur in premature infants.

HEAD

Skull. Parmelee emphasized that the fontanelles of the skull are small in the premature infant; enlargement usually does not take place for one to two weeks after birth. The bones of the skull are soft, and marginal craniotabes is a constant finding.

Scalp. Cephalhematoma and caput succedaneum are uncommon in these infants. Curious round ("punched out") skin defects of the scalp such as those reviewed by Abt have been observed not infrequently in our nursery.

Pseudohydrocephalus. The disproportionately large head size⁵³ is sometimes referred to as "pseudohydrocephalus of prematurity." The differentiation between true hydrocephalus and relative megacephaly in these infants often presents a serious problem (see Chap. 4).

EYES

The eyes of premature infants in the neonatal period have received considerable attention because of *retrolental fibroplasia* (see Chaps. 9 and 16).

External Observations. Inflammation and edema of the eyelids may result from the instillation of silver nitrate solution.

Sjogren studied the secretion of tears in newborn children and found practically no lacrimal secretion in 57 per cent of premature infants as compared with 13 per cent of term infants.

Pupillary reactions can be elicited even in very small premature infants.

Ophthalmoscopic Examination

Ophthalmoscopy is difficult in the first week of life because in many small infants the vitreous is hazy. Fletcher and Brandon recorded the least minus lens of the ophthalmoscope necessary to focus clearly on the retinal vessels at the disc margin of 462 premature babies. They found a mild degree of myopia (0 to -6 diopters) in infants weighing more than 1700 Gm. at birth. The infants weighing less than 1250 Gm. at birth exhibited a myopia of from -10 to -20 diopters.

Although considerable disagreement persists concerning the incidence of retinal hemorrhages in newborn infants, there is agreement that the incidence is not strikingly higher in premature than in mature infants.^{8, 26}

EARS

Pinnae. The pinnae are usually poorly supported by cartilage and fold into bizarre positions.

- ✓ Hilson found that malformed external ears, particularly if asymmetrical, were associated with congenital malformations of the genitourinary tract.

Otoscopic Examination

Visualization of the eardrums is difficult and is usually omitted in routine examination. *Otitis media* is observed not infrequently at necropsy, but the diagnosis is rarely made during life.

NOSE

Infants who are in marked respiratory distress may exhibit distention of the *alae nasi* (see Chap 14).

Bilateral choanal atresia is a rare cause of respiratory difficulty and may be definitely ruled out by passing a catheter through the nose into the pharynx.⁶

MOUTH AND PHARYNX

The difficulty in visualizing the mouth and pharynx of very small infants usually makes this portion of the examination unsatisfactory. Care must be taken to prevent trauma to the epithelial surfaces during examination.

"Mucus." Varying amounts of fluid collect in the oropharynx. In nursery parlance the fluid is called mucus because it is viscid; however, its origin is unknown. Jost's observations (in decapitated rabbit fetuses) which indicated that the lung produces fluid may be pertinent.

The accumulation of large amounts of frothy fluid should suggest esophageal atresia.

Blood-tinged Fluid. When blood or blood-tinged fluid is encountered it is important to determine quickly whether this represents active bleeding or swallowed maternal blood³ (see Differentiation Between Maternal and Infant's Blood) *Dark-red blood in the oropharynx may indicate pulmonary hemorrhage.*

Vomitus. Regurgitation is encountered very commonly in premature infants. Forceful vomiting occurs infrequently. The presence of bile-stained vomitus is presumptive evidence of intestinal obstruction.

NECK

The submental region and neck are often overlooked in the examination of small infants because they remain hidden until the head is retracted. A full in-

spection may reveal fistulas, congenital goiter, etc., that would otherwise be unsuspected. We have on occasion encountered extensive weeping excoriations of this area in very small infants.

THORAX

Appearance. A disproportionately small thorax is a stigma of prematurity (see Chap. 4). The relative disproportion between the thoracic and abdominal girths results in a pearlike shape of the trunk in very small infants.

The soft costal grid, depressed sternum, and barely perceptible thoracic excursions are notable as one watches these infants breathe. Ecchymoses of the thoracic wall should suggest fracture of the ribs.

Auscultation

Auscultation of the chest is difficult with an ordinary stethoscope. Dr. Richard L. Day devised an improved sensing piece for premature infants which we have adapted to an electronically amplified stethoscope (Fig. 8-2). However,

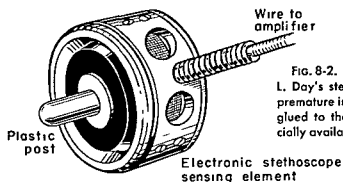


FIG. 8-2. An adaptation of Dr. Richard L. Day's stethoscopic sensing piece for premature infants. A small plastic post is glued to the diaphragm of a commercially available electronic stethoscope.

even with amplification it is difficult to interpret the breath sounds in these infants. The cardiac sounds can be heard very well with amplification, and not infrequently cardiac murmurs are heard (see Chap. 14).

Respiratory Patterns

- ✓ **Rhythms.** The respiratory rhythms of quiet, apparently normal premature infants have been studied by many observers and were reviewed by Cross. The commonest rhythm is the steady cogwheel type, with no pause between inspiration and expiration; the so-called adult respiratory rhythm (inspiration, expiration, pause) is next in frequency; other patterns (inspiration, pause, expiration) also occur.

Sighs interrupting regular breathing are observed frequently. Sometimes the

sigh is followed by an apneic pause. Periodic breathing—defined by Cross as consisting of two or more periods of breathing per minute separated by an apneic pause of 3 seconds or more—is commoner among the smallest premature infants.⁴⁰ Cross considers it likely that anything that increases the minute volume of respiration (increased oxygen,⁵⁰ restlessness, etc.) reduces the incidence of this type of respiration.

Rate. It is difficult to define the normal values for respiratory rate for premature infants, principally because of the uncertainty inherent in any definition of a "normal premature infant." Furthermore, it is virtually impossible to specify the "normal conditions" that should prevail when these values are obtained (Table 8-1).

Miller studied the trends of respiratory rates in the neonatal period and described several respiratory patterns (see Chap 14). He noted that two patterns were associated with a low mortality rate and thus may be considered to be "normal." Infants in the first group breathe at approximately 40 respirations per minute from birth on without significant fluctuations in rate. Those in the second group exhibit rates over 60 in the first hour, show no significant increase, and subsequently decline. A significant increase is considered to be 15 or more respirations per minute above the average rate obtained in the first hour after birth.

TABLE 8-1 MEAN RESPIRATORY AND CARDIAC RATES AT 12 HOURS OF AGE IN "NORMAL" PREMATURE INFANTS

	Birth weight (Gm.)		
	1000 or less	1001- 1500	1501- 2000
Respiratory rate			
No infants	16	67	119
Mean rate/min.	57	56	55
Mean $\pm$ 2 S D	33-81	24-88	23-87
Cardiac rate			
No infants	5	41	40
Mean rate/min	135	138	139
Mean $\pm$ 2 S D	110-162*	114-162	105-173

The means were computed from measurements made in asymptomatic infants who survived the first week of life. The air temperature (88° F, 31.1° C) and relative humidity (80-90 per cent) were the same for all weight groups. All infants were supine and were not receiving supplemental oxygen.

* Observed range

Cardiac Rate

We have attempted to estimate the "expected" first-day cardiac rates in a small group of infants who survived the first week of life and were maintained in a uniform environmental condition (see Table 8-1).

Blood Pressure

Londe made many measurements of the blood pressure in the lower extremities of premature infants. Two inflatable cuffs were placed on the thigh, and the oscillations of the pulse detected in the distal cuff were transmitted and recorded. The systolic pressure was lower on the first day of life than later, the values ranging from 20 to 50 mm. Hg for infants weighing less than 1900 Gm. Systolic blood pressure increased with birth weight and with postnatal age. Estimated diastolic pressures ranged from 26 to 46 mm Hg and changed very little with size and age.

Ashworth and others described a simple device for obtaining the systolic blood pressure (arm) of the newborn which may prove to be quite practical for use with premature infants (see Appendix 10). Two cuffs are used in the manner described by Londe; a visual signal (oscillation of liquid in a capillary tube) is utilized as a pulse indicator.

Holland and Young measured the neonatal systolic blood pressure of premature infants (arm), using the method of palpation. A small number of observations revealed a range of 35 to 70 mm Hg and an apparent positive correlation with birth weight. Many more precise observations are necessary to establish satisfactory standards.

The flush method of obtaining blood-pressure readings¹⁶ has been used in premature infants; a table of values is given in Appendix 10.

ABDOMEN

The abdomen is usually full and soft, ballooning out with each inspiration. The wall is thin and the viscera are easily palpated. With slight distention the intestinal pattern is visible. Distention in small infants very quickly embarrasses respirations, and cyanosis may often call attention to an intra-abdominal complication. The sudden appearance of marked distention should suggest rupture of the stomach in premature infants (see Chap. 18).

Palpation of the abdomen should be as gentle as possible. The liver margin and spleen tip are usually palpable. The kidneys are situated relatively low in the flanks and are usually easily palpable.

If anal atresia has not been ruled out in the delivery room, this should be

done at the time of the definitive physical examination by passing a small, soft catheter into the rectum.

GENITAL TRACT

The more immature the infant, the less well developed are the external genitalia.

Female. The labia majora are incompletely developed, but the labia minora and the clitoris are prominent. Inexperienced observers have often mistaken a female for a male infant.

We have observed pseudomenstruation of the newborn in a few female premature infants.

Male. The testes are frequently undescended. Scorer observed that at birth one or both testes were undescended in 30 per cent of 142 premature infants as compared with 3 per cent of 1500 term infants. He examined all infants with incomplete descent at birth and found that the testicle appeared in the scrotum during the first month of life in 61 per cent of 23 survivors in the premature group and 50 per cent of 48 term infants.

NEUROLOGIC EVALUATION

The reader is referred to the detailed descriptions of Gesell and to the monographs of the French neurologists Thomas *et al.* and St. Anne Dargassies⁴¹ for complete accounts of the behavior of premature infants and the technique of evaluating their neurologic status. The latter author⁴² suggested that the evaluation of neurologic maturation is as reliable as head circumference and body length and weight in fixing the fetal age of the infant who is born prematurely.

The importance of improving our ability to recognize damage to the nervous system among these subjects cannot be overestimated. An extensive experience with long follow-up will be necessary to establish the significance of judgments made in the neonatal period.

Techniques and Normal Responses

The neurologic examination requires considerable patience. The examiner must be prepared to wait until the infant is quiet, and often he must return for re-evaluation of the responses, since many are inconstant. Much of the investigation can be carried out by observation, simple touch, and gentle manipulation.

Ciliary Reflex. In the supine infant a light touch on the eyelashes results in the closure of one or both eyes.⁴¹

- ✓ **Photomotor Reflex.** The photomotor reflex is initiated by directing a bright light against one closed eyelid. A positive response consists of a strong tonic contraction of the orbicular muscles of both eyes which lasts beyond the period of stimulation.⁴¹
- ✓ **Doll's-eye Sign.** If the infant's eyes remain open long enough for observation, turning his head from side to side should reveal that the eyeballs move in the direction opposite to the movement of the head.⁴¹
- ✓ **Setting-sun Sign.** The setting-sun sign (see Chap 13) may be elicited in some premature infants with no other signs of neurologic damage.⁴⁹
- ✓ **Reflex of the Cardinal Points.** A cotton applicator is used to touch lightly (several times in succession) the right and left angles of the lips followed by the median lobes of the upper and lower lips. A positive response consists of turning the head and tongue toward the stimulus, and deflection of the corner of the mouth.⁴¹
- Moro Reflex.** To elicit the Moro response a very small infant may be lifted by the hands when supine sufficiently to change the position of the neck without actually raising the pendent head. When the hands are released the trunk falls back to its original position and this initiates the reflex. Extension of the arms, extension of the fingers, and flexion of the legs are fairly constant. The final adduction of the arms (embrace movement) is the least constant component.⁴¹
- ✓ **Grasp-and-Flexion Reflex.** The grasp is investigated by lightly pressing a small rod into the metacarpophalangeal groove. This produces flexion of all the phalanges. When traction is exerted on the rod grasped in the infant's hand the flexors of the forearm, arm, and shoulder are brought into play, this is the tonic reflex of the flexors, which makes it possible to raise almost the entire weight of the infant by lifting the rod.⁴¹

Tactile stimulation of the metatarsophalangeal groove or pressure on the plantar surface causes flexion of the toes.⁴¹

Crossed-Extension Reflex. With the infant supine the reflex of crossed extension is produced by immobilizing one leg in extension and rubbing the sole of the foot (Fig. 8-3). The contralateral (free) leg first flexes and then extends, with adduction of the extremity (as if in defense) and extension of the toes like a fan. Adduction is the least constant component of this response.⁴¹

Reflex of Trunk Incurvation. The reflex of trunk incurvation is produced by raising the prone infant in the palm of the examiner's hand and repeatedly pricking the skin of the trunk between the twelfth rib and the iliac crest (Fig. 8-4). Normally the trunk curves inward with wrinkling of the skin on the side which has been stimulated.⁴¹

RESULTS OF NEUROLOGIC EXAMINATION

Some of the results of St. Anne Dargassies' ⁴² systematic examination of 100 premature infants are summarized in Table 8-2.

PHYSICAL MEASUREMENTS

Measurements of the infant's external dimensions constitute an important part of the physical examination, not only for the purpose of improving the estimate of the degree of prematurity but also as a baseline for further measurements to evaluate postnatal growth

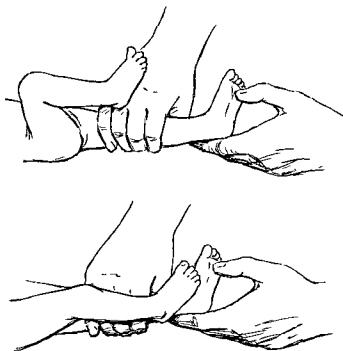


FIG. 8-3. Crossed-extension reflex. (Top) With immobilization of the leg in extension, stimulation of the sole of the foot produces flexion of the contralateral leg followed by (bottom) extension, fanning of the toes, and adduction of the free leg. (Redrawn from Thomas, A., Chesni, Y., and St. Anne Dargassies, S.: *Examen Neurologique du Nourrisson* [Neurologic Examination of the Nursling]. Paris, La Vie Medicale, 1955.)

The greatest occipitofrontal head circumference, chest circumference at the nipple line, and a measurement of length (crown-heel or crown-rump) should be obtained. Standards are given in Chapters 1 and 4 and in Appendix 9.

SUPPLEMENTS TO PHYSICAL EXAMINATION

Infants and children have benefited greatly from recent technologic advances in roentgenology, the analysis of body fluids, instrumentation, and other procedures that the physician uses to improve his discernment. Such diagnostic aids are sorely needed in the care of premature infants; often they are not available. Often the difficulty of adapting many of the existing techniques and apparatus to small subjects has precluded their use. However, an important stumbling

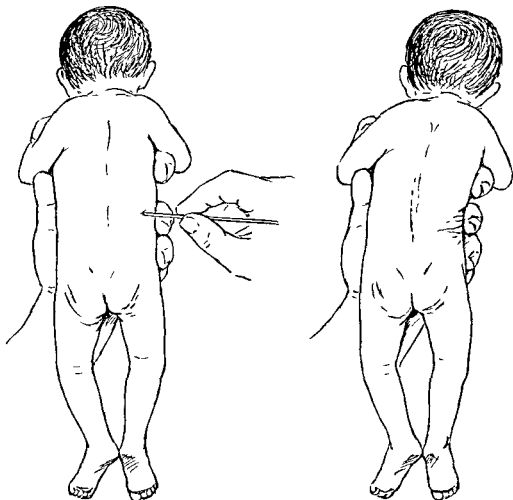


FIG. 8-4. Reflex of trunk incurvation. (Left) With the infant held in the palm of the examiner's hand the skin of the trunk between the twelfth rib and the iliac crest is repeatedly pricked. (Right) The trunk curves toward the side which has been stimulated. (Redrawn from Thomas, A., Chesni, Y., and St. Anne Dargassies, S.: *Examen Neurologique du Nourrisson* [Neurologic Examination of the Nursing]. Paris, La Vie Medicale, 1955.)

TABLE 8-2 NEUROLOGIC STATUS OF THE PREMATURE INFANT AT BIRTH
Some of the Signs Obtained by St Anne Dargassies in a Study of 100 Infants

	<i>Birth weight and approximate gestational age</i>			
	<i>1000 Gm and less, 6 mo</i>	<i>1000-1200 Gm , 6½ mo</i>	<i>1200-1500 Gm , 7 mo</i>	<i>1500-1800 Gm 7½ mo.</i>
Eyes				
Ciliary reflex		Present in all groups		
Photomotor reflex		Present in all groups		
Doll's eye reflex		Present in all groups (difficult to test)		
Pupillary reflex		Present in all groups (difficult to test)		
Ears Response to sound		Present in all groups (motor response variable)		
Cardinal points	Difficult to initiate response, likely to be incomplete	Repeated stimulation is necessary, turning of head is only partial, response rapidly exhausted		Prompt response
General reflexes				
Patellar tendon	Difficult to elicit, may suddenly appear and involve contralateral adductors			
Sucking	Present, easily exhausted			Present
Swallowing	Present, easily exhausted			Present
Gagging		Present in all groups		
Moro	Present in all groups, may be absent in the presence of non neurologic neonatal complications			
Upper extremities				
Passive tone	Extension of the arms is not opposed		Resistance to extension except during sleep	
Grasp	Absent		Present	
Tonic flexors	Present on repeated stimulation		Present	
Lower extremities				
Flexion of toes		Present in all groups		
Crossed extension		Feeble and incomplete		
Spontaneous movement	Varying from immobility to great activity, jerks, tremors, slow majestic movements, frequently generalized and asymmetrical	Spontaneous movements, but progressively fewer during the first week	Movements are moderate, impeded by increasing hypertonicity	
Provoked movement	Rapid withdrawal of the stimulated extremity, repeated stimuli lead to diffuse movements involving trunk and eventually the head		Response tends to be local, less total	Only localized movement
Trunk incurvation		Constant in all groups		

From St Anne Dargassies ⁴²

block has been the general belief that these infants should not be touched or disturbed in any way. It is unlikely that there will be any significant improvement in the care of premature infants until this attitude changes.

EXAMINATION OF THE BLOOD

Hemogram

There is considerable variation in the hemograms of prematurely born infants. Interpretation is particularly difficult in the first few days of life because of the influence of the time of clamping of the cord, gestational age, site of blood sampling (capillary or venous), etc.

Wolff and Goodfellow compared the blood values of infants of low birth weight with those of larger premature infants. They found that in general the smaller infants exhibited lower levels of hemoglobin and erythrocytes and higher values for reticulocytes and leukocytes. A summary of their determinations of normal values in the first three months of life appears in Appendix 10 ✓

Hematocrit

The hematocrit of capillary blood of premature infants was determined by Blanc, according to the method described by McGovern and others. A summary of his values is given in Appendix 10.

Chemical Analysis

Chemical analysis of blood of very small premature infants, until recently not feasible, can be made by the use of microtechniques which are now available for use in the clinical-chemistry laboratory. Kaplan and del Carmen described methods for quantitative analysis for glucose, nonprotein nitrogen, inorganic phosphorus, calcium, alkaline phosphatase, bilirubin, sodium, potassium, chlorides, total cholesterol, total protein, and albumin; pH determination; and the cephalin-flocculation test. The quantities of plasma or serum required for analysis range from 0.02 to 0.1 ml., amounts which can be provided by capillary blood obtained by heel prick. "Normal" values of some chemical constituents of capillary blood are given in Appendix 10.

López-Banús described a method of obtaining venous blood from scalp veins of small infants, a modification is shown in Figure 8-5.

Blood Culture

A modification of the López-Banús method³¹ of obtaining venous blood may

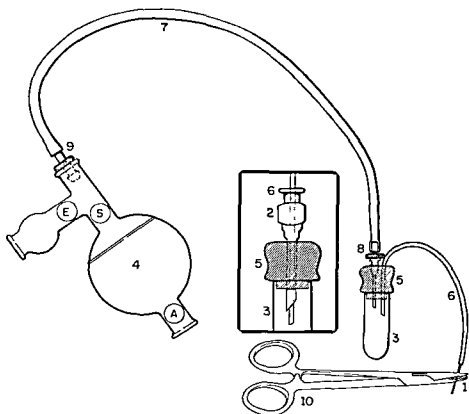


FIG. 8-5. Modification of López-Banús' method for collecting blood from scalp veins. The set is prepared as follows: A small collecting tube (3) is capped with an apron-type rubber cork. A large bore needle (2) is inserted into the cork and the free end of a catheter from a scalp-vein infusion set* (6) is passed into the tube through the needle. When the needle is removed the catheter remains in place. Another needle (8) is inserted into the cork and connected by means of a rubber tube (7) and male Luer adapter (9) to an aspirating bulb (Propipette). The catheters, plastic tubing, and Propipette are exposed to ultraviolet light; the needles, forceps, and sponges are autoclaved.

The set is used as follows: Air is exhausted from the aspirator by pressing the bulb (4) while pinching valve A. Release of the valve prevents air from refilling the bulb; the system is closed. Using a hemostat (10), the Murphy-Gardner needle (1) is inserted into a scalp vein against the flow of blood. When valve S is pinched, blood is aspirated into the collecting tube. (From Ducharme, J. R., and Grumbach, M. M.: A modification of the López-Banús method for collecting samples of venous blood from young infants. *Pediatrics* 23:756, 1959.)

*Silicone-lined with Siliclad, Clay-Adams, Inc., N.Y.C.

also be used for blood cultures in small subjects.* Femoral vein puncture should not be performed in premature infants (see Chap. 19).

Eitzman and Smith demonstrated that the value of blood cultures obtained in the newborn period can be improved by applying hexachlorophene, ethanol, and iodine to the skin before venipuncture to prevent contamination of the blood specimen with organisms from the skin. We have adopted their suggestion, except for the order of application, and prepare the skin as follows: (1) Wash the scalp site with 20 circular strokes of a cotton pledget soaked with a skin detergent containing 3 per cent hexachlorophene. (2) Apply 2 per cent iodine solution with cotton-tipped swabs. (3) Remove iodine with swabs soaked in 70 per cent ethanol. Allow the skin to dry.

LUMBAR PUNCTURE

Technique

Otila performed 200 lumbar punctures in 100 "normal" premature infants. He observed that punctures were most often successful when the infants were placed in the sitting position with the dorsal and lumbar spine mildly flexed. He used needles 4.0 cm. in length and 1.2 mm. in diameter (approximately 18-gauge), with a short bevel and fitted with a stylet. The canal was entered between the first and second lumbar vertebrae (about 2 cm. above a line connecting the iliac crests). The depth of insertion varied from 0.5 cm. in very small infants to a maximum of 2.5 cm. in larger and older infants. Otila removed as much as 5 ml. of fluid from infants whose birth weight was 1500 Gm. or less and 8 ml. in larger infants. No untoward effects were observed. A syringe was not used; in most instances the fluid dripped out freely.

Glaser used a fine hypodermic needle (27-gauge) fitted with a wire obturator for lumbar puncture in premature infants. He also recommended that the infant be held in the upright sitting position in order to distend the lumbar portion of the *dural sac*. Our experience using small needles with infants lying on their sides has not yielded the proportion of atraumatic successes reported by Otila and by Glaser.

Cerebrospinal Fluid Findings

A summary of the cerebrospinal fluid findings in "normal" premature infants is given in Appendix 10.

The fluid in these infants is usually yellow in color. The cell count and the

* Disposable set for obtaining blood samples from infants, Cutter Laboratories, Berkeley, Calif., and Vacutainer blood culture bottle, Becton, Dickinson and Company, Rutherford, N. J.

amount of protein are considerably higher than in the cerebrospinal fluid of term infants. Otila found that concentration of sugar was often at or above the blood sugar level determined simultaneously.

✓ DIFFERENTIATION BETWEEN MATERNAL AND INFANT'S BLOOD

Apt and Downey described a quick method for determining whether red blood that may be encountered in an infant's gastric fluid and stools is swallowed maternal blood or gastrointestinal bleeding in the infant. A hemoglobin solution is prepared by mixing a small amount of the bloody material with tap water in the proportion of 1 part blood to 5 parts water. The mixture is centrifuged to obtain a supernatant pink solution free of solid matter. Approximately 1 ml. of 0.25N NaOH is mixed with 5 ml. of the hemoglobin solution and the color is observed after 5 minutes. If the solution contains maternal blood (adult hemoglobin) the color changes to brown-yellow, if the infant's blood is present, the fetal hemoglobin remains predominantly pink.

OTHER DIAGNOSTIC AIDS

Many physicians are unfamiliar with the appearance of roentgenograms, electrocardiograms,³⁰ and electroencephalograms in premature infants because such diagnostic aids are rarely employed in these subjects. It can only be hoped that technical adaptations^{13,23,46} and increased interest will improve this unfortunate situation.

Studies of the mother may be helpful in elucidating problems of narcosis, infection, anemia,³⁶⁻⁵⁴ thrombocytopenia, etc., manifested in the infant.

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Routine Procedures in Care of the Premature Newborn

Following the examination of the newly admitted infant various routine procedures are carried out in most nurseries for premature infants. Many of these routines have never been subjected to critical testing and therefore lack the support of satisfactory evidence of effectiveness. Harmful influences of drugs, environmental conditions, and so on, have sometimes gone unrecognized for long periods of time because evaluation is so difficult. For these reasons it must be understood that no "routine" for the care of the premature infant should be regarded as immutable and above criticism. Some procedures are, however, standardized and should be carried out unless contraindicated.

The considerations which guide the decisions concerning the conditions of the environment have already been discussed. The duration of the initial fast, the types of feeding, and the administration of vitamins (including vitamin K) are discussed in the next chapter.

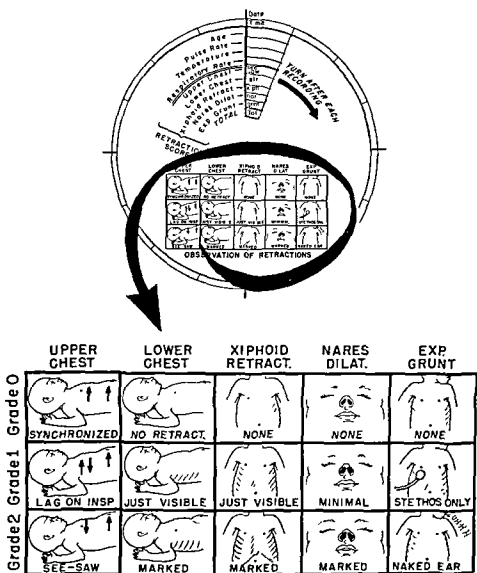
ROUTINE OBSERVATIONS

Vital Signs

Routine observations especially in the first days of life are of particular importance in the management of premature infants. Respiratory rate, axillary temperature, pulse rate, and "retraction score" are important vital signs. In our nursery these are recorded by the nurse at six-hour intervals during the first five days of life (Fig. 9-1).

Passage of Stool and Urine

The time of passage of the first stool and urine should also be recorded. Kramer and Sherry determined these times in 200 normal premature infants (Table 9-1). They recommended close observation for possible gastrointestinal



OBSERVATION OF RETRACTIONS

FIG. 9-1. Vital-signs wheel. Pulse rate, body temperature, respiratory rate, and respiratory performance are recorded on a data sheet at 6-hour intervals. To encourage the examiner to make each observation without knowledge of prior judgments, the preceding record is masked with the wheel. An index of respiratory distress is determined by grading each of five arbitrary criteria; grade 0 indicates no difficulty, grade 1 moderate difficulty, and grade 2 maximum respiratory difficulty. The "retraction score" is the sum of these values; a total score of 0 indicates no dyspnea, whereas a total score of ten denotes maximal respiratory distress. (Courtesy of Mead Johnson & Company, Evansville, Ind.)

TABLE 9-1 TIME OF PASSAGE OF THE FIRST STOOL AND FIRST URINE IN 200 PREMATURE INFANTS

Time	First stool			First urine		
	No. infants	%	Cumulative %	No. infants	%	Cumulative %
Delivery room	26	13		45	22	
Hours						
0-12	63	32	45	86	43	65
12-24	71	36	80	52	26	91
24-48	28	14	94	17	10	100
Over 48	12	6	100			100

From Kramer and Sherry ¹⁸

or urinary-tract obstruction in infants who fail to pass stool or urine by the age of 24 hours

Abnormal Signs

Melena. The passage of grossly bloody stools is not a rare event among premature infants in the neonatal period and requires prompt definition (see Chap. 8).

Apt demonstrated that when large amounts of blood (35 to 40 ml.) were placed in the stomach of newborn infants bloody stools appeared from 9 to 30 hours later and were passed for periods lasting from 12 to 45 hours.

Other Signs. Other important signs during the early days of life are abdominal distention, blood- or bile-stained vomitus, convulsions, apnea, and cyanosis.

The time of appearance of skin icterus may also be regarded as an important sign (see Chap. 13)

CARE OF THE SKIN

Controlled studies of the relative value of different techniques of skin care have not been performed on premature infants.

Dry Care. "Dry care" consists of the removal of excess blood or debris from the face and scalp on admission to the nursery and, after defecation, wiping the soiled skin with sterile, nonmedicated oil. The remainder of the skin is left untreated. This method has been used in many nurseries for premature infants, including ours, for many years.

Hexachlorophene Bathing. Farquharson and co-workers proposed the use of hexachlorophene bathing for the control of pyoderma among newborn term in-

fants. This method of skin care has been considered to be effective in reducing both the incidence of skin infections and the rate of nasal and skin colonization by staphylococci among term infants.^{2, 21}

PROPHYLACTIC CARE OF THE UMBILICAL STUMP

Triple-Dye. Jellard studied the influence of the stump of the umbilical cord as a reservoir for the propagation of staphylococci among term infants in a maternity hospital nursery. In a controlled trial of the influence of daily painting of triple-dye on the cord stump and the surrounding skin she demonstrated that this treatment was effective in reducing air-borne contamination and staphylococcal cross-infection.

For the past 1½ years we have used a modification of this formula in the nursery for premature infants—a solution of brilliant green 2.29 Gm., acriflavine 1.14 Gm., crystal violet 2.29 Gm., and water 1000 ml. Our favorable impressions have not been subjected to a critical test.

Hexachlorophene Powder. The use of hexachlorophene dusting powder on the umbilical stump and surrounding skin of premature infants was shown by Gillespie and associates to reduce the staphylococcal colonization of the unhealed umbilicus.

PROPHYLACTIC TREATMENT AGAINST INFECTION

Very small premature infants usually exhibit few recognizable signs early in the course of serious infections. Moreover, treatment is often unsuccessful. This frustrating clinical problem has been considered at length and a solution has been sought by many.

In contrast to the investigations which have led to an improvement in the care of newborn domestic animals,¹⁷ studies of human infants born prematurely have failed to provide clear-cut evidence on which to base a rational treatment to improve the resistance of these individuals to infections (see Chap. 19).

Antibacterial Drugs

For several years many have been searching for an agent or combination of agents that is both safe and therapeutically effective in infections among premature infants. No satisfactory regimen has been established.

Indications. In an attempt to improve results in the care of premature infants, some advocated prompt institution of antibacterial therapy at the slightest suspicion of infection and prophylactic therapy for those in whom a high incidence of infection is expected.^{5, 20}

In many nurseries antimicrobial drugs are administered to premature infants born after prolonged rupture of the membranes (more than 12 to 24 hours), and to infants transferred to the unit from an extramural place of birth because the incidence of infections has been observed to be relatively high in these groups of infants.^{3, 5, 6, 8} The effectiveness of this policy has never been established by a critical trial.

Effect on Bacterial Flora. A variety of antimicrobial agents appeared to have no appreciable effect on the bacterial flora of the nose and throat of premature infants studied by Stoppelman and by Gialdroni-Grassi *et al.* However, these investigations did not answer the question of whether the routine administration of drugs can reduce the incidence of disease or the mortality rate among premature infants.

Effect on Mortality Rate from Infection. Dahl studied the results of prophylactic treatment of infection in 292 premature infants. On admission to the nursery each infant was assigned in random order to one of three regimens: (1) long-acting penicillin 300,000 units every tenth day (infants weighing less than 1500 Gm. received half the dose); (2) gamma globulin 2 ml. intramuscularly at the time of admission and at the time of discharge from the nursery; and (3) no prophylaxis. The mortality rate between the second day of life and one month after discharge from the nursery was lowest in the infants who received prophylactic penicillin. Among 96 infants who were assigned to the penicillin group there were 16 deaths; infection was considered to be a contributing cause of death in 1 infant. In the control group (96 infants) there were 24 deaths; infection contributed to death in 7 of the 24 fatalities.

Recommendation. The question of *how* antimicrobial drugs should be used in premature infants—whether they should be given routinely for prophylaxis or only for specific indications—has not been completely answered. For example, the possibility that Dahl's results could be achieved by the administration of penicillin only for specific clinical indications has not been excluded. Moreover, the relative magnitudes of the risk of infection and the risk of therapy with many drugs are still unknown.

At present it seems reasonable to recommend that the decision to administer antimicrobial therapy should be based on the results of careful and repeated examinations of each premature infant for signs of the presence of infection.

Gamma Globulin and Other Blood Products

A number of provocative studies have been made of experimental infections in laboratory animals induced by organisms that are commonly encountered in the serious infections of premature infants.^{10, 19, 22, 24} The protective action of

human gamma globulin in combination with various antibacterial drugs was demonstrated. Conflicting evidence is available concerning the effectiveness of gamma globulin prophylaxis in human premature infants.^{7, 18}

There is some interest in the possible prophylactic and therapeutic use of adult blood and blood products in premature infants (see Chap 19). Until a reliable method can be found for destroying trace quantities of virus (particularly hepatitis virus) in blood,¹⁴ the hazard of transmitting disease will hamper large-scale studies of the influence of the prophylactic administration of blood, plasma, and serum.

OPHTHALMOSCOPIC EXAMINATION

Retrolental fibroplasia occurs rarely in premature infants who receive supplemental oxygen only to relieve cyanosis. However, in order to monitor the policy of oxygen administration in our nursery the eyes of all premature infants are examined at weekly intervals until they leave the hospital. Moreover, this routine has provided many resident physicians with the opportunity to become familiar with the technique of examination and with the appearance of the ocular fundus of very small infants. Satisfactory examination of the eyes of most premature infants is possible at the end of the first week of life.⁴

Technique

Dilation of Pupils. One drop of 2 per cent homatropine hydrobromide and one drop of 10 per cent phenylephrine (Neo-Synephrine) hydrochloride in each eye usually produce full dilation of the pupils in one hour. Blanching of the conjunctivae and lids is noted occasionally in very small infants but systemic reactions occur rarely if at all. Atropine should not be used. Particular care should be taken to insure that the mydriatic drops are fresh and that there is no bacterial contamination of the solutions.

Physicians who have never examined the fundi of small infants are often discouraged in their initial efforts. However, with a little persistence even those without training in ophthalmology can become proficient.

The examiner can usually open the lids with his fingers, occasionally assistance is required. We have never used lid retractors. Large infants who protest can be placated with a moistened, sterile sugarit.

MATURATION OF THE OCULAR FUNDUS

Fletcher classified the fundi of premature infants on the basis of serial examinations of 320 infants. The three stages of maturation defined are depicted in Figure 9-2.

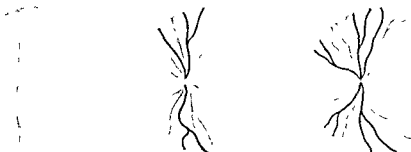


FIG. 9-2. Normal ocular fundi in premature infants. (Left) Immature fundus. The optic disc and blood vessels are barely discernible through the severe vitreous clouding. The disc is oval with indistinct margins and is best seen at -10 to -20 diopters. Small vessels, usually two in number, may be seen emerging from the superior and inferior poles of the disc. Pupillary membranes are common. The periphery of the fundus is gray. (Center) Transitional fundus. Blood vessels are more numerous and larger but still distributed vertically. Vitreous clouding is less. The disc is more circular and the focal distance is less (-8 diopters). Nasal and temporal areas, lacking in visible blood supply, are pale in color. (Right) Mature fundus. The superior and inferior nasal and temporal branches of the retinal arteries and veins are distinguishable, with end branches circling toward the macular and nasal areas. The vitreous is clear. The disc is sharply outlined and pigment may be visible about the margins (-6 to -3 diopters). At the extreme periphery the pink retinal color fades. (Redrawn from Fletcher, M. C.: The developing fundus oculi of the premature infant and its relationship to retrolental fibroplasia. *J. Pediat.* 43:499, 1953.)

At the time of the initial examination (birth to 14 days) the "mature" fundus was seen in none of the infants whose birth weight was less than 1000 Gm., in approximately one-half of those weighing 1500 Gm., and in all whose birth weight was more than 2000 Gm.

The time required (weeks) to attain the mature appearance varied inversely with birth weight. However, in Fletcher's group of infants observed between 1950 and 1953 the incidence of retrolental fibroplasia was high, and it is reasonable to suspect that the rate of maturation was influenced by the high concentration of oxygen in the environment (see Chap. 16). In the past few years we have been impressed that the appearance of the fundus changes from "immature" to "mature" more quickly in infants raised without supplemental oxygen.

It is important to realize that the clinical diagnosis of "mature" fundus does not necessarily indicate that the retinal vessels, in their peripheral outgrowth, have reached the ora serrata and that the infant is immune to the retinal effects of hyperoxia. The extreme periphery of the eye cannot be adequately visualized.

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The Feeding and Nutrition of Premature Infants

The feeding and nutrition of premature infants are difficult because various mechanisms for ingestion and digestion of food are not fully developed. The more immature the infant, the greater the problems. In addition, the needs for rapid growth must be met in the presence of the following handicaps:

- 1 The sucking¹⁹ and swallowing reflexes may be easily exhausted.
- 2 The small capacity of the stomach leads to distention and vomiting.
- 3 The gastric acidity is low.⁷⁰
- 4 The emptying time of the stomach is slow.⁵³

Some infants weighing 2500 Gm. or less do not show these handicaps and may behave as mature infants so far as their digestive tract is concerned.

FEEDING

THE INITIAL FAST AND FEEDING

During the past decade it has been rather generally held that premature infants should not be given water or fluid for periods varying from 12 hours to as long as four days after delivery, until palpable subcutaneous edema is no longer evident. The practice was adopted to reduce the incidence of vomiting and aspiration of fluid in the hope that the pulmonary complications in the neonatal period would be prevented. However, despite strong impressions that fasting is efficacious,²⁷ there is no convincing evidence that it has, in fact, resulted in fewer deaths. On the contrary, Gleiss presented evidence from a controlled trial which indicated that premature infants who received early first feedings (12 to 24 hours) had a significantly lower mortality rate than controls whose first feeding was delayed (average 36 hours).

✓ Ylppö challenged the practice of fasting and advocated that premature infants be fed 5 per cent glucose in water as soon as possible after birth. He suggested

that the total amount for the first day of life should, if possible, equal 5 per cent of body weight, divided into five feedings of 2 to 10 ml. each.

In response to this challenge, Smith⁸³ reviewed the evidence and offered the advice that the initial feeding of premature infants be delayed. In brief, Smith's group⁸⁴ observed that under conditions of thirsting following premature birth, edematous individuals excreted solutes and water in greater quantities than did nonedematous controls of comparable size. This led to the assumption that for unknown reasons some infants are born with relatively large amounts of unnecessary solutes and water that must be excreted by the kidney. The maximum concentrating ability of the kidney was the same in nonedematous and edematous infants, so it was not surprising that the latter kept up a high rate of excretion of solutes and water for a longer time than did the former. Thirsting produced an increase in urine concentration, however, the concentrations of sodium, chlorides, and urea nitrogen in the serum rose.³⁷ Although infants so treated were unable to maintain homeostasis, their clinical status appeared to be satisfactory.

Smith and his colleagues⁸⁴ found that the renal excretion of water and electrolytes could not be hastened by the administration of water (or water and food). Moreover, the hemoconcentration produced by three days without water was rapidly corrected by giving water or water and glucose. They noted that glucose had the effect of conserving body water. Similar observations had been made in adults on limited intakes. In contrast to the findings in adults a sparing effect of glucose on electrolytes and protein was not evident in the newborn infants. The authors concluded that because of the surfeit of electrolytes there is a clinical advantage in providing glucose solutions instead of plain water when fluid is given after fasting in the neonatal period.

O'Brien and others showed that the smallest fluid intake that would maintain normal serum-electrolyte concentration in premature infants was approximately 15 ml. of water per kg. of body weight per day. They estimated that this amount of water may be conserved by reduction of insensible loss by placing the infants in an atmosphere saturated with water. Smith⁸³ reasoned that this method was safer than administering water by mouth.

It is tempting to speculate further concerning the effects of early administration of glucose, calcium, and other nutrients and to cite evidence from experimental animals (see Chaps. 7 and 21), but these speculations cannot be substituted for clinical evidence. The duration of the initial fast and the composition of the initial feedings for premature infants are still highly controversial matters requiring further study. Some of these speculations are being subjected to clinical tests.

Precautions in Early Feeding

It should be emphasized that although the issues have not been settled, the hazard of pulmonary aspiration as the result of overfeeding a newly born premature infant must not be underestimated. When small infants are fed early, the volume of the initial feeds are necessarily exploratory and should be kept very small. Much depends on experienced and vigilant nursing care.

MILK MIXTURES

A detailed comparison of human milk and cow's milk in respect to their composition and effects on the baby starts on page 159 of this chapter.

Human Milk

Many of the advocates of human milk suggest that the early feedings of this milk to small infants be diluted (usually with 5 per cent glucose solution). After several days they are fed either undiluted breast milk⁵⁸ or mixtures of human and cow's milk.^{56, 98} Even the proponents of cow's milk feedings have urged that large premature infants (birth weight over 1750 Gm.) receive milk from their own mothers when it is easily obtainable and that they nurse at the breast as soon as they are able.^{58, 78, 79} Despite these recommendations, in the United States the decline of interest in breast feeding has made human milk a rare commodity and in many places it is virtually unobtainable. In our hospital breast milk has not been used to feed premature infants, with rare exceptions, for more than ten years.

Cow's Milk

Table 10-1 shows two half-skim milk formulas that are used in our nursery to prepare the feedings for infants whose weights at birth are 1750 Gm. and less. The distribution of nutrients is the same in both mixtures. The more dilute mixture (0.67 caloric per ml.) is offered during the first few days of life or during illness, at which time, it is suspected, the concentrating ability of the kidney is minimal. The more concentrated mixture (0.79 caloric per ml.) is given after the early period as a routine to small premature infants who are well. An attempt is made to slowly increase the intake during the first 10 days of life so that at the end of that time the baby is receiving 150 ml. per kg. (approximately 120 calories per kg. per day).

Infants whose birth weight is over 1750 Gm. are fed an evaporated-milk mix-

TABLE 10-1 COW'S MILK MIXTURES USED IN THE PREMATURE
NURSERY OF BABIES HOSPITAL, NEW YORK CITY

HALF-SKIMMED MILK FORMULA—CONCENTRATION NO 1			
<i>Ingredients</i>		<i>Distribution of nutrients (Gm)</i>	
Half-skimmed milk powder	10 Gm	Minerals (ash)	0.7
Dextrose powder U S P	6 Gm	Protein	3.3 (20% of calories)
Water to	100 ml	Fat	1.2 (16% of calories)
		Carbohydrate	10.7 (64% of calories)
		Calories	67.0
HALF SKIMMED MILK FORMULA—CONCENTRATION NO 2			
<i>Ingredients</i>		<i>Distribution of nutrients (Gm)</i>	
Half skimmed milk powder	12 Gm	Minerals (ash)	0.8
Dextrose powder U S P	7 Gm	Protein	4.0 (20% of calories)
Water to	100 ml	Fat	1.4 (16% of calories)
		Carbohydrate	12.6 (64% of calories)
		Calories	79.0
EVAPORATED MILK FORMULA			
<i>Ingredients</i>		<i>Distribution of nutrients (Gm)</i>	
Evaporated milk	33 ml	Minerals (ash)	0.5
Cane sugar	5 Gm	Protein	2.3 (14% of calories)
Water to	100 ml	Fat	2.6 (36% of calories)
		Carbohydrate	8.3 (50% of calories)
		Calories	66.0

ture (see Table 10-1), and the small infants are shifted to this preparation when they reach 1750 Gm.

VITAMINS

During the first three days of life we administer 0.6 ml. of an aqueous preparation of vitamins K₁ (1 mg), E (5 mg), and C (25 mg.). This preparation is given once each day directly into the gavage tube (see Methods of Feeding) or placed on the tongue of the larger infant who is held upright during the procedure.

Beginning on the fourth to the sixth day small amounts (2 drops) of a water-miscible multivitamin preparation are given. The amount is increased (by 2 drops) each day to the final daily dose of 0.6 ml. which contains vitamin A 5000 I.U., vitamin D 1000 I.U., ascorbic acid 50 mg., thiamine 1 mg., riboflavin 0.8 mg., and niacin 6 mg. Iron administration is discussed elsewhere (see Chap. 20).

PARENTERAL FLUID SUPPLEMENTS

During the first week of life, when the intake of the milk feeding in very small infants is considerably below 150 ml. per kg per day, parenteral supplements are provided to approximate the daily fluid requirements. It is often difficult to administer a large amount of parenteral fluid in the smallest infants whose oral intake is minute and, as has been said, there is considerable difference of opinion about the importance of providing fluid until all subcutaneous edema has disappeared. Moreover, there is no agreement on the optimal composition of the supplemental fluid or on the route of administration.

Hypodermoclysis

We have used repeated subscapular hypodermoclyses. When fluid is allowed to drip from a reservoir bottle into the tissues of the upper back (bilaterally), 30 ml per kg can be instilled with little apparent discomfort to the infant. It is rarely possible to use this route more often than twice each day since fluid absorption is usually incomplete in less than 12 hours. The composition of the fluid (final concentration of 2½ per cent dextrose in 0.45 per cent sodium chloride solution) should not be varied, since solutions containing higher concentrations of dextrose are irritating. Hypotonic solutions should not be used. Hyaluronidase is not necessary since diffusion of fluid in the tissues is rapid.

Intravenous Infusion

Nevanlinna described a method of infusion into the umbilical vein. Infants weighing less than 1 kg. were given 30 ml of 5 per cent glucose on the first day of life; the amount was increased by 20 ml. daily during the next few days. For premature infants the experience with this and other routes⁶⁹ is not large enough to permit an estimate of the incidence of possible complications.¹³

METHODS OF FEEDING

Gavage Feeding

For the smallest infants who are unable to suck or who have feeble sucking and swallowing reflexes, feeding by gavage is necessary. The method for gavage, involving an indwelling nasogastric tube,⁸¹ (see Appendix 7) is now used in many institutions almost to the exclusion of the older technique of passing an orogastric tube at each feeding.

Complications. Serious complications such as gastric perforation resulting

from the use of indwelling nasogastric tubes have been infrequent since the practice has been to blunt the distal ends.^{91, 92}

The incidence of purulent rhinitis can be minimized by introducing a new tube into the opposite nostril every five days. It is our impression that tubes of a large caliber are associated with a higher incidence of rhinitis than are small tubes.

Continuous Intragastric Drip

Holmdahl described a method of feeding premature infants by a continuous drip of milk into the stomach. This technique permitted the introduction of greater quantities of formula during a 24-hour period than were possible with intermittent feedings. During a two-year period 72 infants (46 weighed less than 1500 Gm. at birth) were fed this way for periods varying from one week to several months. One infant during the two-year period died of asphyxia due to aspiration of milk. We have used this method for infusing glucose solutions into the stomach but we have hesitated to use milk.

Bottle Feeding

Relatively mature vigorous infants may be fed with a bottle fitted with a small, soft nipple (see Appendix 7). Cineradiographic studies of bottle feeding in mature infants by Ardran and others have suggested that a soft, easily compressible nipple may be important in facilitating feeding.

Other Methods

In our nursery a medicine dropper with a rubber tip has been used on rare occasions.

The Breck feeder should never be used, since forcing milk into the infant's mouth before he is able to suck is dangerous.

FEEDING SCHEDULE

Intervals Between Feedings

The intervals between feedings will vary with the amounts taken in relation to the total volume required. It is usual to begin feeding every 2 hours and to lengthen the interval to 3 hours and then to 4 hours as the amounts taken at each feeding become larger.

It should be emphasized that, in the first days of life particularly, there is great variation in the tolerance of small infants. The physician should review

his decision concerning the intervals of feeding and be prepared to make individual adjustments on the basis of the infant's behavior.

Volume

Rigid feeding schedules for premature infants cannot be dictated. The initial offering of fluid by mouth to a small infant is completely exploratory. If the volume is accepted without regurgitation a base line has been established.

Scammon and Doyle observed that the physiologic capacity of the stomach of the newborn infant is considerably less than the anatomic capacity, and that these capacities do not approximate one another until the fourth day of life. Although their studies did not include small premature infants, their calculation of the relative physiologic capacity of the stomach on the first day of life (2 ml. per kg) provides a satisfactory estimate of the volume of the first feeding.

The observations of Scammon and Doyle on the increase of the physiologic capacity of the stomach in the first 10 days of life (Table 10-2) can be used to estimate the volume of the feedings for premature infants. It must be emphasized that the rate of increase in many infants is significantly slower than indicated and the physician must be prepared to deviate from a rigid schedule of increases. The most frequent error that is made in feeding premature infants consists of overestimating the volume of feedings during the first days of life.

TABLE 10-2. AVERAGE PHYSIOLOGIC CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF LIFE*

<i>Day of life</i>	<i>Stomach capacity (ml /kg birth wt)</i>
1	2
2	4
3	10
4	16
5	19
6	19
7	21
8	23
9	25
10	27

Adapted from Scammon and Doyle **

* Calculated from observations of infants whose birth weight was 2000 to 2500 Gm

TABLE 10-3 COMPOSITION OF 100 ML HUMAN AND COW'S MILK
Representative Values

	Human		Cow
	Colostrum ^a	Mature milk ^b	Mature milk
Water (Gm)	87	88	87
Protein (Gm)	2.7	1.2	3.3
Lactose (Gm)	5.3	7.0	4.8
Fat (Gm)	2.9	3.8	3.7
Calories (no)	58	71	69
<i>Distribution of calories (%)^c</i>			
Protein	24	10	26
Lactose	33	40	26
Fat	43	50	48
<i>Protein distribution</i>			
Casein (Gm.)	1.2	0.4	2.8
Lactalbumin		0.3	0.4
Lactoglobulin		0.2	0.2
Whey protein	1.7	0.6	0.6
Ash (Gm)	0.33	0.21	0.72
Total cations (mEq)	5.86	4.04	13.28
Calcium	1.55	1.65	6.24
Magnesium	.33	.33	0.99
Potassium	1.89	1.41	3.53
Sodium	2.09	0.65 ✓	2.52
Total anions (mEq)	4.75	2.95	10.35
Chlorine	2.57	1.21	2.90
Phosphorus	0.81	0.87	5.58
Sulfur	1.37	0.87	1.87
<i>Vitamins</i>			
A (I U)	383	228	146
D (I U)		0.42	2.36
E (mg)	1.28	0.56	0.06
K (Dam Glavind units)		26	100
Ascorbic acid (mg)	4.4	4.3	1.6
Nicotinic acid (μg)	75	172	85
Pyridoxine (μg)	.	11	48
Riboflavin (total) (μg)	29.6	42.6	157
Thiamine (total) (μg)	15	16	42
B ₁₂ (μg)	0.45	Trace	0.56

From Macy and others.⁴⁶

^a 1-5 days

^b After 10 days

^c The distribution represents "gross" calories

The use of intragastric drip to bypass the limitations of intermittent feedings was discussed earlier.

COMPARISON OF HUMAN AND COW'S MILK

Table 10-3 shows the composition of human colostrum and mature milk compared with cow's milk. It can be seen that cow's milk is much higher than mature human milk in content of protein and minerals but equal in fat. The lactose content of mature human milk is higher than that of cow's milk. The composition of human colostrum with respect to many constituents is intermediate between the mature milks of both species

Protein

The relatively high protein content of cow's milk is accounted for principally by casein. Berfenstam and co-workers observed a difference in the digestibility of cow's- and human-milk proteins. They found that cow's milk proteins were hydrolyzed in the stomach of premature and term infants more rapidly and completely than the proteins of human milk. This difference was also found when they compared the hydrolysis of pure casein prepared from the two types of milk. The amino-acid composition of the proteins is essentially the same in the mature milk of the human and the cow.⁸

Fat

Human milk fat is composed of a larger proportion of unsaturated fatty acids than is found in the fat of cow's milk.⁶⁶ However, the composition of milk fat is influenced considerably by the amount and character of the fat in the maternal diet.

Vitamins

The concentrations of vitamins are affected by maternal intake and by the methods used to sterilize and store milk. The relatively large amount of vitamin E in human colostrum (see Table 10-3) is noteworthy in relation to the tocopherol deficiency of the newborn infant.

Bifidus Growth Factor

György^{33, 35} described a specific substance in human colostrum and mature milk which was required for the propagation of a strain of *Lactobacillus bif-*

idus isolated from the feces of a breast-fed infant. Cow's milk had only a fraction of the "bifidus growth factor" activity exhibited by human milk.

Influence on Growth

Although large premature infants thrive on unmodified human milk, there is general but not complete agreement that the small infants gain weight and mineralize their skeletons more slowly when they are provided with the small amounts of protein and minerals in human milk.^{23, 30, 58} Even term infants should not be given unmodified cow's milk in the neonatal period because of the heightened risk of dehydration under conditions in which extrarenal water losses are increased (to be discussed). Hence most would agree that both human and cow's milk should be altered before either is fed to small premature infants (birth weight 1750 Gm. and less). Modification can be accomplished by dilution, skimming, and supplementation with casein and sugar to produce mixtures of various compositions. It has been shown that by using *either* milk as a base, mixtures can be devised to produce equal rates of weight gain.^{56, 58} For these reasons, in recent years the question of which milk should be fed to small premature infants has become secondary to the question of what should be its composition.

Protection Against Infection

There is a widespread feeling that the incidence of infections and the mortality rate are lower among premature infants who receive human milk than in those fed cow's milk mixtures. It has been suggested that nonspecific immune factors may be transmitted to the newborn infant by colostrum,⁴² mature milk,^{35, 58} or unheated human milk.⁴² Attempts to demonstrate antibody transmission have been generally unsuccessful.^{5, 38, 76}

Crosse and co-workers conducted a large clinical trial in which the effects of human milk were compared with isocaloric cow's milk formulas and human milk reinforced with hydrolyzed casein. The authors concluded that unmodified human milk is the best food for premature babies. They observed the lowest incidence of infection and the lowest mortality rate among 34 infants who received human milk supplemented with vitamins, calcium, and phosphorus. However, the observed differences could easily be explained by chance, and as a result there can be little confidence in an alternative explanation for these results.

Evidence concerning the influence of the type of feeding on infection, neu-

rologic status, and mortality obtained from a rigidly controlled double-blind clinical trial^{40, 61} would be welcomed by all who are concerned with the care of premature infants. This evidence is not available at the present writing.

NUTRITIONAL REQUIREMENTS

The additional nutritional needs of premature infants required to reach the body composition of mature infants may be estimated by referring to the chemical development of the human fetus in utero. Widdowson and Spray⁹⁶ analyzed the bodies of human fetuses and term infants who were stillborn and calculated the probable composition of premature infants at two stages of intrauterine development (1500 Gm. and 2500 Gm.) compared with an infant born at term (Tables 10-4 and 10-5).

PROTEIN

It is reasonable to assume that because of their extremely rapid growth premature infants have special needs for protein.

Absorption

The capacity of these infants to absorb and retain nitrogen from either human milk or cow's milk is efficient.⁵⁹ From postmortem studies it was suggested that premature infants had a deficiency of the proteolytic enzymes of the stomach and pancreas.⁹⁴ This was disputed by Madey and Dancis, who demonstrated normal concentrations of trypsin in the duodenal contents of 16 living premature infants. The latter observers also found that the gain in weight of infants whose diet was supplemented with casein hydrolysate was *not more rapid than that of controls supplemented with whole casein.*

The presumption that protein digestion is not impaired, even in very small premature infants, was also strengthened by the results of studies made by Feinstein and Smith. They demonstrated equally satisfactory nitrogen absorption and weight gain after casein and casein hydrolysate feedings.

Recommended Allowances

High Protein. Levine⁵⁷ advised that premature infants between the ages of one week and one month receive a daily allowance of 6.0-4.4 Gm. of protein per kg. of body weight if the weight is less than 2000 Gm., and 5.0-4.4 Gm. per kg. if the weight is 2000 Gm. or more. For one to three months of

TABLE 10-4. TOTAL AMOUNTS^a OF VARIOUS CONSTITUENTS IN THE BODIES OF PREMATURE INFANTS AND AS PERCENTAGE OF TERM INFANT

	<i>Premature</i>				<i>Term</i>
	<i>Amount</i>	<i>% of term</i>	<i>Amount</i>	<i>% of term</i>	<i>Amount</i>
Weight (Gm)	1500	43	2500	72	3500
Protein (Gm)	160	39	290	70	415
Fat (Gm)	60	13	200	43	470
Sodium (Gm)	3.50	52	5.35	80	6.75
Potassium (Gm)	2.80	47	4.70	78	6.0
Calcium (Gm)	10.2	36	19.0	68	28.2
Magnesium (Gm)	0.35	46	0.60	79	0.76
Phosphorus (Gm)	5.6	35	10.8	67	16.2
Iron (mg)	106	41	184	70	262
Copper (mg)	4.8	35	8.8	64	13.7
Zinc (mg)	26	49	40	76	53

From Widdowson and Spray ²²^a Probable amounts estimated from 19 human fetuses and term infants who were stillbornTABLE 10-5. COMPARISON BETWEEN PERCENTAGE COMPOSITION^a OF PREMATURE INFANTS AND A TERM INFANT

	<i>Premature</i>		<i>Term</i>
	<i>1500 Gm</i>	<i>2500 Gm</i>	<i>3500 Gm</i>
Percentage			
Protein	11.6	12.4	12.0
Fat	3.5	7.6	16.2
Water	82.5	77.3	68.8
Sodium	0.23	0.21	0.19
Potassium	0.19	0.19	0.17
Calcium	0.68	0.76	0.81
Magnesium	0.023	0.024	0.022
Phosphorus	0.37	0.43	0.46
Mg /100 Gm.			
Iron	7.1	7.4	7.5
Copper	0.32	0.35	0.39
Zinc	1.7	1.6	1.5
TOTAL	100%	100%	100%

From Widdowson and Spray ²²^a Probable composition estimated from 19 human fetuses and term infants who were stillborn

age he set the requirement at 4.4–3.3 Gm per kg. These amounts of protein would supply an average of 17 per cent, 15 per cent, and 13 per cent, respectively, of the total calories. These relatively high allowances have been used extensively in this country and to some extent abroad⁹⁹ for the last fifteen or more years

Moderate Protein. Kagan and associates observed that the high protein and mineral content of cow's milk as compared with human milk resulted in the intake of relatively large amounts of ash per unit volume when infants received cow's milk mixtures. They attributed the more rapid weight gains associated with high protein-ash intakes to water retention resulting from the inability of the kidney to excrete the increased solute load of these diets. Kagan's group suggested that pitting edema observed in some premature infants fed cow's milk mixtures may be explained on this basis.

Deleterious consequences aside from the implications for increased water requirement have not been detected following intakes of protein greater than 7 per cent of calories provided by human milk. However, May cautions that the metabolic burden imposed by the absorption of more protein than can be utilized in formation of tissues of fixed protein composition may prove to be disadvantageous. It is unlikely that the arguments^{4, 93} concerning the protein requirements of premature infants will be resolved even when studies of their body composition on various rations are available. For, as May has said, there is no agreement upon a definition of the optimal state of nutrition of human infants.

Babies Hospital practice. For the past 10 years the experience in our nursery has been almost exclusively with high-protein feedings supplying 20 per cent to 14 per cent of calories.

FAT

Widdowson and Spray⁹⁶ indicated that the outstanding deficiency of the premature baby is one of fat (see Table 10-5). In utero the fetus begins to deposit fat when it weighs 800 to 1000 Gm., and by the time a weight of 3000 Gm. is attained the amount of fat is approximately equal to the amount of protein. Widdowson⁹⁵ found that the variation in the proportion of fat in newborn mammals is considerable. The newly born (term) human and guinea-pig both may have a higher proportion of fat than their own mothers; the bodies of some mammals have only 1 to 2 per cent fat at birth. It may be significant that maternal lipemia occurs in the latter part of pregnancy in the human and the guinea pig, but not in two species whose young are lean at birth, the rat and the rabbit.^{11, 95}

fed three groups of premature infants isocaloric mixtures containing approximately the fat content of whole cow's milk (3.2 Gm. per 100 ml.). They contrasted the effects of an unsaturated fatty acid (corn oil substituted, defatted milk powder) and two milk-fat mixtures (evaporated milk and evaporated milk fortified with protein powder). Another group received a half-skimmed milk mixture (1.5 Gm. fat per 100 ml.) with a protein content equal to that of the fortified evaporated milk. Although there was considerable variability, the fat absorption approximated that considered normal for term infants (80 to 90 per cent)⁴⁹ only in the group receiving the mixture in which the fat was derived principally from corn oil.

Recommendations

As can be seen, there is at present no agreement concerning the amount and type of fat that should be offered to cope with the caloric losses resulting from steatorrhea in premature infants.

Gordon and McNamara³¹ suggested that if premature infants failed to gain on human milk or customary cow's-milk mixtures in which fat supplies 35 to 50 per cent of the calories, the caloric loss in unabsorbed fat could be compensated for by reducing the fat and substituting isocaloric amounts of protein or carbohydrate instead of increasing the total caloric intake.

Babies Hospital practice. In our nursery we have offered half-skimmed milk mixtures (1.4 Gm. milk fat per 100 ml., 16 per cent of total calories as milk fat).

CARBOHYDRATE

In contrast to the debates concerning the protein and fat requirements of premature infants, there is general agreement that generous amounts of carbohydrate are required to satisfy the energy needs of these rapidly growing infants. Moreover, it has been demonstrated that the absorption of sugar fed to premature infants is virtually complete.⁴⁵

Relation to Renal Water Requirement

Pratt and Snyderman fed premature infants a mixture in which the calories supplied by carbohydrate were higher (those supplied by protein and fat were lower) than in an isocaloric evaporated milk mixture without added carbohydrate. They demonstrated that the renal solute load, and thus the renal water requirement, was less when these infants received the carbohydrate-modified mixture, since the intake of protein and minerals was reduced.

Calcagno and Rubin found that the osmotic loads of quite high protein intakes (5.6 to 7.4 Gm. per kg.) could be reduced by adding carbohydrate to the milk mixtures for premature infants. Increased retention of nitrogen, presumably as increased protein synthesis, accompanied the addition of carbohydrate. As a result a smaller osmotic load was presented for excretion by the kidney.

McCance and Widdowson⁶⁴ have also emphasized the role of growth in relieving the kidney of the young subject of some of the work this organ must do in adult life

Galactose and Lactose

Haworth and MacDonald have suggested that premature infants may not fully metabolize galactose and lactose. They examined the urine from 26 breast-fed male premature infants during the first month of life. Reducing sugars (glucose, galactose, lactose, and xylose or combinations of these) were found in 77 of 152 specimens of urine examined. This was more frequent than had been found in a group of mature infants. Galactose and lactose were demonstrated once each in the blood of 10 premature infants following breast-milk feedings.

CALORIES

Gordon and co-workers²⁹ made precise measurements of the daily energy exchange of 11 healthy premature infants, age ten to forty-four days, whose weight at birth had been 1130 to 2220 Gm. From these studies the authors concluded that an average of 120 calories per kg. per day covered the maintenance-energy requirements of these infants and permitted an average daily gain in weight of 16 Gm. per kg. *The loss of calories in the stool averaged 18 calories per kg.,* and it was noted that methods of feeding designed to decrease this loss might permit adequate gains on smaller total intakes. Furthermore, the authors cautioned that individual variations in metabolism associated with activity, environmental temperature, and age would modify this estimate.

The energy requirements of premature infants in the first two weeks of life and at different environmental temperatures are not accurately known (see Chap. 7). It is reasonable to assume that since both physical activity and heat production are low during this period,⁸⁹ smaller caloric intakes may permit gain in weight.

WATER

Water accounts for a large proportion of body weight, and this proportion is greater in the fetus than in the infant born at term (see Table 10-5).

Water Balance

The problem of hydrolability of newborn infants, especially premature infants, and their tendency to dehydration has been recognized. Levine and Gordon⁵⁹ studied water balance in 15 premature infants. With daily intakes below 95 ml. per kg. negative water balance and dehydration fever were observed. Intakes of 124 ml. per kg. per day (and more) resulted in positive water balances. The retention of water amounted to 18 to 24 Gm., whether the average daily fluid intake was as low as 124 or as high as 167 ml. per kg. The extra water of higher intakes was eliminated as additional urine. These observations led the authors to state that fluid intakes rarely, if ever, need exceed 150 to 160 ml./kg./day. They adopted relatively low fluid intakes, 130 to 150 ml./kg./day, for routine use in premature infants receiving milk mixtures to supply 120 calories per kg., low fat (2.5 Gm. per kg.), and generous amounts of carbohydrate (18 Gm. per kg.) and protein (6 Gm. per kg.). The relation of the retention of water to total weight gain was between 54 and 70 per cent. This compared favorably with 65 to 68 per cent in 4 premature infants who received human milk.

Renal Water Requirement

The concentration of the urine of premature infants in the early days of life is rarely over 650 milliosmols per liter, which is a little more than twice the concentration of solutes in the serum.⁸⁴ By contrast, the thirsting adult produces urine which has more than four times the osmolar concentration of serum. Thus at any given osmotic load it is presumed that the infant has a relatively high renal water requirement for removal of catabolites.

Pratt and Snyderman pointed out that a large osmotic load resulting from a high protein and mineral intake reduces the margin of safety in water balance among these infants.

Concentration of Milk Mixtures

Darrow *et al.* suggested that the osmotic load of cow's milk be reduced by dilution with water and addition of carbohydrate until the caloric concentration is that of human milk (150 ml. of water per 100 calories).

When concentrated high-protein formulas are used to feed premature infants, physicians should be mindful of their responsibilities with respect to the administration of water, since these infants are of course unable to signal when their needs increase. During illness when the concentrating ability of the kidney

is reduced or when extrarenal losses of water are increased (e.g. diarrhea, overheated incubator, etc.) *it is necessary to supply additional water or to reduce the concentration of the milk mixture.*

Babies Hospital practice. In our nursery two concentrations of half-skimmed milk mixtures are used (see discussion under Feeding) The lower concentration (0.67 calorie per ml.) is fed during the early days of life or during illness, and the higher concentration at other times (0.79 calorie per ml.).

MINERALS

Sodium and Potassium

Concentration in the Fetus. Widdowson and Spray⁹⁶ found that the concentration of sodium in the fat-free body tissue of the fetus decreased until the fetal weight was approximately 2 kg and then remained the same until term. The value reached was the same as in an adult. The concentration of potassium in the fat-free body tissue increased throughout fetal life, but the concentration in the whole body changed very little after the fetus began to deposit fat.

Effects of Loading. McCance and Widdowson⁶³ presented evidence from experimental animals and from premature infants which indicated that the kidney of the neonate continues to reabsorb sodium chloride when that of an adult would excrete it. When these subjects were given excessive amounts of salt they developed hypertonic edema. Interestingly, the catabolism of tissue protein was reduced during the experimental period. These authors have also studied the effects of potassium loading in newborn piglets.⁶⁵ They observed that fasting animals could be intoxicated rather quickly. When potassium was administered in milk they remained in good health. It was concluded that growth was important in maintaining homeostasis, and the authors cautioned that potassium should be administered with greater care in a fasting than in a growing infant.

Calcium and Phosphorus

Antenatal Storage. In the fetus the absolute amount of calcium and phosphorus stored in the tissues increases steadily throughout gestation. Widdowson and Spray⁹⁶ found that the bodies of full-term infants contained 20 or 30 times more of each than was found in fetuses weighing 225 Gm. At term the concentration of calcium in the body was more than twice and of phosphorus a little less than twice as high as in the smallest fetuses examined. There is conflicting evidence concerning the influence of variations in maternal intake

of minerals and vitamin D on the deposition of calcium and phosphorus in fetal bones.^{9, 26}

It is clear that if pregnancy is interrupted before term, storage of calcium and phosphorus will be curtailed.

Postnatal Serum Calcium Level. The concentration of calcium in the serum falls during the immediate postnatal period. A high proportion of premature infants become hypocalcemic (below 8 mg. per 100 ml.). The significance of this *high incidence of hypocalcemia and the relationship of the concentration of calcium in the serum to symptoms* are discussed in Chapter 21.

Source in Cow's vs. Human Milk. Benjamin and her co-workers studied the retentions of calcium and phosphorus by 6 premature infants (age 13 to 41 days) fed human milk and a mixture of skimmed-milk and olive oil. They found that the degree of utilization of the calcium in cow's milk was greater than that in human milk. From their observations these authors concluded that human milk is not the food of choice for the formation of the skeleton of premature infants unless it is supplemented by both calcium and phosphorus.

Eek and others studied 69 premature infants (birth weights below 2 kg.) who were fed different dietaries. They found slight differences in chemical, clinical, and radiologic findings which indicated that cow's-milk feedings were associated with better mineralization of the skeleton than human milk. They concluded, however, that the risk of rickets was probably not greater in those fed human milk if these infants received an adequate amount of vitamin D.

Recommended Allowances. The National Academy of Sciences-National Research Council¹ has recommended a daily dietary allowance of 0.6 Gm. of calcium for a term infant one month of age. At least equal allowances are recommended for phosphorus. No allowance is specified for infants in the first month or for premature infants.

The premature infant needs a greater intake of both of these minerals than the term infant because of his lower antenatal storage and the demands of his more rapid growth. The influence of calcium administration upon morbidity and mortality among premature infants in the first few days of life has not been satisfactorily evaluated (see Chap. 21). As a result we can only speculate about the calcium requirements of these infants during the first week of life.

Iron

Iron functions chiefly as a component of the hemoglobin molecule and in oxidative enzyme systems.

Fetal Store. The percentage of iron in the fetus was found by Widdowson and Spray⁹⁶ to increase during development. They noted that the liver and spleen contained only one-eighth of the iron in the whole body. Josephs emphasized that the largest proportion of fetal iron is stored in the hemoglobin of the circulating blood. Thus the endowment of iron with which each newborn infant starts his extrauterine existence is influenced to a considerable extent by the size of the placental transfusion in the first few moments after birth.

Supplementation. Iron supplementation in premature infants is commonly begun during the first month of life; however, there is evidence that the endogenous supply of iron is adequate to support active hematopoiesis for at least six weeks in most of these infants. A full discussion of iron therapy in premature infants is presented in another chapter (see Chap. 20).

Magnesium and Copper

The concentration of magnesium in the fetal body increases early in gestation but remains almost constant after a weight of 2 kg. is reached.⁹⁶ The retention of this mineral, which is an important cellular constituent and catalyst, tends to parallel protein or calcium intake.¹

Widdowson and Spray⁹⁶ found that the percentage of copper in the fetus increased with development, and approximately one-half of the total amount of this element was present in the liver and spleen. Copper is involved in blood formation. Since human milk has a higher content of copper than does cow's milk, the occurrence of copper-deficiency anemia in an infant fed exclusively on a diet of cow's milk is a conceivable, but apparently rare, possibility.¹²

VITAMINS

The premature infant needs larger amounts of vitamins A, C, and D than does the term infant. Studies of the relation of the vitamin B complex (thiamine, riboflavin, niacin, and other components) to the premature infant's nutrition indicate that supplements of the vitamin B complex may be desirable. The amounts of the vitamins that should be given to the premature infant for prophylaxis and optimum growth on the one hand, and to cure him of deficiency diseases on the other, are as yet undetermined.

Incomplete as is the definite information with regard to the vitamin needs of premature infants, the prophylactic administration of certain vitamins is considered to be important. It should be emphasized that the premature infant cannot get an adequate supply of vitamins from milk. Vitamin A, riboflavin, and niacin are supplied by both human milk and cow's milk in amounts considered

adequate for the term infant, who takes large amounts of milk and whose rate of growth is relatively slow compared with the premature infant. Thiamine is not supplied in large amounts in milk, and amounts of vitamins C and D in milk are inadequate even for the term infant.

Vitamin A

Vitamin A supplies a complex which unites with protein to form in the retina certain substances needed for vision. It exercises control of the development and maintenance of epithelial tissues. Vitamin A is also important in maintaining normal bone growth. Most of the supply of vitamin A is stored in the liver. Carotene is converted into vitamin A in the intestinal wall and perhaps in other sites.⁶²

Infants of low birth weight have less vitamin A in their blood than those of higher birth weight; larger amounts of this vitamin are stored as the maturation process is more prolonged.⁶⁰

A deficiency of vitamin A may appear earlier in the premature infant than in the one born at term. This circumstance is attributed to the low storage of vitamin A in the liver of prematurely born infants, the inadequate absorption by them of this vitamin and of dietary fat, and the low level of vitamin A in their blood plasma. Clinical forms of vitamin A deficiency are rare in the United States but may occur in infants fed on skimmed milk. Cornfeld and Cooke reported that *the signs of vitamin A deficiency in young infants may resemble more closely those seen in rapidly growing experimental animals than in adult humans*. They described an infant who exhibited growth failure, increased intracranial pressure, and gynecomastia in addition to xerophthalmia and epithelial metaplasia. Two examples in infants receiving feeding mixtures derived from soybeans without vitamin A supplements have been described recently.^{5, 97}

Prophylactic Dose. It is generally agreed that prophylactic doses of vitamin A should be added to the diet of premature infants. *The daily administration of 5000 I.U. of vitamin A has been routine in our nursery (see p. 154); however, this dose is more than three times higher than that recommended by the National Academy of Sciences-National Research Council¹ for infants 2 to 6 months of age.*

Thiomine

Thiamine (vitamin B₁) plays an important part in intermediate carbohydrate metabolism. Its lack results in inefficient metabolism of carbohydrate throughout the body, including the nervous system. Thiamine deficiency in infants is ex-

tremely rare in this country. However, an example has been reported in a 5½ month old infant who was receiving a soybean feeding mixture without vitamin supplementation.²²

Requirement. Holt and others⁴⁷ studied older infants (7 to 10 months of age) and estimated the thiamine requirement of artificially fed infants to be 0.14 mg. to 0.20 mg. per day. In other studies Holt and Snyderman⁴⁸ demonstrated that less thiamine is excreted in the urine on a high-carbohydrate than on a high-fat diet. They interpreted this to indicate that there is an increased demand for thiamine when carbohydrate is substituted for fat in the diet.

Prophylactic Dose. The exact requirements for prematurely born infants are unknown. We have administered 1 mg. thiamine per day.

Riboflavin

Riboflavin (vitamin B₂) combines with phosphoric acid and protein to form tissue respiratory enzymes that are necessary for the metabolism of practically all living cells. Deficiency of riboflavin manifests itself in lessened visual acuity, stomatitis, dermatitis, and retardation of wound healing.³⁰ Stevenson described a crusted lesion which developed at the mucocutaneous border of the mouth in a 13-day-old premature infant receiving a half-skimmed milk mixture. This lesion cleared promptly when 3 mg. per day of riboflavin was given, and it was thought that this might be an example of ariboflavinosis.

Requirement. The minimum riboflavin requirement of older infants was estimated by Holt's group⁴⁴ to be between 0.4 and 0.5 mg. per day. They noted that the infant's riboflavin requirement was two to three times greater than that of thiamine, this is a relatively large requirement as contrasted with that of the adult.

Prophylactic Dose. We administer 0.8 mg. per day; this dose is probably generous.

Niacin

Niacin is needed for the formation of two coenzymes which participate in glycolysis and tissue respiration. A marked deficiency results in the symptoms of pellagra.

Requirement. Tryptophan can serve as a precursor of niacin in man.¹ The antipellagra value of milk is related in part to the tryptophan supplied by casein. Holt⁴⁶ showed that when 15 per cent of the calories are supplied by casein the niacin requirements of infants are met. Since milk contains niacin apart from that which can be supplied from tryptophan it would appear that milk-fed infants are in very little danger of developing a deficiency. Intakes of 6 mg. of niacin equiv-

alents have been estimated in infants receiving milk as the only source of food.¹ **Supplementation.** The routine supplementation of 6 mg. niacin present in the multivitamin preparation used in our nursery is probably more than is necessary for premature infants.

Vitamin B₆ Group

Three chemically related compounds, pyridoxine, pyridoxal, and pyridoxamine, are commonly referred to as the vitamin B₆ group. Vitamin B₆, principally as pyridoxal phosphate, serves as a catalyst in many biochemical reactions of amino acids

Holt⁴⁴ observed that a mentally deficient infant who was receiving a pyridoxine-deficient diet developed convulsions that were promptly terminated by administration of pyridoxine. During the years 1951 to 1953 a fairly large number of infants were observed who developed convulsions while receiving an autoclaved liquid milk preparation deficient in vitamin B₆.^{17, 72} Thermal destruction of vitamin B₆ was shown to be the cause of this outbreak.³⁴

Requirement. Although the daily requirement of infants for this vitamin has not been established, it is of interest that the mean pyridoxal phosphate concentration in whole blood of 18 young infants (including 8 prematurely born infants) was higher than in older children and adults.¹⁰ Presumably the subjects were not receiving supplements of B₆ above that found in their usual diets

Cyanocobalamin

Cyanocobalamin (vitamin B₁₂) appears to be involved in nucleic-acid synthesis, thyroid activity, hematopoiesis, and ascorbic-acid metabolism.¹ Deficiency of this substance has been reported in subjects only on vegetable diets, even small amounts of food from animal sources are apparently adequate to satisfy requirements.¹

There is no indication for the administration of this substance to premature infants.¹⁵ A controlled study of the influence of vitamin B₁₂ on weight gain and on hematologic status of premature infants was conducted by Finberg and Chow and no effect could be demonstrated.

Ascorbic Acid

Ascorbic acid (vitamin C) has many functions in the body and enters widely into oxidation-reduction reactions. It is necessary for the function, formation, and maintenance of the intercellular cement substance of the body.

Role in Tyrosine Metabolism. Levine and associates⁶⁰ found that the urine

of premature infants receiving a diet high in protein without added ascorbic acid contained the amino acid tyrosine and one of its metabolites (*p*-hydroxyphenylpyruvate). When ascorbic acid was added to the diet these substances did not appear.

Kretchmer and co-workers⁵⁵ showed that this phenomenon resulted from the relative inactivity of the tyrosine-oxidizing system in the liver of premature infants. Kretchmer⁵⁴ found that tyrosine could be converted to *p*-hydroxyphenylpyruvate in premature infants soon after birth. However, the next step in the degradation of tyrosine was blocked because of the relative inactivity of the enzyme, *p*-hydroxyphenylpyruvate oxidase. Kretchmer⁵⁴ found that large amounts of ascorbic acid activated this enzyme in the liver of premature infants and facilitated the complete metabolism of tyrosine.

Requirement. The level of ascorbic acid in the blood of the newborn infant is higher than the maternal level. There is a rapid fall in the level after birth unless the vitamin is supplied in the diet, as this substance is not synthesized in the body.

Both human milk and cow's milk contain variable amounts of vitamin C. However, for feeding premature infants both are heated to a high temperature or autoclaved, a process that destroys a large part of the vitamin. As a result the premature infant's diet, whether human milk or cow's milk, should always be supplemented with vitamin C.

Prophylactic Dose. *In our nursery we have fed 25 mg of ascorbic acid per day during the first few days of life, 50 mg per day thereafter.*

Vitamin D

Vitamin D promotes calcium and phosphorus absorption from food, reduces the loss of phosphate from the kidney, and renders the stores of calcium and phosphorus in the skeleton accessible for the calcification of cartilage and bone.

Because of lack of direct measurement methods, little is known about antenatal storage of vitamin D by the fetus. There is some evidence, however, that protection of the fetus from vitamin D deficiency may be obtained by an adequate supply of the vitamin to the mother during pregnancy. After birth the body stores vitamin D chiefly in the liver, though it is also found in other organs, and maintains its stores for a considerable period after ingestion.

Prophylactic Dose. *For premature infants a daily prophylactic allowance of 400 I.U. of vitamin D in a water-miscible form is recommended by the National Academy of Sciences-National Research Council¹ as probably adequate. In our nursery we have given 1000 units per day to these infants. (For a dis-*

cussion of prophylactic and therapeutic doses of vitamin D for premature infants see Chap. 21).

Vitamin E

Vitamin E (tocopherol) has an antioxidant action which may be important in inhibiting the oxidation of unsaturated fatty acids, vitamin A, and other oxidizable substances.

Early studies of this vitamin revealed that vitamin E was necessary for reproduction in the rat. Hemorrhagic manifestations have been observed in the tocopherol-deficient fetuses of experimental animals⁷¹ Chicks reared on vitamin E-deficient diets develop edema, which has been termed "exudative," since the edema fluid has a protein content approximating that of plasma.

Gordon and co-workers³² have summarized studies of tocopherol deficiency in infants and children, and the reader is referred to their paper for a complete review of the subject. In brief, they have demonstrated that premature infants at birth have low tissue stores and low concentrations of tocopherol in the plasma

Requirement. On the basis of analogies with the manifestations of tocopherol deficiency in animals, it has been suggested that premature infants receive vitamin E to prevent hemorrhages⁷¹ and to treat sclerema neonatorum (see Chap. 23) However, Gordon's group³² emphasized that there was no convincing evidence of a relationship between tocopherol deficiency and pathologic states in premature infants.

Dosage. The tocopherol content of cow's milk is low. Fresh human milk contains vitamin E, but storage leads to a loss of tocopherol. These considerations led Gordon and co-workers³² to suggest that small supplements of tocopherol may be indicated for premature infants. We now feed tocopherol (5 mg. per day) to newly born premature infants, but must also emphasize that the efficacy of this treatment has not been established.

Vitamin K

For a discussion of vitamin K see Chapter 20.

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Medical Management of Surgery in Premature Infants

With improved techniques of diagnosis, more and more premature infants are found to need operations in the early period after birth or in the later neonatal period. It is likely that their chances for survival will be improved if they have the benefit of skilled care preparatory to operation as well as during and after it. At present the postoperative mortality is high and much remains to be learned about the problems presented by these patients.

For full accounts of extensive experiences in operating on premature infants the reader is referred to the writings of Gross and Rickham.^{14, 15}

PREOPERATIVE CARE

Body Temperature

Special care should be taken to minimize the fall of body temperature during preoperative physical examination, roentgenography, and other diagnostic maneuvers. This can be accomplished by swaddling if the infant must be removed from the incubator.

It should be recalled that when the incubator is moved from room to room the body temperature of an unclothed premature will be influenced not only by the air temperature within the incubator but also by changes in the temperature of the incubator walls brought about by different room air temperatures (see Chap. 7)

Venous Cannulation

Except in the case of minor surgical procedures a polyethylene tube should be

placed ("cut down") into a peripheral vein (ankle or antecubital) so that intravenous fluids can be given during and after surgery.

Preoperative Medications

Vitamin K. Vitamin K is usually recommended prior to surgery in premature infants

It has been shown that vitamin K is less effective in correcting the coagulation defect in newborn premature infants than in term infants (see Chap. 20). Moreover, the relative unresponsiveness of the premature infant cannot be solved by increasing the dose of the drug.

Existing evidence indicates that 1 mg. of vitamin K₁ intramuscularly does no harm, larger doses are not necessary. The dose may be repeated if the infant receives prolonged antibiotic therapy postoperatively

Large doses of water-soluble vitamin K analogues are contraindicated for premature infants (see Chap. 20)

Antibacterial Drugs. In the recent past almost all premature infants requiring major surgical procedures have received antibacterial drugs before and for several days after operation (usually penicillin alone or in combination with streptomycin or with chloramphenicol). Although the need to prevent serious infections in these infants has not lessened, there is increasing concern about the efficacy and safety of this approach to the problem. Little information is available about the concentrations of various antibacterial drugs in the blood and tissues of treated premature infants, particularly in the first few postoperative days when the volume of fluid administered is deliberately minimized. Studies of this problem are urgently needed. (See also Chaps. 9 and 19.)

Other Drugs. Gross advocated that atropine (0.065 mg.) be administered subcutaneously one hour prior to operation, this is not done in our hospital

Sedatives are usually not given

CARE DURING OPERATION

ANESTHESIA

In the past, local infiltration of the operative field with procaine was commonly used, especially in very small infants. The infant was pacified by administering brandy and glucose water in a cotton-stuffed nipple. General anesthesia with cyclopropane through a closed system was advocated by Gross if extensive intra-abdominal manipulation was necessary.

For surgery in newborn infants there has been increasing interest in the use of muscle-relaxant drugs, relatively small amounts of inhalation anesthetic agents, and controlled ventilation through an endotracheal tube.¹³

Controlled-Ventilation Method

Tracheal Intubation. Rees recommended that tracheal intubation of these subjects should be performed before the induction of anesthesia in order to minimize the dangers of regurgitation and aspiration.

However, by using a muscle-relaxant drug before intubation it is possible to introduce an endotracheal tube with the least amount of trauma and to fit a tube into the laryngeal orifice with some precision.⁸ This is an important consideration because a tube with a relatively large bore permits effective suctioning of the trachea. With smaller tubes suctioning is difficult, and secretions are more likely to accumulate, dry out, and subsequently plug the tube during the operation. Every effort should be made to avoid movement of the tube after it is in place to minimize irritation of the walls of the larynx and trachea.

Following intubation positive control of respiration is assured.

Muscle-Relaxant Drugs. Stead observed that newborn infants were abnormally sensitive to a nondepolarizing drug (d-tubocurarine chloride) and recommended that relaxants of the depolarizing type (succinylcholine chloride) should be used. Low body temperature, a common event in neonatal surgery,⁶ may be an important factor influencing the response to neuromuscular blocking agents.¹

It is preferable to administer muscle-relaxant drugs by continuous intravenous infusion to reduce the amount of drug necessary to produce paralysis. In premature infants this is not always possible because in an infusion concentrations of drug low enough to give accurate control of dosage necessitate the introduction of relatively large volumes of fluid. Intermittent injection as an alternative results in a larger total dose and may be followed by prolonged depression of respiration.

BODY TEMPERATURE

Body temperature should be closely monitored during the operative procedure. This can be best accomplished with a thermistor thermometer² that remains in the rectum or axilla during the entire operation.

Desultory attempts are often made to reduce heat loss of premature infants on the operating table by using hot water bottles, electric blankets, or warming mattresses. The fall in body temperature during a prolonged operation may be profound, and available methods of control have not proved completely satis-

factory. Moreover, the ideal rate of rewarming, supportive measures during rewarming, and related questions have not been adequately answered.

POSTOPERATIVE CARE

ENVIRONMENTAL CONDITIONS

Oxygen

The principles governing the administration of oxygen to premature infants are in no way changed by a surgical procedure (see Chap. 7). Whenever it is necessary to administer supplemental oxygen the concentration in the incubator should be routinely measured.

Atmospheric Humidity

Water mists are commonly introduced into the incubators during the postoperative period in the hope that laryngeal edema will be prevented. Most modern incubators can readily achieve an air condition of 90 per cent relative humidity. We have demonstrated that water mist influences insensible fluid loss to only a slight degree when compared with 90 per cent relative humidity, even in very small, thirsted premature infants.¹⁷ It is not known whether the incidence of postoperative laryngeal edema or other respiratory complications is significantly different in these two environments.

The use of a nebulizing device results in violation of the ventilation barrier of the incubator, since nursery air is aspirated and blown into the incubator. In many hospitals oxygen is used to operate the nebulizer; this results in the exposure of small infants to supplemental oxygen for prolonged periods of time. Since these are undesirable concomitants of mist therapy it is a matter of some importance to determine whether the use of mist is necessary.

SPECIAL EQUIPMENT

"Surgical Incubator." Rickham¹⁸ described a "surgical incubator" which incorporated, among other things, transfusion stands and a drawer to facilitate the introduction of roentgenographic cassettes. In this incubator the infant lies on a radiolucent plastic tray which can be tilted.

Intubation Equipment. Suction apparatus, infant laryngoscope, and suitable endotracheal tubes should always be readily available so that aspiration can be applied promptly.

SPECIFIC POSTOPERATIVE MEASURES

Prevention and Treatment of Massive Atelectasis

Rees emphasized that postoperative pulmonary collapse in newborn infants almost always involves the upper lobes. He recommended that the infant be placed on his side with a head-up tilt to reduce the likelihood of this complication.

When a pulmonary collapse occurs the infant should be turned with the collapsed side uppermost. Rees suggested that re-expansion can be promoted by *thumping the chest lightly with the fingertips for about three minutes each hour*. Aspiration of the tracheobronchial tree becomes necessary if re-expansion does not occur after six hours or if the collapse is massive.

Decompression of the Intestinal Tract

Decompression of the intestinal tract is necessary for infants if the abdominal viscera have been manipulated. This is accomplished by constant or intermittent gastric aspiration.

Many surgeons are reluctant to leave a nasogastric catheter in place because it is attended by the accumulation of tenacious secretions in the hypopharynx and incidents of respiratory obstruction. Gastrostomy is often employed in our hospital for decompression and to provide a port for later feedings.

ADMINISTRATION OF FLUIDS AND ELECTROLYTES

Sparing Policy

There is general agreement among pediatric surgeons^{7,11,16,18,21} that in operations on premature infants fluids should be administered sparingly on the first postoperative day and cautiously thereafter. Gross stated that more premature babies succumbed in the postoperative period from overhydration than from any other single cause.

If there is no dehydration and no postoperative fluid loss, Rickham¹⁶ states, the premature infant does not need fluids for two or three days after operation. With continuous gastric suction he advocates 5 ml. per hour (120 ml. per 24 hours) of one-fifth-physiologic* saline (sodium chloride 0.18 per cent) as the *maximum intravenous allotment*.

The gastric and intestinal secretions of newborn infants (the smallest weigh-

* Isotonic saline (sodium chloride 0.9 per cent) provides 154 mEq. of sodium and 154 mEq. of chloride per liter.

ing 1902 Gm.) studied by Rickham¹⁶ contained approximately 100 to 120 mEq./L. chloride, 40 to 60 mEq./L. sodium and 8 to 10 mEq./L. potassium. Rickham¹⁶ used small quantities of one-half-physiologic saline (sodium chloride 0.45 per cent) only when there was marked salt loss.

Potassium is usually withheld on the first postoperative day.²¹ For infants who are maintained on gastric suction for longer than three days, Rickham²¹ advised 1.8 to 2.1 mEq per day of potassium (50 to 60 ml of Darrow's* solution).

There is often disagreement concerning the management of the premature infant after the second postoperative day if it has been necessary to withhold oral feedings and to maintain gastric aspiration because of prolonged ileus. The arguments are centered on the question of whether the premature infant tolerates starvation and "drying out," since the above-noted conservative policy of fluid and electrolyte administration does not result in homeostasis.

Determinative Policy

Pediatric opinion favors the administration of more liberal amounts of fluid and electrolyte for maintenance, particularly after the first two postoperative days.^{3,4,5} This is estimated as follows: 130 ($\pm$ 30) ml of fluid per kg per day, of which one-third is isotonic saline and two-thirds is 5 per cent dextrose in water. Daily allowances of potassium chloride are estimated as 2 to 3 mEq per kg. per day.¹² The volume and electrolyte composition of intestinal fluids aspirated are used to modify these approximates.

It is important to limit the volume of fluid in the reservoir bottle to insure against a "runaway infusion." Strominger and co-workers use a constant-infusion pump to solve this problem.

There has been considerable reluctance to obtain repeated blood samples during the postoperative period because premature infants are often in precarious condition. The use of gentler methods of blood sampling (see Chap. 8) and micro methods of chemical analysis will undoubtedly permit physicians to make clearer individual judgments concerning the administration of fluid and electrolytes.

OTHER SUBSTANCES FOR INFUSION

Parenteral infusions cannot satisfy the infant's caloric requirements, since only 5 per cent glucose solutions are usually employed. On the other hand more concentrated solutions, even when given slowly, may be followed by venous thrombosis.¹⁸

* Darrow's solution provides 35 mEq of potassium, 121 mEq of sodium, 103 mEq of chloride, and 53 mEq of lactate per liter.

Protein Solutions. Repeated infusions of plasma (up to 20 ml. per kg. at any one time) or human serum albumin (approximately 4 ml. per kg.)⁷ are frequently used to elevate the low concentrations of protein in the serum. Small, frequent blood transfusions (10 ml. per kg.), so commonly used in the past, are now given principally to replace blood loss.

Intravenous Fat. Kauste's report of the administration of intravenous fat to 16 premature infants is of interest, but extensive clinical trials have not been reported.¹⁰

ORAL FEEDINGS

Delay in starting oral (or gastrostomy) feedings is made necessary by paralytic ileus, which usually follows operations for intestinal obstruction. When the volume of fluid aspirated from the stomach is less than 5 ml. per hour feedings can be started

The initial exploratory volumes should not exceed 5 ml. every two hours. A tube should be passed into the stomach before each feeding and the stomach aspirated. If more than 10 ml. are returned the feedings must be decreased or stopped.¹¹ The temptation to quickly increase the volume of feedings is usually quite strong; however, the risk of vomiting and aspiration is reduced by a cautious policy.

In gastrostomy feedings the volume can often be increased more rapidly than in nasogastric feedings. Although esophageal regurgitation may occur after gastrostomy feedings, in our hospital there is general agreement that it happens relatively less frequently.

COMPLICATIONS

The usual threats to the existence of premature infants (hemorrhage, pneumonia, septicemia, etc.) loom even larger in the postoperative period. Sclerema, which is discussed elsewhere, is seen with disturbing frequency.¹² The poor healing quality of the tissues of these infants is reflected by the significant proportion of leaks which follow intestinal anastomoses. As a result, mediastinitis, peritonitis, and fistulas are not infrequent. Major congenital malformations, especially of the heart, account for a significant number of postoperative deaths.

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Early Childhood Care of the Prematurely Born Infant

Routine well-baby care similar to that prescribed for term infants is usually advised when premature infants are discharged from the nursery. These children present a fair number of problems during the first few years of life. Some commonly encountered during follow-up are briefly reviewed in this chapter. (See also Chap 5 and Part Two, Section B.)

CAUSES OF MORTALITY AND MORBIDITY

James has reviewed the available evidence which suggests that the high mortality rate of infants born prematurely extends beyond the neonatal period. It is estimated that between the ages of one month and two years the death rate of exprematures is two to three times as great as among children born at term. James found that mortality and morbidity were highest in premature infants of low birth weight and in those under six months of age.

Douglas and Blomfield's observations of English premature children and controls, which were consistent with those made in other countries,^{1, 2, 18} indicated that exprematures spent more time in the hospital during infancy than did controls (Table 12-1). Infections, principally those of the lower respiratory tract, were the commonest cause of illness and accounted for the largest number of deaths (Table 12-2).

From these observations it is evident that in the months after discharge from the hospital expremature children require considerably more care than do those born at term.

Influence of the Social Environment

Wallace and others have emphasized that the after-care of premature infants is a community problem requiring the attention of not only health agencies but

TABLE 12-1 AVERAGE NUMBER OF DAYS OF HOSPITALIZATION OF EXPREMATURE CHILDREN^a

<i>Ages of children (mo)</i>	<i>Average no days in hospital</i>	
	<i>Premature children</i>	<i>Controls</i>
0-12	1.54	0.39
13-24	1.42	0.44
25-36	0.62	0.68
37-51	0.79	0.69

From Douglas and Blomfield.⁷^aExcluding postnatal nursery care and children permanently in institutions

TABLE 12-2 CAUSES OF DEATH OF PREMATURE CHILDREN BETWEEN 1 MONTH AND 4½ YEARS

<i>Causes of death</i>	<i>Yearly death rates per 1000 survivors</i>	
	<i>Premature children^a</i>	<i>4979 mature singletons^b</i>
Bronchitis and pneumonia	4.88	1.35
Other infections	2.17	1.83
Congenital defects	4.33	0.58
Nephritis	1.08	0.05
Other causes	1.62	0.63

From Douglas and Blomfield.⁷^aGroup of 543 infants who had survived 1 month^bGroup of 4979 mature singletons who had survived 1 month

often of welfare and social agencies also. Many of these children are transferred from the cloistered environment of a nursery to homes in which the general level of hygiene and care is grossly inadequate.

However, the fact that expremature infants are more likely to reside in poorer homes than are mature infants does not completely explain the different mortality and morbidity rates in these two groups. Douglas and Blomfield demonstrated that these differences persisted even when the expremature children were compared with controls drawn from similar homes. This evidence suggests that the results of efforts to improve the environment of expremature children may be counteracted by the inherent increased susceptibility of these children to infection. We can only speculate about the reasons for this conspicuous handicap.

Other Influences

Hypogammaglobulinemia. The role of transient hypogammaglobulinemia during infancy cannot be evaluated^{12, 22} at present but deserves further study.

Method of Feeding. A study by Mannheimer of mortality rates of infants in the first year of life in relation to the mode of feeding revealed a higher incidence of deaths caused by respiratory diseases in bottle-fed infants as compared with breast-fed controls. However, he found that this advantage of breast feeding was not evident in the segment of the study population that had been born prematurely. In contrast to this, Crosse and co-workers⁶ observed a lower incidence of infections among breast-fed expremature infants during the first year of life than among controls who were fed cow's milk. In neither of these trials was it possible to be certain that the type of milk fed represented the only important difference between the two groups during the study period.

Recommendations

At the present time no specific measures can be firmly recommended to solve the problem of the high mortality and morbidity among premature infants after discharge from hospital nurseries. Special attention must be given to the early detection and treatment of infection in these children.¹⁶

Recommended combined immunization⁵ should not be delayed in expremature children because of their size. Routine immunization should commence at one to two months of age.

SUDDEN DEATH IN INFANCY

Each year approximately 1 to 2 per cent of the infants who are discharged from our nursery die suddenly and unexpectedly in the first months of life. Further study to determine whether sudden death is in fact unusually common among expremature infants may shed some light on factors which play a role in the syndrome of sudden death in infancy.

Fulminating respiratory infection is considered to be^{24, 27} the most frequent cause (see Chap 19).

HERNIA

Premature infants are prone to hernias, especially umbilical hernia. Ylppö found that premature infants were more frequently subject to hernia than term infants and that the incidence was greater the smaller the infant.

Umbilical Hernia

Umbilical hernia must be differentiated from pouting of the umbilical stump. *True Umbilical Hernia.* In umbilical hernia an impulse can be felt when the in-

fant cries, the protrusion comes through the center of the umbilical scar, and a collar of fibrous tissue can be palpated around the base of the hernia

"Semi-umbilical" Hernia. Browne distinguished a "semi-umbilical" hernia in which the sac emerges through the upper border of the umbilical scar so that part of the bulge is covered by the umbilicus and the remainder by abdominal skin. No collar of fibrous tissue is present, and the margins of the opening in the abdominal wall are thin. Only a small fraction of the umbilical hernias seen in premature children are of the semi-umbilical type

Occurrence. Woods reported the results of a survey of 283 infants with umbilical hernia. She observed that these hernias were rarely present at birth and usually appeared in the first weeks of life. An initial appearance beyond the age of 6 months was rare. There is general agreement that the incidence of umbilical hernia is higher in Negro than in white children.

Management. In Woods' series 93 per cent of the hernias disappeared spontaneously without intervention (strapping, truss, etc.). We have adopted a "no treatment" policy for umbilical hernias and wait for spontaneous cure. There is considerable difference of opinion about how long this wait should last. The absence of symptoms, the rarity of strangulation, and the frequent spontaneous disappearance of even very large hernias as late as six years of age led Woods to consider that surgical repair was rarely required. In our opinion this conservative advice is justified.

Browne noted that semi-umbilical hernias rarely disappear spontaneously and he recommended surgical correction of this type of defect at about three years of age.

Inguinal Hernia

Indirect inguinal hernias which are the result of failure of obliteration of the vaginal process are relatively common in premature infants. The accumulation of fluid in the scrotum (congenital hydrocele) gives evidence of a communication with the peritoneal cavity and should alert one to the presence of an associated hernia

Occurrence. Inguinal hernias occur more frequently in male infants. Right-sided hernia is more common than left-sided involvement; however, bilateral hernias are seen frequently in infancy.

In female infants it is not uncommon to find an ovary present in the sac.¹³

Treatment. The complication of strangulation occurs most frequently in the first few months of life. Therefore, early surgical correction of inguinal hernia is the treatment of choice.¹⁷

HEMANGIOMA

Superficial cutaneous hemangiomas (strawberry nevi) are rarely present at birth. They usually appear during the second half of the first month of life, and enlarge during the following few months.

Occurrence. It was believed for some time that these hemangiomas were more common among premature infants. Holmdahl suggested that this belief was the result of an error in reckoning introduced by the fact that the smallest infants remain in the hospital, and thus under observation, for the longest period of time. In a series of 640 premature and 186 mature infants he found that when the period of observation was the same the incidence of hemangiomas was also the same (12 to 13 per cent).

Management. There is general agreement that superficial hemangiomas usually disappear spontaneously before the second or third year of life. We have followed the conservative policy of watchful waiting recommended by Lister.

ABNORMAL CONDITIONS OF THE DECIDUOUS TEETH

ENAMEL HYPOPLASIA

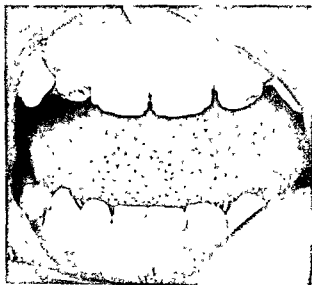
In 1931 Hess and Abramson reported an appreciable incidence of "enamel disease" (*erosions or defects of the dental enamel*) among children two to three years of age in a foundling home. They noted that there seemed to be an unusually high number of prematurely born children in the group with enamel defects

Association with Neurologic Disorders

In Survivors of Hemolytic Disease. Forrester and Miller examined the teeth of 13 children who had recovered from hemolytic disease of the newborn and exhibited clinical signs of kernicterus. They found widespread severe enamel hypoplasia of deciduous teeth in all 13 of these children. The changes consisted of discrete pitting of the enamel of the dental crown or coalescence of the pits to form lines or rings. Sometimes areas of the crown of the tooth appeared to be devoid of enamel. No dental pigmentation was found. Forty-five survivors of hemolytic disease without kernicterus and 105 normal children did not have enamel hypoplasia.

In Expremature Children. Among 99 survivors of premature birth a high incidence of enamel lesions was found.¹¹ The lesions were most extensive in 3 children with definite evidence of retarded neuromuscular development. Fifteen examples of circumscribed enamel hypoplasia (confined almost entirely to

FIG. 12-1. Enamel hypoplasia of incisors in a 3-year-old child (birth weight 1440 Gm.). Neurologic examination negative, hearing normal. (Courtesy of Dr. Solomon N. Rosenstein, Division of Pedodontics, Columbia University School of Dental and Oral Surgery, New York.)



the upper central incisors) were found among the remaining 96 premature children who had no clinical evidence of kernicterus

We examined a group of expremature children at two years of age and found a higher incidence of enamel hypoplasia (Fig. 12-1) in those with evidence of neurologic deficit ($7/14 = 50$ per cent) than in others who were considered to be normal ($9/45 = 20$ per cent).²³ None of the children in the neurologic-deficit group exhibited choreoathetosis or other signs suggestive of kernicterus.

In Term-Born Children. The exact incidence of enamel hypoplasia in term children with cerebral disorders other than kernicterus is in dispute.^{11, 23}

Other Associations

Evans reported a high incidence of enamel hypoplasia in the deciduous teeth of children born to mothers who had rubella during pregnancy. Similar defects are found in the permanent teeth of children who are known to have had rickets in infancy.⁸

Kreshover and co-workers commented that abnormalities of odontogenesis may be considered nonspecific in nature and related to a variety of causative factors.

GREEN TEETH

Green discoloration of deciduous teeth is seen in some children with a history of hyperbilirubinemia in the newborn period. It is of interest, therefore,

that green teeth are rarely observed in expremature children even though a significant proportion of them experience neonatal hyperbilirubinemia (see Chap. 13).

Association with Hemolytic Disease. There are few estimates of the exact incidence of discolored teeth in the survivors of hemolytic disease of the newborn. Marsland and Gerrard found 17 children with green deciduous teeth and 6 with yellow teeth among 170 who survived erythroblastosis fetalis. The duration and depth of jaundice in the neonatal period could not be correlated with the oc-

TABLE 12-3 SUMMARY OF FINDINGS ON EXAMINATION OF THE EYES OF 697 FINNISH CHILDREN SELECTED ON THE BASIS OF BIRTH WEIGHT

	% of exprematures ^a (birth wt under 2500 Gm.)	% of controls ^b (birth wt 2500 Gm. and over)	
Refraction			
Hyperopia	91	94	
Myopia	4	2	
Astigmatism	6	5	
Emmetropia	3	3	
Anisometropia	2	1	
Heterophoria			
Orthophoria	31	33	
Esophoria	43	39	
Exophoria	21	26	
Hyper- and hypophoria	2	2	
Color blindness			
Males	6	5	
Females	1	0	
	% of infants birth wt 1000-2249 Gm (250 children)	% of infants birth wt 2250-2499 Gm. (230 children)	
Strabismus (concomitant)	6	3	2
Amblyopia	5	3	1
Lack of fusion	8	4	3
Lack of binocular sight	8	4	3
Lack of stereoscopic sight	9	5	4

From Castrén.⁴

^a 480 children born during the period 1937-55, average birth weight 2162 Gm. (lowest 1080 Gm.), average age at examination 9.4 years, excluding all examples of retrolental fibroplasia.

^b 217 children born during the period 1940-48, average birth weight 3362 Gm. (highest 4700 Gm.), average age at examination 9.0 years.

currence of discoloration. Histologic examination of the green teeth revealed a green band of pigment in the dentine. The enamel was not discolored. However, a microscopic finding in the enamel, termed a double neonatal line, was found in half of the discolored teeth examined. No correlation between cerebral defect and discoloration could be found. Marsland and Gerrard noted that with the advent of exchange transfusion the incidence of green teeth fell.

EYES

First Year of Life

Fletcher and Brandon made periodic examinations of the eyes of 462 premature infants during the first year of life and found that the majority had small degrees of myopia detectable ophthalmoscopically. However, almost all cases of high myopia occurred in infants who were known to have had acute retrolental fibroplasia in the neonatal period.

Childhood

Castrén conducted a survey of the status of the eyes of expremature children in Finland and compared his findings with those of term-born controls (Table 12-3). The average age of these children was 9 years at the time of the examination. No significant differences in the incidence of refractive errors, imperfect muscle balance, and color blindness were found in the two groups. However, the expremature group had significantly higher incidences of concomitant strabismus, unexplained poor vision, and lack of fusion, binocular, and stereoscopic sight. Moreover, these defects occurred most frequently in the children who had been most premature. Children with known retrolental fibroplasia were excluded from this series. (See also Chap. 16.)

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Part Two

CLINICAL CONSIDERATIONS

Section B • Abnormal Conditions

Neonatal Bilirubinemia

The accumulation of bile pigment in the plasma of infants in the first days of life in concentrations which are associated only with pathologic states at all other ages has in the past been called "physiologic jaundice of the newborn." This term has been used to signify that a high concentration of pigment in the plasma is observed commonly, is the self-limited result of delay in the "development" of the excretory capacity of the liver, and is innocuous. There is increasing concern that these temporary high concentrations may not be well tolerated under all circumstances.

BILIRUBIN METABOLISM

The Bile Pigments

In normal adults bile pigments are formed in the reticuloendothelial system principally, but not exclusively,⁶⁰ from the breakdown of the hemoglobin of mature erythrocytes at the end of their life span.

Unconjugated (Indirect-Reacting) Bilirubin. The resulting lipid-soluble yellow pigment, bilirubin, has been called "indirect-reacting bilirubin" because it reacts with diaotized sulfanilic acid to give a purple color in the presence of alcohol only. Bilirubin is comparatively insoluble in water and exists in the plasma as a complex with certain proteins. There is no agreement about which of the serum proteins are primarily involved in the transport of bilirubin. Various globulin fractions have been found to bind bilirubin.⁷² However, the principal fraction of the total bound bilirubin occurs with albumin.⁹⁷

Conjugated (Direct-Reacting) Bilirubin. In the liver bilirubin is conjugated with the water-soluble sugar derivative glucuronic acid to form mainly bilirubin diglucuronide and it is this pigment which is excreted into the bile.¹⁴ This compound and another similar compound which has been found in the plasma in hepatitis and biliary obstruction, bilirubin monoglucuronide, being water-soluble react "directly" with diazo reagent and do not require the presence of alcohol.

Lathe⁵⁸ proposed that "bilirubin" and "conjugated bilirubin" replace the terms "indirect reacting" and "direct reacting" bilirubin

Metabolic Pathways

Glucuronide Synthesis. The metabolic pathway of glucuronide synthesis for conjugation with bilirubin and many other substances has been the subject of many reports, and the reader is referred to the review of Billing and Lathe¹⁴ for details. Two enzymatic steps, the conversion of uridine diphosphate glucose

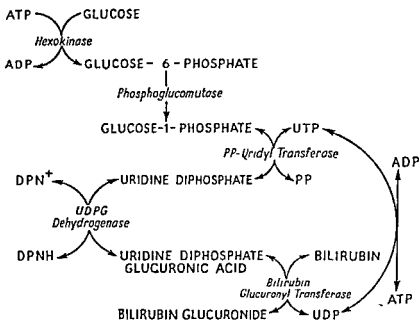


FIG. 13-1. Probable metabolic pathways leading to bilirubin conjugation.¹⁴ Enzymes are italicized. ATP, adenosine triphosphate; ADP, adenosine diphosphate; DPN, oxidized diphosphopyridine nucleotide; DPNH, reduced diphosphopyridine nucleotide; UTP, uridine triphosphate; PP, pyrophosphate. (From Lathe, G. H., Claireaux, A. E., and Norman, A. P.: "Jaundice in the Newborn Infant. I. Non-obstructive Jaundice." In Gairdner, D.: *Recent Advances in Paediatrics* (ed. 2). Boston, Little, Brown & Company, 1958.)

(UDPG) to uridine diphosphate glucuronic acid and the transfer of glucuronic acid from uridine diphosphate glucuronic acid, are of particular interest with respect to the genesis of neonatal bilirubinemia (Fig. 13-1)

Other Pathways. The possibility that bilirubin may be conjugated with other nonglucuronide substances must also be considered.⁵² The role of extrahepatic sites of bilirubin conjugation, particularly the kidney, has not been defined.^{14, 22}

Disposal of Bilirubin in Utero

Newborn infants (and rats with congenital deficiency of glucuronyl transferase) are not icteric at birth, even in the presence of maternal jaundice^{54, 55} The processes which are responsible for this phenomenon have not been elucidated. It is tempting to think that the placenta clears fetal blood of bilirubin before birth, and this notion is strengthened by the demonstration⁷⁹ (in the guinea pig) that unconjugated bilirubin injected into the fetal placental circulation appeared promptly in maternal blood, however, there is no direct evidence in the human on this point

Conflicting observations have been reported concerning the presence in the human placenta of activity of the enzymes involved in glucuronide formation^{22, 79}

CAUSES OF NEONATAL BILIRUBINEMIA

The rate at which the unconjugated bilirubin concentration in the plasma of the neonate rises is dependent upon the rate of bilirubin production (principally erythrocyte breakdown) and the bilirubin-conjugating capacity of the liver (degree of hepatic "maturity") The fairly rapid fall of bilirubin concentration in the plasma which follows the rise, four to seven days after birth, presumably results from an increase in activity of the enzymes concerned with glucuronide synthesis.

INCREASED ERYTHROCYTE BREAKDOWN

Mollison⁶⁶ calculated that the rate of breakdown of the newborn infant's erythrocytes in the first 10 days of life is approximately twice that of adult red cells and that the production of bilirubin from this source is proportionately three times as great as in the adult

Schulman's group estimated that there is a slight reduction in the life span of the erythrocytes of newly born premature infants. The macrocytic cells which represent a small proportion of the total population of red blood cells in the circulation of the newborn infant are probably destroyed more rapidly than the normocytic majority.^{66, 80}

LOW HEPATIC CLEARANCE OF BILIRUBIN

Increased production of bilirubin cannot, however, account for the levels of plasma bilirubin which are observed in the neonatal period. The normal adult liver can excrete an amount of bilirubin accounted for by all the hemoglobin

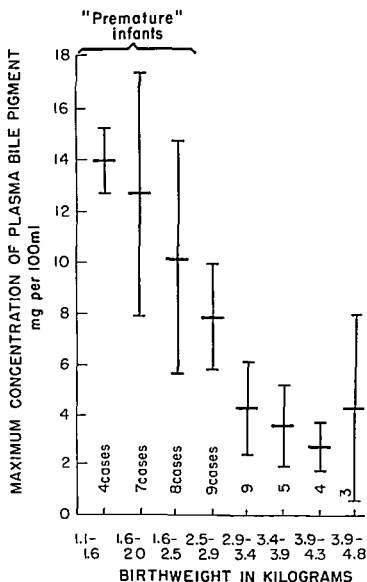


FIG. 13-2. Relationship between birth weight and the maximum concentration of bilirubin (total) in the plasma during the neonatal period. Mean value and the limits of one standard deviation are shown for each group. (Redrawn from Billing, B. H., Cole, P. G., and Lathe, G. H.: Increased plasma bilirubin in newborn infants in relation to birth weight. *Brit. M. J.* 2:1263, 1954.)

in the body in the course of ten hours, and the daily production of bilirubin of a newborn infant would be excreted by an adult in fifteen minutes.¹³ From these considerations and a study of the concentrations of bilirubin in the plasma of newborn infants in relation to birth weight, Billing *et al.*¹³ estimated that the capacity of the liver of a newborn premature infant to excrete bilirubin is 1 to 2 per cent of that of the normal adult liver.

The Glucuronide Conjugating System

Lathe and Walker⁵⁹ found a very low level of activity of the enzyme glucuronyl transferase in the livers of several human newborn infants. Brown and Zuelzer²¹ demonstrated lowered activity of this and another enzyme involved in the formation of glucuronides (UDPG dehydrogenase) in the fetal and newborn guinea pigs. These findings and the studies of Vest support the contention that the accumulation of unconjugated bilirubin in plasma during the neonatal period is the result of a delay in the development of the glucuronide conjugating system.

BILIRUBIN CONCENTRATION

"NORMAL" VALUES

The multiple influences on the degree of bilirubinemia in the newborn premature infant make it necessary to describe the "normal" values with wide margins of uncertainty.

White infants⁶⁰ and male infants¹⁹ have higher degrees of bilirubinemia than do their respective Negro⁴⁹ and female controls of similar birth weights. These observations would appear to be explicable on the basis of the fact that white infants and males are more immature than their coevals. Zetterström and others¹⁰¹ explained the high incidence of hyperbilirubinemia among infants of diabetic mothers on this basis.

In general the most immature newborn infants display the highest concentrations of bilirubin in the plasma (Figs 13-2 and 13-3), and achieve the maximal value latest in the first week of life (Fig. 13-4).

As has been stated, the principal pigment in the plasma of the neonate is unconjugated bilirubin. Since the concentration of conjugated bilirubin rarely (except in biliary obstruction and in inflammatory disorders of the liver) exceeds 2 mg. per 100 ml. plasma, most published studies report only "total bilirubin" (unconjugated plus conjugated) in newborn premature infants.

Lucey's group^{61, 62} summarized studies of the bilirubin concentration in the

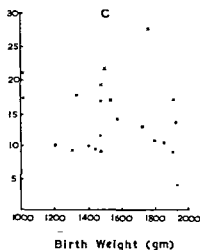
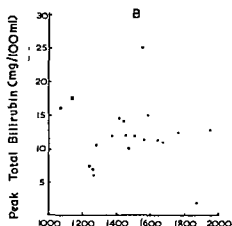
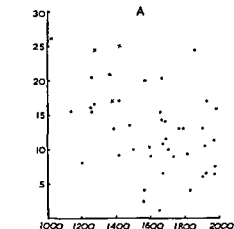


FIG. 13-3. Highest concentration of total bilirubin in the plasma during the neonatal period as estimated from daily determinations in 87 premature infants: by birth weight.

A, 45 white infants, major blood group of infant and mother compatible.

B, 20 Negro "compatible" infants.

C, 22 infants, major blood groups incompatible with that of the mother (18 white and 4 Negro). $x \pm$ values in 10 infants in whom a pathologic state could not be excluded (sepsis, 7; excessive vitamin K administration, 2; and ABO hemolytic disease, 1 infant). (From Rapmund, G., Bowman, J. M., and Harris, R. C.: Bilirubinemia in nonerythroblastotic premature infants: I. The correlation of peak plasma total bilirubin concentration with clinical course and postmortem findings in 140 newborn premature infants. *A M A. J. Dis. Child.* 99:604, 1960.)

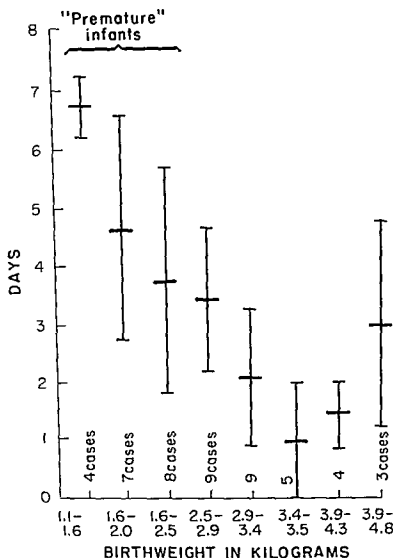


FIG. 13-4. Relationship between birth weight and the day on which the maximum concentration of bilirubin was observed in the neonatal period. Mean value and the limits of one standard deviation are shown for each group. (Redrawn from Billing, B. H., Cole, P. G., and Lathe, G. H.: Increased plasma bilirubin in newborn infants in relation to birth weight. *Brit. M. J.* 2:1263, 1954.)

plasma of premature infants (Table 13-1, Fig. 13-5). As can be seen, a wide variety of results has been reported. This is not surprising since, apart from the technical variations, a large number of factors have been demonstrated to influence the degree of bilirubinemia in newborn subjects and there can be very little assurance that the groups of infants reported in these studies are comparable with respect to these factors.

HYPERBILIRUBINEMIA

Due to Excessive Hemolysis. Some of the conditions which are associated with increased production of bilirubin as the result of excessive hemolysis are erythroblastosis fetalis, septicemia, cytomegalic inclusion disease, syphilis, toxoplasmosis, and congenital spherocytosis.⁸³ Relatively large doses of water-soluble vitamin K may also be associated. (See Chap 20.)

TABLE 13-1 SUMMARY OF REPORTS OF PEAK BILIRUBIN CONCENTRATION IN PLASMA OF PREMATURE INFANTS

Author	Weight (Gm)	Days sampled	Selection excludes					Peak bilirubin (total) % of cases			Comment
			No cases	Septis	Incom- patibles	Sulfa	Vit K	> 10 mg	> 15 mg	> 20 mg	
Rapmund <i>et al</i> ⁷⁴	< 2000	1-7	60	Yes	Yes	Yes	Yes	70	27	10	All on Terramycin
Hsia <i>et al</i> ⁵⁰	< 2000	1-8	7	No	Yes	No	No	86	28	0	
Hsia <i>et al</i> ⁵⁰	2000-2250	1-8	8	No	Yes	No	No	60	25	12	
Obrinsky <i>et al</i> ⁷⁵	< 2000	1-7	27	No	No	No	No	?	0	0	77% Negroes
Dunc ⁸⁴	< 2500	1-3 4 or 5	100	If fatal	If Rh disease	No	No	75	50	39	
Bound <i>et al</i> ¹⁷	< 2500	5	51	No	No	No	Yes	53	16	0	
Freedman ⁴⁰	2100	Until peak passed	308	No	No	No	No	66	23	6	All Negroes
Jelso ⁵³	< 2500	1-7	109	Yes	Yes	Yes	Yes	?	18	3	50% Negroes
Holman ⁴⁸	< 2500	1-7	39	Yes	Yes	Yes	Yes			> 18 36	64% Negroes
Lucey ⁶¹	< 2500	2, 4, 6	60	Yes	Yes	Yes	Yes	50	27	10	

From Lucey⁶¹

Other Associations. Hyperbilirubinemia in association with cyanosis¹⁰² and respiratory difficulty⁶⁵ has also been reported in premature infants, but no acceptable explanation for this association has been proposed.

The relationship between the state of hydration of the newborn premature infant and the level of bilirubin in the plasma has not been subjected to critical study. Rudolph and co-workers found that when feedings were given soon after birth (three to four hours) to infants of diabetic mothers the bilirubin concentrations in the serum at 2 to 5 days of age were lower than among controls who were fasted for the first 48 hours of life.

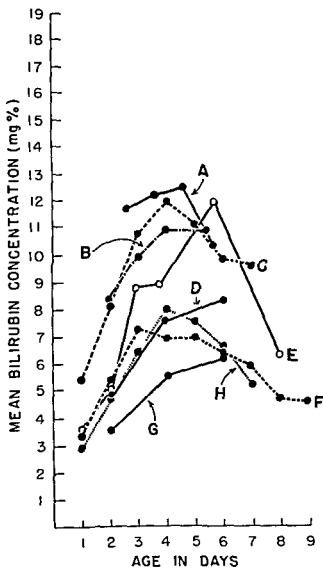


FIG. 13-5. Reported mean concentrations of bilirubin in the plasma by age. Key: Author (number of infants), birth-weight groups —A, Taylor *et al.*⁸⁸ (27), < 2500 Gm. B, Rapmund *et al.*⁷⁴ (60), < 2000 Gm. C, Hsia *et al.*⁸⁰ (12), 980–2500 Gm. D, Crosse *et al.*²⁷ (47), < 2500 Gm. E, Miller *et al.*⁶⁵ (12), 1000–1750 Gm. F, Miller *et al.*⁶⁵ (57) 1750–2500 Gm. G, Meyer⁶³ (46), < 2500 Gm. H, Obrinsky *et al.*⁷¹ (27), < 2000 Gm. (Redrawn from Lucey, J. F., and Dolan, R. G.: Hyperbilirubinemia of newborn infants associated with the parenteral administration of a vitamin K analogue to the mothers. *Pediatrics* 23:553, 1959.)

FACTORS WHICH LOWER BILIRUBIN CONCENTRATION

Sulfonamides have been implicated as a cause of lowered bilirubin concentrations in the plasma of premature infants⁴⁷ and experimental animals.⁵⁴ Odell presented evidence which suggests that salicylate has a similar effect.

Cremer and others observed that the exposure of newborn premature infants to light (sunlight and artificial light) was followed by small reductions in the level of bilirubin in the plasma

EXTRAVASCULAR BILIRUBIN

The yellow color of the skin and other organs is considered to be due to bilirubin bound to elastin in the tissues and not to the bilirubin content of tissue fluid or plasma.⁹⁷ Tissues which are rich in elastin (skin, intima of blood vessels, scleral conjunctivae) show the most intense color.

SKIN

Threshold of Detectable Jaundice

The threshold of visible jaundice in newborn infants has been the subject of much study in the past and this has been reviewed by With.^{96, 97}

The infant must be examined in daylight (or fluorescent light) and pressure applied to blanch the hyperemic skin if slight jaundice is to be discovered. If circulation to the skin is impeded by bandaging or compression as in the natural skin folds, the development of yellow color can be prevented.⁴⁸

The threshold of visible jaundice in 34 white adults with obstructive jaundice was found by Larsen and With to be 1.5 to 2.5 mg. bilirubin per 100 ml. plasma; in 45 newborn infants it was about four times as high, 8 to 9 mg. bilirubin per 100 ml. plasma. This suggests that water-soluble conjugated bilirubin can diffuse into the tissues with greater ease than lipid-soluble bilirubin or that the bile pigments may be bound in different ways to tissue proteins.¹⁴

Latent Period After Bilirubinemia

With⁹⁷ noted that a latent period of several days between hyperbilirubinemia and the development of recognizable icterus occurs in man and experimental animals. Although this delay has been cited in support of the thesis that the yellow color of jaundiced tissues is due to the binding of bilirubin to the tissues themselves, it is of interest that the latent period can be shortened by the injection of bile salts in experimental animals.¹¹

It is not known what influences affect the plasma threshold for icterus or the

latent period between hyperbilirubinemia and icterus during the neonatal period. A rapidly rising level of bilirubin in the plasma does not appear to be a satisfactory explanation for the early appearance of icterus in erythroblastosis fetalis, and the wide variation in apparent plasma thresholds for icterus in neonates³⁰ cannot be entirely explained on the basis of errors of observation. Odell's studies, which indicated that heme pigments may influence the diffusion of bilirubin from the vascular compartment, are of interest in this connection.

URINE

Bilirubin does not appear in the urine in neonatal icterus unless the level of bilirubin in the plasma is very high.⁵⁶ In contrast, pigment regularly appears in the urine during the course of obstructive jaundice. This difference is understandable on the basis of a difference in renal thresholds which Larsen and With estimated to be 10 to 20 mg per 100 ml. plasma for bilirubin and 3 to 6 mg per 100 ml. for water-soluble conjugated bilirubin.

MECONIUM AND FECES

The concentration of bilirubin in meconium of premature infants has been reported to be lower than in term infants.^{90, 99}

Larsen and With attempted to correlate the maximal value of bilirubin in the serum during the first six days of life with the total fecal bilirubin excretion during this period in 25 full-term infants. Although there was an association between high values of bilirubin in the feces and low values of bilirubin in the serum, in this small series chance remained the most likely explanation for the correlation.

CEREBROSPINAL FLUID

Nasralla and co-workers investigated the relationship between the concentrations of bilirubin (total) in serum and in cerebrospinal fluid among 100 newborn infants, including 49 normal premature infants. Although a significant positive correlation was obtained between the concentration of bilirubin in these two body fluids, the association was not close.

The authors expressed the relation between the concentrations in the form of a ratio: serum bilirubin/cerebrospinal-fluid bilirubin. The ratio was lowest among the smallest and youngest infants; for infants weighing less than 2.0 kg the ratio varied from 18.8 (± 10.6) in the first two days of life to 27.3 (± 8.5) in the age interval 6 to 9 days. The concentration of bilirubin in the serum had little effect upon the ratio.

Nasralla *et al.* found a significant positive correlation between the concentrations of bilirubin and of protein in the cerebrospinal fluid

BILE PIGMENTS IN OTHER FLUIDS

The color of bile in the gallbladder of premature infants who succumb in the first few days of life is yellow or muddy brown. This is in contrast to the colorless bile described by Schmid *et al.*⁷⁷ in the gallbladder of children with congenital nonhemolytic jaundice.

In adults bilirubin concentrations in edema fluid, exudates, and transudates are generally lower than in the plasma.⁹⁷ Sweat, tears, gastric and intestinal juice, pancreatic secretion, and vaginal secretions are free of bilirubin in jaundiced adults.⁹⁷ However, Smith observed that tears and nasal secretions may be yellow in markedly icteric infants

SYMPTOMATIC EFFECTS OF NEONATAL BILIRUBINEMIA

Those who care for newly born premature infants with icterus commonly observe drowsiness, apathy, feeble nursing, and regurgitation, but there are no satisfactory data from which it is possible to judge the relationship. The question of whether these signs are the result of the influence of moderate levels of bilirubin upon the central nervous system must go begging.

There have been conflicting reports on the correlation between tachypnea and hyperbilirubinemia in premature infants.^{65, 86}

KERNICTERUS OF PREMATURITY

Following the discovery in 1940 of the Rh factor in human blood it was generally held that most, but not all, instances of bright-yellow staining of the basal ganglia (kernicterus) found at necropsy were associated with isoimmunization.³⁵ In 1946 Vaughan⁸⁸ observed that prematurity played a role in the development of kernicterus associated with erythroblastosis fetalis. He also noted the occurrence of kernicterus in premature infants who had no evidence of isoimmunization.

In 1950 almost simultaneous reports from this country (Detroit)¹⁰² and from England (Bristol)⁴ called attention to an appreciable incidence of kernicterus in premature infants who did not have erythroblastosis fetalis.

INCIDENCE

"Usual" Frequency. It is virtually impossible at the present time to make a statement concerning the "expected" or "usual" incidence of kernicterus of pre-

maturity. In general terms the incidence has been relatively low in nurseries for premature infants except in association with the administration of sulfisoxazole and large doses of synthetic vitamin K (Table 13-2).

TABLE 13-2 SOME REPORTS OF THE "INCIDENCE" OF KERNICTERUS OF PREMATURETY

City	Years	Iatrogenic factors		Denominator population		No examples of kernicterus of prematurity ^a at necropsy
		Vitamin K analogue (mg)	Sulfonamide	Live-born prematures	Necropsied prematures	
Detroit ¹⁰²	1940-1950	?	?	?	?	23
Bristol (England) ⁴	1948-1950	?	?	?	144	23
New Orleans ¹	?	?	?	?	84	7
Helsinki (Finland) ³	1946-1952	?	?	?	(628) ^b	18
Hiroshima (Japan) ⁸⁵	1950-1953	?	?	?	(451) ^b	(27) ^b
London (England) ⁸⁶	1948-1952	?	?	?	(376) ^b	9
Birmingham (England) ⁸⁷	1945-1948	1-5	?	1234	?	10 ^c
	1949	10	?	243	?	4 ^c
	1949-1954	30-50	?	2208	?	54 ^c
	1950-1953	< 5	?	?	216	3
	1953-1954	< 5	SZL ^d	?	141	29
New York City ⁸⁷	1955	< 5	SZL ^d	?	44	19
	1955	< 5	?	?	22	1
	1956	< 5	?	?	87	1
	1957	< 5	?	?	37	3

^a Not associated with isoimmunization

^b Term plus premature infants

^c Necropsy diagnosis plus survivors with kernicterus

^d Sulfisoxazole

Relation to Birth Weight. Harris *et al.* found no relationship between the frequency of occurrence of kernicterus of prematurity and birth weight among infants who weighed less than 2 kg. at birth.

CLINICAL COURSE

The signs exhibited by infants with kernicterus of prematurity are indistinguishable from those seen in association with erythroblastosis.

Onset

Age at Time of Onset. The first signs of kernicterus of prematurity rarely appear before the fourth day; in those associated with erythroblastosis the onset is usually on the second or third day of life.

It is noteworthy that in children with congenital familial nonhemolytic jaun-

dice with kernicterus the onset of signs has been later than the first week of life,²⁶ and in one child not until 3 years of age.⁷⁵

Rapidity of Onset. In our experience the manifestations appear rather abruptly. Although premature infants with moderate bilirubinemia may be lethargic and may feed poorly, the change in clinical state that occurs in the infant with kernicterus is a distinct and quick one, rather than a slow and imperceptible worsening. Alert nurses have often timed the onset to the hour.

Manifestations

Early Signs. The most frequent initial manifestation, apart from jaundice, is feeding difficulty. This takes the form of the rather sudden onset of marked anorexia and regurgitation.

Opisthotonos, rigidity, flexed arms, and bradypnea follow quickly (Fig. 13-6). The muscles become firm to the touch, the skin, however, is not "bound" to the subcutaneous tissue as in sclerema.

The eyes are often open and the infant stares vacantly. Rolling and jerking movements of the eyes may also be present. If the trunk is raised and then quickly lowered to the supine position the eyes slowly drift downward ("setting-sun" sign²⁷).

An abnormal Moro response is seen, in which the infant exhibits an exaggerated startle reaction, the arms are thrown out in rigid extension, and the expected embrace movement does not appear. The results of formal neurologic examination of affected infants in the neonatal period have unfortunately not been reported.

Late Manifestations. Bouts of apnea and cyanosis soon become frequent, and

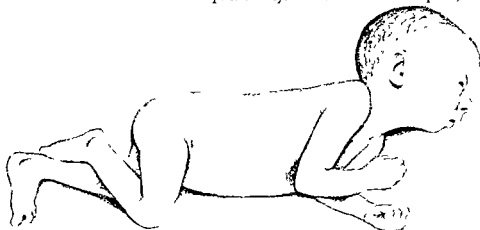


FIG. 13-6. Characteristic appearance of a premature infant with kernicterus.

late in the course peripheral vascular collapse becomes evident. With deepening jaundice the skin takes on a muddy yellow color. Convulsions, in our experience, appear late, if at all. In the terminal stages, fever has been described,^{41, 42, 45} a sign which we have not observed. Blood-stained froth or frank, bright-red hematemesis is a frequent terminal manifestation.^{43, 45}

Outcome

Death. If death occurs, the usual time is late in the first week of life ("sixth day" disease⁵). In kernicterus associated with isoimmunization infants die most commonly on the fourth day of life.⁴³

Mortality Rate. Although the clinical picture is usually quite definite, the diagnosis rests entirely on the physician's judgment. This judgment is usually, but not always, borne out by the necropsy findings. As a result, an exact mortality rate cannot be calculated. It has been estimated that two-thirds to three-quarters of affected infants die in the neonatal period,^{27, 43} but in our experience the presumed neonatal fatality rate has been even higher.

Survival. In the few infants with the clinical picture of kernicterus of prematurity who survive the neonatal period, a curious temporary improvement occurs. Gerrard described this phenomenon in infants with kernicterus associated with erythroblastosis fetalis. The improvement may be so marked that the infants are regarded as normal at one or two months of age. However, later in the first year of life they usually become quite hypotonic. Gerrard noted that with the advent of hypotonia, between the second and ninth months, involuntary ("jerking") movements usually make their first appearance. Some patients exhibit a variable degree of rigidity and opisthotonos during infancy.

Most surviving children with kernicterus associated with erythroblastosis fetalis exhibit choreoathetosis and severe mental retardation.^{38, 43} Gerrard reported that the choreic or athetoid character of the involuntary movements may not be fully developed until the child is three to five years of age. He also noted that perceptive deafness was a frequent manifestation of kernicterus.

PATHOLOGIC FINDINGS

Criteria for Pathologic Diagnosis

Johnson's group proposed the following criteria for the definition of kernicterus:

1. Distinctive evidence of central nervous system dysfunction during life in jaundiced subjects.

2. Canary-yellow staining of nuclear masses of brain, spinal cord, or both, in postmortem specimens.
3. Persistence of the yellow color for several weeks when the brain is fixed in Formalin, without the appearance of a permanent green color as in most other icteric tissues.
4. The presence of intracellular pigment in frozen sections.
5. Evidence of degeneration of nerve cells in specimens prepared for microscopic examination.

Pigment Deposits

In Brain. The distribution of pigment in the brain has been shown to be essentially the same in kernicterus associated with prematurity and in that associated with erythroblastosis fetalis.^{81, 102} The areas most frequently involved are the hippocampus, thalamus, hypothalamus, corpus striatum, nuclei of pons and medulla in the floor of the fourth ventricle, olives, dentate nucleus, flocculus, vermis, gray matter of the spinal cord, and occasionally the cerebral cortex.⁸¹

The pathologic diagnosis of kernicterus is usually made on the basis of grossly visible areas of yellow staining in cut sections of Formalin-fixed brains. There is considerable difference of opinion about the histologic findings in kernicterus; however, typical microscopic findings have been described.^{16, 43, 45, 54}

In Kidney. Zuelzer and Mudgett described "bilirubin infarcts" in the renal papillae of infants who have succumbed with kernicterus associated with erythroblastosis fetalis. Similar lesions have been reported in experimental animals with (unconjugated) hyperbilirubinemia^{54, 78} but not in infants with kernicterus of prematurity.¹⁰²

Other Findings

Although other pathologic findings have been reported in association with kernicterus of prematurity (principally sepsis¹⁰²), the meaning of the relationships remains in doubt

Pulmonary Hemorrhage. One associated finding that has been commented upon by many observers^{2, 4, 43, 102} is that of focal, at times massive, intra-alveolar pulmonary hemorrhage. Similar pulmonary findings have been observed in infants with kernicterus associated with erythroblastosis fetalis and in experimental animals with kernicterus.⁵⁴ However, in our experience, pulmonary hemorrhage was not noted more frequently in premature infants who died with kernicterus than in others who died without kernicterus.⁸¹ (See also Chap. 15.)

PATHOGENESIS

Specificity of Bilirubin

The nature of the pigment responsible for yellow staining of the brain in kernicterus was the subject of much speculation in the past, and conflicting evidence on this point was presented.^{91, 94}

Claireaux and others examined brain extracts obtained from infants who died with both types of kernicterus (associated with prematurity and associated with erythroblastosis). The brain pigment was identical in both groups and was identified as (unconjugated) bilirubin. A bilirubin-retaining lipid was also demonstrated in the brain tissue which selectively concentrated (unconjugated) bilirubin and had no affinity for conjugated bilirubin.

This evidence is in harmony with a number of studies which have indicated that (unconjugated) bilirubin is not only the staining agent⁹³ but is also responsible for the brain damage of kernicterus.^{17, 18, 42, 55, 92, 100} Conjugated bilirubin²⁴ and biliverdin^{32, 33, 100} are presumed to be innocuous. Thus it can be stated with some assurance that the noxious substance which is responsible for kernicterus has been identified. However, there remains considerable question about how and under what circumstances the pigment leaves the vascular compartment and enters the cells of the basal ganglia

Role of Hyperbilirubinemia

In Erythroblastosis Fetalis. When it became established that exchange transfusion reduced the number of neonatal deaths by preventing kernicterus in erythroblastosis fetalis,^{6, 8} there was no agreement about how this effect was accomplished. The observation that there was an association between severe jaundice and kernicterus in hemolytic disease^{67, 89} led to studies of the concentration of bilirubin in the plasma of these infants during the first days of life. English⁶⁸ and American⁵⁰ observers agreed that the incidence of kernicterus was related to the degree of bilirubinemia and that its occurrence was rare if the concentration of bilirubin (total) in the plasma remained below 20 mg. per 100 ml. On the presumption that there was a threshold beyond which bilirubin entered brain tissue, these studies formed the basis for a successful approach to the management of infants with erythroblastosis fetalis.

In Overdosage of Vitamin K. Observations were made on a group of premature infants with no evidence of isoimmunization who developed hyperbilirubinemia following large doses of vitamin K analogue (Synkavit).^{27, 84} These studies supported the idea of a critical concentration of bilirubin in the

plasma, since the incidence of kernicterus rose when the level of bilirubin (total) exceeded 18 mg. per 100 ml.

In Uncomplicated Prematurity. Kernicterus of prematurity unassociated with either erythroblastosis fetalis or large doses of vitamin K cannot be completely explained on the basis of hyperbilirubinemia. In some series^{19, 74} an appreciable proportion (one-third to one-tenth) of premature infants accumulated bilirubin (total) in the plasma in concentrations exceeding 18 mg. per 100 ml., yet the incidence of kernicterus among infants who died in the neonatal period was lower than would be expected from experience with erythroblastosis and large doses of vitamin K. On the other hand, in association with the use of sulfisoxazole in premature infants whose bilirubin (total) concentrations in the plasma remained well below 18 mg. per 100 ml., the incidence of kernicterus was higher than would be expected^{47, 81} if serum bilirubin concentration were the sole determining factor. It seems clear that although the presence of bilirubin (unconjugated) is required for the production of kernicterus, the concentration of this pigment in the plasma may be only one of a number of factors which influences its penetration into the brain.

Factors in the Distribution of Bilirubin in Body Fluids

Protein Binding of Bilirubin. As discussed previously, sulfonamides cause a fall in the concentration of bilirubin in the plasma of experimental animals³⁴ and premature infants.⁴⁷ Odell conducted *in vitro* studies which showed that sulfonamides and salicylate can uncouple protein-bound bilirubin and allow it to diffuse.

Odell also observed that hematin and bilirubin *in vitro* compete with one another for protein binding. Thus it is possible that the distribution of bilirubin may be influenced by the presence of other pigments produced by hemolysis.^{1, 87}

Odell postulated that low concentrations of protein in the plasma or the presence of ions that interfere with the binding of bilirubin may result in low concentrations of pigment in the vascular compartment and the accumulation of unbound bilirubin in extravascular body fluids. In such circumstances the concentration of bilirubin in the plasma may not accurately describe the threat to the central nervous system.

Role of the Blood-Brain Barrier. Numerous experiments have established the fact that there is a barrier to the passage of vital dyes, toxins, viruses, and drugs from the blood to the central nervous system of the adult.⁴¹ This barrier has been localized in the capillaries of the brain, which have a selective permeability. The transcapillary passage of substances into the central nervous sys-

tem is influenced by a number of factors that include particle size, lipid-solubility, etc.³¹

Palm showed that blood vessels of the retina have similar barrier characteristics.

Studies have been made of the barrier to the passage of substances from within blood vessels to the brain and from blood vessels to the cerebrospinal fluid in human fetuses and experimental animals. They have indicated that the permeability of these barriers is greater in the fetus and the young subject than in the adult¹⁰ and greater in prematures than in term infants.⁶⁹ These observations have been invoked to explain the susceptibility of newborn subjects in general and premature infants in particular to the neurotoxicity of bilirubin.^{9, 37, 42, 84}

However, the evidence on this point is not completely clear. It is difficult to be certain that conclusions about the interchange of substances between blood and nervous tissue can be drawn from evidence obtained from studies of the cerebrospinal fluid.³¹ Furthermore, there remains the possibility that in premature infants the barrier (or barriers) to the passage of bilirubin into the nervous system is usually intact but the pathologic conditions which interfere with the function of the barrier occur more frequently among these subjects.⁴⁶

Other Possible Influences

Septicemia,¹⁰² hypoxia,⁴⁵ hypoglycemia,⁴³ ammonemia,⁴⁴ and other states¹⁵ have been proposed as possible contributing causes of kernicterus of prematurity. We can only speculate about these relationships. It is conceivable that these conditions could act not only by promoting the accumulation of bilirubin but also by modifying the distribution of bilirubin in body fluids.

Until we have more complete information relating to the effects of protein concentration in the blood, protein fractions of plasma, hydrogen-ion concentration, etc., upon the distribution of bilirubin our understanding of the pathogenesis of kernicterus will remain incomplete.

MANAGEMENT OF INFANTS WITH BILIRUBINEMIA

As evidence has accumulated that unconjugated bilirubin is a toxic substance, there has been increasing concern about the clinical management of bilirubinemia in premature infants.

Accurate Diagnosis

It should be recalled that a fairly large number of pathologic conditions may

accentuate bilirubinemia (see p. 206). As a result of a fairly exhaustive clinical search is often necessary to establish an accurate diagnosis.

Exchange Transfusion

In the Presence of Increased Hemolysis. Abundant evidence supports the contention that when increased hemolysis is associated with erythroblastosis fetalis or vitamin K overdosage, for best protection of the central nervous system the concentration of bilirubin (total) in the plasma should not be allowed to exceed 18 to 20 mg. per 100 ml.^{27, 51, 63, 68} At present this can be accomplished promptly and reliably only by exchange transfusion (see Chap. 20).

Without Increased Hemolysis. The same criteria and treatment have been used in the absence of increased hemolysis.^{12, 20, 28, 36, 70} In the present state of our knowledge these efforts must be considered to be entirely exploratory.

To satisfactorily remove bilirubin from the infant by perfusion it is necessary to perform the exchange transfusion over a period of several hours²³ and to effect an exchange of blood equal to several blood volumes⁵⁷ (175 to 200 ml./kg. at a rate of 1.8 ml./kg./min.³⁹) There is at this time no satisfactory proof that such rigorous treatment of uncomplicated hyperbilirubinemia results in the survival of an increased number of undamaged premature infants.

The incidence of kernicterus among premature infants who die is low, and the precise differentiation between this condition and other forms of brain damage in survivors is difficult. For these reasons it would be necessary to conduct a fairly large trial with concurrent controls to establish the efficacy of exchange transfusion. The large experience with exchange transfusion in premature infants reported by Crosse and her co-workers²⁸ is difficult to evaluate since no concurrent controls were used. In the controlled trial reported by Forfar *et al.* the long term follow-up is not concluded.

Other Proposed Methods of Treatment

Preliminary reports on the use of other methods^{25, 29, 98} to promote the excretion of bilirubin in premature infants must be interpreted with caution. It is incumbent upon the investigators to prove that the lowering of the concentration of the pigment in the vascular compartment is safe and that there is no change in the distribution of bilirubin. Specifically, it must be shown that increased permeation of the brain does not occur.

There is every reason to hope that a safe method will be found either to promote the excretion of unconjugated bilirubin or to contain it within the bounds

of the vascular system and that our present state of uncertainty about managing these infants is temporary.

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Respiratory-Distress Syndrome

Few subjects have provoked more controversy and produced a more voluminous recent literature than the one concerning the causes of the symptoms of respiratory difficulty among premature infants in the first few days of life.

The subjects "respiratory distress" and "pulmonary hyaline membranes" have recently been thoroughly reviewed, and the reader is referred to these monographs for complete accounts of the historical background and of the many controversies which exist.^{26, 33, 58, 104, 123}

CLASSIFICATION

Postmortem Diagnosis

There is little agreement on the classification of infants who exhibit the symptoms of respiratory distress. In the past the classification has been determined from the point of view of the pathologist who assigned diagnoses after careful study of the gross and microscopic appearance of the lungs of infants who succumbed. The commonest lesion observed was marked capillary engorgement, widespread collapse of alveoli, and membrane-like layers of homogeneous eosinophilic material lining dilated alveolar ducts.

When the clinical course of these infants was reviewed it was found in retrospect that virtually all had exhibited signs of respiratory difficulty. Thus the term "hyaline membrane disease" was applied widely.

Clinical Criteria

In the past few years observations of the respiratory performance of premature infants have been made more frequently, clinical criteria have been defined and it has become clear that many but not all of the infants who exhibit signs of respiratory difficulty have hyaline membrane formation in the lungs.

From the point of view of the clinician the term "idiopathic respiratory dis-

ress syndrome"^{26, 62, 70, 98} is a useful one, for it designates a group of infants with a characteristic set of clinical signs. Not only does it include the infants who die and become known to the pathologist as examples of cases with "pulmonary hyaline membranes"; but in addition others are included who exhibit identical clinical signs. Some of the latter survive. Some die and have no demonstrable pulmonary hyaline membranes.

In the discussion which follows the term "pulmonary hyaline membranes" will be used only when referring to instances in which the characteristic eosinophilic material was seen by the pathologist.

INCIDENCE

Relation to Birth Weight

Clinical Signs. There have been no large-scale clinical studies of the frequency of occurrence of respiratory distress among premature infants. In reported series different criteria have been used for the clinical diagnosis, and thus different estimates of the incidence of respiratory difficulty have been reported (Table 14-1). However, there is agreement that the arbitrary clinical signs of distress are exhibited least frequently by the largest premature infants and most frequently by the smallest infants.

Pulmonary Hyaline Membranes. Latham and others estimated the incidence of pulmonary hyaline membranes (as found at necropsy) to be 2 to 4 in 1000 premature live births, as compared with less than 1 in 1000 term live births.

TABLE 14-1 ESTIMATES OF THE INCIDENCE OF RESPIRATORY DISTRESS
AMONG CONSECUTIVELY BORN PREMATURE INFANTS

Birth weight (Gm)	Criterion of distress			
	Respiratory rate ^a		Retractions ^b	
	No. infants	% with distress	No. infants	% with distress
2001-2500	223	13	.	.
1501-2000	92	47	57	26
1001-1500	35	89	27	45
1000 or less	.	.	18	72

^aFrom Miller,²⁶ based on a study of 350 premature infants consecutively born in University of Kansas Medical Center. Increased rate was considered to be a rise of 15 or more respirations per minute over the average rate in the first hour of life.

^bFrom Bauman,¹⁰ based on a study of 102 premature infants (birth weight less than 2001 Gm) consecutively born in the Sloane Hospital for Women, excluding those who died before the age of 6 hours. Retractions were scored according to an arbitrary scheme (see p. 144) at 6 hours of age. A total score of 2 or greater was considered to indicate significant retractions.

The frequency of occurrence of this pathologic entity among premature infants has often been computed on the basis of the number of infants examined at necropsy. This has led to the widely held view that pulmonary hyaline membranes occur relatively more frequently among infants in the middle birth-weight

TABLE 14-2 "INCIDENCE" OF PULMONARY HYALINE MEMBRANES BY BIRTH WEIGHT AND AGE AT DEATH

	<i>Birth weight (Gm)</i>		
	<i>1000 or less</i>	<i>1001-1500</i>	<i>1501-2000</i>
Total no infants	116	216	360
Died 0-23 hours			
No died	56	33	20
No necropsies	52	32	18
No with hyaline membranes	15	24	14
% necropsied cases affected	29% ^a	75%	78%
"Incidence" in total population	13% ^b	11%	4%
Died 24-47 hours			
No died	22	21	21
No necropsies	20	17	19
No with hyaline membranes	3	9	14
% necropsied cases affected	15%	53%	74%
"Incidence" in total population	5%	5%	4%
Died 48-71 hours			
No died	9	8	7
No necropsies	8	8	6
No with hyaline membranes	1	2	4
% necropsied cases affected	13%	25%	67%
"Incidence" in total population	3%	1%	1%

Based on 692 premature infants, whose birth weight was below 2001 Gm, consecutively born in the Sloane Hospital for Women, 1950-1957, and admitted to the premature nursery of Babies Hospital.¹¹⁴

For the purpose of this calculation the assumption is made that the mortality rate associated with pulmonary hyaline membranes was the same in the three birth weight categories

^a% necropsied cases affected = hyaline membranes/number necropsies $\times 100$, e.g., $15/52 = 29\%$

^b"Incidence" in total population = hyaline membranes/total number of infants admitted (less those who died in the previous age interval), e.g., 1000 Gm or less, 0-23 hours, $15/116 = 13\%$, 1000 Gm or less, 24-47 hours, $3/116 = 3\%$

groups. However, when the incidence was estimated on the basis of live births^{31, 67} and due allowance was made for the differences in age at the time of death¹¹⁴ it was shown that pulmonary hyaline membranes occur with equal

or greater frequency in the smallest premature infants (Table 14-2). These estimates of the incidence of pulmonary hyaline membranes together with clinical estimates of the incidence of respiratory distress favor the view that there is an intimate relationship between the degree of prematurity and the incidence of respiratory distress.

Association with Other Conditions

Retrospective calculations of the coincidence of pulmonary hyaline membranes with various maternal, parturient, and fetal factors have been made repeatedly. The meaning of these associations is difficult to judge because the interpretation is affected by the choice of a contrast population of infants. For example, it has been shown by some, but not all, observers that a history of maternal diabetes, antepartum bleeding, multiple pregnancy, birth by cesarean section, or breech presentation is obtained more frequently among infants with pulmonary hyaline membranes than among others who have died without this lesion.^{17, 28, 31, 67, 81, 88, 106, 120} Gellis and Hsia⁴⁵ observed that the incidence of respiratory distress among infants of diabetic mothers was not greater in 510 individuals who were delivered by cesarean section than in 201 others who were delivered by the pelvic route. There is conflicting evidence on the point of whether the incidence of pulmonary hyaline membranes is greater in the second-born of twins³¹ or the same in both members of the pair.¹¹³

None of the reported clinical studies of consecutively born premature infants has been large enough to permit a valid comparison of pulmonary-hyaline-membrane incidence rates specific for degree of maturity, method of birth, complications, and other factors. It is entirely possible that the relationship of each of these factors to the occurrence of pulmonary hyaline membranes is dependent upon a common association with prematurity.⁶

ETIOLOGY

PULMONARY HYALINE MEMBRANES

Composition of the Membranes

Much of the controversy concerning respiratory distress has been centered on the composition of pulmonary hyaline membranes. There is now convincing evidence that the membranes are made up principally of insoluble fibrin.^{48, 129} Although all are not agreed,^{1, 116} it appears likely that, except for thromboplastic material, amniotic-fluid remnants do not commonly contribute elements to the membranes.^{38, 48}

The pulmonary membranes have been alleged to result from necrosis and hyalinization of epithelial cells lining respiratory bronchioles.^{9, 125}

Effusion of Fluid into the Respiratory Tract

Many recent studies have been concerned with attempts to determine the factors that influence the effusion of fluid from pulmonary capillaries into the alveoli.³⁹

Cardiopulmonary Factors. There has been considerable interest in the cardiopulmonary events that occur in the first moments of extrauterine life^{37, 60, 97} and speculation about the effect of these changes upon pulmonary capillary pressure, particularly as it determines the effusion of fluid.^{18, 19, 25, 31, 44, 53, 69, 70, 93}

Development of Pulmonary Arterioles. O'Neal *et al.*, studying the formation of fetal pulmonary arterioles, demonstrated that the media of these vessels is poorly developed in premature infants and postulated that in consequence such infants may be predisposed to disturbances of pulmonary circulation.

Increased Capillary Permeability. Ylppo many years ago noted marked permeability of the blood vessels of premature infants. This imperfection probably accounts for the generalized edema so regularly manifested by premature subjects and has been invoked as an additional predisposing cause for the accumulation of pulmonary fluid.^{31, 96} Edema fluid obtained from premature infants has been shown to be rich in protein, particularly albumin.³¹

In attempting to account for such increased capillary permeability one cannot judge, from the existing evidence, the relative importance of the roles of incomplete development versus injury as the result of hypoxia.¹⁰⁵

Role of Supplemental Oxygen

Pulmonary hyaline membranes have been noted in newborn and adult experimental animals after exposure to high concentrations of oxygen (above 85 per cent),^{12, 22, 124} and exposure to high oxygen concentrations has been shown to interfere with the ciliary activity in the respiratory tract of experimental animals.¹³

There is considerable doubt about the effect of oxygen in the production of pulmonary hyaline membranes in human premature infants. The experience in our nursery for eight years is interesting in this regard. During this time the policy of oxygen therapy was changed from one of prolonged administration of high concentrations of oxygen for all infants (1950 through 1952) to a policy of oxygen only to relieve cyanosis and rarely above 40 per cent concentration (1953 through 1957). The annual incidence of retrolental fibroplasia fell sharply fol-

TABLE 14-3 ANNUAL OCCURRENCE OF PULMONARY HYALINE MEMBRANES AND RETROLENTAL FIBROPLASIA IN CONSECUTIVELY BORN PREMATURE INFANTS

	<i>Distribution (%) of intramural admissions by birth weight</i>				<i>% with active retrolental fibroplasia</i>	<i>"Incidence" of pulmonary hyaline membranes*</i>	
	<i>1000 Gm or less</i>	<i>1001-1500 Gm</i>	<i>1501-2000 Gm</i>	<i>Total</i>			
				<i>%</i>			<i>No</i>
1950	16	56	48	100	85	8%	11%
1951	23	40	37	100	84	26%	11%
1952	11	35	54	100	79	16%	11%
1953	18	22	60	100	88	1%	5%
1954	14	30	56	100	89	0	11%
1955	10	32	58	100	78	0	19%
1956	20	25	55	100	85	0	15%
1957	20	30	50	100	104	0	13%

Based on 692 premature infants, whose birth weight was less than 2001 Gm, who were born consecutively in the Sloane Hospital for Women, the intramural obstetrical service of the Columbia-Presbyterian Medical Center 1950-1957. The crude annual mortality rate and proportion of dead infants examined at necropsy did not vary significantly from year to year.

* Frequency of occurrence of pulmonary hyaline membranes at necropsy per 100 intramural admissions

lowing the restricted use of oxygen but the incidence of pulmonary hyaline membranes was essentially unchanged (Table 14-3).

Other Factors

Much of the previous work on the subject of pulmonary hyaline membranes was concerned with various extrapulmonary fluids as sources of the hyaline material itself.^{17, 74, 130} More recent studies have attempted to determine the thromboplastic activity of these fluids to account for the conversion of fibrinogen of the pulmonary transudate into fibrin.^{48, 118}

There has also been interest in determining the fibrinolytic activity of materials that might enhance the disintegration of the fibrin masses.^{27, 68} Lieberman suggested that deficient tissue-fibrinolytic activity resulting from the absence of plasminogen activator in the lung might be a predisposing factor in hyaline-membrane formation.

RESPIRATORY DISTRESS WITHOUT PULMONARY HYALINE MEMBRANES

Preoccupation with the origin and nature of pulmonary hyaline membranes leaves untouched the entire subject of idiopathic respiratory distress without

hyaline membranes. Some have questioned the significance of the membranes even when they are present.^{52, 98}

Role of Surface Tension

Postmortem studies have shown that when the lungs of premature infants contain only moderate amounts of air they tend to assume a distinctive pattern of expansion characterized by distended respiratory bronchioles and collapsed alveoli. Gruenwald⁵⁰ suggested that this pattern is produced as the result of surface tension which develops at the gas-fluid (moist surface) interface. This force opposes the expansion of the lung by air since it determines that the gas will collect as bubbles of the smallest number and largest possible size and this collection tends to occur in bronchioles at the expense of the alveoli. When fluid is instilled into the respiratory tree it encounters no such opposing force.

The lungs of dead premature infants can readily be expanded with liquid. This results in a uniform pattern of expansion as compared with the "swiss cheese" appearance that follows the instillation of air at comparable pressures.

Gruenwald⁵² has shown that in premature infants the total volume of the alveoli is low compared to the volume of the bronchial tree and that with increasing maturity this ratio becomes larger. As a result, when a significant amount of air is lost from the lungs, as during a period of apnea in a small premature infant, a large proportion of the remaining air can be accommodated in the bronchial tree and an unduly large number of alveoli become airless.

These studies led Gruenwald⁵² to regard the respiratory-distress syndrome as the clinical manifestation of the characteristic atelectasis of premature infants. He further postulates that the collapse of alveoli is not caused by hyaline membranes obstructing the flow of air into the terminal passages of the lung. According to this view the atelectasis is related to the structural characteristics of the lung and to the phenomenon of surface tension. These properties are in turn inherently related to the degree of development of the lung.⁵²

Avery and Mead⁷ measured the surface tension of washings and extracts of the lungs of small premature infants and of infants with hyaline-membrane formation. As compared with the lungs of older infants and children they found differences which suggested that the immature subjects were deficient in an alveolar lining layer (presumably protein) that would tend to stabilize the alveoli by reducing their tendency to collapse at low lung volumes.

Importance of Rib-Cage Recoil

Rahn emphasized that the elastic distending force provided by the rib-cage recoil is important in maintaining a functional residual volume in the lungs and

in preventing their collapse with each expiration. It has been frequently suspected that the premature infant's chest cage is much too soft to provide efficient recoil.^{73, 79}

These interpretations of "nonhyaline membrane" factors that may interfere with pulmonary function in premature infants do not exclude the possibility that the transudation of protein-rich fluid into the alveoli and precipitation of fibrin along the walls of the air passages constitute complications of the basic disturbance and make the re-expansion of alveoli even more difficult.^{28, 52}

ROLE OF CHEMICAL DISTURBANCES

The studies of James's group⁵⁹ have indicated that some degree of asphyxia occurs during delivery in all infants. Although this is usually brief and of no consequence, if respirations are not established promptly the biochemical changes (respiratory and metabolic acidosis) may be profound.

The role of severe acidemia and other biochemical aberrations in the production of pulmonary changes has not been defined. However, once the pulmonary changes have occurred it is possible that the outcome of the idiopathic respiratory-distress syndrome is determined by the severity of the chemical derangement¹⁰¹ which results from the reduced capacity of the lung to diffuse gas across the alveolar-capillary boundary.⁸ If this proves to be true, there will be ample justification for the concept of a single clinical entity, respiratory-distress syndrome, associated with various degrees and combinations of alveolar collapse, fluid and fibrin block, and disordered pulmonary blood flow.

CLINICAL MANIFESTATIONS

Condition Immediately After Birth

The majority of infants who die with pulmonary hyaline membranes exhibit initial apnea, inadequate respirations, or bradypnea (less than 40 breaths per minute) during the period immediately after birth.^{67, 85} James⁵⁸ observed that the incidence of respiratory distress was higher among premature infants whose condition at birth was poor than in others who were classified as vigorous at birth (Fig. 14-1).

Some infants who later develop signs of respiratory distress breathe spontaneously at birth and are considered to have normal pulmonary function in the first moments of life. In the Johns Hopkins Hospital series⁶⁷ 20 per cent of the infants who died with pulmonary hyaline membranes had been described as in good condition at birth.

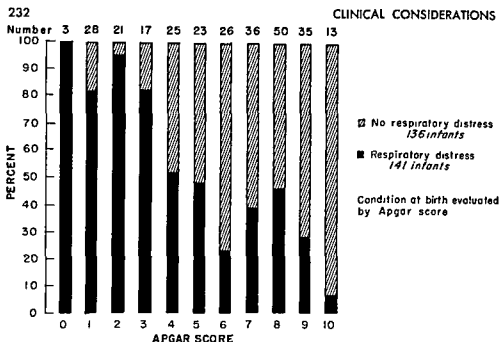


FIG. 14-1. Incidence of respiratory distress in relation to vigor at birth in 277 premature infants (birth weight 2000 Gm. or less). Vigor at birth was judged by an arbitrary scoring system (see p. 95), 0 indicating the poorest and 10 the best clinical condition at the age of one minute. Infants whose "retraction score" (see p. 144) was 2 or greater during the first day of life were considered to have respiratory distress. (From James, L. S.: Physiology of respiration in newborn infants and in the respiratory distress syndrome. *Pediatrics* 24:1069, 1959.)

Symptom-Free Interval

Many have stated that an asymptomatic "free period" precedes the onset of respiratory difficulty.^{17, 95, 96, 123} In the planned study of Feinberg and Goldberg roentgenograms obtained in the first hour of life revealed abnormalities which on occasion preceded clinically detectable signs of labored respirations. In seven of ten infants, symptoms developed within 15 minutes to 3 hours after birth; in the three remaining infants clinical signs did not appear for 3 to 9 hours after birth. Rarely¹¹ some premature infants with pulmonary hyaline membranes have exhibited no signs of distress during life.¹⁶

However, a precise definition of the first recognizable clinical sign of the syndrome has not been made, and until this is agreed upon it is unlikely that estimates of the length of the "free period" will agree.^{83, 96, 106}

Expiratory Grunt

An expiratory grunt often becomes audible with a stethoscope or with the unaided ear within minutes after birth. Often this manifestation is displayed before

any other and in our experience has been a valuable heralding sign of impending distress.

Trends of Respiratory Rates

Precise respiratory rates are difficult to obtain in premature infants because of their irregular breathing patterns³⁰ and the influence of a number of factors including ambient temperature, body position, oxygen, etc. (see Chap. 8).

Respiratory Distress. Despite the difficulties, it has been shown by Miller's group^{83, 87} that an increase in respiratory rate of 15 or more breaths per minute above the average rate during the first hour identifies an infant in respiratory distress.⁸²

Benign Course. The trend exhibited by infants whose neonatal course is benign consists of either no fluctuation from an average rate of approximately 40 per minute in the first hour or a first-hour rate of over 60 breaths per minute and subsequent decline within a few hours or days of birth.⁸²

Influence of Rate on Regularity of Respiration. Cross²⁹ has expressed the view that anything that increases the minute volume of respiration reduces the incidence of irregular breathing. In this regard it is interesting that in the infant with respiratory distress the rapid respirations, often above 80 per minute,⁸⁴ are usually quite regular until the terminal stage.

Signs of Respiratory Obstruction

Infants with the respiratory-distress syndrome gradually develop a characteristic pattern of obstructive breathing within the first six hours of life. With each descent of the diaphragm on inspiration the abdomen balloons out and the lower end of the sternum and the intercostal spaces retract. As the degree of retraction becomes more marked, the *alae nasi* distend and the chin descends with each inspiration. Often the entire lower end of the sternum remains sunken during the full respiratory cycle, and a conspicuous concave deformity of the chest is created (Fig. 14-2). The upper chest often appears overinflated, presenting a prominent ("pouter pigeon") contour when viewed from the side.

Miller⁸⁴ described "see-saw" respirations in normal newborn infants (on inspiration the anterior chest wall is drawn down and inward as the abdomen expands). In our experience this type of respiration has been observed in premature infants in association with other signs of respiratory distress.

Retraction Score. We devised an arbitrary scheme in an attempt to quantitate the severity of retractions among premature infants who exhibit signs of respiratory obstruction (see Chap. 9). Routine recordings of the retraction score at six-hour intervals have focused attention upon respiratory performance. Also the



FIG. 14-2. Characteristic appearance of a premature infant with the respiratory-distress syndrome.

presence or absence of retractions at six hours of age has provided a prognostic criterion similar to that described for the trend of respiratory rates (see Table 14-4)

Other Signs

Skin Color. The skin color of the infant with respiratory distress is dependent upon the severity of the retractions and the oxygen concentration of the inspired air. The infant becomes increasingly cyanotic as retractions become more severe. Although the pink color can usually be restored if oxygen is administered (36 to 40 per cent oxygen concentration), infants with severe dyspnea remain cyanotic even when the concentration of oxygen is increased to 60 per cent and above. Often the skin color remains pink until with crying it becomes intensely blue.

Cry. The cry of a premature infant with respiratory distress is often accompanied by grimacing and restless movements of the head, so that the infant appears to be irritable or in pain. Nurses have often described this as a "complaining cry." Each cry is terminated abruptly and expiration is completed with the characteristic expiratory grunt.

Breath Sounds. The inspiratory phase of the respiratory cycle is quick, the expiratory phase is prolonged. The breath sounds are difficult to interpret in infants with respiratory distress. Usually only a short inspiratory click is heard, but with amplification (see Chap. 8) fine crackling râles are sometimes audible. An expiratory grunt or moan is commonly heard on auscultation.

Cardiac Signs. *Murmurs.* Burnard^{23, 24} described a crescendo systolic cardiac murmur and occasionally a continuous murmur in association with dyspnea in mature and premature infants. Usher *et al.*¹²⁸ found cardiac murmurs in infants recovering from respiratory distress.

Heart Rate. Burnard²⁵ observed a fixed heart rate between 110 and 120 per minute at the height of respiratory distress; with improvement the rate became labile and often rose to 140 or 150 per minute.

Blood Pressure. The blood pressure of premature infants with respiratory distress was studied by Usher and co-workers,¹²⁸ who found that the pressure was low at birth and remained low during the first 48 hours, in contrast to a rise in unaffected premature infants. Neligan described a transient fall in systolic pressure to below the normal range (see Appendix 10) in the first half-hour of life among infants who developed respiratory difficulty.

Edema. The association of respiratory distress and edema was studied by Sutherland and others. They made serial measurements of the lower limbs of premature infants and demonstrated that, as compared with unaffected infants, in those with respiratory distress there was a relative increase in the volumes of the leg during a time of decreasing body weight. The authors considered that this phenomenon was due to a redistribution of body fluid and they suggested the possibility that the peripheral edema was the result of disturbed pulmonary physiology rather than merely coexistent with it.

Preliminary studies by Smull have shown that total body water is increased in premature infants with respiratory distress

Prognostic Signs

Signs of Impending Death. In infants with unremitting symptoms of respiratory distress the skin color becomes ashen, and the general appearance suggests peripheral circulatory collapse. Body temperature falls. Ominously the rate of respirations slows down,^{16, 82, 85} retractions become less marked, and repeated bouts of prolonged apnea usually indicate that the infant will soon die.

Favorable Course. Not all infants who manifest the clinical signs of respiratory distress die.^{10, 15, 87, 98} Some develop only moderate retractions and never develop cyanosis in atmospheric air, and the respiratory difficulty is short-lived.

Others exhibit marked signs of distress and rather dramatically (and spontaneously) improve between the ages of 72 and 96 hours.

OUTCOME

Relation to Clinical Signs

Bauman^{10, 11} estimated that somewhat more than half of premature infants (birth weight under 2001 Gm.) who exhibit signs of respiratory distress die (Table 14-4). Among a group of infants in our nursery who died after exhibit-

TABLE 14-4 ESTIMATES OF MORTALITY RATE OF PREMATURE INFANTS WITH AND WITHOUT RESPIRATORY DISTRESS

Birth weight (Gm.)	Criterion of distress							
	Respiratory rate ^a				Retractions ^b			
	"Normal"		Increased		"Normal"		Retractions	
	No infants	% dead <7 da	No. infants	% dead <7 da	No infants	% dead <7 da	No. infants	% dead <7 da
2001-2500	194	0	29	7				..
1501-2000	50	0	42	24	42	2	15	46
1001-1500	4	0	31	35	15	7	12	58
1000 or less					5	60	13	69

^a From Miller,⁹ based on a study of 350 premature infants consecutively born in University of Kansas Medical Center. Increased rate was considered to be a rise of 15 or more respirations-per minute over the average rate in the first hour of life.

^b From Bauman,¹⁰ based on a study of 102 premature infants, whose birth weight was less than 2001 Gm., consecutively born in the Sloane Hospital for Women, excluding those who died before the age of 6 hours. Retractions were scored according to an arbitrary scheme (see p. 144) at 6 hours of age. A total score of 2 or greater was considered to indicate significant retractions.

TABLE 14-5 AGE AT DEATH OF 33 PREMATURE INFANTS WITH CLINICAL SIGNS OF RESPIRATORY DISTRESS (RETRACTIONS) DURING THE FIRST DAY OF LIFE, BY NECROPSY DIAGNOSIS

	Necropsy diagnosis	
	Pulmonary hyaline membranes	No pulmonary hyaline membranes
No infants	19	14
Age at time of death (hrs)		
Median	25	78
Range	6-56	6-144

From Bauman¹⁰

ing retractions, approximately one half were found at necropsy to have pulmonary hyaline membranes;¹⁰ the other half had various other pulmonary lesions. Although the clinical manifestations of these two groups of infants could not be distinguished, the infants who had pulmonary hyaline membranes died at earlier ages (Table 14-5).

TABLE 14-6 AGE AT DEATH OF 94 PREMATURE INFANTS WITH PULMONARY HYALINE MEMBRANES FOUND AT NECROPSY, BY BIRTH WEIGHT

	<i>Birth weight (Gm)</i>		
	<i>1000 or less</i>	<i>1001-1500</i>	<i>1501-2000</i>
No infants	20	40	34
Age at time of death			
Median	12 hrs	13 hrs	18 hrs
Range	2 hrs-8 days	2-122 hrs	3-109 hrs

Based on 692 premature infants, whose birth weight was less than 2001 Gm, consecutively born in the Sloane Hospital for Women, the intramural obstetrical service of the Columbia Presbyterian Medical Center, 1950-1957

Time of Death

Observers who have determined (in retrospect) the time of death of premature infants with histologic evidence of pulmonary hyaline membranes are agreed that approximately one half of these infants do not survive the first 24 hours of life, in the remainder, death occurs with few exceptions before the age of 72 hours^{17, 21, 31, 47, 65, 66, 67, 108}

Although small premature infants with pulmonary hyaline membranes tend to die earlier than large infants the differences in survival times are not great (Table 14-6).

DIAGNOSTIC STUDIES AND LABORATORY FINDINGS

Roentgenography

Appearance of the Lungs. The lungs in premature infants who are subsequently found at necropsy to have pulmonary hyaline membranes have been variously described as having an appearance roentgenographically^{40, 41, 78, 92, 117} of ground glass,³² miliary mottling,³⁷ and diffuse bilateral reticulogranular pulmonary images of increased density¹¹ (Fig. 14-3). As has already been stated, in one study the abnormal roentgen signs were occasionally evident before the development of recognizable clinical signs.⁴¹

In a series of 104 consecutive infants admitted to our premature nursery roentgenograms obtained on admission revealed reticulogranular changes in the chest roentgenograms of 35 infants.¹¹ However, clinical signs of respiratory distress were observed in only 16 of the infants whose roentgenograms were abnormal;

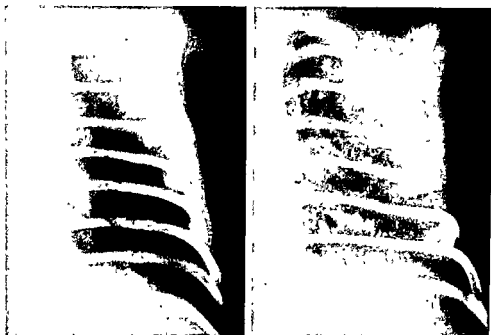


FIG. 14-3. (Left) Normal roentgen appearance of a lung field in a 27-hour-old premature infant. (Right) Marked, diffuse reticulogranular pulmonary images of increased density ("increased reticulogranularity"). Note air-filled bronchi extending into the periphery. (From Bauman, W. A., and Nadelhaft, J.: Chest radiography of prematures: A planned study of 104 patients including clinico-pathologic correlation of the respiratory distress syndrome. *Pediatrics* 21:813, 1958.)

the clinical signs were present in 3 infants whose roentgenograms were normal. When the clinical, roentgenographic, and pathologic diagnoses of those who died were correlated it was concluded that there was a significant association between the independent diagnoses of "respiratory distress," "reticulogranularity," and "pulmonary hyaline membranes." In addition it was noted that the clinical and roentgenographic signs either alone or combined were exhibited by some infants who survived and others who died without pathologic evidence of pulmonary hyaline membranes.

Cardiothoracic Ratio. Burnard²³ estimated heart size by measuring the cardiothoracic ratio⁷⁶ in serial roentgenograms of newborn infants. This measurement was increased in infants with dyspnea and diminished as the infants improved.

Chemical Abnormalities

Hypercapnea and Acidosis. A rise in the carbon dioxide tension ($p\text{CO}_2$), fall in oxygen tension ($p\text{O}_2$), and considerable reduction in the pH of the blood

has been observed in infants with signs of respiratory difficulty.^{15, 86, 100} Although asymptomatic premature infants often have alterations of chemical constituents of the blood in the first few days of life indicating a moderate uncompensated metabolic acidosis,^{5, 14, 102} those with normal pulmonary function do not have an increase in the carbon dioxide tension of the blood.^{14, 100}

Studies of infants with respiratory distress revealed that the total carbon dioxide content of plasma was not increased despite the rise in carbon dioxide tension; this indicated that there was a combined metabolic and respiratory acidosis.^{15, 86, 100} The changes have been interpreted to mean that inadequate alveolar gas exchange is the cause of the rise in carbon dioxide tension; reduction in alkali reserve probably occurs secondarily in these infants.

Reardon¹⁰⁰ observed the association of acidosis and hypoglycemia in infants with respiratory distress who are born of diabetic and prediabetic mothers.

Hyperkalemia. Keitel noted that in premature infants the values obtained in clinical measurements of the concentration of potassium are subject to a number of technical variables. Perhaps this is responsible for a considerable difference of opinion concerning the interpretation of many studies of this subject.

Usher¹²⁷ presented evidence that premature infants with respiratory distress developed significant hyperkalemia.

Measurements of Pulmonary Function

Detailed measurements of the respiratory function of premature infants with respiratory distress have demonstrated that the most important abnormality consists of an increase in the physiologic dead space^{26, 62} (Table 14-7). As a result the affected infant must increase his respiratory rate to maintain adequate ventilation since decreased lung elasticity prevents him from adjusting by increasing tidal volume. Cook and others estimated that the work of respiration is increased 200 to 400 per cent above normal in these infants.

Miller's group⁸⁵ compared the respiratory activity of distressed premature infants who died with those who survived. These studies indicated that the latter were able to develop and sustain higher respiratory rates than the former.

Other Findings

Venous Pressure (Umbilical Vein). Bonham Carter and others¹⁸ measured venous pressure by passing catheters for distances of 5.0 to 8.5 cm. in the umbilical veins of 25 infants with respiratory distress in the first six hours of life. These were compared with pressures obtained in 35 normal infants. The venous pressures of infants with distress who survived were significantly higher than normal controls. The pressures of affected infants who died were significantly lower than

TABLE 14-7 COMPARISON OF RESPIRATORY PARAMETERS IN NORMAL NEWBORN INFANTS AND IN THOSE WITH RESPIRATORY DISTRESS

	<i>Normal 2.5 kg. infant</i>	<i>Infant with respiratory distress*</i>
Minute volume	498 ml	+75%
Rate	34/min	+90%
Tidal volume	15 ml	-8%
Vital capacity (crying)	140 ml.	-50%
Alveolar ventilation	355 ml/min	-50%
Arterial carbon dioxide tension	32 mm Hg	+30%
Functional dead space	5 ml	+70%
Functional residual capacity	70 ml.	-45%
Negative pressure change during quiet respiration	5 cm H ₂ O	+300-500%
Maximum negative pressure change during respiration	50 cm H ₂ O	±
Lung compliance	5 ml/cm H ₂ O	-80%
Pulmonary work per minute	1450 Gm. cm.	+400%

From Cook and others²⁸

* Average changes with respiratory distress

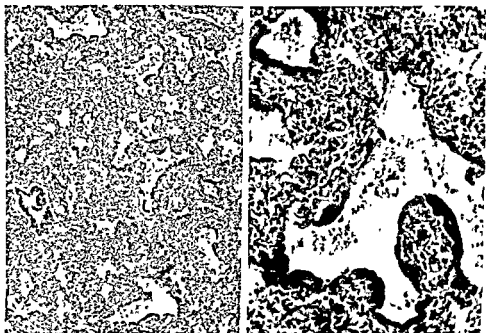


FIG. 14-4. (Left) Section of lung, showing the typical picture of hyaline membrane with resorption atelectasis. The surfaces of the alveolar ducts that are open are almost entirely covered by a layer of homogeneous hyaline-like material. The remaining alveolar ducts and all alveoli are airless and appear solid. (Right) Higher power view of the lung shown on the left. (From Potter, E. L.: Pathology of prematurity. *J. Am. M. Women's A.* 5:391, 1950. Photographs No. 237954-1 and 2 by Armed Forces Institute of Pathology.)

those in affected survivors. Oddly, the venous pressures in the infants who died were similar to those obtained in normal controls.

Cardiac Catheterization. Cardiac catheterization studies of infants with respiratory distress have indicated that a relatively large volume of blood may be shunted through a widely patent ductus arteriosus.¹⁰⁸ James⁵⁸ noted that both *right-to-left* and *left-to-right* shunts may be present with each cardiac cycle in both normal and distressed infants. He emphasized that the volume of the blood shunted is the most important factor in determining eventual cardiac failure in these infants.

Electrocardiography. Usher¹²⁷ described abnormalities in electrocardiographic tracings of infants with respiratory distress. Ahvenainen and Landtman also found abnormal electrocardiograms in infants with asphyxia.

Pharyngeal Smear. Österlund and Hjelt, in a preliminary report, suggested that the presence of pulmonary hyaline membranes may be detected by the demonstration, using special stains, of a membrane-like structure in smears obtained from the pharynx with an ordinary throat swab.

PATHOLOGY

Potter⁹⁴ described the pathologic findings in the lungs of infants with pulmonary hyaline membranes under the heading "congestive pulmonary failure (*resorption atelectasis with hyaline-like membrane*)" (Fig 14-4):

The lungs have a striking appearance. They are the size of well expanded lungs but have the consistency of liver. Instead of being the yellow-pink of lungs containing air or the light violet of the nonexpanded fetal lungs they are a uniform dark red-purple. If the infant continued to have symptoms and survived more than 48 hours, an inflammatory process is usually superimposed. In such instances the lungs seem on palpation to be slightly granular; ordinarily, however, they are of uniform consistency. The whole lung or individual portions sink when placed in water despite the fact that a little air always remains in the proximal portions of the pulmonary tree.

Histologic examination reveals widespread resorption of air and the walls of many alveolar ducts and most of the alveoli are collapsed, giving a solid appearance to the lung tissue between the few alveoli that remain open. This picture is entirely different from that of normal unexpanded lung and has led to the mistaken belief that this condition is a result of primary maldevelopment of pulmonary tissue. If an attempt is made to expand such lungs with air after removal from the body, the proximal spaces become greatly hyperdistended and the distal ones even more completely collapsed. If fluid is injected, however, the spaces gradually open and the fact that the lungs are normally developed is immediately apparent on microscopic examination.

Intense capillary engorgement is responsible for the color and the increase in weight

and is one of the most striking findings on histologic examination. The inner surfaces of the alveolar ducts that remain open are covered by an irregular layer of homogeneous acidophilic material. It forms a mechanical barrier to normal respiratory exchange by blocking off some portions of pulmonary tissue and by coating the remainder in such a way that the capillaries are deprived of contact with the oxygen-containing atmosphere. A few polymorphonuclear leucocytes may be present, especially in infants who survive more than 36 hours, but in the majority there is no evidence of infection.⁸⁴

A number of investigators^{2, 10, 21, 31, 66, 67} have emphasized that the histologic appearance of the lung of infants with respiratory distress is closely related to the age at the time of death. Extreme atelectasis of the type seen with pulmonary hyaline membranes but without the acidophilic material has been described in infants who died early in the first day of life.^{21, 51} Pulmonary hemorrhages and pneumonia were observed more frequently in infants who died after two days of life, a time when pulmonary hyaline membranes were not as common.

Increased amounts of cerebrospinal fluid and edema of the leptomeninges have been observed postmortem coincidentally with pulmonary hyaline membranes,^{31, 94} however, these findings are also common in premature infants who die without pulmonary hyaline membranes.⁹⁵

TREATMENT

As of this writing there is no satisfactory evidence of the efficacy of any mode of treatment for the respiratory-distress syndrome of premature infants. For complete details of proposed treatments the reader is referred to the survey and evaluation by Cook's group.

Careful consideration should be given to the possible presence of other clinical entities such as diaphragmatic hernia and bacterial pneumonia for which specific treatment is available.

PROPOSED PROPHYLACTIC MEASURES

Clamping of the Umbilical Cord

The influence of the time of clamping of the umbilical cord upon the subsequent development of respiratory distress has been the subject of speculation and study.^{18, 19, 53, 75, 93}

Although the results of a controlled trial indicated that the incidence of respiratory signs was lower among premature infants whose cords were clamped early, there is no convincing evidence that the outcome of the respiratory-distress syndrome can be influenced by giving or withholding transfusions of placental blood to premature infants (see Chap. 6).

Gastric Aspiration

Gastric aspiration following birth by cesarean section and after premature birth has been widely practiced during the past decade. This maneuver was originally proposed by Gellis and others⁴⁶ as a technique for preventing the development of neonatal respiratory difficulty among infants delivered by cesarean section from diabetic mothers.

In the original study the effect of gastric aspiration was judged on the basis of a reduction in the incidence of clinical signs of respiratory difficulty. Other studies measured the influence of gastric aspiration upon neonatal mortality. *These clinical trials did not produce convincing evidence of a beneficial effect of the prophylactic treatment.* Evidence based on experiences in which there were no deaths in either treated or control groups cannot be used to answer the question concerning the efficacy of this procedure in reducing neonatal mortality among premature infants.⁴³ Other trials were conducted without concurrent controls or revealed differences that could easily be the result of chance alone.^{31, 72, 131}

Body Position

Prone vs. Supine. In a discussion of the treatment of atelectasis with hyaline membranes in premature infants Crosse advocated that they be placed in the prone position.

We have adopted a modification of a supine position advocated by Rossier (see Chap. 7).

Although Kravitz and others demonstrated that the respiratory rates of normal small premature infants who were in prone position were significantly more rapid than the rates of controls who were supine, it has not been established that the course or outcome of the respiratory-distress syndrome can be influenced by the position of the infant.

Postural Drainage. Mathesius proposed that "anoxic" newborn infants be placed in the head-down position to promote postural drainage and forestall the development of respiratory distress.

PROPOSED THERAPEUTIC MEASURES

Stabilization of the Thoracic Cage

There is no reason to question the argument that it is important to stabilize the soft sternum and rib cage of the premature infant with respiratory distress. However, the practical methods which have been proposed to achieve chest-wall stabilization have not been satisfactorily evaluated.^{26, 73, 79, 122} Theoretically, if the distending force provided by the rib-cage tension is inadequate the resting

lung volume can be expected to drop markedly with each expiration. Rahn pointed out that such a loss of the functional residual gas volume of the lung would be expected to have important consequences, since this alveolar air buffer acts as an important protective device to provide homeostasis of carbon dioxide and oxygen

Increased Humidity and Lowered Environmental Temperature

There have been numerous proposals to the effect that the symptoms of respiratory distress can be alleviated by increasing humidity, nebulizing water⁹⁶ or detergent mists,⁹⁹ or lowering the environmental temperature^{61, 119} in the incubators of affected infants. Controlled studies have failed to demonstrate any beneficial influence of these factors as judged by the respiratory performance of premature infants who survived or necropsy findings among those who died^{20, 56, 109-112}

Glucose and Electrolyte Solutions

Glucose and Hypotonic Saline. Reardon *et al.*¹⁰¹ administered 60 ml. per kg. per day of 5 per cent glucose in 0.45 per cent saline to 37 infants with respiratory distress who were born of diabetic or prediabetic mothers. This treatment was associated with clinical improvement in all but one patient and a return of arterial carbon dioxide tension to normal within 24 hours, 3 of these infants died, 1 had pulmonary hyaline membranes. In another group of 18 infants who were given either 10 per cent glucose or received no fluids 6 died and all exhibited pulmonary hyaline membranes at necropsy.

No further statement concerning the efficacy of this treatment is possible until the results are available from a properly controlled trial in infants of diabetic mothers or premature infants.

Glucose and Sodium Bicarbonate. Usher¹²⁶ reported the survival of 20 of 21 premature infants with the respiratory-distress syndrome after intravenous infusions of a glucose-bicarbonate solution. The solution contained 10 Gm. of glucose and 5 mEq. of sodium bicarbonate per 100 ml. and was infused at the rate of 60 ml. per kg. per day. The results of a controlled trial have not been published.

Other Proposed Treatments

Various other treatments that have been suggested either formally or informally include gastric oxygen,^{4, 42} digitalization,^{25, 26} phlebotomy,²⁶ electrophrenic respiration,³⁴ augmented respiration,³⁵ intermittent positive pressure,⁴⁹

thoracotomy,¹³³ rocking,⁸⁰ and transfusion and perfusion with oxygenated heparinized blood.^{132, 133, 134} The clinical impressions of the effectiveness of these measures have not been subjected to critical trials.

The use of anticoagulants⁶⁸ and fibrinolysins²⁷ has been suggested, but no clinical experiences with these agents have been reported.

Reichelderfer and Nitowsky could find no evidence of effectiveness of the Bloxsum air lock at the conclusion of a controlled study.

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Other Noninfectious Pulmonary Conditions

PNEUMOMEDIASTINUM AND PNEUMOTHORAX

There have been many reports of pneumomediastinum and pneumothorax in newborn infants, and the reader is referred to other sources for a review of the literature on this subject.^{4, 10, 13}

INCIDENCE

Recent studies indicate that the incidence of pneumomediastinum and pneumothorax is low in unselected premature infants³ and appreciable among newborn infants with respiratory distress.¹⁵

Peterson and Pendleton observed that pneumothorax was particularly frequent in a group of term (or postmature) infants whose respiratory difficulty was probably caused by aspiration of amniotic-sac contents.

MECHANISMS

Macklin and Macklin demonstrated that overinflation of alveoli from a variety of causes may on occasion be complicated by rupture of alveolar bases, with escape of air into the sheaths of the pulmonary vessels resulting in pulmonary interstitial emphysema. *If these conditions continue, air makes its way to the hilus of the lung and mediastinum, and by rupture of the mediastinal pleura air may enter the pleural cavities.* The Macklins emphasized that any condition which induces atelectasis, particularly if the collapse occurs suddenly, may initiate pulmonary interstitial emphysema because of compensatory overdistention of areas of the lung which have not collapsed.

Positive-pressure breathing apparatuses are commonly implicated as the cause of alveolar rupture. However, since escape of air can occur spontaneously, it is often impossible to prove the charge.

Air may enter the pleural cavities directly through a rent in the visceral pleura or through a bronchopleural fistula

DIAGNOSIS

Clinical Manifestations

Appearance of Infant. Manifestations of respiratory and circulatory difficulty are dependent upon the volume of air which accumulates in the mediastinum or in the pleural cavities. When a large amount of extrapulmonary air is present respirations are rapid and shallow. The neck veins may be distended.

Salmon and others emphasized the striking appearance of the chest which is expanded at or near-full inspiration, because of minimal expiratory movements respiratory excursions are limited. They used the term "airblock" to describe this condition and advised that the appearance of the chest together with cyanosis should suggest the diagnosis. In unilateral pneumothorax limitation of respiratory movements may be confined to the affected side.

Subcutaneous emphysema and bulging of the precordium may occur, but these signs are unusual.

Physical Signs. The chest is hyperresonant to percussion; cardiac dullness may be absent. Depending on the site of the accumulated air, auscultation may reveal displaced heart sounds, or the sounds may be distant. Breath sounds are sometimes diminished over the affected areas of the thorax.

Crackling sounds, synchronous with each heart beat, have been described in pneumomediastinum.⁹

Differentiation from the Respiratory-Distress Syndrome. Retractions of the chest on inspiration are conspicuously absent in infants with respiratory difficulty due to pneumomediastinum and pneumothorax. This sign, i.e. retractions of the chest, usually serves to distinguish these conditions from the respiratory-distress syndrome (see Chap. 14). Both conditions, however, may coexist in the same infant so that the presence of retractions cannot be used to rule out pneumomediastinum and pneumothorax.

Roentgenographic Diagnosis

Pneumomediastinum. In roentgenograms of the chest the pneumomediastinum is seen as a longitudinal radiolucent band along the borders of the mediastinum (paracardiac halo¹⁸) in the frontal view.⁸ In the lateral view encapsulated air is visualized just beneath the sternum.

Pneumothorax. Free air in the pleural space is characterized by a band of

diminished density surrounding the lung. Large amounts of air displace the mediastinal structures and the involved hemithorax is radiolucent.

Currarino and Silverman noted that tension pneumothorax cannot always be distinguished from intrapulmonary cysts

TREATMENT

The treatment of pneumomediastinum and pneumothorax in newborn infants should be conservative. Many infants with aberrant air in the chest exhibit no signs of difficulty and require no treatment.

When oxygen is used the concentration should be no higher than is just necessary to relieve cyanosis, and it should not be administered to premature infants for a prolonged time (see Chap. 7).

MASSIVE PULMONARY HEMORRHAGE

Pulmonary hemorrhages are not rare among infants dying during the first week of life.^{12, 16, 20} Although these may simply be nonspecific agonal complications of a number of unrelated conditions, there is some evidence that large intrapulmonary hemorrhages are the result of a fairly specific pathologic process. Ahvenainen and Call² reviewed this subject in detail and made observations in a series of infants who died in the neonatal period; later Ahvenainen¹ made a similar survey in Helsinki, Finland.

Definitions. To distinguish the major hemorrhages in the lung from small petechial hemorrhages, Ahvenainen and Call² used the term "massive pulmonary hemorrhage" when gross examination revealed that one-third or more of the lung was severely involved.

The term "hemorrhagic pneumonia" has been used in connection with pulmonary hemorrhage in newborn infants, even in the absence of inflammatory cells. Potter advised against the use of this designation.

SITE OF HEMORRHAGE

The site of hemorrhage may be subpleural, intra-alveolar, interstitial (septal), or perivascular. In lungs that were placed in the "massive hemorrhage" category,² the site of hemorrhage was either intra-alveolar alone or both intra-alveolar and interstitial. In practically all cases the bleeding originated from alveolar capillaries and from veins in the intralobar septa. Ahvenainen and Call made observations which suggested that perivenous and septal localization of hemorrhage is more likely in premature than in term infants because of the relative weakness of the walls of intrapulmonary veins in premature infants.

ASSOCIATED CONDITIONS

Prematurity

Potter noted that diffuse intra-alveolar hemorrhage is the most difficult form of pulmonary hemorrhage to interpret. She found that except in erythroblastosis fetalis it was usually limited to infants with a birth weight of less than 2000 Gm.

TABLE 15-1 FREQUENCY OF OCCURRENCE OF MASSIVE PULMONARY HEMORRHAGE AT NECROPSY BY BIRTH WEIGHT*

Birth weight (Gm)	No necropsies	Massive pulmonary hemorrhage	
		No	% of necropsies
Under 1000	32	4	13
1010-1250	51	4	8
1260-1500	62	3	5
1510-1750	70	10	14
1760-2000	65	6	9
2010-2500	124	12	10
2500 or less	404	39	10
Over 2500	337	21	6

Adapted from Ahvenainen.¹

* Live born infants who died before 30 days of age

In Ahvenainen's study¹ massive pulmonary hemorrhage was encountered somewhat more frequently in necropsies performed on premature than term infants (Table 15-1).

Congestion of Pulmonary Veins

Congenital Malformations of the Heart. Ahvenainen and Call² suggested that any condition which produces congestion of pulmonary veins in newborn infants may at times be complicated by massive pulmonary hemorrhage. They cited the frequent association of intrapulmonary bleeding with congenital malformations of the heart in support of this view.

Excessive Transfusions. Ahvenainen and Call² reported six examples of massive pulmonary hemorrhage following excessive transfusions; three were premature infants who each received from 50 to 80 ml of blood and died at from 2 to 10 days of age.

Lack of Association with Pulmonary Hyaline Membranes. In contrast to

the above-noted relationships massive pulmonary hemorrhage is not a frequent complication of the intense capillary engorgement which occurs with pulmonary-hyaline-membrane formation. Although there is not complete agreement,^{5, 6} most studies have also failed to reveal a significant association between pulmonary-hyaline-membrane formation and all degrees of pulmonary hemorrhage in newborn infants.^{1, 2, 11}

Erythroblastosis Fetalis

Potter noted that infants with erythroblastosis fetalis occasionally die suddenly of pulmonary hemorrhage on the second day of life.

Kernicterus. In the American² and Finnish¹ surveys, massive pulmonary hemorrhage appeared to occur relatively frequently in association with kernicterus. In an outbreak of kernicterus that occurred in our nursery we were unable to demonstrate an association between pulmonary hemorrhage and the central nervous system lesion (see Chap. 13).

Hemorrhagic Disease of the Newborn

The relationship, if any, between massive pulmonary bleeding and hemorrhagic disease of the newborn is obscure, for, with the exception of intracranial hemorrhage, coincident extensive bleeding in other locations is unusual.^{1, 16}

Neonatal Cold Injury

Mann and Elliott described the findings at necropsy among a group of infants who died in the newborn period after accidental exposure to cold. Massive pulmonary hemorrhage with no evidence of an inflammatory reaction in the lung was the dominant finding. This report stimulated us to review the pulmonary findings among premature infants who died during the course of a trial designed to determine the influence of environmental temperature on survival during the first five days of life.¹⁹ Although the incidence of pulmonary hemorrhage was somewhat higher among infants who were in cooler incubators (83–85° F., 28.3–29.4° C.), the difference could be explained so easily by chance that an alternative explanation appeared unlikely.

Other Associations

At least two observers^{1, 12} noted a fairly frequent history of maternal toxemia in infants who died with bleeding from the lung.

Previously suggested causes of pulmonary hemorrhage in newborn infants, such as aspiration of gastric contents¹⁷ and pulmonary infection,⁷ did not appear to play a role in the series of cases studied by Ahvenainen.¹ Generalized infection, however, has been seen frequently in association with massive pulmonary hemorrhage.^{1, 2}

CLINICAL DIAGNOSIS

Outward Manifestations. Ahvenainen¹ reported that most of the patients who are subsequently found to have massive pulmonary hemorrhage are severely ill on their last day of life, many being in a state resembling shock. Dyspnea, cyanosis, convulsions, and unconsciousness are also observed.

The only distinctive clinical manifestation is the sudden appearance of a discharge of unclotted dark blood or blood-stained frothy fluid from the nose and mouth, death usually occurs shortly thereafter.

Roentgenography. Roentgenograms of the chest in infants with intrapulmonary hemorrhage reveal no distinctive pattern. Both a fine reticulogranular pattern and a coarse irregular increase in density of the lung may be seen.^{3, 15}

TABLE 15-2 FREQUENCY OF OCCURRENCE OF MASSIVE PULMONARY HEMORRHAGE AT NECROPSY BY AGE AT DEATH AND MATURITY*

Age at death (days)	Premature				Term	
	No necropsies	Massive pulmonary hemorrhage		No necropsies	Massive pulmonary hemorrhage	
		No.	% of necropsies		No	% of necropsies
Less than 1	40	0	0	35	2	6
1	62	8	13	34	1	3
2	35	6	17	37	3	8
3	29	4	14	30	4	13
4	35	4	11	24	3	13
5	28	5	18	20	3	15
6	17	3	18	11	1	9
Less than 7	246	30	12	121	17	9
7-13	82	8	10	59	3	5
14-20	41	1	2	38	1	3
21-29	35	0	0	49	0	0

Adapted from Ahvenainen.¹

* Live born infants who died before 30 days of age.

AGE AT DEATH

Except for the first day of life, when massive pulmonary hemorrhage is distinctly rare, the lesion is found with essentially equal frequency at any time during the first two weeks of life. In the Finnish study it was distributed fairly uniformly among the deaths that occurred during the first two weeks of life in both the premature and term groups (Table 15-2). In this respect the distribution was different from that seen for pulmonary-hyaline-membrane formation and pneumonia (see Chaps 14 and 19). Landing found a similar distribution for all pulmonary hemorrhages among infants who died in the first week of life.

TREATMENT

No satisfactory treatment for massive pulmonary hemorrhage is known

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Retrolental Fibroplasia

A full account^{13, 57} of the rise and fall of the incidence of retrolental fibroplasia would make an instructive and colorful story. However, from the vantage point of the 1960's it is possible to assemble the individual bits of knowledge not necessarily in the order of discovery and certainly not in the order of clinical recognition, and to present a clearer if not historically correct outline of the development of understanding about this condition.

Before leaving history entirely, acknowledgment must be made of Terry's contribution in 1942, when he called attention to this condition and related it to prematurity. In the original note he considered the possibility that "... some new factor has arisen in extreme prematurity to produce such a condition."

Our present understanding of this entity is still not complete in terms of chemistry¹⁵ and physics. However, principally as the result of the observations of the following investigators, we arrived at an appreciation of the iatrogenic cause of retrolental fibroplasia which has led to its virtual disappearance. Owens and Owens⁴¹ described its postnatal development; Crosse, Evans, and K. Campbell each suggested that high-oxygen environments might be the cause; and Patz,⁴⁵ Gyllenstein and Hellström,²³ and Ashton, Ward, and Serpell⁶ defined the role of oxygen in the pathogenesis of retrolental fibroplasia.

DEVELOPMENT OF THE INNER OCULAR BLOOD VESSELS

NORMAL DEVELOPMENT

To understand the pathologic condition known as retrolental fibroplasia it is necessary to know some of the details of the development of the blood supply to the eye.

Hyaloid Artery

Mann described the hyaloid artery at the 4.5-mm stage in the human embryo. It is a branch derived from the internal carotid, entering a cleft in the under side

of the optic cup. The hyaloid artery branches to form the intraocular blood supply of the fetus, but these radicles never appear to come in direct contact with the retina.

Vascularization of the Retina

Up to the third month of fetal life the retina has no blood supply of its own,³⁷ indicating that this tissue can be adequately nourished by the neighboring choroidal capillaries. As the retina develops and becomes thicker, and Michaelson³⁷ has presented evidence which indicates that the critical thickness is $140\ \mu$, the nutritional needs cannot be fully met by the choroid. It is at this stage of development (third to fourth month of gestation) that capillary buds appear to be attracted into the retina from neighboring vessels. Thus at the 70-mm stage fine vessels appear along the hyaloid artery in the optic nerve which are destined to become the retinal veins, and at the 100-mm stage a small swelling appears on the trunk of the hyaloid artery as it passes through the optic disc, the site of origin of the retinal arteries. Buds of cells, preceded by mesenchymal cells laden with glycogen,³⁸ grow into the nerve-fiber layer of the retina from the swelling on the hyaloid artery.

The temporal arteries bud earlier than the nasal vessels and are longer at all stages of development. The greater temporal area of the retina in the human eye is the result of the medial insertion of the optic nerve. Campbell¹⁰ suggested the possibility that an oxygen debt occurs sooner on the temporal side and so stimulates an earlier invasion of blood vessels. In the eighth month of gestation when the vessels reach the ora serrata the retina is considered to be fully vascularized (Fig 16-1).

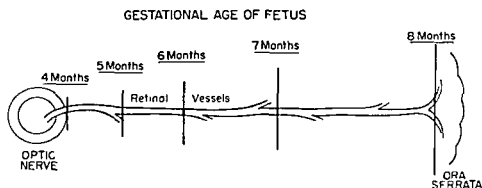


FIG. 16-1. Chronology of retinal vascularization in the human fetus. (From Patz, A.: The role of oxygen in retrolental fibroplasia. E. Mead Johnson Award address. *Pediatrics* 19: 504, 1957.)

Development of the Retinal Capillaries

As early as 1948 Michaelson³⁶ published the results of a detailed study of the development of the retinal capillaries in the human eye. However, the relevance of these observations to the disease retrolental fibroplasia went virtually unnoticed. He found retinal capillaries budding from pre-existing vessels which had grown out from the optic disc and that these parent vessels were predominantly veins. Where the veins and arteries were close to one another capillary growth took place initially from the side of the vein away from the artery (Fig. 16-2). Michaelson^{36, 37} observed that in the space between the arteries and veins a reticular capillary system of varying density developed. Around the arteries there was a zone which was free of capillaries, as the neighborhood of the veins was approached the capillary bed became more dense.

INFLUENCE OF A LOW-OXYGEN ENVIRONMENT

The development of the retinal vascular system in the rat is similar to that in man. Campbell¹⁰ in 1951 studied the influence of low-oxygen tensions on the development of the retinal system of newborn rats. He demonstrated that the

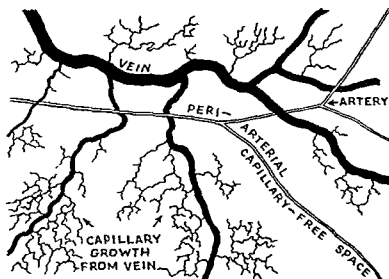


FIG. 16-2. Injected retina of a human fetus showing capillary growth from the veins and the formation of a capillary-free space around the arteries. The venules which cross the artery do not branch into capillaries until they have passed the artery by a certain distance. (Drawn from a photograph in Michaelson, I. C.: *Retinal Circulation in Man and Animals*. Springfield, Ill., Charles C Thomas, Publisher, 1954.)

capillary-free zones around the arteries were significantly narrower in animals which were in hypoxic environments than in control rats of the same age. However, the rate of outward growth of the vascular system from the optic disc was diminished. Others later made similar observations^{5, 24, 44} in newborn mice, rats, and kittens. Under conditions of hypoxia, intense engorgement of the retinal vessels and narrowing of the capillary free zones occurred; however, intravitreal proliferation (to be discussed later) was never observed.

INFLUENCE OF A HIGH-OXYGEN ENVIRONMENT

Vaso-obliteration

Ashton *et al.*⁶ observed that when neonatal animals whose retinal vascular system had not yet matured were exposed to oxygen concentrations greater than 35 per cent a marked constriction of the arteries and arterioles occurred. The arterioles and arterial side of the capillary bed were the first to close down and this was followed by contraction of the entire capillary bed. Finally, the main arteries and veins closed leaving an avascular retina. Ashton *et al.*⁶ noted that the vasoconstrictive process began peripherally and spread posteriorly; the optic disc area was the last to shut down completely. These changes developed after 5 minutes' exposure to a hyperoxic atmosphere. After about six hours of exposure a delayed vaso-oblitative effect was described. When secondary closure was achieved the circulation could be either opened by exposure to air or closed again by placing the animal in oxygen. After longer periods the process seemed to become irreversible. Total obliteration occurred after exposure to oxygen for three or more days and the retinal circulation could not be restored to normal on return to air.

Specificity of the Hyperoxic Effect. This vaso-oblitative phenomenon has been shown to be unique, as it has been observed only in the ingrowing retinal vessels. Studies of the influence of hyperoxia upon retinal vessels that have matured (reached the ora serrata), corneal vessels, and the immature blood vessels of other organs in chick, cat, and rat embryos have all failed to record a comparable effect.^{2, 3, 38, 43}

An additional condition for this singular effect of hyperoxia was discovered by Ashton and Cook³ when they made direct observations upon living retinal vessels. They found that the vaso-oblitative effect of hyperoxia could only be sustained or induced when the immature retina was in place, for when retinal detachment occurred the effect was reversed.

Mechanisms Responsible for the Hyperoxic Effect. The possible mechanisms involved in this unusual type of vaso-obliteration have been reviewed by

Ashton.² The elaboration of a vasoconstrictor substance has been postulated, but extracts of retinas in which vaso-obliteration had been induced had no effect when transferred to normal retinas or preparations of rat colon.⁴ The fact that the effect of hyperoxia is so selectively restricted to immature retinal vessels is an important argument against the possibility that the phenomenon is the result of removal or neutralization of a vasodilator substance by oxygen.

Ashton⁴ proposed that the vessels might be closed by external pressure as the result of imbibition of fluid by cells surrounding the capillaries. The reader is referred to Ashton's writings for the full statement of his hypothesis. It will have to suffice here to report that Ashton and co-workers^{4, 19} have been able to produce vaso-obliteration of immature retinal vessels in experimental animals by introducing either sodium fluoride or iodoacetate (glycolytic inhibitors) into the vitreous. The similarity between this effect and that induced by hyperoxia was made even closer by the findings that the enzyme-inhibitor effect did not occur in mature retinal vessels and that it was reversed by retinal detachment.

Vasoproliferation

Patz *et al.*⁴⁴ observed that following hyperoxic obliteration of the retinal circulation, when experimental animals were returned to air, proliferation of the retinal vessels, budding of capillary tufts into the vitreous, and retinal edema and hemorrhages occurred. Endothelial nodules in the nerve-fiber layer of the retina, indistinguishable from those seen in human retrolental fibroplasia, have been observed under the microscope. These proliferative lesions have also been observed by Patz⁴³ in some animals while still surrounded by high concentrations of oxygen. Ashton *et al.*⁶ showed that proliferation occurred only when the retinal vessels had been completely obliterated by oxygen.

Despite earlier conflict on the question of the influence of the rate of withdrawal from oxygen, it has been shown by Patz⁴³ and by Gyllenstein and Hellström²⁵ that gradual withdrawal does not reduce the degree of vascular proliferation.

The vascular lesions of hyperoxia in animals usually subside over a matter of months.²⁵ The extremely low incidence of cicatricial ocular lesions in animals,⁴³ in conspicuous contrast to human retrolental fibroplasia, remained unexplained.

INCIDENCE

The extreme variability in the reported incidence of retrolental fibroplasia, once the subject of much confusion and speculation,³¹ resulted from varying practices of oxygen administration in nurseries for premature infants (Table 16-1).

TABLE 16-1 INCIDENCE OF RETROLENTAL FIBROPLASIA AMONG SURVIVORS OF PREMATURE BIRTH IN NURSERY POPULATIONS

Source	Period of observation	Birth weight (Gm)	Oxygen administration		Incidence (% and no. infants/pop.)	
			Concentration (%)	Duration	Active (vascular)	Cicatrical ^a
<i>"Routine" oxygen administration</i>						
U.S.A. ²⁹	1948-1952	800-1360	"	"	57-(73/128)	32-(41/128)
U.S.A. ³⁴	1949-1951	<2000	>50	3-63 da	27-(75/280)	7-(19/280)
U.S.A. ⁴⁵	<1952	<1588	65-70	4-7 wks	60-(17/28)	25-(7/28)
England ⁹	1952	≤2041	"Routine"	"	24-(14/57)	2-(1/57)
U.S.A.	1953	≤1500	>50	28 da	70-(33/47)	17-(8/47)
{singletons} ¹⁰	{3 mo }					
U.S.A.	1953	≤1500	>50	28 da	83-(5/6)	66-(4/6)
{multiple births} ³⁰	{3 mo }					
U.S.A. ³²	<1954	1000-1850	69±7	≥14 da	61-(22/36)	22-(8/36)
Sweden ²⁸	<1954	1000-2250	≈45	>14 da.	25-(31/121)	2-(2/121)
<i>Curtailed oxygen administration</i>						
U.S.A.	1953-1954	≤1500	<50	"Indication"	31-(133/425)	5-(20/425)
{singletons} ¹⁰						
U.S.A.	1953-1954	≤1500	<50	"Indication"	42-(45/108)	14-(15/108)
{multiple births} ³⁰						
U.S.A. ³²	<1954	1000-1850	38±8	"Indication"	7-(2/28)	0-(0/28)
U.S.A. ⁴⁵	<1952	<1588	<40	1-14 da	16-(6/37)	0-(0/37)
U.S.A.	1954-1958	≤2000	<40	"Indication"	0.4-(5/1060)	0.3-(3/1060)
{Babies Hosp. }						

^a One or both eyes.

Effect of Duration of Supplemental Oxygen

The findings from studies conducted in this country and abroad³² are in agreement that the incidence of cicatricial retrolental fibroplasia increases rapidly with increased duration of exposure to supplemental oxygen during the first week or ten days of age.

Estimates of the risk of cicatricial retrolental fibroplasia after exposure to oxygen for less than 48 hours after birth are tenuous. The cooperative study³⁰ enrolled infants who survived 48 hours. Data obtained from the experience of infants in this study prior to their enrollment indicated that exposures to supplemental oxygen for periods of less than 48 hours were attended by some increased risk of cicatricial retrolental fibroplasia. However, there have been no controlled studies of the influence of oxygen administered during the first hours of life. (See also Chap. 7.)

Effect of Oxygen Concentration

In experimental animals the incidence of vascular changes in the retina increases with increasing concentrations of oxygen. However, it has not been clearly shown in humans that the incidence of cicatricial lesions is increased over the ranges of oxygen concentration ordinarily used clinically. A lower limit (30 per cent) has been established below which vascular changes have never been produced in experimental animals. No such lower limit (so-called safe concentration) has been established for human cicatricial retrolental fibroplasia.

In our nursery, oxygen is administered only to relieve cyanosis, rarely in concentrations greater than 40 per cent, and never continuously. This policy has been followed by the virtual disappearance of this condition in our nursery and in others.²²

Occurrence Without Supplemental Oxygen

The rare examples of retrolental fibroplasia that now occur, usually in association with no exposure or a very brief exposure to an oxygen-enriched environment, continue to be the cause of much speculation. We have not considered that another etiology must be brought in to explain these infrequent cases. The evidence available from experimental animals makes it difficult to accept the possibility that very brief exposures to hyperoxia can increase the risk of retrolental fibroplasia. If 21 per cent oxygen concentration in normal air is accepted as a rare cause of retrolental fibroplasia, no further explanations are required. This remains a moot point, and at the present time it is not known whether the incidence of retrolental fibroplasia can be reduced to zero.

Other Associations

Although an increased ocular susceptibility to oxygen, reflected by a higher incidence of retrolental fibroplasia, has been reported in males⁸ and in infants of multiple birth³⁰ these associations have not been uniformly found.

CLINICAL COURSE OF HUMAN RETROLENTAL FIBROPLASIA

ACTIVE PHASE

Age at Onset

Unrestricted Supplemental Oxygen. The age at the time of appearance of the first recognizable signs of retrolental fibroplasia was shown to be correlated

with the length of stay in oxygen, particularly for exposures exceeding several weeks. The length of stay in oxygen in the past was determined to a great extent by the degree of prematurity.

In the cooperative study of retrolental fibroplasia³⁰ the heaviest infants' average stay in oxygen was less than 4 days; the mean age at onset of retrolental fibroplasia was 5.3 weeks. The average age at onset for the lighter infants was 6.8 weeks, and their stay in oxygen was 30 days or more.

Oxygen Only for Clinical Indications. During recent years, under a policy of careful restriction of oxygen, we have observed several examples of retrolental fibroplasia in very small infants who received only the briefest exposure to oxygen. The age at the time of onset in these infants has been late (6 to 10 weeks). **Latest Age at Onset.** Normal ocular fundi at 90 days of age may be taken as virtual assurance that retrolental fibroplasia will not occur, since an onset beyond this time has never been reported

Appearance of the Fundi Early in the Disease

Although a hazy vitreous in the first two weeks of life was shown²¹ to be associated with a higher incidence of retrolental fibroplasia, this finding is not usually regarded as the earliest sign of the disorder. La Motte and Tynen reported a transient threadlike attenuation of the retinal vessels as an early sign which occasionally preceded other signs.

It is generally agreed that the first pathognomonic signs of active retrolental fibroplasia detectable on ophthalmoscopic examination are dilatation and tortuosity of the retinal vessels.⁴⁰ The veins are often three to four times their normal caliber, and the arteries are extremely tortuous. An arborized appearance, indicative of new vessel formation, may be seen at the end of vessels in the temporal periphery more often than in the nasal field

Later Signs

As the process progresses the vitreous becomes hazy and new vessel formation more profuse. Retinal hemorrhages are often seen. Gray areas which represent elevation of the retina appear in the periphery of the fundus. If the condition continues, strands of newly formed vessels extend into the vitreous from the areas of retinal detachment. Finally, the areas of detachment become larger, until in the most severe stage the entire retina becomes detached.

Both eyes are usually but not always involved to the same degree in the active phase.

For the sake of uniformity of terminology, we reproduce below an arbitrary classification of the successive stages of retrolental fibroplasia in the active phase

that was suggested in 1953 by the Joint Committee for the Study of Retrolental Fibroplasia²⁹ and has been generally accepted.

STAGES OF RETROLENTAL FIBROPLASIA IN THE ACTIVE PHASE

- I Dilatation and tortuosity of retinal vessels
Hemorrhage may or may not be present.
Early neovascularization, especially in the extreme periphery of the visible fundus, may be present.
- II Stage I plus neovascularization and some peripheral retinal clouding.
Hemorrhages are usually present.
Vitreous clouding may or may not be present.
Spontaneous regression may occur.
- III Stage II plus retinal detachment in the periphery of the fundus
Spontaneous regression unlikely.
- IV Hemispheric or circumferential retinal detachment.
Elevation of the retina over a large area, but still with some retina in position.
- V Complete retinal detachment

Duration of the Active Phase

The duration varies. It may be extremely rapid or, by contrast, smolder for weeks. Rarely does the active phase continue beyond the sixth month of life. Although there have been examples of active retrolental fibroplasia beginning while the infant was still receiving oxygen,³⁰ it usually begins and runs its clinical course long after oxygen has been discontinued.

Extent of Involvement During the Active Phase

In a group of 128 infants with active retrolental fibroplasia, Owens³⁹ observed that one-third showed minor activity, one-third developed intermediate changes, and one-third progressed to the most severe form of the disease.

Relation to Birth Weight. Although the incidence and severity of the active phase have not been shown to vary significantly with birth weight, Owens³⁹ found that active retrolental fibroplasia was both less frequent and less severe in infants whose birth weight was over 1300 Gm

Pathology of the Active Phase

The first recognizable pathologic lesion is found in the nerve-fiber layer of the retina.^{1, 18, 49} Here endothelial and mesenchymal cells proliferate to form nodules. Whorls of capillaries are seen which resemble renal glomeruli.

At progressive stages of the disease hemorrhages appear in relation to these

abnormal vessels, and tufts of capillaries sprout into the vitreous through the internal limiting membrane. Detachment of the retina results from transudate in the retina and from organization of intravitreal hemorrhages.

SPONTANEOUS REGRESSION

Spontaneous regression from the active phase was shown by Owens³⁹ to be characteristic of this disease.

Subsidence of the Active Phase

The first signs of regression are a lessening of the degree of vascular dilatation and tortuosity. Following this the vitreous becomes less hazy, and finally the gray retinal areas regain their normal pink color.

Owens³⁹ observed that after the active phase in 44 per cent of infants with the disease no residual changes were visible by ophthalmoscopic examination. The amount of damage in those with residua was dependent upon the severity of activity during the active phase.

Factors Influencing Frequency of Regression

In the cooperative study³⁰ a significantly lower rate of spontaneous regression was found for infants of multiple birth than for single born prematures. In the same study the rate of occurrence of spontaneous regression to normal was not significantly different in infants who received prolonged oxygen and in those who received curtailed oxygen.

There have been so few examples of retrolental fibroplasia in the more recent era of marked restriction in the use of oxygen that no statement is possible concerning the incidence of regression.

CICATRICAL RETROLENTAL FIBROPLASIA

Many ocular changes can result after subsidence of acute retrolental fibroplasia. The detectable residua range from small retinal scars to the formation of a mass of tissue filling the entire retrolental space. The cicatricial lesions have been arbitrarily classified²⁹ into five grades, as shown below.

GRADES OF RETROLENTAL FIBROPLASIA IN THE CICATRICAL PHASE

- I. Small mass of opaque tissue in periphery of the fundus without visible retinal detachment.
 - The fundus may have a pale appearance.
 - The blood vessels may be attenuated

- II. Larger mass of opaque tissue in periphery of the fundus, with some localized retinal detachment.

The disc is distorted by traction toward the tissue, usually to the temporal side.

Cases ending in grade I or II have useful vision.

- III. Larger mass of opaque tissue in periphery incorporating a retinal fold which extends to the disc.

Visual acuity varies from 5/200 to 20/50

- IV. Retrolental tissue covering part of pupillary area.

Small area of attached retina may still be visible, or only a red reflex over a sector of the fundus may be seen.

- V. Retrolental tissue covering entire pupillary area

No fundus reflex present.

Eyes that have advanced to grade V of the cicatricial stage sometimes show corneal opacifications, posterior synechias, iris atrophy, pupillary membrane, and occasionally cataract. Also they may show secondary glaucoma and buphthalmos. All of these later sequelae occur in grade V and are therefore properly classified as such.

Retinal Lesions

Owens³⁹ found that 30 per cent of infants who developed retrolental fibroplasia were left with minor retinal changes (grades I, II, and III) and 26 per cent with the more severe changes (grades IV and V). The cooperative study³⁰ revealed that the severity of the cicatricial lesions was not dependent upon either duration of oxygen or concentration of oxygen to which the infants were exposed. In this study the severity of the cicatricial lesions was not related to birth weight.

Other Ocular Manifestations

A full description of the many types of ocular manifestations that may follow this disease (e.g., strabismus, nystagmus, microphthalmia, etc.) is beyond the scope of this book and the reader is referred to descriptions in the ophthalmologic literature.^{12, 20, 50}

A high incidence of myopia has been noted in the survivors of premature birth. It is not certain that this represents a complication of retrolental fibroplasia.^{17, 20} (see Chap. 12).

Association with Mental Retardation

Although early reports of retrolental fibroplasia pointed out an association with cerebral defect it is now thought that these were mistaken examples of retinal dysplasia.⁴⁸

The question of whether mental retardation is more frequent among children with retrolental fibroplasia than among other survivors of premature birth has not been clearly answered. Mental retardation has been reported in a high proportion of children blind with retrolental fibroplasia,⁵⁶ but Parmelee *et al.*, found the incidence of mental retardation among such children to be not significantly different than among controls blind from other causes. Further follow-up studies of children with no residua, others with varying grades of ocular damage, and carefully chosen controls are necessary before this point can be settled.

DIFFERENTIAL DIAGNOSIS

Persistence and Hyperplasia of the Primary Vitreous

Cicatricial retrolental fibroplasia may be mistaken for persistence and hyperplasia of the primary vitreous,⁴⁷ which manifests itself as a dense, opaque, retrolental mass. The latter condition usually occurs in term infants and generally affects only one eye. The opacity decreases in density peripherally, where a red reflex may be seen.

Retinal Dysplasia

Retinal dysplasia (encephalo-ophthalmic dysplasia)⁴⁸ is an ocular condition that is present at birth. It is always bilateral and is manifested by a mass behind the lens producing a white pupil. The eyes are usually microphthalmic. This disorder is not associated with prematurity and occurs in association with multiple congenital defects including cerebral agenesis.

Retinoblastoma

Retinoblastoma was reported by Hix and Danielson in an infant who weighed 1750 Gm. at birth. The first changes were observed during the course of weekly ophthalmoscopic examinations of the fundi; they appeared on the twenty-third day of life. Dilatation and tortuosity of the retinal vessels were noted initially; later retinal hemorrhages occurred. A diagnosis of retrolental fibroplasia was considered until macular masses appeared. The latter findings made retinoblastoma very likely. This was later confirmed on histologic examination of one of the eyes, which was enucleated.

Peripheral Choroiditis

Peripheral choroiditis, probably due to syphilis, was discovered by Harley and Mather during the course of routine eye examination in a premature infant (birth

weight 1336 Gm.). Gray elevations in the periphery of the fundus resembled those seen in retrolental fibroplasia. However, it was notable in this infant that the retinal veins and arteries appeared normal. (See also Chap. 17.)

TREATMENT

Active Phase

Because no satisfactory evidence has been presented that treatment can influence the course of active retrolental fibroplasia, no treatment of the acute process can be recommended. The administration of adrenocortical steroids has no effect on the course of retrolental fibroplasia. Earlier suggestions that the severity of the acute process might be reduced by placing infants back in oxygen have not been substantiated in animal or clinical studies.

Oxygen Weaning. Slow withdrawal of premature infants from hyperoxic environments was advocated⁵¹ in the hope of preventing the vascular changes or reducing the severity of changes already present. There is no satisfactory evidence that slow return from hyperoxic conditions to normal air can reduce the incidence of cicatricial retrolental fibroplasia in humans. Such evidence must be forthcoming before oxygen weaning can be accepted, since this policy results in an increased duration of exposure to hyperoxia.

Cicatricial Phase

The treatment of the cicatricial phase of retrolental fibroplasia is at present limited to attempts to ameliorate complications.⁷

The problems of blind children require special attention and the families are often in need of expert guidance.⁴⁶

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Congenital Malformations

The classification of congenital malformations is a difficult nosological problem which has not been satisfactorily solved. As a result it is extremely difficult to interpret the results of most clinical studies of the subject. Despite this limitation it can be stated with some assurance that congenital malformations are more common among premature than among mature infants.

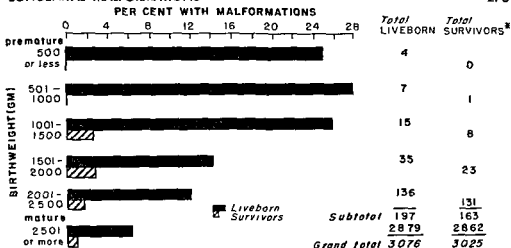
INCIDENCE IN RELATION TO PREMATURITY

Live-Born Infants

Hendricks observed that the incidence of prematurity among live-born infants with malformations (as reported on birth certificates) was more than $2\frac{1}{2}$ times that among all live births. He was unable to determine the degree to which birth weight reflected actual prematurity, since the malformations may have been associated with slower growth in utero. He concluded that both inadequate growth and premature delivery were involved because a similar relationship was observed when gestational age was used as a criterion of prematurity.

White Infants. Comparable findings have been observed in a prospective study of the incidence of congenital malformations in 3076 white single-born infants (Fig. 17-1) In this study conducted at Babies Hospital, New York City,⁴⁸ the congenital defects were found at postmortem examination in those who died and on examinations at birth, 6 months, and 1 year of age in those who survived. Six per cent of the 2879 white term infants (birth weight over 2500 Gm.) had congenital malformations. In 197 live-born white infants whose birth weight was 2500 Gm. or less, the incidence of malformations was 14 per cent; the percentage appeared to increase with decreasing birth weights and was higher in premature females than in premature males.

Nonwhite Infants. Among nonwhite premature infants (birth weight 1001-2500 Gm.) who died in the neonatal period (U.S., early 1950), the National Office of Vital Statistics⁷² reported that with increasing birth weight there was a decreasing incidence of congenital malformations reported as the cause of death. This trend was not apparent in the nonwhite population of the



* Survived 28 days or more

FIG. 17-1. Incidence of congenital malformations among 3076 white, single, live-born infants and among 3025 who survived 28 days or more, by birth weight. (From unpublished data of Mellin, G. W., and Merritt, K. K.: Fetal Life Study. Columbia University, College of Physicians and Surgeons, New York.)

Babies Hospital study;⁴⁸ however, as a group, nonwhite infants weighing 2500 Gm or less had a relatively higher incidence of malformations

Stillborn Infants

In a group of stillborn infants examined in the Babies Hospital study,⁴⁸ defects were noted in 12 out of 60 subjects who weighed 2500 Gm. or less; 2 infants with malformations were found among 22 stillborn infants who weighed more than 2500 Gm.

Neonatal Deaths

Congenital malformations play an undeniable role in the death of premature infants. Bundesen and his co-workers found that 42.3 per cent of 1326 neonatal deaths from congenital malformations were of premature infants. Malformations as a cause of death ranked fourth among infants whose weight at birth was less than 1749 Gm. and second among those weighing between 1750 and 2500 Gm.

CAUSES

Information as to the causes of developmental anomalies is gradually increasing.⁷⁵ Briefly, it may be said that the interactions of both genetic and nongenetic factors are important in the etiology of congenital malformations.

The arguments in the past about whether defects were exclusively hereditary or environmental in origin now seem redundant.²⁴ Studies in experimental animals have indicated that teratogenic agents can alter developmental processes in the same way as can genetic change.

The number of experimental teratogenic agents (as well as "negative" influences such as dietary deficiency, and so on) that have been described is now very large.⁴¹ As a result there is considerable discussion about the specificity of action of these agents. This point was discussed by Wilson, who concluded that the effects of teratogenic agents are related to definite stages or events in embryonic development, and when due allowance has been made for variations in dosage of the agent, varying reactions of different species, etc., distinctive malformations can be associated with particular agents.

For a complete discussion of this important subject, the reader is referred to other sources.^{23 41, 52, 55 74}

VIRAL DISEASES IN THE MOTHER

Rubella

Attention was first drawn to the association between rubella (German measles) in the mother during pregnancy and fetal malformations by the report of Gregg in 1941. Of 78 infants with congenital cataract, 68 were born to mothers who had had rubella in the early months of pregnancy. In 44 of these infants a congenital heart lesion was also present. The average birth weight of all the infants in this study was 2268 Gm. (5 pounds).

Following the publication of Gregg's report there were numerous studies of this association, and most, but not all, indicated that the incidence of malformations following maternal rubella early in pregnancy was extremely high. This evidence was critically reviewed by Greenberg and others who concluded that it was impossible to estimate the incidence from retrospective studies. Prospective studies indicated that the incidence of malformations following maternal rubella was considerably lower than had first been suggested; however, since these investigations were conducted without concurrent controls, the results were also very difficult to evaluate.

Hill and co-workers examined 44 infants born alive to women who developed rubella just preceding or during pregnancy. In each instance the fact of the occurrence of rubella had been recorded *before* the child was born. Major congenital defects (congenital heart disease, cataract, and deafness) occurred only in the infants whose mothers developed rubella early in pregnancy. The birth weights of all of the infants were not known, but of 6 infants with de-

fects 4 weighed 2500 Gm. or less; among 35 unaffected infants only 1 weighed 2500 Gm. or less. Hill's group combined their results with those of three other similar prospective studies (Table 17-1) and arrived at an estimate of the risk of congenital defect from rubella at successive four-week periods during pregnancy. However, the possibility that these estimates might be subject to geographic and temporal variations could not be refuted

TABLE 17-1 RISK OF DEFECT IN THE INFANT FOLLOWING
MATERNAL RUBELLA DURING PREGNANCY

<i>Week of pregnancy at which rubella commenced</i>	<i>No of cases</i>	<i>Infants with major defects</i>	
		<i>No</i>	<i>%</i>
1-4	12	6	50
5-8	20	5	25
9-12	18	3	17
13-16	18	2	11
17-24	17	1	6
25 or more	19	0	0
TOTAL	104	17	

Combined data from four prospective studies as summarized by Hill and others **

Jackson and Fisch obtained a list of women in whom a diagnosis of rubella had been made during the first 18 weeks of pregnancy. Fifty-seven children of these mothers and 57 controls matched with the rubella group for age, sex, county of birth, and maternal age and parity were examined at 4 years of age. Fifteen children in the rubella group had major congenital defects, in the control group no major defects were found. Only three children in the rubella group exhibited malformations that had been diagnosed early in life. Fourteen were later found to have congenital deafness; in 12 it was the sole defect, in 5 it was unilateral. In 9 of the 14 children the deafness had gone undetected in examinations prior to the age of 4 years. The authors concluded that to obtain a reliable estimate of the risk of deafness in a child resulting from maternal rubella investigations must be prospective and the children must be followed for at least 4 years. (See also Chap. 3.)

Mumps, Rubeola, Varicella

The evidence for an association between other maternal viral infections and malformation of the fetus is not completely satisfactory. In the prospective study conducted by Hill and others, no deleterious effect on the product of

conception was observed after maternal mumps (29 cases), rubella (6 cases), and varicella (25 cases). The proportion of live-born children with low birth weights was relatively high after maternal varicella, but chance could not be excluded as the explanation for this finding. A national prospective inquiry into the effects of virus infections during pregnancy has been undertaken in Britain but the results are not yet published.

Cytomegalic Inclusion Disease

The virus of cytomegalic inclusion disease may be transmitted to the fetus and produce infections which result in serious malformations of the developing nervous system (see Chap 19)

OTHER MATERNAL CONDITIONS

Carter^a reviewed the antenatal records of mothers who delivered children with malformations and was unable to find any noninfectious maternal condition that was followed by a significantly increased rate of malformations.

McDonald conducted a prospective investigation into the relationship between maternal health in the first 12 weeks of pregnancy and the incidence of malformations evident at birth. He reported that as compared with mothers of unaffected infants, a higher proportion of mothers of infants with major defects had had an acute febrile illness, pulmonary tuberculosis, or had been engaged in heavy work.

Toxoplasmosis

An association between cleft palate and cleft lip in the infant and infection of the mother with the parasite *Toxoplasma gondii* has been suggested, but the evidence is tenuous (see also Chap 19)

Hypothyroidism

Man and others reviewed the available evidence concerning the association between maternal hypothyroidism and congenital anomalies. They concluded that, although the magnitude of the risk could not be estimated from the limited number of observations, there was suggestive evidence that a variety of abnormalities, often including permanent defects of the central nervous system, occurred with increased frequency in pregnancies complicated by maternal hypothyroidism.

Age

There is not complete agreement on the influence of maternal age on malformation of the fetus. *Hendricks* found that the incidence of malformations reported on birth certificates was higher in infants whose mothers were at either the lower or the upper range of child-bearing age.

In some series the age of the mother was not found to be related to the incidence of malformations when children with mongolism (*q.v.* this chapter) were excluded from the reckoning.

Diabetes

There is little agreement on the relationship between maternal diabetes and congenital malformations in the infant (see Chap. 22).

Nutrition During Pregnancy

Although there is some evidence from clinical studies that the nutrition of the pregnant woman is related to the welfare of the product of conception, evidence of this relationship in the production of fetal malformations is less satisfactory. *Burke* and her associates found a higher incidence of malformations among the offspring of women whose antenatal diets were poor than in mothers whose diets were excellent. However, there was no assurance that the difference in antenatal diet was the most important difference which existed between these groups of women.

EFFECTS OF ANTENATAL RADIATION

First Generation

From what is known of the sensitivity of experimental animals to radiation it would be anticipated⁵⁶ that in humans the effects of diagnostic irradiation at the ordinary dosage level would be difficult to recognize in the first postexposure generation.

This was the case in a study by *Stewart* and others who found no increase in the number of congenital malformations in the offspring of women who had had roentgen examinations of the abdomen and other sites during their pregnancies, as compared with controls. Moreover, *Neel* and *Schull*⁵⁷ found no significant, consistent effect in the offspring born to survivors of the atomic bombings in Hiroshima and Nagasaki, Japan.

Subsequent Generations

The effects of radiation on subsequent generations are much more difficult to study in human populations. Gentry and co-workers undertook a study of the long-range effects of exposure to radiation. They studied the birth and death certificates among residents in certain areas in upper New York State where there were increased natural deposits of radioactive materials. Many of the families had lived in these areas for several generations. The authors found that the malformation rate was 15.8 per 1000 live births in these areas compared with a rate of 12.8 in areas with relatively little radioactive materials.

SPECIFIC DEFECTS AND THEIR STATUS IN PREMATURE INFANTS

DIAGNOSIS

The existence of congenital malformations may be suspected before birth by such signs as relatively feeble fetal movements, hydramnios,⁶⁷ marked fetal bradycardia,⁴⁹ and others (see Chap. 6). Following delivery all observers of the newborn infant must maintain a careful watch for the presence of malformations, particularly the types that are amenable to surgical correction (see Chap. 8).

TABLE 17-2 AGE OF INFANTS* WHEN MALFORMATIONS OF VARIOUS ORGAN SYSTEMS WERE FIRST SUSPECTED OR NOTED

System	Total no malformations	% of malformations first suspected or noted			
		Birth	6 mo	12 mo	Over 12 mo
Cardiovascular	42	36%	48%	12%	5%
Central nervous	65	42	32	25	2
Gastrointestinal	41	24	46	29	
Genitourinary	41	71	24	5	
Musculoskeletal	173	46	41	11	3
Respiratory	7	43	29	14	14
Skin	91	40	40	17	4
Other	5	40	40	20	.
TOTAL	465 ^b	43	39	15	3

From McIntosh *et al*,⁶⁸ study conducted at Babies Hospital

* 386 infants with malformations who survived the neonatal period among total 5530 live-born including 486 weighing 2500 Gm. or less at birth

^b Each malformation is counted once. There were 465 malformations found in 386 live-born infants (premature and term) who survived the neonatal period

The diagnosis of developmental anomalies, except for gross defects, is usually difficult, even in term infants. In the longitudinal study of the incidence of congenital malformations conducted at Babies Hospital⁴⁸ it was found that, despite an organized effort to detect defects, less than half were recognized at birth (Table 17-2).

Since it is not practicable to discuss methods of diagnosis and correction for every type of congenital defect, the discussion which follows will be limited to the most frequently occurring defects and the particular aspects that are relevant to premature infants. The main points to bear in mind are that: (1) premature infants are especially likely to have congenital abnormalities; (2) the abnormalities may not be apparent at birth; (3) early diagnosis is important in giving a prognosis for survival and in planning specific treatment and general care, (4) most of the laboratory tests for diagnosis can be applied to the premature infant, although modifications of some of the tests may be necessary, and (5) success in operations of premature infants calls for special medical as well as surgical skill (see Chap. 11).

MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM (Including the Eyes)

The frequency of the various types of defects of the nervous system reported in the Babies Hospital study is shown in Table 17-3. All the infants with malformations of the nervous system who were stillborn or who died in the neonatal period had multiple malformations involving one or more systems. Among the infants with nervous-system defects who survived the neonatal period, more than two-thirds had only a single defect.⁴⁸

Mongolism

The frequency of mongolism among newborn infants is estimated to lie between 1 : 500 and 1 : 1500.³ The true incidence cannot be determined accurately since the diagnosis is often deferred in infancy, and children with mongolism have a high mortality rate in early life.

Smith and McKeown observed that the proportion of children who weighed less than 2500 Gm. at birth and were born before the thirty-seventh week of gestation was significantly greater in 103 children with mongolism than in a control population.

The clinical diagnosis of mongolism is notoriously difficult to make at birth and in the first few weeks of life in very small premature infants.⁴⁹ With the aid of roentgenographic signs⁷ and the pattern of dermal configurations^{18, 73} a diag-

TABLE 17-3 DISTRIBUTION OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM (INCLUDING EYE) AMONG 5739 INFANTS WEIGHING MORE THAN 500 GM. AT BIRTH, ACCORDING TO OUTCOME OF DELIVERY

	<i>Outcome of delivery</i>	
	<i>Stillborns and neonatal deaths (209)</i>	<i>Infants live-born^a (5530)</i>
Mongolism		11
Anencephaly	8	
Meningomyelocele and meningoencephalocele	3	4
Hydrocephalus	3	2
Microcephaly		2
Other malformations of brain ^b	2	23 ^b
Cataract	1	11
Prosis		4
Nystagmus		3
Microphthalmia	2	1
Other malformations of eye		4
TOTAL NO. MALFORMATIONS	19	65

From McIntosh *et al.*,⁴⁸ study conducted at Babies Hospital

^a Infants who survived 28 days or more

^b Includes 18 with marked mental deficiency

nosis can usually, but not always, be established before the infant leaves the nursery.

Spina Bifida

Spina bifida is a developmental defect in the closure of the lamina of the vertebral bodies with or without protrusion of the cord membranes. When the cord membranes do not protrude the condition is known as spina bifida occulta. Spina bifida with myelomeningocele (nerve fibers in the sac) is more common than meningocele and has a more serious prognosis. The presence of nerve tissue within the sac can often be detected by transillumination of the lesion with a strong light in a dark room.

Arnold-Chiari Malformation

An anomaly of the hindbrain termed the Arnold-Chiari malformation is related to low dorsal and lumbar myelomeningoceles. It consists in a downward displacement of the cerebellum and brain stem through the foramen magnum into the cervical portion of the bony spinal canal. In this condition cerebrospinal

fluid usually has direct access to the spinal subarachnoid space, as the fourth ventricle opens caudally below the level of the foramen magnum. The fluid is often prevented from passing forward normally as the result of obliteration of the basilar cisternal pathways at the level of the foramen magnum.

Other defects in the brain and skull (such as microgyria and craniolacuna) are usually present and may be demonstrated in roentgenograms. Ingraham and Matson stated that it is probable that the Arnold-Chiari malformation exists in virtually all patients with spina bifida who have hydrocephalus at birth or develop it later, particularly those with myelomeningocele.

A comprehensive discussion of the management of these malformations is given by Ingraham and Matson.

Hydrocephalus

The diagnosis of congenital hydrocephalus in the early stages is difficult because the premature infant's head normally appears large in relation to his size. Figure 17-2 shows the marked disproportion between the circumference of the head and the shoulders in a premature infant with hydrocephalus.

Since the growth of the head of premature infants is normally very rapid, hydrocephalus often goes undetected until the condition is fairly well advanced. Frequently there is a period of indecision because the limits of the normal rate of growth are difficult to define. The results of a series of measurements of the circumference of the head in a group of small premature infants in our nursery (see Chap. 4) have proved useful in distinguishing between normal rate of growth and early hydrocephalus.

Other diagnostic signs are separation of the skull sutures, bulging and tenseness of the fontanelle, vomiting, and convulsions. If spina bifida is present at birth the diagnosis of hydrocephalus is highly probable.

The condition must be differentiated from meningitis (see Chap. 19); chronic subdural hematoma; megaloccephaly; and hemorrhage due to birth trauma (see Chap. 18).

Diagnostic procedures and the various methods of treatment of hydrocephalus in infancy are presented fully in Ingraham and Matson's book.

Malformations of the Eyes

Among the numerous malformations of the eye only three will be discussed: developmental cataract, ptosis of the eyelid, and strabismus. For a complete description of all of the anomalies of the eye, the reader is referred to Mann's book on the subject.

Developmental Cataract. Cataracts may be present at birth or may not form



FIG. 17-2. Hydrocephalus in a premature infant, showing marked disproportion between head and shoulders. (Courtesy of John L. Parks, M.D., and the late Lewis K. Sweet, M.D., Wash., D.C.)

until some time during infancy²⁹ or childhood. In either case they should be termed as Mann suggests, "developmental" (rather than congenital), since in the growth of the lens fibers before the completion of the adult nucleus at 25 years, the moment of birth is only an incident. A variety of toxic substances may lead to cataract formation.

Mann noted that lamellar or zonular cataracts are associated with disorders of development involving the whole individual. In a given case the time in development when the disorder took place can be estimated with considerable accuracy by determining which zone of the lens is opaque. She observed that other calcium-containing structures are similarly affected, for example, permanent teeth may exhibit definite lines of hypoplasia of the enamel corresponding in time with the opaque zones of the lens. These observations are of interest to those concerned with prematurity, since a relatively high incidence of enamel hypoplasia is observed in the deciduous teeth of expremature children (see Chap. 12).

The incidence of developmental cataracts in premature infants is low, and it is uncertain whether they occur more frequently than in the general population. Castrén examined the eyes of 480 expremature children and found cataracts in the eyes of 3; none were present among 217 controls whose weight at birth had been over 2500 Gm.

Ptosis of the Eyelids. Congenital inability to raise the upper lid may be due to absence of the levator palpebrae superioris. Ptosis following birth injury may be part of an *ophthalmoplegia of central nervous system origin involving all the extrinsic muscles of the eye.*

Strabismus. Strabismus may be the result of a developmental abnormality or due to birth injury. If the lesion is developmental the aplasia may be in the central nervous system or in the muscle. Any and all combinations of ocular palsies can occur; Mann notes that many of them are central in origin. The increased incidence of concomitant strabismus in expremature children (see Chap. 12) may be related to the relatively frequent occurrence of brain damage.

Strabismus occurred frequently in expremature infants with cicatricial retrolental fibroplasia during the period when the latter condition was rampant (See also Chap. 16.)

MALFORMATIONS OF THE GASTROINTESTINAL TRACT

Diagnosis

Congenital abnormalities may result in partial or complete obstruction at certain points in the gastrointestinal tract (stenosis or atresia). A maternal history of hydramnios,⁴⁵ inability to pass a catheter into the stomach, or the recovery of more than 30 ml. of fluid by gastric aspiration following delivery should all raise the suspicion of intestinal obstruction even before the onset of other manifestations.

Clinical Manifestations. The following clinical signs appear soon after birth (as soon as fluids are given): (1) vomiting (particularly of bile-stained fluid); (2) distention of abdomen; (3) abnormal meconium; and (4) absence of fecal material or presence of a small amount combined with other symptoms of obstruction.

Roentgenography. Santulli regards the use of four-position roentgenograms of the abdomen (i.e., supine anteroposterior, upright anteroposterior, horizontal right-lateral, and horizontal left-lateral) as the most important diagnostic measure to be taken when intestinal obstruction is suspected in newborn infants. Rarely is contrast medium needed and, in Santulli's opinion, it should be avoided in the usual case.

Improvement in the results of treatment can be achieved through early recognition of intestinal obstruction in newborn infants.

Atresia of the Esophagus with Tracheoesophageal Fistula

There are a number of types of malformations of the esophagus, all relatively rare. The commonest is atresia with fistulous opening into the trachea. The upper part of the esophagus usually ends in a blind pouch and the lower part communicates with the trachea. As has been stated, this condition may be detected immediately after birth by the inability to pass a rubber catheter into the stomach. It is often diagnosed by the recognition of an excessive flow of frothy saliva from the mouth. Later when the infant is given fluids he regurgitates and immediately shows signs of distress such as choking, coughing, and cyanosis. These symptoms are due to overflowing from the esophageal pouch into the larynx and will result in aspiration pneumonia if the condition is not speedily corrected. Acute gaseous abdominal distention should raise the suspicion of tracheoesophageal fistula.

Although there are no precise data available, it is generally agreed that esophageal atresia is encountered with greater frequency in premature infants than among those born at term. Gross noted that 25 per cent of a series of 233 infants with esophageal atresia had been born prematurely. During a seven-year period operations for atresia of the esophagus and tracheoesophageal fistula were performed on 72 infants in Babies Hospital; 33 had a birth weight of 2500 Gm. or less.³⁸

As has been demonstrated in several surveys,^{12, 28, 31, 38, 63} the majority of deaths in newborn babies with esophageal atresia occur in the group who are prematurely born and in those with other malformations. The importance of anesthetic techniques in the management of the high-risk group is stressed in these reports.

Congenital Pyloric Stenosis

Henderson and others reviewed the literature on the occurrence of pyloric stenosis in premature infants and concluded that although the evidence was very unsatisfactory there was nothing to suggest that this condition was more frequent in premature than in mature infants. Corner observed that the birth-weight distribution of 117 cases of pyloric stenosis (8 in premature infants) was not significantly different from that of the general population.

Henderson's group noted that the clinical features that seemed to be peculiar to premature infants and tended to make the diagnosis more difficult to establish were anorexia, the absence of projectile vomiting, and peristaltic waves that were not notably greater than those seen in normal premature infants. On the other hand, palpation of the pyloric tumor through the thin abdominal wall was relatively easy. The authors reviewed the time of onset of symptoms in 17 reported

cases and found that there was no relationship to the degree of prematurity. In an infant who weighed 1.8 kg. at birth and whose gestational age was estimated to be 32 completed weeks, anorexia appeared on the tenth day of life and vomiting began on the twelfth day.

Prompt surgical treatment of pyloric stenosis is indicated in premature infants.³²

(See Rupture of the Stomach in Chap. 18 for congenital defect of the muscular coat of the stomach)

Intestinal Malformations

Malformations of the intestinal tract are among the commonest of all congenital defects found in premature infants.

Antenatal Development. During early embryonic life the intestine communicates with the yolk sac. The opening into the yolk sac narrows gradually to form the vitelline duct, which then becomes the yolk stalk. This structure finally loses its connection with the intestine.

At first the intestines lie in the cavity of the umbilical cord and outside the abdominal cavity. Later they are drawn back into the abdominal cavity, rotation takes place about the superior mesenteric vessels in two stages, so that the final positions of the various parts of the intestine are assumed in relation to the right and left sides of the abdomen, to the mesentery, and to one another. In addition, the intestine is a hollow tube in early fetal life; at the end of the second fetal month the epithelial lining grows rapidly, filling the primitive gut tube ("epithelial plug stage") particularly in the esophagus, upper part of the small intestine, and the rectum.^{33, 39} Failure to develop beyond the epithelial plug stage is considered to be the cause of some instances of congenital atresia.

Injury to the Intestines During Fetal Life. The belief has been widely held that persistence of the solid stage of development is also the cause of jejunoileal atresias. However, it is more than likely^{31, 38} that the various types of atresia and stenosis in the distal part of the small intestine result from injury to the developing bowel. The commonest injury is considered to be volvulus resulting from meconium ileus, malrotation, mesenteric anomalies, or persistent fetal umbilical hernia. Evidence of meconium peritonitis is frequently present.^{38, 64}

Duodenal Obstruction. The dominant symptom in duodenal obstruction is vomiting; in the majority of instances the obstruction is distal to the ampulla of Vater,²⁰ and in these cases the vomitus is bile stained. Intrinsic obstruction may be caused by complete discontinuity of the duodenum and by areas of atresia or stenosis. Extrinsic causes are volvulus of the midgut loop in association with malrotation, peritoneal bands, and annular pancreas.

Bodian and others noted the frequent association of duodenal obstruction and

mongolism. A similar association with prematurity has also been described.^{2, 20} **Malrotation.** When intestinal obstruction is associated with malrotation it usually results from volvulus of the midgut loop.⁶⁶ The clinical signs are those of incomplete duodenal obstruction. Less frequently obstruction may be caused by incomplete rotation of the cecum without volvulus of the midgut.

Meconium Ileus. Approximately 10 per cent of individuals with fibrocystic disease of the pancreas are born with intestinal obstruction due to inspissated meconium which plugs the distal portion of the ileum.¹⁷ Young and others demonstrated that the addition of human serum albumin to meconium from normal infants resulted in a viscid, tenacious product which appeared to be identical to the meconium in a patient with meconium ileus. They suggested that the proteins in amniotic fluid that are unable to be hydrolyzed are mixed with components of normal meconium to produce viscid material characteristic of meconium ileus.

Boyer found that the mean birth weight of children with fibrocystic disease of the pancreas was significantly lower than that of a control population. Twelve per cent of the fibrocystic group (173 patients) had a birth weight of 2500 Gm. or less, 7 per cent of the control group were in this weight category.

Congenital Megacolon. Infants with megacolon may exhibit delayed or infrequent passage of meconium in the newborn period. Some have clinical signs of intestinal obstruction⁷⁰ that may be difficult to differentiate from ileal obstruction.

There is no evidence that congenital megacolon occurs with unusual frequency in premature infants. However, delay in passage of the first meconium stool occurs more frequently in premature than in mature infants (see Chap. 9). As a result, the diagnosis of congenital megacolon is entertained more often in the former group.

Meconium-Plug Syndrome. Anorectal plugs of meconium may also produce symptoms of obstruction that are relieved by passage of the plug.^{13, 18} Some, but not all, of the infants who exhibit the meconium-plug syndrome are later found to have congenital megacolon.

"Pseudo-obstruction" in Premature Infants

Following Treatment of the Mother with Hexamethonium. Paralytic ileus simulating intestinal obstruction has been reported in premature infants whose mothers received hexamethonium bromide therapy for toxemia of pregnancy.^{30, 53} In these cases abdominal distention and obstipation became apparent in the first days of life.

Unexplained Cases. In agreement with others⁶⁰ we have observed a number of

premature infants who developed abdominal distention, obstipation, and vomiting after an interval of normal bowel function. These manifestations appeared at the end of the first week or during the second week of life. Several were explored surgically without the disclosure of any abnormality. In most of these children the duration of symptoms was less than one week. A few died.

These manifestations appeared to bear no relation to congenital megacolon (or functional intestinal obstruction in the newborn²¹), since recovery in the survivors was complete. Most of the infants with these signs were not receiving drugs. Although examples continue to occur in our nursery, the exact nature of the condition has remained obscure. We have dubbed this syndrome "pseudo-obstruction" in premature infants.

Rupture of the Stomach. This is discussed in Chapter 18

Anal and Rectal Malformations

The anus may be absent, occluded by a complete or partial membrane (stenosis), or abnormally located, or there may be atresia. The rectum may be absent, imperforate, or with a fistulous opening into the urethra or vagina. In all of these malformations the symptoms are those of obstruction. No meconium is passed, or it may emerge ribbon-like, or be passed through fistulous openings.

In 507 children with anorectal anomalies reported by Gross, more than one-third had other malformations (congenital heart disease, malformation of vertebrae, esophageal atresia, etc.). No association with prematurity has been apparent.

Malformations of the Biliary Tract

Jaundice that results from obstruction to the flow of bile into the intestine on the basis of developmental anomalies of the biliary system must be differentiated from other causes in the neonatal period (see Chap. 13) and in infancy.³⁵ There is no indication that biliary-tract anomalies occur with unusual frequency in prematurely born infants.

MALFORMATIONS OF THE CARDIOVASCULAR SYSTEM

Incidence in Premature Infants

Perceptible Defects. Richards and others⁶² found a relatively high incidence of cardiovascular malformations among premature infants; 1.7 per cent of 463 live-born infants whose birth weight was 2500 Gm. or less as compared with 0.5 per cent among 5067 term infants.

Cardiac Murmurs. Richards *et al.*⁶³ also determined the prevalence of car-

TABLE 17-4 PREVALENCE OF CARDIAC MURMURS AMONG PREMATURE INFANTS

Age at examination	Birth weight (Gm.)						Total	
	501-1500		1501-2000		2001-2500			
	No infants ^b	% with murmurs	No. infants ^b	% with murmurs	No infants ^b	% with murmurs	No infants ^b	% with murmurs
1-60 da.*	23	13	61	3	277	1	361	2
6-9 mo	20		53	2	255	6	328	5
12-15 mo	21	10	55	6	242	7	318	7

From Richards *et al* ⁶³

^a The age at initial examination in infants whose birth weight was 1500 Gm. or less varied from 8 to over 60 days, 1501-2000 Gm., 1-60 days, 2001-2500 Gm., 1-30 days

^b Number of infants examined

diac murmurs in 364 premature infants who survived the neonatal period (Table 17-4). Murmurs at the various ages occurred somewhat more frequently in the premature as compared with the term infants, but the observed differences could easily have been the result of chance. Of 36 premature infants who had cardiac murmurs at one or more examinations during the first year of life, 14 per cent were found to have congenital malformations of the heart. The corresponding value for 353 full-term infants was 5 per cent.

Other Considerations

The increased incidence of heart defects and the difficulties of diagnosis in small infants combine to make the recognition of cardiovascular diseases a challenging problem in the premature nursery. Advances in the surgical and medical care of heart disease in infancy make it important that the diagnostic difficulties be solved. Methods of treatment are not different from those employed for term infants.

The reader is referred to other sources^{42, 54, 71} for descriptions of the many types of malformations of the cardiovascular system and for the principles of management of congenital heart disease.

MALFORMATIONS OF THE GENITOURINARY SYSTEM

The incidence of defects of the genitourinary system is difficult to estimate because many of the malformations present no external signs and may go unrecognized for a long time. In the Babies Hospital prospective study abnormalities of this system were observed in 4 per cent of stillbirths, 14 per cent of neonatal deaths, and 1 per cent of infants who survived the neonatal period.⁴⁸ There are no reliable estimates of the frequency among premature infants.

Complete expositions of this topic are to be found in the books by Campbell, by Kjellberg *et al.*, and by Jones and Scott.

DIAPHRAGMATIC HERNIA

Types of Hernia

Herniation of the intestines and other abdominal viscera through the diaphragm into the thoracic cavity may occur through one of the pleuroperitoneal hiatuses or, much less frequently, the foramen of Morgagni in the retrosternal portion of the diaphragm. Herniation through a left posterolateral defect is observed much more frequently than on the right.

Diagnosis

Clinical Signs. The infant with diaphragmatic hernia usually has severe respiratory difficulty and cyanosis. Since premature infants frequently have respiratory difficulty and the frequency of occurrence of diaphragmatic hernia is not notably high among them, the respiratory signs of diaphragmatic hernia are often mistakenly attributed to the respiratory-distress syndrome (see Chap. 14)

In infants with diaphragmatic hernia, inspection reveals that with each breath one side of the chest (usually the left) moves less than the other. The abdomen appears small and scaphoid. The heart is displaced (usually to the right) away from the affected side. The possibility of dextrocardia is often considered. Breath sounds may be diminished on the affected side or may be inaudible.

Roentgenography. Roentgenograms of the chest quickly confirm the diagnosis. The use of a contrast medium in the colon is rarely necessary.

Treatment

The indications for operation in affected premature infants are not different from those in mature subjects.

(For a discussion of inguinal and umbilical hernias see Chap. 12.)

CLEFT LIP AND CLEFT PALATE

Incidence

It has been estimated that the incidence of cleft lip, cleft palate, or both is 1.3 per 1000 live births.¹⁴ Approximately 25 per cent of the clefts involve the lip only, 35 per cent the palate only, and 40 per cent both lip and palate.

Management

Feeding. When these malformations occur in premature infants they do not present a feeding problem that is unique in a premature nursery. Indwelling nasogastric tubes are used to feed these infants initially; a "cleft-lip feeder"⁴⁶ is introduced later.

Surgical Correction. Surgical closure of the lip is usually delayed until the infant is gaining weight steadily; an arbitrary weight of 2.7 kg. has been suggested.⁴⁶

There are widely divergent views on the optimum age for closure of the palate. MacCollum and Richardson have suggested that this be performed when the infant is approximately 14 months of age, weighs 9.9 kg., and is in good health.

A helpful guide for those who must plan for the ongoing care of children with facial clefts has been prepared by the Committee on Child Health of the American Public Health Association.¹⁹

PREVENTION OF CONGENITAL MALFORMATIONS

As Fraser²² has emphasized, the causes of congenital defects are numerous and often multiple, and we are a long way from taking any rational measures to appreciably reduce the frequency of human malformations.

Counseling

The anomalies with clear-cut genetic causes represent a minority of the total number of defects. If affected individuals and other carriers of abnormal genes refrained from reproducing, the number of such defects could be reduced.

Parents who have just had a child with a malformation frequently ask their physician to help them decide whether or not to reproduce. In the usual clinical situation there is often a dearth of information about the family of the propositus and incomplete knowledge about the genetic basis of the malformation in question. Even a skilled geneticist would have difficulty estimating the risks under these circumstances.⁴¹ Physicians, pressed by the frequent demands which are made upon them, must remain mindful of their limited ability to render judgments in these matters.

Avoidance of Exposure to Rubella During Pregnancy

The relation of congenital malformations to maternal rubella during early pregnancy has been shown. Pregnant women should avoid exposure to rubella and other virus diseases.

Use of Gamma Globulin. In a study conducted on human volunteers Krugman and Ward demonstrated a rubella-neutralizing antibody in gamma globulin. On the basis of this evidence they recommended the early administration of large doses of gamma globulin (at least 20 ml.) to the pregnant woman who has been exposed to rubella

Other Preventive Measures

Pregnant women should avoid all radiation exposure. Diagnostic roentgenography should be limited to specific, strict indications and efforts should be made to shield the fetus as much as possible.

The use of potentially teratogenic agents, such as androgenic steroids, anti-metabolites, etc (see Chap 6), in pregnant women should be avoided

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Birth Injuries

The term "traumatic birth injury" is used here to include contusions, lacerations, fractures, and hemorrhage caused by mechanical factors during delivery. These injuries should be differentiated from the injury caused by anoxia or asphyxia. In many surveys of the subject this distinction is not consistently made, notably in the case of intracranial hemorrhage (discussed in this chapter)

INCIDENCE

No satisfactory reports have been found of the over-all incidence of birth injuries among premature infants

Birth-Certificate Reports

Wallace and others found that among 14,242 live-born premature infants in New York City in 1953, birth injuries were recorded on the birth certificates of 23 (1.6 per thousand), this incidence was approximately the same as in the term group (Table 18-1). The neonatal mortality rate among infants with birth injuries was higher in premature than in term infants. The authors pointed out that these data represented merely minimal estimates of the extent of the problem.

Wallace's group reported the incidence of birth injuries by type and site for live-born infants, both mature and premature (Table 18-2). There is little information as to the incidence of various types of birth injuries among premature infants

Death-Certificate Data

An estimate of neonatal mortality rates among premature infants in association with injuries to the central nervous system and other birth injuries (reported on death certificates) is available in an analysis by the National Office of Vital Statistics. As can be seen in Figure 18-1, with increasing birth weight the proportion of live-born infants whose death was attributed to birth injuries fell sharply. However, at higher weights, birth injuries, particularly injuries to the central nervous system, assumed added importance in over-all mortality.

TABLE 18-1 BIRTH INJURIES REPORTED ON CERTIFICATES OF LIVE BIRTH, INCIDENCE AND NEONATAL MORTALITY, BY BIRTH WEIGHT

New York City, 1953

	<i>Birth weight (Gm.)</i>						<i>Not stated</i>
	<i>1000 or less</i>	<i>1001-1500</i>	<i>1501-2000</i>	<i>2001-2500</i>	<i>2500 or less</i>	<i>2501 or more</i>	
Live births	903	1,065	2,497	9,777	14,242	146,730	
Birth injuries							
Number	2	11	3	7	23	275	7
Incidence ^a	2.2	10.3	1.2	0.7	1.6	1.9	
Mortality ^b (%)	100	55	33	14	44	3	

Adapted from Wallace *et al.*³⁰^a Incidence per 1000 live births^b Neonatal mortality rate among infants with birth injuries

TABLE 18-2 BIRTH INJURIES REPORTED ON CERTIFICATES OF LIVE BIRTH, BY TYPE AND SITE

New York City, 1953

	<i>Birth injuries reported</i>		<i>Mortality (%)^b</i>
	<i>No.</i>	<i>Incidence^a</i>	
Paralysis	79	0.49	2.5
Facial	46	0.29	
Erb's	18	0.11	
Brachial	11	0.07	
Miscellaneous	4	0.02	
Fracture	67	0.41	7.5
Clavicle	26	0.16	
Lower extremities	12	0.07	
Humerus	18	0.11	
Upper extremities	9	0.06	
Other	2	0.01	
Intracranial injury or hemorrhage	19	0.12	42.1
Miscellaneous ^c	140	0.87	3.6
TOTAL	305	1.89	6.6

From Wallace *et al.*³⁰^a Incidence per 1000 live births^b Neonatal mortality rate^c Includes contusions, abrasions, bruises, hematomas, lacerations, etc

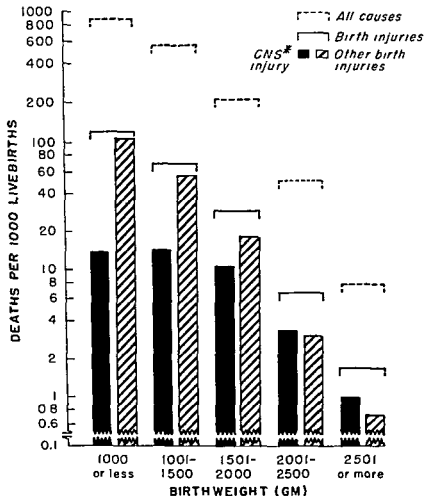


FIG. 18-1. Neonatal mortality rates (per 1000 live births) for all causes and birth injuries, by birth weight, United States, early 1950. *CNS = intracranial and spinal injury at birth. (Adapted from U.S. National Office of Vital Statistics: Relation of weight at birth to cause of death and age at death in the neonatal period; United States, early 1950. *Vital Statistics—Special Reports* 39: [No. 6], 1956.)

It is obvious that the shortcomings of "cause of death" diagnoses on death certificates and the classification of all intracranial hemorrhages in a single category limit sharply the interpretations which can be made of these data.

CAUSES

Traumatic birth injuries are related to a variety of factors associated with labor and delivery. A single injury or several injuries may occur in combination (to the



FIG. 18-2. Massive intraventricular hemorrhage in a premature infant. Note blood clot forming a cast of the lateral ventricle. (Case of Institute of Pathology, University of Geneva, Switzerland. Courtesy of William A. Blanc, M.D., Babies Hospital, New York.)

skin, subcutaneous tissues, bones, nervous system, and viscera). Since some of these injuries affect the infant's welfare and others are of slight importance they will be referred to as major and minor injuries.

Premature infants are particularly prone to certain types of birth injury because of the fragility of the various body structures which make them more liable to injury from slight trauma (see Chap. 8), the relative frequency of breech presentation, and the shortness of labor and the rapidity of expulsion from the birth canal.

In this discussion only those birth injuries will be discussed for which there is some evidence that they are particularly common among premature infants.

INTRACRANIAL HEMORRHAGE

Predisposing Factors

Hemorrhages from veins in the subependymal area with subsequent rupture into the ventricle (Fig. 18-2) are the most frequently occurring types of intracranial bleeding in premature infants. Gruenwald¹⁴ observed single or multiple areas of hemorrhage in the subependymal tissue that were not regularly connected with large vessels in the area, and, in agreement with earlier observers, felt that this appearance argued strongly against mechanical trauma as a cause. He studied the histologic appearance of intracerebral blood vessels of premature infants and observed that the subependymal veins had thinner walls than veins in the differentiated white matter. Gruenwald¹⁴ suggested this structural weakness as the basis for the predisposition of subependymal veins to rupture more easily than those in other parts of the brain when the pressure in the lumen rises. He noted that undifferentiated subependymal tissue is particularly abundant and well vascularized over the surface of the caudate nuclei, a frequent site of hemorrhage. The close relationship to the vein of Galen via the terminal veins was considered to be a factor which exposed the veins in this area to unusually high back-pressure.

Role of Asphyxia. Grontoft reached conclusions similar to those of Gruenwald concerning the mechanism of production of this type of hemorrhage. He considered that asphyxial venous stasis plays an important causal role. He produced venous stasis experimentally and observed hemorrhages which were similar to those found in a group of asphyxiated infants.

Classification

On the basis of these considerations intracranial hemorrhages in newborn infants may be divided into two major categories, those produced by mechanical trauma and those initiated by asphyxia (anoxia).

In both categories hemorrhages into the meningeal spaces, with rare exceptions, come from veins. In the traumatic group subdural hemorrhages are found with or without visible tears of the dura (Fig. 18-3). Asphyxial (anoxic) intracranial hemorrhages are generally found in the ventricular and subarachnoid spaces (see Fig. 18-3).

Incidence

Postmortem Estimates. Haller's group reviewed the cases of brain hemorrhage in 1043 premature and term infants whose death occurred in the perinatal

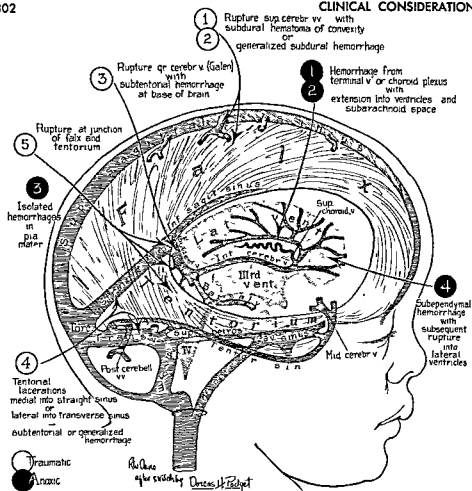


FIG. 18-3 Intracranial dural and venous relationships showing frequent sites of injury and common sources of hemorrhage in newborn infants. Traumatic lesions are indicated by black numbers on white and asphyxial (anoxic) lesions are shown by white numbers on black. (From Haller, E. S., Nesbitt, R. E. L., Jr., and Anderson, G.W.: Clinical and pathologic concepts of gross intracranial hemorrhage in perinatal mortality. *Obst. & Gynec. Surv.* 11:179, 1956.)

period The study was made during a 13-year period (from 1937 to 1949). The total number of deaths with intracranial hemorrhage (94 cases) were almost equally divided between premature and term infants. The distribution of types of hemorrhages was quite different however (Table 18-3); most of the hemorrhages in term infants were traumatic (41/50), but in the premature group two-thirds were classified as anoxic (29/44). Similar distributions were observed by Grøntoft (Fig. 18-4) and by others.^{1, 5, 6, 14, 26}

Haller's group noted a reduction in the incidence of deaths from traumatic brain hemorrhage among term infants in the more recent years of their study, but

TABLE 18-3 DISTRIBUTION OF BIRTHS, DEATHS, AND TYPES OF INTRACRANIAL HEMORRHAGE BY BIRTH WEIGHT

	<i>Birth weight (Gm)</i>			<i>Total under 2500</i>	<i>Term (2500 Gm. and over)</i>
	<i>1000-1499</i>	<i>1500-1999</i>	<i>2000-2499</i>		
Number of births	350	639	2,019	3,008	23,768
Total deaths	207	190	169	566	477
Intracranial hemorrhage	18	10	16	44*	50 ^b
Traumatic hemorrhage	6	5	4	15	41
Tentorial tear	0	1	0	1	8
Falx tear	0	0	0	0	2
Falx and tentorial tear	0	0	1	1	1
Subdural without tear	6	4	3	13	30
Anoxic hemorrhage	12	5	12	29	9
Ventricular only	4	0	2	6	0
Ventricular and subarachnoid	2	1	3	6	3
Subarachnoid only	6	4	7	17	6

From Haller *et al*¹⁵

*Including 5 stillbirths

^bIncluding 15 stillbirths

deaths associated with traumatic and with anoxic brain hemorrhages did not occur less frequently among premature infants during the same period.

Total Incidence. The over-all incidence of intracranial hemorrhage in premature infants is not known, since all who die are not examined postmortem and since the diagnosis in survivors cannot be established with certainty. From the relatively high incidence of brain damage among the survivors of premature delivery (see Chap. 5) it is reasonable to assume that most estimates¹⁷ are too low.

Clinical Diagnosis

The diagnosis of intracranial hemorrhage in premature infants in the early neonatal period is especially difficult because the symptoms and signs are usually not specific; moreover, in most instances cerebral hemorrhage is not the sole disorder.

History. Gröntoft reviewed the clinical histories of infants with intracranial hemorrhage and noted that in contrast to the traumatic group, those infants with asphyxial hemorrhages were more frequently premature, less frequently stillborn, had longer survival times, and had mothers under the age of 30. Foot and breech

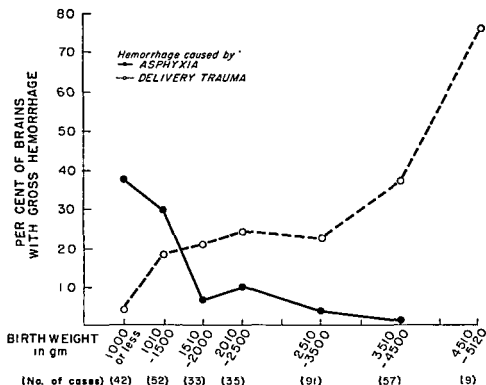


FIG. 18-4. Frequency of occurrence of intracranial hemorrhages caused by asphyxia and delivery trauma, by birth weight in 319 autopsies. Asphyxial hemorrhages comprised 43 cases (hemorrhage from terminal vein, 27; choroid plexus, 1; in the parenchyma, 3; and circumscribed hemorrhage in the leptomeninges, 12); 77 cases with subdural hemorrhage were classified as traumatic (tentorial tear with severe hemorrhage, 38; with slight hemorrhage, 25; with hemorrhage occurring after fetal death, 9; and hemorrhage without tentorial tear, 5). (Redrawn from Gräntoft, O.: Intracranial haemorrhage and blood-brain barrier problems in the new-born: A pathologico-anatomical and experimental investigation. *Acta path. et microbial. scandinav.*, Suppl. 100, 1954.)

presentations, use of forceps for delivery, and toxemia in the mother were less frequent in the asphyxial group.

Signs. Haller *et al.* found it difficult to differentiate the two major types of brain hemorrhage on the basis of clinical observations. In general the infants in the anoxic group were found to be in better condition at birth and to exhibit less initial apnea. These authors stressed the following clinical signs of intracranial hemorrhage:

- 1 Apathy or restlessness.
- 2 Cyanosis or pallor.
- 3 Bulging fontanelles
- 4 Convulsions or twitching tremors

5. *Difficult resuscitation.*
6. *Feeble, high-pitched cry.*
7. *Irregular breathing.*
8. *Unequal pupils or nystagmus.*
9. *Poor nursing or refusal to nurse.*
10. *Vomiting*
11. *Rapid or slow pulse rate.*
12. *Exaggerated or absent Moro reflex.*
13. *Presence of altered blood in the spinal fluid*
14. *Paralysis*

Cerebrospinal-Fluid Findings. The difficulty in establishing a diagnosis of intracranial hemorrhage on the basis of changes in the cerebrospinal fluid in premature infants was discussed in detail by Otila. He pointed out that xanthochromia, elevated protein content, and increased cells are observed frequently in the spinal fluid of asymptomatic premature infants (see Appendix 10). The findings may reflect a high incidence of small hemorrhages in these infants; however, the practical problem of distinguishing a clinically significant cerebral hemorrhage usually is not resolved by examining the cerebrospinal fluid.

Hematocrit Determinations. Blanc *et al.* obtained serial (micro) hematocrit determinations in a group of premature infants and demonstrated a significant association between a sudden drop in the hematocrit ratio during life and intraventricular hemorrhage at postmortem examination. The usefulness of this method of diagnosis is being evaluated in our nursery at the present time.

Early recognition of intracranial hemorrhage in live premature infants remains a serious problem for the clinician. Perhaps increased interest and improved diagnostic methods will improve this situation.²³

Treatment

Vitamin K Prophylaxis. Grøntoft reviewed the evidence concerning the influence of vitamin K prophylaxis (see Chap. 20) and concluded that, although the incidence of large hemorrhages over the convexity has been lowered, this prophylaxis has not changed the frequency of asphyxial hemorrhages. There is no evidence that vitamin K is effective in the treatment of existing intracranial hemorrhages.

Supportive Measures. Although supportive measures (warmth, elevation of the head, sedation, etc.) are advocated in the treatment of cerebral hemorrhage in premature infants there is little or no evidence that these measures are effective.

Lumbar Puncture. According to Matson lumbar puncture is indicated in the presence of a bulging fontanelle. If bloody fluid under pressure is demonstrated,

the pressure should be gradually reduced to normal levels by drainage of cerebrospinal fluid.

Other Measures. If the spinal fluid is clear or under normal pressure, if the fontanelle still bulges, or if there is no symptomatic relief after lumbar puncture, Matson advised that the subdural spaces should be punctured bilaterally. Emergency intracranial operative procedures to remove blood clots or stop bleeding in the newborn are not indicated.¹⁸

Massive intraventricular hemorrhage in premature infants resulting from asphyxial venous congestion presents a challenging and as yet unsolved problem in management

Prognosis

Intracranial hemorrhages are observed frequently in newborn premature infants who die, and clinical signs of localized brain damage are observed frequently in survivors (see Chap. 5); it is tempting to relate these two observations and to suggest that intracranial hemorrhage may be the leading cause of brain damage in premature infants. Clearly, much more evidence is needed before one can be certain about this point

SPINAL-CORD AND PERIPHERAL-NERVE INJURY

Injuries to the spinal cord and peripheral nerves as the result of mechanical trauma are observed more commonly in large than in small infants. The reader is referred to other sources for a discussion of these problems.^{7, 8, 32}

VISCERAL INJURIES

Among premature infants who die in the neonatal period, injuries of the liver and adrenal glands are observed more frequently than injuries of other internal organs.^{10, 21}

Hepatic Hemorrhage

Although the diagnosis of rupture of the liver is rarely made during life, there are occasional case reports of infants successfully treated during the neonatal period. The fairly extensive literature on the subject of hepatic hemorrhage in the newborn infant has been reviewed by several authors in the past few years.^{5, 13, 31} There is general agreement that this entity occurs more frequently among premature and very large infants than in average-size newborns.

Cause. Injury to the liver may occur as the result of trauma from compression of the chest or abdomen¹³ during and after delivery.

Clinical Course. An asymptomatic interval of one to seven days has been described which probably corresponds to a first (subcapsular) stage of hemorrhage. In rare instances the capsule is torn by the original trauma, and as a result these infants die very promptly.

After a symptom-free interval the hematoma may rupture, at which time the infant suddenly becomes pale and limp. There is often abdominal distention and the liver is found to be enlarged on palpation. Blood obtained on abdominal paracentesis establishes the diagnosis.

Treatment. Prompt transfusion and laparotomy are indicated.

Adrenal Hemorrhage

Associated Conditions. Adrenal hemorrhage (Fig. 18-5) is seen at postmortem examination most often in infants delivered from a breech position. It is gen-



FIG. 18-5. Rupture of both adrenal glands with massive hemorrhages (breech delivery). (Courtesy of John L. Parks, M.D., and the late Lewis K. Sweet, M.D., Washington, D.C.)

crally thought to be the result of trauma inflicted on the fetal abdomen during delivery of the head²¹

Hemorrhage into the adrenal gland is also found relatively frequently in premature infants^{4, 24} and in infants who succumb with other conditions in the neonatal period (infection, intracranial hemorrhage, etc.).

Clinical Findings. An antemortem diagnosis is rarely made. Snelling and Erb reviewed the clinical findings in infants who died with adrenal hemorrhage and found that the signs were not specific (collapse, cyanosis, irregular respirations, etc.). Palpation of a mass in one or both flanks is probably the most important physical sign.

Adrenal Calcification. Not all infants with hemorrhage into the adrenal gland die. It is possible to identify some of the survivors by roentgenography, since calcification may occur in as short a period as 10 days²⁴ Jarvis and Seaman collected 26 examples of adrenal calcification in infants and children which were discovered either in roentgenograms during life or at postmortem examination, six of these children were premature (birth weight 2500 Gm or less).

Rupture of the Stomach

Causes. Although rupture of the stomach is classified here as a birth injury, only a small proportion of the cases are caused by mechanical birth trauma. For a complete discussion of the various causes of rupture of the stomach the reader is referred to several reviews of the subject^{9, 25, 27}

In our hospital, over a 12-year period²⁹ 11 cases of perforation of the stomach in newborn infants were seen. Six of these infants were prematurely born. In three cases among the premature infants the rupture was thought to be due to trauma from an unblunted polyethylene feeding catheter, in two to congenital defect of the muscular coat, and in one to ulceration of the stomach associated with sepsis.

Clinical Manifestations. The clinical picture of rupture of the stomach is so characteristic that there should be little difficulty or delay in establishing the diagnosis. The infant usually appears well at birth and for several days thereafter. Occasionally refusal to feed may be a heralding sign of rupture, but the sudden appearance of marked abdominal distention is the usual and most striking clue. Dyspnea and cyanosis soon follow. Examination reveals a tense, tympanitic abdomen. A plain upright roentgenogram of the abdomen (Fig. 18-6) establishes the diagnosis.

Treatment. Prompt surgical correction is indicated.



FIG. 18-6. Subdiaphragmatic collection of air following perforation of the stomach, visible in an upright anteroposterior plain roentgenogram. (Courtesy of Thomas V. Santulli, M.D., Babies Hospital, New York.)

Intestinal Perforations

Perforations at all levels of the gastrointestinal tract have been described in newborn infants; some perforations probably occur in utero.^{11, 22} Premature infants are not especially subject to these lesions.

MINOR INJURIES

Injuries to the skin and subcutaneous tissues such as abrasions, lacerations, localized edema, and hemorrhage due to pressure in the birth canal or from forceps may be classified as "minor" in contrast to those previously discussed.

Pressure Injuries of Breech Delivery

In frank breech deliveries the skin may be bruised by the pressure of the operator's fingers. Sudden or prolonged changes in pressure exerted on the presenting part may cause edema of, or extravasation of blood into, the tissues around the rectum and the labia or scrotum. Less marked pressure changes may cause merely edema, particularly of the scrotum. Extensive hemorrhage may cause serious injury of the testicles and scrotum during breech delivery.

Fractures

Bone injury probably occurs infrequently in premature infants because of the relative ease with which they are delivered.

We have observed multiple fractures of the ribs in an infant whose chest was squeezed in an attempt to initiate respirations.

PREVENTION OF BIRTH INJURIES

Descriptions of recommended techniques for the conduct of premature labor to minimize birth injury are found in the obstetric literature, and the reader is referred to these sources for full discussions (see also Chap. 6).

Although administration of vitamin K to women in premature labor was at one time advocated as a means of preventing hemorrhagic disorders in the infant, it has been demonstrated (see Chap. 6) that this is not more effective than vitamin K given only to the infant after birth.

Minkowski advocated that women in premature labor receive vitamin E to prevent cerebral hemorrhage in the offspring. This suggestion has not been subjected to a critical trial.

Mechanical trauma (squeezing the abdomen, compressing the chest, etc.)

should be avoided during resuscitation. The influence of prompt and effective resuscitative measures on the incidence of asphyxial cerebral hemorrhages in premature infants is of considerable current interest but this has not been evaluated.

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Infection

The distinction between infection and disease, which is so difficult to delineate in other subjects, is particularly confusing in the case of the prematurely born infant. Considerable disagreement exists concerning the role of infections as a cause of death in small infants who are examined postmortem, and the diagnoses are very often in doubt among the living. Despite the uncertainty which surrounds this topic there is more or less general agreement that premature infants are unusually susceptible to infection, disseminated infection is a frequent primary cause of death ²² (See also Chaps 7, 9, and 10.)

SUSCEPTIBILITY AND RESISTANCE

The defects in resistance to infections which exist in premature infants are incompletely understood. A brief review will be given of some studies which have been made of this subject.

Circulating Antibody

Gamma Globulin Concentration. The concentration of gamma globulin in the serum increases during fetal development;¹¹¹ at birth the concentration is lowest in individuals with the lowest birth weight (see Appendix 10). The infant is unable to synthesize appreciable amounts of gamma globulin during the first few weeks of life and the level in the plasma falls, reaching about one third of the birth value at one month of age ^{84, 120} *The level remains essentially unchanged between one and three months of age, when the rate of synthesis of gamma globulin equals that of catabolism. During this period of hypogammaglobulinemia premature infants reach levels of about 90 to 210 mg. per 100 ml.;¹¹⁸ term infants fall to a low of about 140 to 450 mg. per 100 ml.¹²⁰*

In this connection Janeway and Gitlin observed that individuals with congenital agammaglobulinemia appear to remain free of serious bacterial infections when the concentration of circulating gamma globulin is kept above 100 to 150 mg. per 100 ml.

Good found that premature infants begin to synthesize gamma globulin after

a postnatal delay period that is the same or even shorter than that of term infants.

Bacteriostatic Activity of Serum. Dancis and Kunz³¹ tested the bacteriostatic activity of the serum of young infants in vitro. During the first month of life, a higher proportion of the sera of premature as compared with term infants was unable to inhibit the growth of a test organism. It was shown that this defect was related to low levels of gamma globulin rather than to deficient complement activity.

Response to Immunization. In agreement with an earlier study,¹⁵⁷ Dancis and co-workers³² demonstrated that the antibody response of a group of premature infants who received an injection of diphtheria toxoid at birth was slightly but not significantly lower than that of term controls. When the premature subjects received an injection at a time estimated to be their normal birth date, they exhibited a response that was greater than that of term infants immunized at birth but not superior to that of term infants immunized at one month of age.

These studies indicate that when compared with term infants the prematurely born individual receives a smaller endowment of antibody from his mother but has, if anything, only a slight handicap with respect to the ability to form antibody in response to an adequate stimulus. The extent to which these differences account for the high incidence of infection in premature infants as compared with term subjects has not been determined.

Plasma Cells. In Young Infants. Good reported that plasma cells (which probably synthesize antibodies)⁴⁹ make their appearance in the bone marrow of young infants at two or three months of age, while in the presence of infection they appear as early as the third week of life.

Observations in Experimental Animals. Dixon's observations in experimental animals indicated that the environment provided by the neonate influences antibody production. When appropriately sensitized lymph node cells from adult animals were transferred to newborn recipients, they produced antibody poorly. Cells from neonatal animals were, however, capable of making antibody better when transferred to an adult. Dixon suggested that lymphocytes cannot be transformed into plasma cells in a neonatal animal. The nature of the defect responsible for this inadequacy could not be identified, but there was evidence that the environment in the newborn animal could be favorably influenced by the transfer of large numbers of adult normal lymph node cells.

Phagocytic Ability of Leukocytes

Gluck demonstrated that the leukocytes of premature infants exhibited significantly less phagocytic ability than did those of term controls and adults; phago-

cytosis approached adult propensities with increasing birth weight. The addition of fresh adult serum *in vitro* enhanced the phagocytic activity of the leukocytes of premature infants. The phagocytosis-inducing factors in the serum were identified in the fractions containing the alpha and beta globulins.^{70, 156}

Localization of Infection

It is well known that newborn infants (and neonatal animals)⁶² frequently fail to localize bacterial and certain viral infections, but the defects responsible for this characteristic are not accurately known

Other Factors

In addition to undoubted other deficiencies^{42, 103} premature infants suffer from certain handicaps which are circumstantial. The mothers of premature infants often have received little or no antenatal care. These women have a relatively high incidence of complications of pregnancy, including infections and premature rupture of membranes. As compared with term infants, premature infants remain in the hospital for relatively long periods of time and therefore are at greater risk with respect to exposure to hospital infections.

INCIDENCE

There is no way of accurately estimating the "usual" incidence of infections among premature infants, principally because of the inherent difficulty in establishing a diagnosis. In addition the number of manifest infections in any nursery waxes and wanes with the passage of time.

On the basis of crude observations we are aware of continuous fluctuations in the incidence in our nursery ranging from interludes of virtual freedom from infections to small outbreaks that are very alarming. Major epidemics due to bacterial and viral agents are, of course, not uncommon in nurseries for premature infants.

The distribution of infections encountered in two premature nurseries widely separated from one another is presented in Table 19-1.

INTRAUTERINE INFECTION

A variety of infectious agents may be transmitted to the fetus through the placenta. Potter¹²⁶ commented that the protective function of the villous surface has been greatly overrated, since it is probable that most bacteria, viruses, or parasites in the general circulation of the mother can pass the placental barrier

TABLE 19-1 APPROXIMATE DISTRIBUTION OF INFECTIONS
IN TWO PREMATURE NURSERIES

	I ^a	II ^b
Total admissions	362	174
Total infections	86	62
	% of infections	
Respiratory		80
Pneumonia	14	
Upper respiratory	5	
Intestinal infection	2	10
Skin and eyes		10
Pyoderma	2	
Conjunctivitis	13	
Omphalitis	4	
Other		
Major ^c	3	
Minor ^d	57	
TOTAL	100	100

Adapted from Hardymen⁷³ and Kasanen⁸⁸^a Premature nursery, Vancouver General Hospital, 1956-57, 266 premature infants and 96 larger infants admitted for special care^b Premature nursery, Children's Clinic of the University of Turku, Finland, 1951-53, 362 premature infants, largely but not exclusively intra-mural.^c Septicemia, meningitis^d Candidiasis, lymphadenopathy, pyrexia of unknown origin, infected cut down wound.

and enter the fetal circulation. Some of the intrauterine infections which are important in premature infants will be discussed.

SYPHILIS

In recent years the incidence of florid congenital syphilis has decreased so markedly that many newly trained physicians in this country have never seen a case. The reduction is in great part due to the success of public-health measures to detect and treat syphilitic women during pregnancy (see Chap. 3). The outlook for the infant is related to the time of infection in utero, the adequacy of the treatment of the mother, and the adequacy of treatment after birth.

It is obviously important to determine for an infant born of a syphilitic mother, treated or untreated, whether there are indications that he should be

treated for syphilis. The importance of making a definite diagnosis in the infant cannot be overemphasized

Diagnosis

The diagnostic criteria for syphilis in premature infants differ in no way from those used for the diagnosis in term infants

History. A history of maternal syphilis, previous pregnancies resulting in stillbirths or premature births, and the birth of previous syphilitic infants are suggestive of the presence of syphilis

Clinical Criteria. The clinical features of early congenital syphilis most commonly encountered¹²⁵ are arranged in Table 19-2 in order of frequency. Jaundice and hemorrhages into the skin and from mucous membranes can also be added

TABLE 19-2. FEATURES MOST COMMONLY ENCOUNTERED IN
UNTREATED EARLY MANIFEST CONGENITAL SYPHILIS

<i>Feature*</i>	<i>% of cases with manifestation</i>
Osseous lesions	76
Cerebrospinal-fluid abnormalities	64
Rhinitis	60
Eruptions	58
Anemia	52
Generalized glandular enlargement	47
Hepatomegaly	44
Malnutrition	40
Splenomegaly	37
Pseudoparalysis	14

From Platon¹²⁵

* Not all are necessarily specific for syphilis

to this list. None of these criteria is alone pathognomonic of syphilis and any of them may occur in other infections; the presence of other criteria is required, such as roentgenologic or serologic evidence.

Dark-Field Examination. The diagnosis of congenital syphilis can be established directly by the demonstration of spirochetes in tissue fluid collected from lesions of mucous membranes or from abraded skin lesions.

Roentgenography. The diagnosis of syphilis from roentgenograms of the bones of the newborn premature infant is difficult unless the lesions are characteristic and multiple at the growing ends of the bones, and unless there are

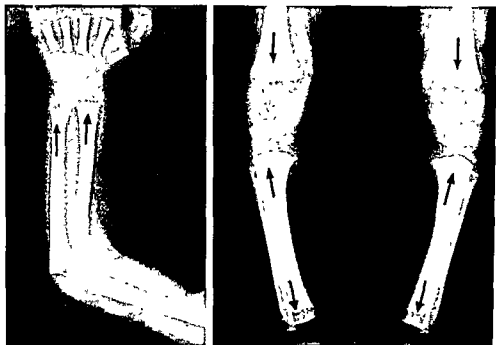


FIG. 19-1. Syphilitic metaphysitis in a premature infant one month of age. In each affected bone the deep terminal layer of spongiosa in the metaphysis is destroyed; this results in a uniform band of diminished density extending the full width of the shaft. (Courtesy of John Caffey, M.D., Babies Hospital, New York.)

evidences of bone destruction as well as increased calcium deposition. Non-specific changes, including double contours and a cupped and spurred appearance of the epiphyseal line, have been described in the long bones of healthy premature infants.^{68, 74}

Figure 19-1 shows the earliest roentgenographic signs of bone syphilis in a premature infant one month of age. Other changes (not shown in this illustration) may be periostitis, fine serration of the epiphyseal line, and in severe cases destructive lesions occurring near the ends of the bones—frequently on the median surface of the tibia near the knee (osteochondritis)

Serologic Diagnosis. Positive reactions for syphilis in the infant's blood in the first month or two of life are not necessarily evidence of syphilitic infection of the infant because the specific antibodies circulating in the infant's blood may be maternal antibodies transmitted through the placenta. Serologic tests for syphilis (STS) employing both flocculation and complement-fixation techniques can be quantitated, and serial tests to demonstrate a progressive fall or rise in titer must be performed to distinguish between passive transfer and actual infection. Platou estimated that at least 40 per cent of newborn infants who have

positive STS are not syphilitic, and practically all of these become seronegative by the age of three months; rarely the tests remain positive for as long as five or six months.

The treponema immobilization test (TPI) is useful in the study of false-positive reactions. It has been infrequently employed in infants and children because it is a technically difficult test and can be performed in relatively few laboratories.¹²⁵

Treatment of the Infant

Indications. Indications for giving antisyphilitic treatment to a premature infant are:

1. Evidence that the mother has syphilis and has been untreated or very inadequately treated.
2. A positive, quantitative, specific blood reaction, the titer of which increases or fails to decrease on repeated tests.
3. Roentgenographic evidences of osteochondritis or periostitis combined with (a) history, (b) positive serology on repeated quantitative tests, or (c) clinical evidences of syphilis.
4. Classical signs of syphilis with a positive blood reaction or positive roentgenogram.

Platou advises that when there is reasonable suspicion of congenital syphilis, premature infants may be better treated than exposed to the risks involved in the delay for absolute proof.

Supportive Treatment. It is important to realize that supportive measures, including maintenance of body fluids and nutrition and appropriate treatment of complicating infections, are often necessary in addition to the specific consideration of eliminating the spirochete.

Penicillin. The treatment of the premature infant should consist of a total dosage of 100,000 units or more of penicillin per kg. of body weight distributed over a period of eight or more days. A regimen which has been satisfactory in Platou's experience consists of 150,000 units of repository penicillin daily by intramuscular injection for 10 days in infants up to two years of age; this usually exceeds a total dosage of 100,000 units per kg.

The significance and frequency of reactions to penicillin therapy (Herxheimer reaction) is still controversial. On the basis of the fear that these may be serious in premature and debilitated infants it is occasionally suggested that therapy be started with very small doses of penicillin.¹¹² This view has gained little support in the course of time.

Follow-up of Treated Infants

Recovery. The results of postnatal penicillin therapy of syphilitic infants have been considered satisfactory in nearly 90 per cent of all infants treated before 3 months of age.^{72, 125}

During the first month after treatment about 10 per cent become seronegative. At 6, 18, and 24 months the proportions with negative STS are about 50 per cent, 80 per cent, and nearly 95 per cent respectively.¹²⁵

Relapse. Relapse has occurred in approximately 6 per cent of the patients, usually between 3 and 10 months following completion of therapy; infants with relapses have responded satisfactorily to retreatment with penicillin.

Mortality. Between 5 and 10 per cent of infants die either during or within 6 months of the start of treatment.^{72, 125}

Prevention of Congenital Syphilis

Early antenatal care, including a serologic test for syphilis and adequate treatment of infected women, will not only prevent infection of the fetus but also will reduce the incidence of premature birth (see Chap. 3). It is obvious that not only must access to antenatal clinics and treatment centers be made easily available but also public-health and welfare agencies must make cooperative efforts in the finding and follow-up of cases. In addition a program for education of the public in regard to the importance of early and continuous antenatal care must be one that is constantly in action.

That more intensive efforts should be made to prevent congenital syphilis is shown by studies made in two large metropolitan areas. According to one report¹⁶² the 14,599 live-birth certificates recorded in New York City in May, 1951, showed that only 42 per cent of the expectant mothers made the first antepartum visit during the first trimester and only 34 per cent received a serologic test for syphilis in the first trimester. Another study⁵⁶ showed that among 1005 women who entered Boston City Hospital in 1951 for delivery, 169 (16.8 per cent) reported that they had had no antenatal care. All of these 1005 women were given serologic tests for syphilis within 48 hours of delivery and 24 were found to be infected. Eight of these 24 women had had no antenatal care.

CONGENITAL TOXOPLASMOSIS

The first examples of proved human infection with *Toxoplasma gondii* were of the congenital form of this disease.¹⁷² Since this first description there have been innumerable studies of the manifestations of toxoplasmosis in humans and

animals. The reader is referred to recent reviews of the extensive literature on this subject.^{28, 41, 52}

Mode of Infection

In the majority of cases mothers of affected infants have been healthy with no history of illness prior to or during the pregnancy. It is presumed that the placenta and subsequently the fetus become infected as the result of parasitemia during the course of an unapparent initial infection acquired during the pregnancy. On the basis of the available evidence, Feldman⁵² suggested that infections acquired after the first trimester are more likely to spread to the fetus than those acquired just before or soon after the onset of pregnancy. Among 141 infants with congenital toxoplasmosis collected by him, 29 per cent were born prematurely.

Diagnosis

Clinical Manifestations. At the time of birth the clinical condition of the infant with congenital toxoplasmosis varies between the extremes of stillbirth to that of an outwardly normal newborn infant. The frequency with which certain recognizable evidences of active infection have occurred in reported cases is summarized in Table 19-3. Jaundice, hepatomegaly, splenomegaly, maculopapular eruption, purpura, and fever also occur. Occasionally routine examination of the ocular fundi of premature infants (see Chap. 9) discloses evidence of unsuspected infections.

TABLE 19-3 FREQUENCY WITH WHICH CLINICAL MANIFESTATIONS WERE REPORTED IN COLLECTED CASES OF CONGENITAL TOXOPLASMOSIS

<i>Manifestation</i>	<i>Total no. cases*</i>	<i>% of cases with manifestation</i>
Chorioretinitis	150	94
Cerebral calcification	158	59
Psychomotor retardation	142	45
Convulsions	131	39
Microphthalmia	135	36
Hydrocephalus	147	22
Microcephalus	150	21

From Feldman.⁵²

*Case reports from which the presence or absence of the manifestation could be determined.

Laboratory Findings. A stained smear of the sediment from the cerebrospinal fluid may reveal the parasite. It is often possible to isolate the protozoa by injecting infected sediment into laboratory-reared mice.

The Sabin-Feldman dye test is the most sensitive and specific of the various serologic methods available for the diagnosis of toxoplasmosis. In active infection the dye-test antibody titers in the sera of the mother and her infant are high at birth, usually more than 1:1000.⁵² Transplacental transfer of antibodies does occur, and as a consequence a false positive dye-test in the infant is possible. Whenever there is doubt the test should be repeated after several months, since in the unaffected infant the passively acquired antibody would be expected to largely disappear.

The complement-fixation test may be negative in the infected newborn infant even in the presence of a high maternal titer of complement-fixing antibodies.

Prognosis

The outlook for cure of infants with congenital toxoplasmosis is poor, although several have survived for years. The prognosis in subsequent pregnancies is unimpaired, no instance has been reported of a second case of congenital toxoplasmosis in the offspring of an individual mother.

Treatment

Sulfonamides (principally sulfadiazine, sulfamethazine, and sulfamerazine) and pyrimethamine (a folic-acid antagonist) have been shown to act synergistically against toxoplasmosis in laboratory animals and in acquired forms of human toxoplasmosis.⁴⁸ The efficacy and safety of the sulfonamide-pyrimethamine combination in the treatment of active congenital toxoplasmosis has not been established.

Sum recommended that when pregnant women exhibit inexplicable fever, lymphadenopathy, and fatigue they should be carefully examined for the possibility of acquired toxoplasmosis. However, there would be some hesitancy in the use of pyrimethamine for the antenatal treatment of toxoplasmosis, because another folic-acid antagonist (4-amino-pteroylglutamic acid) has been observed to have an abortifacient and teratogenic effect in humans.¹⁵²

CYTOMEGALIC INCLUSION DISEASE

The disseminated form of cytomegalic inclusion disease acquired in utero was, until recently, recognized only at the time of autopsy in infants who were still-

TABLE 19-4 CLINICAL CHARACTERISTICS OF 42 NEWBORN INFANTS
WHO WERE ASSUMED TO HAVE DIED OF GENERALIZED
CYTOMEGALIC INCLUSION DISEASE

<i>Clinical characteristics</i>	<i>% of infants</i>
Hemorrhagic diathesis	74
Jaundice	71
Enlargement of the liver and the spleen or both	62
Prematurity	55
CNS disease	38

From Medearis ¹⁰¹

born or died shortly after birth.¹⁴¹ The clinical diagnosis is now being made with increasing accuracy during life and, contrary to previous opinion, survivors are not rare

Mode of Infection

This condition results from a generalized infection with an agent which is either identical or closely related to human salivary-gland virus.¹⁴⁰⁻¹⁶⁸ The virus is placentally transmitted from an apparently healthy mother.¹²⁷ The available evidence indicates that subsequent pregnancies are not affected.¹⁴ In a recent review, Medearis noted that more than half of the reported newborn infants with generalized cytomegalic inclusion disease were classified as premature.

Diagnosis

Early Clinical Signs. The clinical manifestations in newborn infants with cytomegalic inclusion disease resemble those of erythroblastosis fetalis, congenital toxoplasmosis, syphilis, or neonatal sepsis. Medearis described the usual features in 42 cases (Table 19-4); these included prematurity, early jaundice, hepatosplenomegaly, petechiae, lethargy, and respiratory distress

Laboratory Findings. The hemogram usually reveals anemia and thrombocytopenia. Exfoliated inclusion-bearing epithelial cells (Fig. 19-2) may be found in urinary sediment,⁵³ gastric washings,¹⁵ and cerebrospinal fluid.¹⁰⁴

Roentgenograms of the skull may reveal periventricular calcification that is quite different from the irregular distribution of calcification in toxoplasmic encephalomyelitis.⁷⁷ However, this distinctive pattern may not persist in infants who survive.⁷³

Human salivary-gland virus produces characteristic intranuclear inclusion



FIG. 19-2. Characteristic "owl-eye"¹⁰⁴ cells of cytomegalic inclusion disease. (Left) A cytomegalic cell in the urinary sediment. The huge cell probably originated in the lower part of the collecting tubules; it contains a basophilic intranuclear inclusion body surrounded by a clear halo which separates it from the nuclear membrane. A normal desquamated renal tubular cell is shown at the lower left. (Right) Cytomegalic cell and two normal cells from the gastric mucosa in the sediment from a gastric washing. (Hematoxylin and eosin, $\times 782$). (Courtesy of William A. Blanc, M.D., Babies Hospital, New York.)

bodies in human fibroblasts maintained in tissue culture. This method of virus detection may be applied to urine and other body fluids.¹³³

Late Manifestations and Prognosis. Newborn premature infants with generalized cytomegalic inclusion disease usually die early in the neonatal period. Those who survive commonly exhibit signs of severe brain damage (e.g., progressive hydrocephalus, microcephaly, hydranencephaly, etc.). However, complete recovery without residua is apparently possible.^{14 100}

Burns described the ocular findings in a premature infant with cytomegalic inclusion disease who developed chorioretinitis at the age of 42 days. He pointed out that the retinal lesions were multiple, were present in the periphery of the eye, and showed less tissue destruction than in chorioretinitis due to toxoplasmosis.

Pulmonary forms of cytomegalic inclusion disease (interstitial pneumonia, bronchopneumonia, etc.) have been described in children who had passed the neonatal period.⁶⁴

Treatment

No specific treatment for cytomegalic inclusion disease is available. Cortisone (or prednisone),^{14, 106, 160} gamma globulin,¹⁰⁶ and exchange transfusion¹⁴ have been used for the treatment of this condition. At the present time there is no convincing evidence that the course of the disease can be altered.

OTHER INFECTIONS

Common Infectious Diseases. A number of viral infections including measles,⁸⁵ varicella,⁶¹ poliomyelitis,¹⁷⁰ herpes zoster,⁵¹ equine encephalomyelitis,¹⁰⁸ and Coxsackie virus infection^{11, 90, 148} may on occasion be transmitted from mother to fetus. Although these infections may be associated with premature delivery the clinical picture in the premature infant is not unique. The reader is referred to other sources for descriptions and full discussions of this subject^{18, 127, 171}

Tuberculosis. Tuberculosis is in rare instances transmitted to the fetus in utero.⁸²

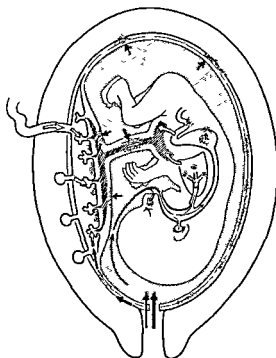
INTRAPARTUM INFECTION

AMNIOTIC INFECTION

Mode of Infection

The fetus can be infected as the result of an infection of the amniotic sac. The routes of infection of the amniotic fluid and the fetus are depicted in Figure 19-3. The factors favoring invasion of the amniotic cavity with vaginal bacteria or fungi^{12, 24, 40} are premature rupture of membranes with long delay in the onset of labor, long labor, excessive manipulation, and a long period of dilation of the cervix even with intact membranes.

Role of Premature Rupture of Membranes. There is little agreement on the interval between rupture of the membranes and delivery that should be considered "prolonged" and considerable difference of opinion upon the significance of rupture of membranes before the onset of labor. Kjessler considered that rupture of the membranes 17 hours prior to the birth of the child was critical and classified periods greater than this as "long intervals." He concluded that it was not the long interval *per se* but this factor in combination with abnormally protracted labor and uterine inertia which accounted for congenital pneumonia. Eastman³⁸ found that when the membranes ruptured prematurely near term perinatal mortality increased after latent periods exceeding 48 hours; however, a prolonged latent period had no apparent influence on perinatal mortality in cases in which the infant was premature. Both authors observed a somewhat higher incidence of spontaneous rupture of membranes with prolonged latent period in pregnancies that terminated prematurely.



- ↑ Ascending amniotic infection
- ♀ Possible ways of contamination of fetal blood
- Fetal circulation

FIG. 19-3. Routes of infection in the amniotic-infection syndrome. The amniotic fluid may be contaminated by ascending infection through intact or ruptured membranes, hematogenous spread to placenta with secondary invasion of the fluid, or through the fallopian tube. Infected amniotic fluid is aspirated and swallowed and penetrates the respiratory and gastrointestinal tracts where bacteria may produce local inflammation and enter the fetal circulation. The fetal circulation can also be invaded by hematogenous spread from the placenta or from superficial chorionic vessels which have been invaded from infected amniotic fluid. (From Blanc, W. A: Amniotic infection syndrome: Pathogenesis, morphology, and significance in circumnatal mortality. *Clin. Obst. & Gynec.* 2:705, 1959.)

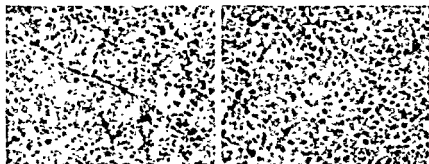


FIG. 19-4. Subamniotic accumulation of polymorphonuclear leukocytes in amnionitis as seen in a whole mount of the amnion. (Left) Photomicrograph focused at subamniotic level. (Right) Focus on the amniotic epithelium. The whole mount is prepared as follows: A square inch of amnion is taken from the placental surface in an area overlying chorionic vessels. It is dipped in 95% alcohol for one minute, floated in water, stained one minute in 1% aqueous cresyl violet, rinsed in water, and mounted on a slide. While held with a glass rod it is flooded with three successive rinses (20 seconds each) of absolute alcohol and two rinses of toluol and mounted in balsam. Care should be taken to mount the specimen with the amniotic epithelium in contact with the slide. (Courtesy of William A. Blanc, M.D., Babies Hospital, New York.)

Sites of Infection

The various fetal and maternal tissues that may be invaded include the intervillous tissue, chorion, amnion, umbilical cord, skin, conjunctiva, cornea, middle ear, mouth, nose, paranasal sinuses, respiratory tract, and gastrointestinal tract. Septicemia may be secondary to these local infections.

Not all fetuses exposed to contaminated amniotic fluid contract infections. Conversely, however, there is good evidence that pneumonia, otitis, gastroenteritis, meningitis, and sepsis may occur in utero and result in still-birth.^{8, 17, 97, 100, 124} In live-born infants many of the examples of infection which are detected in the first few days of life are the result of intrauterine infection

Diagnosis

Blanc¹⁶ showed that the diagnosis of amniotic infection could be established from smears of the chorionic surface of the amnion or from the gastric content obtained by gastric aspiration of the newborn infant's stomach (see Chap. 6) He has described a new method of examining the fetal adnexa (Fig. 19-4) Benirschke and Clifford¹⁰ proposed that frozen sections of the mid-portion of the umbilical cord be examined to determine the presence of umbilical vasculitis

Bacteriologic Findings. In amnionitis Blanc¹⁷ observed that the most common bacteria found on culture were *E. coli*, *Streptococcus fecalis*, nonhemolytic and hemolytic *Staphylococcus albus* and *aureus*. A similar distribution of bacteriologic findings was observed by Bowie in cultures of high-vaginal swabs from 400 patients with puerperal pyrexia.

Treatment

The treatment of intrauterine bacterial infections is hampered not only by the uncertainty of antenatal diagnoses but also by the paucity of data concerning the distribution of available drugs between mother and fetus. Page recently reviewed the subject of the transfer of materials across the human placenta. He emphasized that since almost any substance can cross the placenta, for a given substance the important considerations are the predominant mechanism of transport (i.e., diffusion, carrier systems, leakage through pores, or pinocytosis) and the rate of transfer. This information is not available for most antibiotic drugs.

Antenatal Administration of Antibacterial Drugs. Charles administered a single dose of antibiotic to parturient women at varying intervals before delivery. Samples of maternal blood, cord blood, and amniotic fluid were assayed for the

antibiotic by a microbiologic method. In a group of ten women who received 1,000,000 units of penicillin, therapeutic concentrations were reached in all three compartments. The concentration of penicillin in the amniotic fluid remained high long after the level in the maternal and cord blood fell. Charles believed that this phenomenon was due to rapid renal excretion of penicillin by the fetus; however, selective absorption by the amnion or an unexplained property of penicillin was also considered.

Other groups of ten women each received a single dose of streptomycin (1.0 Gm. intramuscularly), chloramphenicol (0.5 Gm. orally), tetracycline (0.5 Gm. orally), or oxytetracycline (0.5 Gm. orally). It was demonstrated that all these antibiotics reached therapeutic concentrations in the cord blood, although in each instance the levels were lower than in maternal blood. There is conflicting evidence concerning the concentration of these agents in amniotic fluid^{3, 35}

Speert demonstrated that the human placenta was permeable to sulfadiazine; equilibrium between maternal and fetal blood was established within two to three hours after a single intravenous dose of 0.5 Gm. The drug appeared in the amniotic fluid but more slowly than in the fetal blood. Ziai and Finland¹⁷⁵ administered a single dose (2.0 Gm.) of a long-acting sulfonamide (sulfamethoxypyridazine) to ten mothers in labor and demonstrated levels in umbilical-cord blood that approached those of the maternal blood within four hours. This was confirmed by Sparr and Pritchard, however, they noted that after delivery the rate of disappearance of sulfamethoxypyridazine from the newborn infant's serum was considerably slower than from maternal serum and that appreciable concentrations could be found as long as four days after delivery and five days after the administration of a single dose of 2.0 Gm. to the mother. They warned that in the presence of prematurity or erythroblastosis fetalis, administration of a long-acting sulfonamide to the mother before delivery might expose the newborn infant to the risk of kernicterus (see Chap. 13). Moreover, they found limited penetration of the sulfonamide into amniotic fluid and predicted that sulfamethoxypyridazine would have little value in maintaining bacteriostasis in the amniotic cavity following rupture of the membranes.

Therapeutic Trials. Smith and others¹³⁹ gave antibacterial therapy (streptomycin 1.0 Gm. twice each day and oxytetracycline 0.5 Gm. every 6 hours) to 69 mothers with presumed infection (antepartum fever), 68 concurrent controls with similar manifestations did not receive therapy. Five offspring of the treated women died, none of these infants had pneumonia; there were 10 infant deaths in the untreated group, 5 of the 10 had pneumonia. There was suggestive evidence that the perinatal death rate was lowered when the mother was treated for at least 48 hours before delivery. von Friesen conducted a controlled trial of the influence of the routine administration of sulfamerazine (1.0 Gm. per day) to

women in labor. The stillbirth rate was significantly higher in the control than in the prophylaxis group. This difference was attributed to the effect of sulfamerazine on intrauterine infection associated with prolonged labor, primary uterine inertia, and maternal fever.

Eastman³⁹ questioned the value of administering antibiotics to mothers during prolonged latent periods after premature rupture of membranes. He found that the perinatal mortality rate during a period when penicillin was given to mothers was not different from the rate observed before the discovery of penicillin. A trial using concurrent controls has not been reported.

Recommendations. At the present time there is considerable difference of opinion concerning the criteria that should be used to guide the use of antibiotics in the mother to protect the infant. Moreover, the most suitable agent, particularly when premature delivery is imminent, has not been determined.

It has not been established that the prophylactic administration of an antibacterial drug (or combination of drugs) to all premature infants who have been exposed to amnionitis is both safe and effective in reducing the number of deaths due to congenital bacterial infections. In the present state of our knowledge it can only be said that when a diagnosis of amniotic infection or umbilical vasculitis is made the infant should be closely observed for signs of infection (particularly respiratory difficulty) and treated with antibacterial drugs when the signs are present.

DISSEMINATED HERPES SIMPLEX INFECTION

Zuelzer and Stulberg described the syndrome of generalized herpes simplex infection in newborn infants and noted that premature infants were especially susceptible.

Mode of Infection

Exposure is presumed to occur during passage through a birth canal infected with herpes virus. Conjunctiva, oral mucosa, and skin are the usual portals of entry. Zuelzer and Stulberg stressed that surface lesions of the conjunctiva or skin in the first few days of life should make one consider the diagnosis of herpes. They observed that in some instances the lesions were inconspicuous; in one case there were no external lesions, suggesting that transplacental infection may also occur.

Clinical Manifestations

The clinical features in Zuelzer and Stulberg's cases were not strikingly different from those of other severe infections in newborn infants. Systemic reac-

tions began between the fifth and the seventh day of life; these included fever or hypothermia, increasing icterus, lethargy, respiratory distress, and rapid circulatory collapse. Enlargement of the liver and occasionally of the spleen and a tendency to severe bleeding also were noted. All the affected infants died, and extensive visceral lesions were described.

Florman and Mindlin described an example of generalized herpes simplex infection in a premature infant who survived. This infant developed extensive chorioretinitis and brain damage, which were presumed to be the result of herpes infection.

Treatment

No effective treatment for this condition has been proposed. Zuelzer and Stulberg reported that a small dose of gamma globulin given at birth failed to protect one premature infant.

EYE INFECTIONS

The term "ophthalmia neonatorum" is applied to several forms of acute conjunctivitis in newborn infants. Gonorrheal ophthalmia, or gonococcal conjunctivitis, has been so reduced in incidence in this country by the widespread use of prophylactic measures that other organisms are now found more frequently to be the cause of ophthalmia in newborn infants. The symptoms, diagnosis, and treatment of these conditions in premature infants are the same as in term infants.

Gonorrheal Ophthalmia

Differential Diagnosis. In the early acute stage of conjunctivitis differential diagnosis must be made between gonorrheal conjunctivitis and other specific infections and from chemical conjunctival irritation due to prophylactic treatment. *In the latter the symptoms are not nearly so acute and subside rapidly.* To rule out a gonorrheal infection, however, smears and cultures should be made. **Prophylaxis.** Gonorrheal ophthalmia is preventable by routine instillation of a prophylactic in the conjunctival sac of the infant at birth. The use of a solution of silver salts, preferably one drop of a 1 per cent solution of silver nitrate in the conjunctival sac of each eye, has been found effective. This type of prophylactic treatment was until recently required by law or regulation in almost all the states in the United States.

At the present time there is no general agreement on the answer to the question of whether prophylaxis with silver nitrate or any other agent is necessary. The reader is referred to a paper by Mellin and Kent for a review of

the arguments and a survey of the recent literature on this topic. We continue to use silver-nitrate prophylaxis (see Chap. 6).

Inclusion Bleorrhoea

Inclusion bleorrhoea (viral conjunctivitis) is caused by a virus which is morphologically similar to the viruses of trachoma and other members of the psittacosis-lymphogranuloma group, with which it shares a complement-fixing group antigen.⁸⁶

Mode of Infection. Like gonorrhoeal ophthalmia the virus of inclusion bleorrhoea is transmitted from the genital tract of the mother during birth.

Clinical Signs. Outward manifestations usually appear later than those of gonorrhoeal infection, between the fifth and tenth day. Symptoms are similar to those of gonorrhoea, with acute inflammation and copious discharge in severe cases. Both eyes are usually affected. The cornea does not become involved. According to Howard⁸¹ there are no recognizable complications or sequelae.

Diagnosis. The diagnosis is established by the demonstration of cytoplasmic inclusion bodies in conjunctival scrapings.

Treatment. Ormsby and others reported that the infection responded readily when treated topically for 14 days with either sodium sulfacetamide (10 per cent), chlortetracycline (0.1 per cent), or oxytetracycline (0.1 per cent) in ointment base.

Thygeson noted that the incidence of this form of abacterial ophthalmia neonatorum has been steadily decreasing in the United States. He speculated that this may be due to the widespread use of antibiotics which has reduced the incidence of inclusion virus cervicitis.

POSTNATAL INFECTIONS

NEONATAL SEPTICEMIA (SEPSIS)

In the neonatal period the infant may suffer from a general blood-stream bacterial infection which has been acquired antenatally or postnatally. In the newborn, especially in premature infants, the primary site of infection is usually not obvious, and the symptoms are generalized and varied. Ylppö pointed out in 1919 that septicemia is an important and relatively frequent cause of morbidity and mortality of newborn infants. He reported that in 10 of 14 infants dying between the fourth and the fifteenth day bacteria were demonstrable in the blood stream. Since that time improvement in obstetric and pediatric techniques has undoubtedly reduced the incidence of septicemia.

Periodic reviews of this topic^{37, 119, 138, 143} present evidence that septicemia

still occurs and that it remains a very difficult clinical problem. There is general agreement that the incidence of neonatal septicemia is disproportionately high in premature infants and is higher in males than in females.

Clinical Manifestations

The initial symptoms of bacterial sepsis in premature infants are varied and often indefinite. Listlessness, anorexia, and vomiting are frequently the only early clinical manifestations.

The body temperature of small infants with septicemia may be elevated without reaching a level that is ordinarily recognized as fever,¹¹⁰ but many exhibit a drop in body temperature.

Increasing jaundice, hepatomegaly, splenomegaly, abdominal distention, bleeding, petechiae, sclerema, and subcutaneous abscesses may all occur. The kidneys may be found to be enlarged when there is associated pyelonephritis.

Impetiginous skin lesions, the result of *Pseudomonas aeruginosa* infections, are characterized by a green or violet hue or by areas of purple cellulitis which resemble septic infarcts.^{66, 119}

The early symptoms and manifestations of bacterial septicemia are so similar to those of abacterial infections^{79, 148} that a distinction can rarely be made at the beginning of illness.

Complications of Bacterial Septicemia

Meningitis. Meningeal infection is a relatively frequent and usually occult complication of septicemia.^{164, 176} Kagan's group noted that bulging fontanelle, nuchal rigidity, convulsions, and spasticity were more often absent than present in a series of premature infants with meningitis. Failure to feed and cyanotic episodes were the two most frequent manifestations reported by Brody and others.

Pyarthrosis. Howard⁸⁰ called attention to the localization of septic infection in the hip of premature infants. Subcutaneous swelling may be present in the upper portion of the thigh and the region of the hip or it may involve the entire thigh, leg, and foot. The area of swelling is usually indurated and is rarely inflamed; it is often mistaken for simple edema.

Other Complications. Other sites may be involved becoming manifest as pneumonia, peritonitis, osteomyelitis,^{27, 153} parotitis,⁸³ or pericarditis.¹⁵⁸ In several very small infants we have observed septicemia and panophthalmitis due to *Pseudomonas aeruginosa*;¹⁴⁶ in these cases the eye appeared to be either the portal of entry or the site of hematogenous metastasis.

Diagnostic Aids

The clinical signs of infection are often so vague in premature infants that it is entirely justifiable to begin treatment simply on the grounds of reasonable suspicion. However, when such a decision is made it is very important to collect specimens of body fluids before treatment is started, in order to prevent hopeless muddling of the clinical problem, which is difficult to interpret even in ideal circumstances. Hemogram, urinalysis, lumbar puncture, blood culture, nasopharyngeal culture, umbilical-stump culture, and culture of skin lesions should be obtained. (For the technique of lumbar puncture and blood culture in small infants see Chap. 8.)

Leukocytosis¹¹⁵ and anemia are suggestive of septicemia, but these signs are not always present. The infecting organism can often be recovered on culture of the urine and cerebrospinal fluid even in the absence of pyuria or pleocytosis, when these fluids are purulent it is often possible to identify bacteria in stained smears of the sediment.

Skeletal roentgenograms should be obtained when osteomyelitis is suspected. Electrocardiograms may be helpful in distinguishing bacterial sepsis from encephalomyocarditis of the newborn infant associated with Coxsackie group B virus infections.⁶⁵

Bacteriologic Findings

Nyhan and Fousek noted that in recent years the distribution of causal agents has changed. Prior to 1944 beta-hemolytic streptococcus was the most frequently occurring organism; since that time infections with coliform organisms have been more common. The distribution of organisms responsible for septicemia in 43 premature infants is presented in Table 19-5.

Premature infants accounted for seven out of eight cases of septicemia due to streptococci of groups B, D, or F which were reported by Nyhan and Fousek.

Septicemia due to *Pseudomonas aeruginosa* in premature infants is of particular interest, because this organism usually does not invade human beings except in the presence of debility or prolonged treatment with antibiotics. Among newborn premature infants it may be associated with a fulminating infection.⁷⁸ Nyhan and Fousek reported that among 13 newborn infants with septicemia due to *Ps. aeruginosa* 10 were premature.

Neter and Weintraub studied an "outbreak" of a *Ps. aeruginosa* carrier state which occurred in a nursery for premature infants. In the majority of these subjects the presence of the microorganism was not associated with systemic

TABLE 19-5 DISTRIBUTION OF ORGANISMS RESPONSIBLE FOR SEPTICEMIA OF THE NEWBORN IN 43 PREMATURE INFANTS

Organism	% of infants
Hemolytic streptococcus, group A	12
Hemolytic streptococcus, group B, D, or F	16
Hemolytic staphylococcus	9
Pneumococcus	5
<i>E. coli</i>	27
<i>Pseudomonas</i>	23
Other organisms	8
TOTAL	100

Adapted from Nyhan and Fousek.¹¹⁹

infection. The authors speculated on whether only certain serotypes or phage types of *Ps. aeruginosa* might be associated with infection. Similar questions have been raised with respect to coagulase-positive hemolytic *Staph. aureus*.¹³¹ Recently Eichenwald's group⁴⁶ and Sprunt have suggested that bacteria-virus interaction may be important in the dissemination of staphylococci and in the causation of disease.

Reports of epidemics or sporadic examples of infections in premature infants caused by unusual gram-negative bacilli appear from time to time.^{21, 105, 143}

Treatment

Treatment of sepsis in premature infants consists in giving appropriate antibacterial drugs (see p. 346 for choice of these agents and dosage).

The advent of antibacterial therapy resulted in some decline in mortality due to neonatal septicemia among premature infants, but the rate is still high. Poor results are due, in part, to delay in diagnosis. It is strongly suspected that defective resistance among these subjects is also a factor. In desperately ill premature infants we have on occasion resorted to nonspecific measures, including transfusion of fresh adult blood and intramuscular injection of relatively large doses of gamma globulin (1.0 ml. per kg.). The efficacy of these measures has not been established.

RESPIRATORY-TRACT INFECTIONS

Upper Respiratory-Tract Infection

Stuffy-Nose Syndrome. Eichenwald⁴³ described a syndrome in premature infants consisting of a stuffy nose with intermittent mucoid nasal discharge.

Hyperemia of the nasal and pharyngeal mucosa was present and in addition mild hyperplasia of the pharyngeal lymph tissue. The condition lasted for a week or more and rarely progressed to more serious respiratory illness. This "stuffy-nose syndrome" involved a significant proportion of the premature infants admitted to an infected unit, and the outbreak was not easily eradicated.

Eichenwald⁴³ demonstrated that this syndrome resulted from bacterial-viral synergism involving a coagulase-positive hemolytic staphylococcus and adenovirus type 1. In another outbreak he isolated a different viral agent, which appeared to be acting synergistically with a staphylococcus. When the staphylococci were eliminated with antibacterial drugs the condition improved. The presence of either infective agent alone was not associated with disease.

Purulent Rhinitis. Persistent purulent rhinitis occurs not infrequently in premature infants who are fed with indwelling nasogastric catheters (see Chap. 10)

Inhalation (Aspiration) Pneumonia

Mode of Infection. Congenital Pneumonia. As has already been discussed, the respiratory tract may be contaminated in utero by the aspiration of infected amniotic fluid. Penner and McInnis found the highest incidence of intrauterine and neonatal pneumonia in premature infants who were born following early rupture of membranes.

Massive aspiration of meconium-filled amniotic fluid occurs relatively infrequently in premature infants.

Aspiration of Feedings. Postnatal aspiration pneumonia may occur as the result of regurgitation and aspiration of milk feedings by a feeble infant or by an infant with esophageal atresia and tracheoesophageal fistula.

Diagnosis. The infant may die of pneumonia before or shortly after birth. The clinical manifestations of congenital pneumonia are difficult to distinguish from those of cardiac and neurologic disorders. In the series observed by Schaffer *et al.*, live-born infants with pneumonia appeared limp, pallid, flaccid, or cyanotic at the time of birth. Ahvenainen noted that the most common clinical symptoms of neonatal pneumonia were cyanosis, tachypnea, and dyspnea. In agreement with others,^{9, 134} he observed that although dyspnea was common it was usually not severe. On examination of the chest dullness and râles can be discerned sometimes.

Roentgenograms may reveal areas of consolidation; right-upper-lobe involvement is particularly characteristic of aspiration pneumonia.³⁰ In severe infections diffuse clouding of both lungs is seen. In the chest roentgenograms of

12 newborn premature infants with pneumonia, Bauman and Nadelhaft observed in 6 of them a reticulogranular pattern (see p. 238).

Specimens of body fluids from the infant and the mother should be obtained and cultured, since it is usually very difficult to be certain about the identity of the infecting agent(s) in aspiration pneumonia. The bacteriologic findings in amnionitis have already been discussed (p. 327); the findings in postnatal aspiration pneumonia are similar.

Other Bacterial Pneumonias

Briggs and Hogg analyzed the pulmonary findings in a series of 110 infants dying in the first seven days of life, of whom 90 weighed 2500 Gm. or less at birth. When the pathologic findings were related to the length of life, the incidence of pneumonia was represented by a bimodal distribution curve. Increased frequency of pneumonia in the early hours of life was caused by intra-uterine infection; in the later hours the high incidence was the result of infections contracted within the nursery. After 48 hours of life, the frequency of pneumonia seen at necropsy exceeded that of all other pulmonary conditions.

Associated Conditions. Often pneumonia is the terminal complication in infants with serious congenital malformation, intracranial hemorrhage, etc. The lung is a frequent site of localization of infection in postnatal septicemia. Landing observed that acute pneumonia is relatively infrequently found in association with pulmonary hyaline membranes.

Clinical Signs. Premature infants with pneumonia may or may not show recognizable signs of respiratory-tract infection (such as cyanosis, rapid and labored breathing, and fever). Although physical examination may reveal abnormal signs, chest roentgenograms usually provide more definite evidence in the form of localized areas of increased density.

Pathologic Findings. Postmortem examination of the lungs reveals alveolar exudate consisting of leukocytes, bacteria, and fibrin. Potter¹²⁶ noted that fibrin is rarely present in pneumonia of intrauterine origin. She observed that in very small premature infants with pneumonia the lumens of the air spaces are filled with leukocytes and the pulmonary tree distal to the bronchioles is lined with a single layer of cells which resemble macrophages.

Bacteriologic Findings. Studies of the bacterial flora in the upper respiratory tract of unaffected newborn infants¹⁴² and in the lungs of infants dead of pneumonia¹³² indicate that coliform microorganisms are responsible for a high proportion of the cases of pneumonia in the neonatal period. Severe staphylo-

coccal infections of the lung may occur sporadically or in nursery-wide epidemics

Interstitial Plasma-Cell Pneumonia

Interstitial plasma-cell pneumonia (*pneumocystis pneumonia*) was well known in central Europe following pathologic descriptions in 1938. Until recently it was considered to occur elsewhere only rarely. This unusual infection has now been reported in other parts of the world including North America. The extensive literature on this topic has been the subject of several reviews.^{34, 63, 67}

Interstitial plasma-cell pneumonia affects principally premature and other debilitated infants between the ages of one and six months.

Vaněk reported that this condition was caused by *Pneumocystis carinii*, a protozoan parasite which has a wide geographic distribution of natural infection in the lungs of wild and domestic animals of many species. Gajdusek reviewed the many, and for the most part unsuccessful, efforts that have been made to propagate this microorganism in culture and in experimental animals. There is some difference of opinion whether the organism should be classified as a protozoan or a fungus.

Mode of Infection. The mode of transmission of the disease in infants has not been proved. It has been suggested that the agent passes to the newborn from a clinically unapparent infection of the mother. Gajdusek noted that the epidemiologic pattern of outbreaks occurring in nurseries and institutions suggests that infant-to-infant or personnel-to-infant transmission probably takes place.

Pathogenesis. There is evidence that latent infection with *Pneumocystis carinii* is not rare in man and that in the pathogenesis of active infection with this relatively avirulent microorganism an impairment of host resistance is necessary.¹³⁶ It may be of some importance that the peak incidence of pneumocystis pneumonia coincides with the period of transient hypogammaglobulinemia in infancy.^{13, 136} However, in these infantile cases the lung is infiltrated with the very elements (plasma cells) which are considered to be responsible for the production of gamma globulin. This finding was interpreted by Sheldon to reflect severe impairment of body defenses *not* related to gamma globulin.

Interstitial plasma-cell pneumonia has been reported^{13, 136} in patients with hypo- and agammaglobulinemia. In these cases plasma cells were notably sparse or lacking in the interstitial infiltrate.

Diagnosis. The first signs of illness appear insidiously and consist of non-specific restlessness or languor and abnormal nursing behavior.⁶⁴ Tachypnea (respiratory rate more than 40 to 50 per minute), dyspnea, and cough may next become evident.⁶⁵ Intercostal retractions, distention of the alae nasi, and intense cyanosis are evident at the height of the illness. These signs are reminiscent of those seen in neonatal respiratory distress (see Chap. 14). Despite marked respiratory embarrassment, abnormal findings on physical examination of the chest are usually slight; fine crepitant râles and slight impairment of resonance may be discerned.

Gajdusek described the facies as anxious, with wide-open eyes and the head covered with perspiration. There is usually little if any fever.

Roentgenographic examination of the chest reveals widespread consolidation radiating from the hili of the lungs. The gross changes in the roentgenogram are in striking contrast to the meager signs obtained on physical examination of the chest and may even be present before the onset of respiratory symptoms. Other laboratory signs are variable.

A complement-fixation test has been developed which offers a means of serologic diagnosis by the demonstration of a significant rise in antibody titer between specimens of serum obtained early and late in the course of the illness.⁶⁵

Gajdusek reported that the parasites have been demonstrated in lung-puncture material from living patients and occasionally in thick-drop preparations of peripheral blood. He suggested that a search for organisms in Giemsa-stained smears of gastric contents and in material obtained from retropharyngeal swabs may provide a means of establishing a diagnosis during life.

Course. The duration of the illness is usually four to six weeks, with slow recovery. The disease progresses to a fatal outcome in 20 to 25 per cent of the cases.⁶⁵

Occasionally the course is very rapid. Subclinical pneumocystis pneumonia has been observed in association with otherwise unexplained sudden death in infancy.¹³⁶ (See Chap. 12.)

Treatment. Gajdusek reported in 1957 that no specific therapy for pneumocystis pneumonia had been demonstrated. Antiprotozoal drugs have been used without convincing evidence of beneficial effect. A variety of therapeutic measures, including gamma globulin, adrenocorticotropin, cortisone, blood transfusion, and short-wave therapy, also were apparently ineffective.

The administration of oxygen, humidification of the ambient air, and careful nursing have been recommended as important supportive measures.

Pathologic Findings. The morphologic appearance of the lung of infants who die with pneumocystis pneumonia is distinctive. The histologic changes

consist of a diffuse interstitial infiltration by mononuclear cells (plasma cells); an alveolar exudate, composed of faintly granular amorphous material, large cast-off alveolar wall-lining cells, and hyaline-like masses. The microorganisms cannot be seen in ordinary hematoxylin-and-eosin-stained sections; under high magnification these preparations reveal a characteristic honeycomb-like structure of the exudate. Vaněk showed that the exudate, colored with Giemsa stain, was composed of masses of parasites

Imprints of fresh lung tissue reveal cystlike structures containing small, round bodies which are basophilic.¹³

Other Abacterial Pneumonias

Outbreaks of abacterial interstitial pneumonitis, presumably of viral origin, that occurred in premature infants were reported by Adams *et al.*

INFECTIONS OF THE MUCOUS MEMBRANE AND THE SKIN

Infections of the mucous membranes of the mouth, eyes, or vagina may occur after birth from contact with infected material. The symptoms, diagnosis, and treatment have been discussed in the section on intrapartum infections.

Thrush

Thrush is oral infection with *Candida albicans*, a yeastlike organism, which may spread to other parts of the body. The disease may have been transmitted during birth from a maternal vaginal candidiasis, or later through contact with infected infants, contaminated nipples or other equipment, or contaminated hands of the person caring for the infant.

Kozinn and co-workers⁹³ noted that thrush lesions rarely appeared before the eighth day of life. These authors found that when differences in age at the time of discharge from the hospital were taken into account, the incidence of oral thrush was no higher among premature than among term newborns.

Diagnosis. The clinical diagnosis is made by the observation of white patches on the mucous membrane of the mouth that look like deposits of coagulated milk. They do not wipe off easily and bleed readily if traumatized. For confirmation of the diagnosis smears should be made on a clean glass slide after swabbing the oral lesions. Upon the addition of a 15 to 20 per cent solution of sodium hydroxide the organism, a fungus, can be identified from its morphology.

Complications. Newborn infants with thrush harbor *Candida albicans* in the

intestinal tract; the infected stools may constitute a focus for infection of the perianal skin.⁹² Esophagitis and pneumonia⁹⁹ may also occur.

Treatment. The buccal lesions usually respond promptly to topical treatment. An applicator is dipped in a mild antiseptic (e.g., 1 per cent aqueous gentian violet) and rolled over the mucosal surfaces several times each day.

Kozinn's group⁹³ suggested that treatment should be designed to eliminate candidal organisms from the intestinal tract, since infected stools are a source of contagion for the nursery population. Harris and others conducted a controlled trial of the prophylactic effect of the daily oral administration of nystatin (100,000 units in 1 ml) to newborn infants in a nursery. They demonstrated a significant effect and suggested that by this method thrush could be successfully eliminated from hospital nurseries. Further observations indicated that the oral administration of nystatin on only the second and fifth day of life might be equally effective.

Prevention. Apparently neonatal candidiasis can be prevented by administering nystatin vaginal tablets to pregnant women with candidal vulvovaginitis.⁹³

Infants with oral thrush and cutaneous candidiasis should be isolated until they are proved free of infection. Kozinn and co-workers⁹³ have challenged this recommendation and are conducting studies to determine the preventive value of isolation.

The scrupulous technique required for the prevention of the spread of any infection is also recommended. This should include thorough washing of hands before and after handling or feeding each infant and careful sterilization, preferably by autoclaving, of bottles, nipples, and utensils used in preparing feedings.⁴

Umbilical Infection (Omphalitis)

Mode of Infection. After delivery the umbilical arteries contract and the umbilical cord, deprived of a blood supply, becomes necrotic. Morison¹¹⁴ noted that as the necrotic tissue of the umbilical stump separates an active reaction by leukocytes is provoked. This is a reaction limited to the granulation tissue which forms at the site of separation and in the floor of the ulcer left when the cord separates. Since bacteria can be readily recovered from the cord stumps of a high proportion of newborn infants⁵⁰ and since the incidence of umbilical sepsis is relatively low, it is assumed that the umbilical granulation tissue is a fairly effective barrier to the passage of microorganisms.

Morison¹¹⁴ observed that the inner layers (media and intima) of the umbilical arteries undergo necrosis unaccompanied by an inflammatory reaction. The umbilical vein has no sheath. The clot which forms in its lumen organizes and a

barrier of granulation tissue probably prevents intraluminal spread of infection.

Extension of Infection. Infection may occur early before active reaction occurs or later when reaction is poor, as with a large moist umbilical cord. The process may extend beyond the umbilical site either in the loose tissue sheath around an artery, in its dead tissue, or through its lumen. Infection does not appear to extend along the periadventitial tissues of the umbilical vein, but septic thrombophlebitis may occur.

Morison¹¹⁴ considered that infection may also spread from an umbilical infection by the smaller blood vessels and lymph channels of the abdominal wall.

Diagnosis. Evidences of infection of the umbilicus are redness, moisture, or purulent discharge. Forshall noted that infection delays obliteration of the umbilical vessels and that umbilical bleeding is a common manifestation.

Complications. Forshall found that septic umbilical arteritis may be manifested by chronic or intermittent umbilical discharge, or pus may track along the course of the artery to point as an abscess in the scrotum or thigh. Peritonitis and septicemia may also occur.

Organisms may invade the blood clot in the umbilical vein and be carried as emboli to the liver or conceivably through a patent ductus venosus to the lungs. In a group of infants with remote infections of this kind studied by Morison¹¹³ there was delay in healing of the umbilical site but no lesion at the umbilicus. The clinical manifestations were those of septicemia.

Management. The routine treatment of the umbilical wound has already been discussed (see Chap. 9).

Whenever there is a suspicion of omphalitis or septicemia, cultures of the umbilical exudate and of other body fluids should be obtained. When premature infants develop omphalitis it is virtually impossible to be certain that the infection is a local one. For this reason it is usually unwise to depend solely upon the topical administration of antibacterial drugs. Systemic therapy should be used in the same way as for septicemia.

Impetigo Neonatorum

Superficial skin infections occur frequently in newborn infants. Since 1864 when Fox drew attention to the contagious nature of certain of these skin lesions, there have been innumerable reports of epidemics of impetigo in nurseries and institutions. Recently renewed interest has been aroused in nosocomial infections in general.^{5, 128, 131, 135, 173}

Clinical Findings. The earliest manifestations of impetigo consist of solitary thin-walled vesicles or vesicopustules on any part of the skin surface, but especially in the folds of the neck, axilla, or groin. Occasionally the first lesions

appear as periumbilical satellites. The pustules soon rupture, leaving a red, denuded base with very little reaction in the surrounding skin

Parmelee noted that the epidermis of the skin of the newborn is loosely attached to the underlying dermis, permitting epidermolysis to take place much more readily than it does in later childhood. He suggested that this may explain the propensity of the skin of the newborn infant to form vesicles or blebs with infection, in contrast to furuncles and skin abscesses which are characteristic of later childhood.

Other eruptions of the skin that result from abrasions or drugs may resemble impetigo, not infrequently nonspecific papular rashes become secondarily infected. The complications of impetigo include paronychia, mastitis, and septicemia

Bacteriologic Findings. Culture of the purulent fluid from the pustules usually yields coagulase-positive staphylococci; occasionally other pyogenic organisms are recovered

Treatment. Routine management of the skin of premature infants has been discussed elsewhere (Chap. 9). When pustular lesions are present active treatment against staphylococci should be instituted while awaiting the results of culture. The infant should be isolated. The response to antibacterial agents administered locally is usually prompt. Systemic therapy is indicated if the lesions are extensive, if there is an epidemic, or if there is a suspicion that septicemia may be present. Wheeler suggested a plan for use in nurseries in event of the occurrence of epidemic impetigo or epidemic diarrhea (Table 19-6).

Other Skin Infections

Other forms of pyoderma are less common in premature infants. Pemphigus neonatorum is considered to be a severe and progressive form of simple impetigo.

Erysipelas, a streptococcal infection of the skin, usually has its origin in umbilical-cord infections, forceps lacerations, or circumcision wounds. Similar lesions due to staphylococci have been reported in a newborn infant.²³

Ritter's disease is a rare exfoliative dermatitis of newborn infants, probably the result of bacterial infection.¹⁰²

(See also discussion of septicemia in this chapter.)

DIARRHEA AND INTESTINAL INFECTION

The premature infant is apt to develop diarrhea and vomiting, which may be symptoms of overfeeding or of infection in the intestinal tract or elsewhere. Any evidence of diarrhea in a premature infant must be regarded with concern, since

TABLE 19-6 PLAN FOR THE CONTROL OF EPIDEMIC DISEASE IN NURSERIES FOR NEWBORN OR PREMATURE INFANTS

	<i>Allocation</i>	<i>Culture and treatment</i>
Original patient	Discharge from unit immediately	Culture and treat immediately
Patient's mother	Isolate	Culture; treat if positive or if baby positive
Nursery contacts	Retain in original nursery	Culture and treat if original patient positive
Nursery personnel	Retain in original nursery until report of culture	Culture, if carrier, may not work in nursery
	Reopen nursery only after it has been evacuated and cleaned	Keep testing for development of antibiotic resistance
New patients	New nursery with new personnel, close down if cases appear in new nursery	Culture frequently

Adapted from Wheeler¹⁴⁹

these infants tend to become dehydrated rapidly. Diarrheal disease in premature, as compared with mature, newborn infants is characterized by the severity of the symptoms and the high fatality rate.

The reader is referred to the report of a conference on infantile diarrhea held by the New York Academy of Sciences⁶ for a complete discussion of the recent advances which have been made in our knowledge of the causes, pathogenesis, diagnosis, specific therapy, and prophylaxis of epidemic and endemic diarrheal diseases of infants.

Pathogenesis

Enteropathogenic strains of *E. coli* are responsible for many of the epidemics and for a significant proportion of the sporadic cases of diarrhea in newborn infants. Some outbreaks are caused by other bacterial pathogens and viruses⁴⁵

Eichenwald⁴⁷ observed that viral agents which produce respiratory signs in term infants may cause gastrointestinal manifestations in premature subjects.

Diagnosis

Clinical Manifestations. The first sign of enteric infection may be the sudden appearance of watery stools or explosive defecation in an infant who has

previously appeared well. On the other hand, the onset may be insidious, with such signs as lack of appetite, listlessness, drowsiness, failure to gain or actual loss of weight, and occasional vomiting and distention.

The body temperature is usually normal or subnormal in the early stages. As the disease progresses the infant becomes dehydrated rapidly and develops a shock-like appearance, with marked peripheral vascular collapse.

Enteric infection may not always cause diarrheal disease in newborn infants. Watt and others reported an outbreak of salmonellosis in a large premature nursery unaccompanied by diarrhea or any other signs of illness.

Cultures and Serologic Tests. At the first suspicion of diarrhea in a premature infant, rectal material for bacterial culture should be obtained by swab. It is important that *E. coli* isolated from stools be submitted to a laboratory equipped to perform serogrouping and typing tests.

If more than one infant in a nursery is affected, specimens of stool should be frozen and stored so that virus studies can be performed. Other studies should include the collection of two specimens of the patient's blood, one taken at the onset of the illness and the other one or two weeks later for serologic tests.

Management of Epidemics

Wheeler presented a plan designed to prevent the spread of enteropathogenic *E. coli* in nurseries (see Table 19-6). He recommended that after a broth culture is made of rectal material obtained by swab, the patient with diarrhea should be transferred from the nursery and be treated immediately with neomycin sulfate, 50 mg. per kg. per day in four divided doses by mouth.

If enteropathogenic *E. coli* are recovered from the original patient, Wheeler recommended that the nursery be closed to all new admissions, the patient's mother, nursery contacts, and nursery personnel should be treated with neomycin. Vitamin K was recommended when neomycin is administered for more than two days.

Svirsky-Gross reported that an outbreak of diarrhea among premature infants was controlled with human-milk feedings.

Supportive Treatment

Oral feedings should be discontinued for 24 hours or longer depending on the severity of the diarrhea.

If parenteral replacement therapy is indicated it should be planned on the basis of a clinical estimate of the degree of dehydration and the volume of gastrointestinal losses, and the results of chemical examination of the serum to deter-

mine the concentration of the major ions. There are wide variations in the derangement of body water and electrolyte from infant to infant, and a standard formulation for the administration of fluid and electrolyte is not possible. The reader is referred to other sources for a complete discussion of this important subject^{29,33,129,151,163,168}

Initial Infusion. In severe diarrhea emergency treatment is often required to combat dehydration and shock. This can be accomplished by the intravenous infusion of 5 per cent glucose in 0.45 per cent saline (77 mEq. sodium per liter), 30 ml per kg. in one-half hour, followed by 10 ml. per kg. of compatible whole blood.

The finding of normal skin turgor in infants with diarrhea and weight loss should suggest the possibility of hyponatremia;⁹⁸ under these circumstances the repair solution should be relatively dilute with respect to sodium—40 mEq./L. or less.⁵⁵

Replacement Therapy. When the chemical composition of the infant's serum becomes known the remainder of the fluid and electrolyte regimen can be planned; the daily allotment should be administered in a continuous manner.¹¹⁷ Fluids containing potassium should not be given intravenously to newly born premature infants unless there is definite laboratory evidence of a deficit of potassium, in older infants potassium should not be started until the infant gives evidence of adequate urine formation by voiding.

Wallace¹⁶³ observed that in the majority of infants dehydration can be repaired and the infants simultaneously maintained with quantities of total fluid in the order of 150 to 180 ml. per kg. per day. Although occasionally dehydrated premature infants are encountered for whom the total calculated need for water may be very high, he suggested that as a rule the total quantity of fluid administered should not exceed 200 ml. per kg. per day. In many cases this fluid can be composed of equal parts of isotonic electrolyte solution (isotonic saline or Darrow's solution; see p. 185) and 5 to 10 percent glucose. On this schedule dehydration can often be repaired in two days.

Maintenance. During maintenance therapy approximately one-half of the quantity of fluid required during the phase of dehydration is required and only one-third need consist of isotonic electrolyte solution. When clinical improvement is evident oral feedings with dilute milk mixtures should be started.

TETANUS NEONATORUM

Neonatal tetanus is rare in areas of the world where aseptic technique is used in the care of the umbilical cord and in performing circumcision. Since the clinical problems presented by this condition are not peculiar to the premature infant,

the reader is referred to other sources for a review of this subject¹⁵³ and for reports of controlled therapeutic trials that are being conducted in an effort to improve treatment.¹⁰¹

ANTIBACTERIAL DRUGS

The choice of drugs for the treatment of infections in premature infants has, in the past, been dictated principally by the knowledge of their specific activity against different types of microorganisms. Since unexpected harmful effects of several drugs have been demonstrated, it has become clear that when premature infants are treated other factors require careful consideration and may even take precedence over the sought-for antibacterial effect.

Kretchmer noted that the neonatal infant demonstrates characteristic organ and tissue functions quite different from those encountered in the mature individual. For example, it has been demonstrated that a number of drugs that are metabolized through the action of enzymes present in the liver microsomes of adult experimental animals are not metabolized in livers of the newborn of the same species.^{59, 55} For most of the available antibacterial drugs the absorption, distribution, excretion, or metabolism in premature infants is unknown. Kretchmer postulated that if an agent were given to an infant, lack of formation of conjugation products would lead to prolongation of action. New conjugation products might be formed that could be toxic; or, in contrast to the mature subject, the active agent might act to cause difficulty in a metabolic area particularly sensitive in the infant. He urged that the pharmacology of a drug be investigated in the laboratory, with the use of fetal and neonatal animals, before it is administered to human infants.

Kempe reviewed the modes of action, antibacterial spectra, and pediatric dosages of a large number of agents which are currently available. The discussion which follows will be limited to the drugs for which some data are available concerning the absorption, distribution, fate, and excretion in premature infants. At present this information is, however, woefully inadequate.

PENICILLIN

Barnett and co-workers showed that renal clearance of penicillin is appreciably reduced in premature infants as compared with older children. They suggested that if dosages are given in proportion to the infant's weight, levels of penicillin should be maintained in the blood three times as long as in the blood of children and adults.

Renkonen found that small doses of penicillin (4000–10,000 units) given orally to premature infants were sufficient to elevate the penicillin titer of the blood to an adequate therapeutic level. Eichenwald's⁴⁴ group administered phenoxymethyl penicillin (penicillin V) orally to premature infants in a dose of 30,000 units per kg. every 8 hours. Concentrations of more than 1 unit per ml were maintained in the sera of the majority of the infants. No correlation was found between level in the blood and body weight or postnatal age. In this study diarrhea did not occur even after two weeks of continuous administration of oral penicillin.

SULFONAMIDES

Contraindication. Sulfonamides should not be given to premature infants in the presence of neonatal bilirubinemia (see Chap. 13). Since a quantitative relationship has not been established, there can be no definition of the concentration of bilirubin below which sulfonamides may be safely administered. During the first week of life, when a relatively high proportion of premature infants have a significant bilirubinemia, if these drugs are to be used at all they should be given with great caution.

Dosage. Fichter and Curtis determined that in premature infants a single dose of sodium sulfadiazine given subcutaneously (100 mg. per kg.) on the first day of life maintained therapeutic concentrations of sulfonamide in the blood (more than 5 mg per 100 ml.) for 48 hours. In infants older than two days of age the authors recommended subcutaneous sodium sulfadiazine, initial dose 100 mg. per kg., followed in 12 hours by 50 mg. per kg. every 12 hours. The same dosage schedule proved to be satisfactory for a triple sulfonamide suspension which was given by mouth to premature infants who were more than two days old.

CHLORAMPHENICOL

Toxicity. A number of independent observers noted that following the administration of chloramphenicol to newborn infants (premature and term) some developed abdominal distention, occasionally vomiting, irregular respirations, and peripheral vascular collapse. In some of these patients who died, postmortem examination failed to disclose any specific morphologic changes. The clinical picture became so distinctive that clinicians began to refer to it as the "gray syndrome." Although the evidence was entirely circumstantial there was a strong suspicion that chloramphenicol was the responsible agent. The mechanism of the presumed toxicity remains speculative.⁹⁴

In older individuals daily doses of chloramphenicol between 50 and 100 mg. per kg. result in concentrations of chloramphenicol in the blood that are generally below 20 μ g. per ml. It was noted that all of the newborn infants who developed symptoms received more than 50 mg per kg per day. Subsequent studies revealed that when chloramphenicol was given to newly born premature infants the concentration in the blood remained elevated for a relatively long period of time after each dose, and repeated doses (75 mg. per kg. per day or more) resulted in unusually high blood levels.

Metabolism and Excretion. When chloramphenicol is administered to human subjects only 5 to 10 per cent of the administered dose is excreted unchanged in the urine⁶⁹ and from 75 to 90 per cent of the administered dose is accounted for by degradation products which appear in the urine. Chloramphenicol is detoxified primarily by the formation of glucuronides and in this form is eliminated mainly by renal tubular excretion.⁹⁴ Free chloramphenicol is excreted by glomerular filtration. Only free chloramphenicol exhibits significant antibiotic activity.

Sutherland and others found that, as compared with adults, when infants were given chloramphenicol a relatively large proportion of the drug circulating in the blood was in an inactive form, in the urine a relatively small proportion existed in the altered form. These results suggested that the high, prolonged blood levels in newborn infants were related principally to poor renal excretion of conjugated chloramphenicol.

Dosage. Moderate concentrations of chloramphenicol (generally below 40 μ g. per ml) were found in the blood of newborn premature infants after the intramuscular administration of 12.5 mg of chloramphenicol acid succinate per kg. every 12 hours.¹⁶⁷ There were, however, marked variations in the ability of infants to excrete the drug. As a result it may be necessary to individualize dosage by determining the concentration of chloramphenicol in the blood or the antibacterial activity of the serum for each infant so treated.

TETRACYCLINE

Eichenwald's group⁴⁴ found that orally administered tetracycline was irregularly absorbed by premature infants. Doses of 25 mg per kg every 6 hours resulted in inadequate concentrations in the first 24 hours; at 72 hours there was evidence of a cumulative effect. They observed that when 1 ml. of fluid per mg of tetracycline was given with each dose the absorption of the drug appeared to be improved.

At present there are no satisfactory data on which to base a recommendation for the dose of tetracycline appropriate for premature infants.

KANAMYCIN

Eichenwald and co-workers⁴⁴ administered kanamycin (7.5 mg. per kg. every 12 hours intramuscularly) to premature infants for periods of 1 week or less. Therapeutic levels of 10 μ g. per ml. of serum were achieved, no evidence of a cumulative effect was evident. Urinalyses revealed no signs of renal toxicity.

OTHER DRUGS

Many other antibacterial drugs have been given to large numbers of premature infants, these include streptomycin, chlortetracycline, and oxytetracycline. Until exact data are available concerning the absorption, distribution, and excretion of these and other agents by newly born premature infants, there can be no confidence that arbitrary dosage schedules are either safe or efficacious if the estimates are based on experience with mature subjects. It is hoped that present deficiencies in our knowledge in this area will not persist for long.

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Abnormal Blood Conditions

ANEMIA IN THE NEWBORN

There is not complete agreement concerning the hemoglobin concentration which should be considered as indicative of anemia in newly born premature infants.

Antenatal Hemoglobin Concentration

Walker and Turnbull found that there was a steady rise in hemoglobin concentration from the tenth week of gestation. The hemoglobin formed in early fetal life is entirely of the fetal type. Adult-type hemoglobin appears at about the thirteenth week and rises slowly thereafter.¹⁸

Cord Blood. Although there is some difference of opinion concerning the values which are to be expected after the twenty-second week, Gairdner¹⁶ suggested that in normal subjects it is likely that from about 30 weeks onward the hemoglobin concentration of umbilical-cord blood remains unchanged (Fig. 20-1).

Walker and Turnbull found a wide scatter of values after the thirty-sixth week of pregnancy which they attributed to variations in the oxygen environment of the fetus in utero. They considered that high umbilical-cord concentrations of hemoglobin were the result of intrauterine hypoxia;¹⁹ others¹⁰ believe they may be the result of hemoconcentration.

In infants with erythroblastosis fetalis a hemoglobin concentration of 14.8 Gm. per 100 ml. (or less) in the umbilical-cord blood is considered to indicate anemia.^{31, 63}

Neonatal Blood. In the first hours after birth the concentration of hemoglobin in the infant's blood rises in the majority of subjects. When the umbilical cord is tied late the hemoglobin value a few hours after birth is considerably higher than that of the cord blood; after early clamping the rise is minimal.

Gairdner and co-workers¹⁷ attributed the rise in hemoglobin concentration to a shift of fluid (mainly whole plasma) out of the vascular compartment.

Allen and Diamond considered that at birth hemoglobin concentrations below 15 Gm. per 100 ml. in capillary blood (13 Gm. per 100 ml. in venous blood) indicate anemia in infants with erythroblastosis fetalis. The results of several

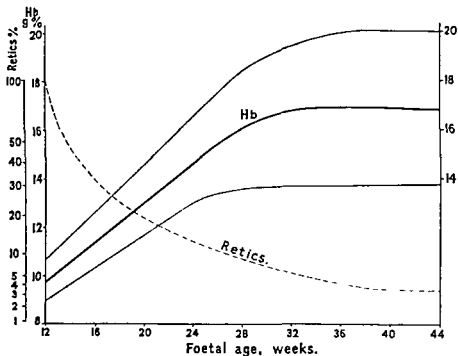


FIG. 20-1. Hemoglobin concentration (mean [heavy line] and range) and reticulocyte percentage in fetal life. Adapted from several sources. (From Gairdner, D.: "The Haematology of Infancy." In Gairdner, D. (Ed.): *Recent Advances in Paediatrics* (ed. 2). Boston, Little, Brown & Company, 1958.)

studies of the capillary hemoglobin concentration of premature infants in the first three days of life^{44, 47} indicate that there is a wide variation in the observed values among apparently normal children (see Appendix 10). As a result the diagnosis of anemia is often uncertain.

CAUSES OF ANEMIA AT BIRTH

Potter³⁷ reviewed the causes of anemia at birth; these are (1) deficient formation of red blood cells, (2) hemorrhage, or (3) abnormal destruction of red cells. She observed that hypochromic anemia is rare at birth. Anemia from the failure of blood formation in utero is also rare; most of the examples of anemia at birth are the result of blood loss or failure to compensate for blood destruction.

Hemorrhage

External Bleeding. Wickster and Christian urged that the possibility of occult bleeding from placental or umbilical vessels in the last trimester be considered whenever one is confronted with a pallid, flaccid newborn premature infant. These authors emphasized the role of posthemorrhagic shock in the death of the newborn premature infant in association with placenta previa, abruptio placentae, abnormal placenta, and incision into the placenta during cesarean section. They recommended that repeated hemoglobin, cell volume, and red cell counts be performed on all premature infants born following these complications.

Parabiotic Circulation in Twins. In monochorionic twins, on rare occasions, *mixing of the separate circulations may occur and a disproportionate amount of blood may accumulate in one circulation at the expense of the other.*²³

In this circumstance one twin appears anemic at birth and the other is plethoric. **Fetomaternal Transfusion.** Following Chown's demonstration that fetomaternal transfusion caused anemia in several newborn infants there has been renewed interest in the possibility that thin-walled vessels within the chorionic villi may on occasion break and permit fetal blood to escape into the maternal circulation. The possibility of fetomaternal transfusion may be anticipated if the mother develops jaundice just before delivery or has a systemic reaction suggestive of transfusion of incompatible blood.⁵¹ Depending on the rapidity and volume of blood loss the clinical picture of the infants at birth may vary from pallor to acute hemorrhagic shock.³² The diagnosis can be confirmed by the demonstration of fetal hemoglobin³² or fetal erythrocytes⁶⁹ in the maternal circulation.

Treatment. Newborn infants with posthemorrhagic shock should be transfused without delay. The amount of compatible whole blood given at one time to premature infants should not exceed 10 ml. per kg. of body weight.

Erythroblastosis Fetalis (Hemolytic Disease of the Newborn)

In erythroblastosis fetalis there is increased destruction of the infant's red cells due to the action of specific antibodies derived from the mother by placental transfer. This condition results from the immunization of the mother against a fetal blood-group antigen (principally one of the Rh antigens) not possessed by herself. The disorder has been the subject of several complete reviews, and the reader is referred to these sources for full discussions and a survey of the extensive literature.^{2, 30, 41, 70}

Premature Induction of Labor. The incidence of erythroblastosis fetalis is not markedly higher among premature infants, except as the result of a policy of premature induction of labor in an attempt to prevent stillbirth.

The uncertainties which surround the antenatal estimates of gestational age (see Chap. 1) are not the least of the problems which plague the physician who must decide whether to allow the pregnancy of an immunized Rh-negative mother to proceed to term. Walker *et al*⁶⁴ reviewed the existing evidence on this point and concluded that because so many stillbirths due to hemolytic disease occur very early in pregnancy the value of premature induction is limited. He recommended the procedure in families in which a previous infant has been stillborn or very severely affected and when the father is homozygous. There is no general agreement on the value of maternal antibody titer in predicting stillbirth.¹⁴

Antenatal Screening. Most cases of erythroblastosis fetalis can be predicted antenatally. Walker⁶⁵ advised the following plan

1. Every mother receiving antenatal care should have her Rh type determined, if it is not already known

2. All Rh-negative mothers should be tested for antibodies between the thirty-second and the thirty-sixth week of each pregnancy unless the father has been shown also to be Rh-negative.

The presence of Rh antibodies indicates that any subsequent Rh-positive fetus may be affected

Preparations for the care of infants with erythroblastosis fetalis can be made antenatally by cross-matching the mother's serum with blood from prospective group O Rh-negative donors

It is important to understand that antenatal screening does not exclude the possibility of hemolytic disease due to rarer antibodies

Umbilical-Cord Blood Tests. The cord blood of all infants born to Rh-negative mothers should be tested for the presence of antibody globulin on the infant's red cells with the direct (Coombs) antiglobulin test. A positive direct antiglobulin test establishes the diagnosis of erythroblastosis fetalis.

The severity of the disease can be predicted to some extent by determination of the hemoglobin and bilirubin concentration of umbilical-cord blood.

Clinical Signs. Many of the early signs of erythroblastosis fetalis cannot be distinguished from those of infections in newborn infants, and the differential diagnosis must often be made on the basis of evidence obtained from laboratory tests (see Chap. 19).

The most important sign of erythroblastosis fetalis in premature and term in-

fants is the appearance of jaundice during the first twenty-four hours of life. When splenomegaly, hepatomegaly, and anemia are also present the diagnosis is more certain. Petchial hemorrhage may be present in the sickest infants.² Edema is also an unfavorable sign and should be considered a sign of congestive heart failure.

Treatment. The treatment for erythroblastosis fetalis is exchange transfusion. The reader is referred to Allen and Diamond's book for a complete discussion of the principles of treatment and a description of the technique of exchange transfusion (see also Chap. 13).

Walker⁶³ proposed the following criteria for immediate treatment:

1. Cord hemoglobin 14.8 Gm. per 100 ml. or less.
2. Cord hemoglobin 14.8–17.7 Gm. per 100 ml. and cord serum bilirubin 2.8 mg. per 100 ml. or more.
3. Cord bilirubin more than 4 mg. per 100 ml.

Allen and Diamond advised that except in the mildest cases prematurity in the infant with erythroblastosis fetalis should be considered an indication for exchange transfusion.

The purpose of immediate treatment is primarily to reduce elevated venous pressure, if present, and simultaneously to correct anemia. The majority of deaths in the first few hours after birth are the result of heart failure, not of anemia per se or hyperbilirubinemia. If a satisfactory exchange transfusion can be carried out approximately 85 per cent of the infant's red blood cells and unfixed antibody may be removed, thus minimizing the subsequent rise in the concentration of bilirubin in the serum (see Chap. 13). In a severely affected premature infant it is often advisable to correct the elevated venous pressure and anemia by means of a small and incomplete exchange transfusion, reserving the full procedure for the time when the infant's general condition has improved.

The objective of delayed or repeated exchange transfusions is that of keeping the concentration of bilirubin in the serum below 18–20 mg. per 100 ml.^{2, 60} Walker⁶³ observed that among 652 infants with erythroblastosis fetalis who were treated by exchange transfusion, the need for repeated procedures was related more directly to prematurity than to the initial severity of the hemolytic process or the delay before performing the initial exchange transfusion. Repeated exchange transfusions were required in 8 per cent of mature infants, in 30 per cent of those weighing 2500 Gm. or less at birth, and in 50 per cent of those whose birth was induced at 35 weeks gestation.

Complications. Walker⁶³ noted that in recent years unexplained death during exchange transfusion has constituted the principal circumstance in fatalities asso-

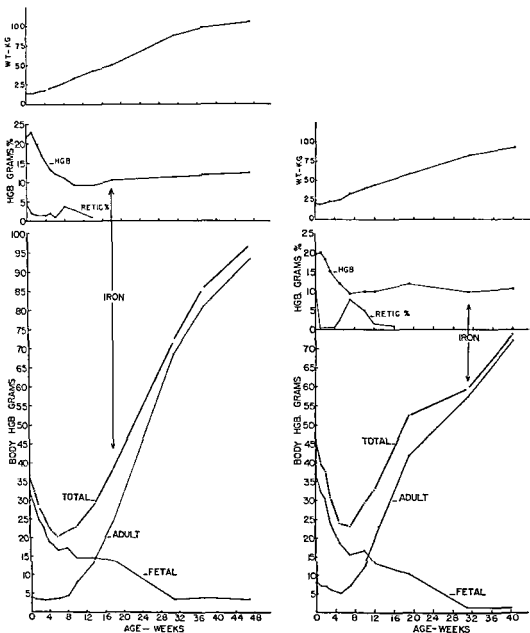


FIG. 20-2. Changes with age in the blood constituents. (Left) For an infant whose birth weight was 1560 Gm. (Right) For an infant whose birth weight was 2100 Gm. (From Schulman, I., and Smith, C. H.: Studies on the anemia of prematurity: III. The mechanism of the anemia. *A.M.A. Am. J. Dis. Child.* 88:582, 1954.)

ciated with hemolytic disease. In his series of cases, 16 infants died during exchange transfusion; 10 of these infants weighed 2500 Gm. or less, 2 were hydropic, and all but one were severely affected.

(For a discussion of kernicterus and bilirubinemia in premature infants see Chap. 13.)

ANEMIA OF PREMATURITY

EARLY PHASE

In all premature infants, after the first week of life the hemoglobin concentration falls for five to eight weeks and then levels off.⁵ This results in an anemia (i.e., hemoglobin concentration below 10 Gm. per 100 ml.) in most subjects. Since the red cell count falls proportionately the early anemia is normochromic. In general, the smallest infants exhibit the most rapid fall in hemoglobin concentration and develop the most marked degree of anemia⁴⁴ (see Appendix 10).

Mechanisms

Schulman and Smith⁴⁶ demonstrated that the fall of hemoglobin concentration during the early phase is the result of a steady decrease in total circulating hemoglobin mass (Fig. 20-2). The mechanisms involved in the drop in body hemoglobin include a marked decrease in hematopoietic activity and a decrease in the life span of the red cells. A fall in the reticulocyte count gives evidence of diminished synthetic activity.

The early anemia of prematurity is usually self-limited. Increased hematopoiesis is manifested by reticulocytosis and deceleration of the fall in hemoglobin concentration despite rapid weight gain. Schulman⁴⁴ reviewed the evidence on the mechanisms involved in the decrease and subsequent increase in erythropoietic activity and concluded that these phenomena are not the result of a maturational process. It is more likely that anemia itself is the stimulus that is responsible for the release of a humoral erythropoiesis-stimulating factor from the kidney or pituitary. Schulman⁴⁴ emphasized that, in a given infant, the postnatal age at which active regeneration begins is dependent upon factors that influence the hemoglobin mass with which the infant begins life. When the minimum hemoglobin concentration is reached hematopoiesis is resumed at the normal rate.

Storage of Iron

At the time of birth the largest proportion of iron is stored in the hemoglobin

of circulating blood (see Chap. 10). Since iron is not excreted from the body, there is a progressive accumulation of iron in the liver, spleen, and bone marrow during the period of fall in circulating hemoglobin mass.⁴⁹ The administration of iron would be expected to have little influence on anemia under these circumstances, as has been shown in a number of studies.^{45, 52, 67}

Blood Transfusion

In the past blood transfusions were frequently given to correct the early anemia of prematurity. There is general agreement that this treatment is rarely necessary. In the presence of infection, which may delay the erythropoietic response to anemia, transfusion may be required. Schulman⁴⁴ advised that reticulocyte counts be obtained in such instances and that the infant be carefully evaluated.

INTERMEDIATE PHASE

During this period active erythropoiesis produces an increase in total circulating hemoglobin mass (see Fig. 20-2). However, rapid growth and expansion of blood volume also proceed at the same time so that the net effect is a minimal increase in the peripheral hemoglobin concentration. During this period iron that was stored during the early phase is utilized in the synthesis of hemoglobin, which is principally of the adult type (see Fig. 20-2).

When the available iron stores are exhausted the intermediate phase of anemia of prematurity comes to an end. The time when this occurs varies considerably and is dependent for the most part upon variations in the size of the initial hemoglobin mass and the rate of postnatal growth.

Treatment

There is some disagreement concerning the effectiveness of exogenously administered iron during this period.^{49, 52} Schulman⁴⁴ could find no convincing evidence that the administration of iron will accelerate the rate of hemoglobin gain if adequate iron stores are present.

LATE PHASE

The late anemia of prematurity is an iron-deficiency anemia that follows the depletion of endogenous supplies of iron. This phase is manifested by a fall in hemoglobin concentration. As iron deficiency affects hemoglobin synthesis more than red cell generation, the late anemia is hypochromic and microcytic instead of the normochromic anemia of the earlier phases.⁴⁷

Supplemental Iron

In order to prevent the development of the iron-deficiency phase of anemia of prematurity it is necessary to administer medicinal iron, since the amount of iron required is usually greater than can be supplied from dietary sources

Initiation of Therapy. As has been stated, the time at which this supplementation is needed varies from infant to infant. Schulman⁴⁴ noted that very few premature infants require iron before the sixth week, while virtually all require it by the fourteenth week of life

For routine administration starting times of 3 weeks of age¹⁸ and 8 weeks of age⁴⁴ have been advocated. We have found it expedient to begin the administration of iron just before each infant is discharged from the nursery so that we may instruct the mother in its use; generally the infants are less than 1 month of age. Small infants who remain in the nursery for a long time are followed with blood counts at two-week intervals. In these infants iron is started at 8 weeks of age unless blood counts indicate an earlier need

Oral Dosage. The dosage of iron necessary to prevent the late anemia of prematurity has been estimated to be between 15 and 35 mg. of elemental iron daily.^{18, 44} When iron deficiency is already present, Schulman⁴⁴ advocated from 50 to 100 mg. daily.

Duration of Therapy. Most premature infants require oral iron supplementation for the entire first year of life, and some may manifest a need during the second year. Schulman⁴⁴ advised that periodic checks of hemoglobin concentration be made in premature infants during the first two years

Parenteral Iron. Often as the result of poor mothercraft, language barriers and other circumstances, premature infants are not brought back for medical supervision after they have been discharged from the hospital. It was advised that under these circumstances an iron-dextran complex should be administered intramuscularly before the infant left the nursery in a dose sufficient to insure adequate iron stores for the first year of life.^{18, 33} However, iron-dextran complex should not be given routinely to premature infants until it has been demonstrated that there are no long-term harmful effects.⁴⁰

COAGULATION DISORDERS

The reader is referred to a monograph by Schulman and Smith⁴⁷ for a review of the coagulation disorders of infancy and childhood and for a description of a modern concept of the clotting mechanism.

NORMAL COAGULATION CYCLE

An outline of the normal coagulation cycle is presented in Table 20-1. It may be noted that the clotting of the blood itself is thought to differ somewhat from the manner in which clotting occurs in the tissues. This distinction, as given in the table, should be kept in mind, particularly since tissue thromboplastin is

TABLE 20-1 NORMAL COAGULATION CYCLE

A. Plasma System

Phase I: Formation of Plasma Thromboplastin (Prothrombinase)

Plasma Thromboplastin Precursors + Platelet Thromboplastic Factor + (Antihemophilic globulin) (Plasma thromboplastin component) (Plasma thromboplastin antecedent) (Proaccelerin (labile factor)) (Stuart-Prower factor) (Hageman factor)	$\text{Ca}^{++} \rightarrow \text{Plasma Thromboplastin}$ (Prothrombinase)

Phase II Prothrombin Conversion

Plasma Thromboplastin + Prothrombin + $\text{Ca}^{++} \rightarrow \text{Thrombin}$
 (Prothrombinase)

Phase III Fibrin Formation

Thrombin + Fibrinogen $\rightarrow$ Fibrin

B. Tissue System

Phase I. Tissue Thromboplastin + Proaccelerin (labile factor) + Proconvertin (stable factor) + Stuart Prower Factor + Ca^{++}	}	$\rightarrow \text{Prothrombinase}$

Phase II and III as above

Courtesy of Irving Schulman, M D, Children's Memorial Hospital, Chicago, Ill.

utilized in one of the most commonly employed tests of the coagulation mechanism (prothrombin time).

Plasma System. Under physiologic conditions the antihemophilic globulin, plasma thromboplastin component, plasma thromboplastin antecedent, proaccelerin (labile factor), Stuart-Prower factor, and Hageman factor react with the platelet thromboplastic factor and calcium to form a complete plasma thrombo-

of coagulation factors which are synthesized in the liver and which are dependent upon vitamin K for normal production.^{1, 15, 48, 57, 58, 59} These factors are plasma thromboplastin component, plasma thromboplastin antecedent, Stuart-Prower factor, proconvertin, and prothrombin. Thus in hemorrhagic disease of the newborn an abnormality exists in the formation of thromboplastin and in the conversion of prothrombin to thrombin.

In the term infant the above-noted coagulation factors tend to reach minimal concentrations at 48 to 72 hours of postnatal life and then rise spontaneously. In the premature infant the neonatal fall is greater and the subsequent increase is slower.

Response to Vitamin K. All the coagulation abnormalities respond rapidly to the administration of vitamin K. Most of the aberrations are corrected in 24 to 48 hours; complete normality is usually established in 48 to 72 hours. The deficient factors respond in a specific sequence: Prothrombin and plasma thromboplastin component increase most rapidly, this is followed by a rise in the concentration of proconvertin, and finally the Stuart-Prower factor concentration increases. In premature infants the response to vitamin K is slower than that observed in term infants.^{1, 57}

Fibrinogen Concentration. The fibrinogen concentration in the plasma of newborn infants has been reported as slightly decreased. Conflicting opinions have been expressed about the correlation between the fibrinogen concentration in maternal and cord blood and about the relationship between birth weight and fibrinogen concentration^{34, 42, 55, 56} (also see Appendix 10). However, there is general agreement that, except in the rare examples of congenital afibrinogenemia,³⁸ the concentrations of fibrinogen in the plasma of premature and term infants are not low enough to interfere with the adequate formation of fibrin.⁵⁷

Diagnostic Aids. Exact diagnosis in an infant with an abnormal tendency to bleed must rest upon the results of laboratory tests designed to identify specific abnormalities in the coagulation cycle. The reader is referred to the monograph by Schulman and Smith⁴⁷ for a clear discussion of the laboratory aids to the diagnosis of coagulation disturbances. Improved methods of blood collection in premature infants have made it possible to perform these tests in the smallest infants (see Chap. 8).

Congenital Abnormalities

The incidence of congenital deficiencies of the various factors necessary for coagulation is not higher among premature infants. The reader is referred to other sources for complete descriptions of these disorders.^{39, 54}

Secondary Disturbances

Maternal Ingestion of Drugs. Van Creveld⁵⁷ observed that maternal ingestion of drugs may produce coagulation defects in newborn infants. The drugs included phenobarbital, coumarin derivatives, salicylates, sulfonamides, and anti-convulsant drugs.

Thrombocytopenia. Bleeding in the neonatal period may be the result of thrombocytopenia. This subject was recently reviewed by Kaplan, who noted the wide variety of clinical circumstances which are associated with a reduction in the number of circulating platelets in newborn infants. The classification following is adapted from Kaplan's review.²²

A. Due to maternal antibodies

1. With maternal purpura

- a Maternal idiopathic thrombocytopenic purpura
- b Maternal drug sensitization (quinine, sulfonamides, quinidine, Sedormid, para-aminosalicylic acid and certain anticonvulsant drugs)

2 Without maternal purpura

- a Maternal isoimmunization to platelets
- b. Maternal isoimmunization to erythrocytes (severe erythroblastosis fetalis)

B. Transfusion thrombocytopenia (replacement transfusion)

C. Neonatal infection (bacterial, viral, spirochetal, protozoan)

D. Acute neonatal thrombocytopenia, etiology obscure

There are no satisfactory estimates of the incidence of thrombocytopenic purpura in premature infants. Kaplan reported 75 examples of acute thrombocytopenia that occurred in a nursery for premature infants during an 18-month period. In the majority the etiology was obscure and the manifestations consisted of mild rectal bleeding or cutaneous and mucosal hemorrhages. We have been impressed with the frequency with which unexplained thrombocytopenic purpura occurs in our nursery. In this connection the reader should be cautioned that the interpretation of platelet counts in newborn premature infants is made difficult by the marked variation in asymptomatic subjects (see Appendix 10).

Decreased Proaccelerin. Van Creveld and others⁵⁸ described three examples of intrauterine melena caused by a decreased concentration of proaccelerin; two of the infants were born prematurely. Bloody amniotic fluid and rectal hemorrhage immediately after birth were the outstanding clinical signs. The authors considered that this syndrome was caused by a temporary disturbance in the formation of proaccelerin by the fetal liver, since the concentration of this substance eventually increased and the hemorrhages ceased. The condition was not influenced by the administration of vitamin K.

Other Conditions. Coagulation disturbances accompanying hepatic disease and erythroblastosis fetalis have been reported.⁵⁹

TREATMENT OF COAGULATION DISORDERS

Vitamin K

Vitamin K is essential for the synthesis of prothrombin by the liver. Two forms of vitamin K occur in nature; both are fat-soluble and both have anti-hemorrhagic activity. The richest sources of vitamin K₁ for man are green plant tissues; vitamin K₂ is formed in the intestine by the action of bacteria.

In 1939 it was demonstrated that hypoprothrombinemia in asymptomatic newborn infants and in infants with hemorrhagic disease could be corrected by the ingestion of naturally occurring vitamin K.^{13, 61} Since then the relationship between vitamin K, hypoprothrombinemia, and hemorrhagic disease has been the subject of innumerable investigations.

The original forms of vitamin K for intramuscular injection were prepared as oily solutions that were often irritating and sometimes produced an abscess at the site of injection. Subsequently numerous water-soluble compounds (naphthoquinone derivatives) were found to have vitamin K activity. Aqueous solutions of vitamin K analogues proved to be useful clinically because they were nonirritating after intramuscular injection and because absorption was rapid.

For many years it was advocated that synthetic vitamin K be given by injection to all premature infants at the time of birth.

Effective Dose. Sells and others found that 1 mg. of synthetic vitamin K (the recommended prophylactic dose) exceeded, by almost a thousandfold, the minimal daily requirement of term newborn infants. Lehmann showed that a single intramuscular injection of 0.5 mg. of synthetic vitamin K given one hour after birth was as effective as 5 mg. in preventing or minimizing hypoprothrombinemia in the first week of life among term infants.

Neonatal Hemorrhages. There has been considerable difference of opinion concerning the influence of vitamin K prophylaxis on the incidence of sporadic neonatal hemorrhages which occur in association with trauma, asphyxia, infections, etc.^{33, 36, 43} In a large experience with parturient women who received vitamin K prophylaxis and with concurrent untreated controls, Dam and others¹² reported an apparent beneficial influence of vitamin K on the incidence of hemorrhages in newborn infants. An analysis of the intracranial group of hemorrhages revealed that the difference in frequency was more marked in premature than in term infants.

Gröntoft reviewed his experience with intracranial hemorrhages and concluded

that vitamin K prophylaxis appeared to protect premature and medium-sized infants against large hemorrhages over the cerebral convexities but had no influence on intracranial hemorrhage of the asphyxial type (see Chap. 18).

Vitamin K Analogues

Overdosage. Since vitamin K prophylaxis was not always completely effective in controlling bleeding states in premature infants, many physicians attempted to improve the results by using large doses of vitamin K analogues and by repeating the doses at frequent intervals.

In 1953 Gasser¹⁹ suggested that synthetic vitamin K might be the cause of Heinz-body formation in red blood cells and severe hemolytic anemia in 14 premature infants, and in 1955 Allison³ reported a small series of cases of kernicterus and hemolytic anemia in premature infants whose only treatment had been relatively high doses of a water-soluble vitamin K analogue. Since then a number of studies have made it clear that excessive amounts of synthetic vitamin K (more than 10 mg.) produce hyperbilirubinemia^{6, 7, 28} in premature infants that may result in kernicterus^{11, 24, 25} (see Chap. 13). Asteriadou-Samartzis and Leiken found that, in contrast to the effects of water-soluble vitamin K analogues, large doses of vitamin K₁ (25 mg. orally and intravenously), did *not* produce hyperbilirubinemia in premature infants.

Toxic Action. The mechanism leading to hyperbilirubinemia in premature infants receiving vitamin K analogues by injection has not been completely elucidated. Toxicity may be due to a primary effect on the erythrocytes. This is supported by clinical observations and findings in experimental animals that vitamin K analogues may produce Heinz bodies in red blood cells and acute hemolytic anemia^{3, 19, 29, 65}

Since newborn premature infants have low tocopherol concentrations in the blood it was of particular interest that the hemolytic effect of vitamin K analogues in experimental animals could be enhanced in the presence of vitamin E deficiency.⁴ Vitamin K₁ on the other hand, appeared to be harmless when injected into animals deficient in vitamin E and the toxic vitamin K substitute had no hemolytic effect when it was given by mouth.

Zinkham investigated the possibility that hemolysis following high doses of water-soluble analogues of vitamin K might be related to an abnormality of glutathione metabolism in red blood cells of newborn infants. He found that except for a small percentage of infants with an inherited abnormality of metabolism of red cells (deficient activity of glucose-6-phosphate dehydrogenase) the drug sensitivity could not be explained on the basis of glutathione instability, which is observed in the erythrocytes of newborn infants. He observed that added glucose

corrected the *in vitro* instability of glutathione; alpha-tocopherol had no effect

Lucey and Dolan reviewed the possible mechanisms that might be responsible for the toxicity of vitamin K analogues and advanced the hypothesis that these compounds exert their effect on the liver.

Vitamin K Prophylaxis

At present it is generally agreed that vitamin K should be administered prophylactically to premature infants; the daily dose should not exceed 1 mg. per day. The availability of an aqueous dispersion of vitamin K₁ which can be administered intramuscularly has made it unnecessary to use vitamin K analogues parenterally.

Gasser²⁰ warned that even vitamin K₁ should not be regarded as a harmless drug in the premature infant. He observed hemolytic Heinz-body anemia in a premature infant who received 8 mg. of vitamin K₁ between the sixth and the twelfth days of life.

Van Creveld³⁷ recommended 1 mg. of vitamin K₁ intramuscularly for premature infants on the first day of life. We give 1 mg. of vitamin K₁ by mouth to all premature infants once each day for the first three days of life (see Chap. 10).

Treatment of Transitory Deficiencies

Vitamin K. There is general agreement that vitamin K is the treatment of choice for frank hemorrhagic disease of the newborn.³⁵ Schulz and van Creveld reported that several infants with severe bleeding responded promptly to the injection of 1 mg. of vitamin K₁. In infants with hemorrhagic disease van Creveld³⁷ advised that the initial prophylactic dose be repeated on the second day of life either intramuscularly or, when melena persists, as a powder by mouth.

Blood Transfusion. For severe hemorrhagic manifestations transfusions of fresh blood should be given (not more than 10 ml. per kg. at one time).

Management of Thrombocytopenia

In thrombocytopenia among premature infants treatment is usually directed against an associated condition. Specific measures to increase the number of circulating platelets, such as platelet transfusions or steroid therapy, are rarely indicated.

Treatment of Congenital Coagulation Abnormalities

Transfusions of fresh blood and fresh plasma are temporarily effective in most of the coagulation disorders caused by congenital abnormalities in the hemostatic

mechanism and in bleeding secondary to other diseases. Specific therapy can be planned only after a diagnosis has been established.

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Metabolic and Nutritional Disorders

ACIDOSIS

The hydrogen-ion concentration of the blood is more unstable in newborn infants than in older individuals. Instability is most marked in premature infants.^{1, 43, 46} Since many apparently asymptomatic small infants have chemical signs of acidosis it has been tacitly assumed that these frequently observed deviations are "physiologic "

Mechanisms

Role of the Kidney. Tudvad and co-workers investigated the role of the kidney in the production of "physiologic" acidosis of premature infants. In agreement with Day and Franklin they found that the acidosis could not be explained on the basis of low concentrations of carbonic anhydrase in the kidney, despite the fact that the blood of premature infants exhibits lowered activity of this enzyme.⁴⁹

Observations on healthy premature infants indicated that bicarbonate reabsorption by the kidney was unimpaired and that acidosis could be corrected by the administration of bicarbonate. Tudvad *et al.* concluded therefore that the most likely explanation for the acidosis is that the quantity of metabolic acids requiring excretion exceeds the capacity of the premature infant's kidney to conserve fixed base by excretion of ammonia and titratable acids

Birth Asphyxia. James and co-workers demonstrated that a brief period of asphyxia which occurs as the result of the delivery process produces a temporary mild respiratory acidosis with elevated carbon dioxide tension of the blood in most newborn infants (see Chap. 6). When asphyxia is prolonged a marked reduction in buffer base occurs, indicating that a metabolic acidosis has been superimposed on the respiratory acidosis. Weisbrot and others reviewed the various explanations that have been offered for the observation that the blood of newborn infants has a low carbon dioxide content and low carbon dioxide tension as compared with adults. In their opinion it was unlikely that this phenome-

non could be entirely accounted for by an unusual capacity for anaerobic metabolism in these infants with an end point in their carbohydrate breakdown short of that of carbon dioxide and water, resulting in the accumulation of organic acids, such as lactic and pyruvic acid.⁵⁹ These authors suggested that carbon dioxide retention during parturition might induce a fall of buffer base in the infant.

The relationship between pulmonary function in the neonatal period and acid-base disturbances is of considerable current interest and is being investigated by a number of workers (see Chaps. 14 and 23).

DIAGNOSIS

Clinical signs of mild acidosis in the early neonatal period are not pathognomonic. Later in the neonatal period premature infants may develop severe acidosis as a complication of various illnesses, but even then the clinical signs are rarely specific. An exact diagnosis can be made only by performing chemical studies, which should include plasma pH, carbon dioxide content, sodium, potassium, chloride and protein, and hematocrit⁴³ (see Appendix 10).

TREATMENT

It has been stated repeatedly that the mild "physiologic" acidosis of prematurity does not require treatment.^{46, 47, 59} Although this advice may be correct, it has not been subjected to a satisfactory critical test.

Severe acidosis and dehydration accompanying diarrhea and infections must be treated with appropriate amounts of fluid and electrolytes (see Chap. 19). Reardon⁴⁵ advised that it is not practical to attempt a correction of carbon dioxide content to the normal adult level by fluid therapy in the first few days after birth. She suggested that the requirements of premature infants may be calculated in the same manner as that used for term infants after the first three or four days of life.

HYPOGLYCEMIA

Blood-Sugar Concentration During the Neonatal Period

Studies of the concentration of sugar in the blood of premature infants which were conducted prior to 1950 were reviewed by Norval. With the wide range of values reported it was difficult to be sure whether the variations were real or the result of technical differences. Norval made 798 measurements in 33 asymptomatic premature infants during the first two weeks of life. In general her results were similar to those reported previously. The mean values for premature infants

TABLE 21-1 BLOOD SUGAR CONCENTRATION IN RELATION TO AGE IN ASYMPTOMATIC PREMATURE INFANTS*

Day of life	No. infants	Blood sugar ^b (mg. per 100 ml.)	
		Mean	S.D.
1	33	44.9	±14.7
2	33	53.3	±13.0
3	33	55.3	±16.2
4	33	59.8	±15.5
5	33	59.8	±16.4
6	33	58.5	±11.0
7	33	63.0	±13.8
8	28	63.1	±14.5
9	25	65.7	±14.7
10	24	65.0	±14.4
11	23	70.6	±19.9
12	23	65.0	±11.3
13	23	62.9	±15.4
14	22	63.9	±13.6

Adapted from Norval.⁴⁰

* Birth weight 1430-2280 Gm, fasted for at least the first 24 hours after birth, a few were not fed for 48 hours. When feedings were started blood samples for the determination of sugar were obtained two or three hours after the last feeding. Blood was obtained from a skin puncture in the heel of each infant.

^b "True sugar" as determined by a modification of Somogyi's micro method.

were lower than those for term infants, but the range was approximately the same. No correlation between birth weight and blood-sugar concentration was evident. The sugar concentrations tended to fall rapidly in the first hours after birth and were lowest during the first day of life, the average values rose during the first week and were relatively stable during the second week of life (Table 21-1). Unlike the observations of Haass, Norval found that declines in blood sugar concentration and markedly low values were not necessarily associated with low body temperatures or with a fall in body temperature.

Cornblath and others⁵ proposed that studies of capillary-venous differences in sugar concentration might provide better estimates of peripheral utilization of glucose by newborn infants than measurements in capillary blood alone. They studied 55 normal term infants and found that when glucose was administered during the first hours of life an increase in peripheral utilization occurred.

Response to Epinephrine. The infants studied by Cornblath *et al.*⁵ responded

to epinephrine by an increase in concentration of sugar in the blood and an inhibition of peripheral utilization. Both of these responses were similar to those of older children and adults; however, the peak hyperglycemic response to epinephrine was delayed and prolonged in the term newborn babies as compared with older infants.

Desmond had shown previously that premature infants responded to epinephrine with hyperglycemia, but the increase was less than that noted in term infants.

Response to Glucagon. Cornblath's group⁶ observed that the administration of glucagon to newly born premature infants produced a prolonged hyperglycemia similar to that produced by epinephrine. The degree of hyperglycemia after glucagon in premature infants was less than in term infants. The authors speculated on the cause of the lessened response of premature subjects to glucagon and likened it to the responses of adults with liver disease. After 5 days of age the glucagon-induced hyperglycemia in term infants was shorter and resembled that of older infants and children, premature infants still exhibited a lower peak concentration than term infants

Causes of Neonatal Hypoglycemia

Numerous theories have been proposed to explain the hypoglycemia that occurs in the first hours of life; these include exhaustion of liver glycogen, altered hepatic threshold for glucose, withdrawal from maternal hormones with delayed response to epinephrine, adrenocortical hypofunction, and insulin hypersecretion or hypersensitivity.^{5, 10, 15, 31, 52, 55} The relationship of the relatively high concentration of amino acids in the blood of newborn infants⁴⁸ to glucose metabolism in the neonatal period has not been explored.^{4, 60}

It is very likely that a number of factors operate to produce the phenomenon of hypoglycemia immediately following birth, and much further study is needed before the mechanisms are clearly understood.

CLINICAL DIAGNOSIS

Farquhar¹⁶ reviewed the many attempts that have been made to correlate neonatal deaths or clinical symptoms such as cyanosis, irritability, listlessness, and hypotonicity with the concentration of sugar in the blood of term infants, infants of diabetic mothers, and premature infants. He added his own observations of 90 infants of diabetic mothers and concluded that there was no relationship between the development of a morbid neonatal course and the blood-sugar level at the time or the extent and rapidity of the fall.

Observations among premature infants have not been as extensive as those in infants of diabetic mothers. Premature infants may have other primary disorders in the neonatal period, and in individual cases it is impossible to evaluate the role of hypoglycemia as the cause of symptoms

TREATMENT

At present there are conflicting opinions, accompanied by considerable speculation, concerning the need or efficacy of early administration of glucose to premature infants (see Chap. 10). Trials in infants of diabetic mothers have failed to demonstrate that treatment with glucose relieves such symptoms as apneic spells, irritability, etc. A properly controlled critical test of the influence of glucose administration on *mortality* among infants of diabetic mothers and premature infants has not yet been reported. Since the neonatal survival of some newborn animals can be favorably influenced by the administration of glucose,^{8, 26, 39} it is important that the evidence on this point, as it concerns human newborn infants, be more firmly established than it is at present. (See also Chap. 22.)

NEONATAL HYPOCALCEMIA

Incidence in Premature Infants

The homeostatic mechanisms for maintaining a stable concentration of calcium in the serum appear to be incompletely developed at birth in premature infants.² Gittleman and co-workers measured the concentrations of calcium in the blood of 111 premature and 908 term infants on the first day of life. The incidence of hypocalcemia (serum calcium concentration less than 8 mg per 100 ml.) was 50 per cent in the premature group as compared with an over-all incidence of 4 per cent among term infants. In term infants the incidence was considerably higher in those born by cesarean section and in those born after a complication of pregnancy or labor. Bruck and Weintraub studied 51 premature infants and found that 34 became hypocalcemic during the first 2 weeks of life; of 21 term controls only 2 reached levels below 8 mg. per 100 ml. and both were considered to be "sick" infants. There was no significant difference in the concentration of inorganic phosphorus between premature and term infants.

Relation to Birth Weight. Gittleman and co-workers observed a significant correlation between mean serum calcium concentration on the first day of life and birth weight that ranged between 1001 and 2500 Gm. (see Appendix 10). In the study conducted by Bruck and Weintraub the minimum calcium concentration

attained was not related to birth weight within the range between 1400 and 2500 Gm.

Relation to Feeding. Bruck and Weintraub observed that in the majority of infants the lowest concentration of calcium in serum was reached during the postnatal fasting period, in general, the longer the fasting period was extended the lower was the concentration of calcium.

Human Milk. When human milk was fed after the initial fast, the concentration of calcium consistently increased, phosphorus rose in about one-third of the cases and fell in two-thirds.

Cow's Milk. Cow's milk feedings resulted in an initial increase in the concentration of calcium in 60 per cent of the cases and a fall in 40 per cent. However, in almost all cases the calcium concentration subsequently increased and reached normal values by the end of the first or second week of life.

In 73 per cent of the infants fed cow's-milk mixtures the phosphorus concentration increased; in 27 per cent it fell.

Classification of Neonatal Hypocalcemia

Gribetz used the term "first-day hypocalcemia" to categorize the transitory decrease in calcium which has been described above. He noted that it is not known whether this condition is a variant of classical neonatal tetany,^{11, 23} which usually occurs several days after birth. Neonatal tetany probably occurs more frequently in premature than in term infants.¹¹

Causes of Tetany of the Newborn

Tetany of the newborn is considered to be due to transient hypoparathyroidism aggravated by limitation of renal excretion of phosphate and a high phosphate intake associated with the feeding of cow's-milk mixtures.^{22, 27, 37}

Walton described two examples of neonatal tetany in premature infants (siblings) associated with maternal hyperparathyroidism.

DIAGNOSIS OF HYPOCALCEMIA IN THE NEWBORN

Clinical Manifestations

The usual signs of tetany of the newborn are neuromuscular hyperirritability and convulsions. There is considerable difference of opinion about the interpretation of other signs that have been associated with hypocalcemia in the neonatal

period; these include vomiting, cyanosis, edema, abdominal distention, apnea, melena, tachycardia, tachypnea, and hollow or squeaky cry.^{2, 7, 11} It has not been established that these nonspecific manifestations are causally related to the concentration of calcium in the serum. Moreover, there have been frequent observations of hypocalcemia on the first day of life and later in the neonatal period in asymptomatic premature infants.^{2, 7}

Laboratory Criteria

These observations have led to some speculation about whether it is appropriate to consider 8 mg per 100 ml as the lower limit of normal for calcium in the serum of newborn premature infants. Bruck and Weintraub suggested that the low concentrations of protein in the serum of premature infants would permit a relatively large fraction of the calcium in the serum to exist in the unbound state. However, even according to these calculations, a "normal" value for ionized calcium would not be expected with a total calcium concentration of less than 7 mg. per 100 ml. These authors advised that in all patients a total calcium concentration of 6 mg. or less per 100 ml. should be regarded with alarm.

In classical neonatal tetany the low serum calcium concentration is almost always associated with an elevated phosphorus level (above 7 mg per 100 ml.).²⁷ In a high proportion of the cases of hypocalcemia observed within 36 hours of birth by Craig and Buchanan, the serum phosphorus concentration was below 6 mg. per 100 ml.

TREATMENT

Emergency Treatment of Convulsions

Convulsions due to hypocalcemia usually respond promptly to the administration of calcium salts. For emergency treatment Gribetz advised a 10 per cent solution of calcium gluconate to be given intravenously at a rate of less than 1 ml per minute. The injection should be discontinued at the first sign of bradycardia or as soon as the desired clinical result is obtained. Calcium should never be given intramuscularly, and care must be taken to prevent leakage into the tissues when the solutions are infused into a vein.

Gribetz warned that calcium salts must be administered with great caution in children who have received digitalis, since the calcium ion may potentiate the effect of this drug.

Treatment of Hypocalcemia with Mild Symptoms

Calcium Chloride. Therapy may be initiated by the administration of a dilute solution of calcium chloride by gavage or by diluting the salt in regular feedings. The concentration of calcium chloride solutions placed in the gastrointestinal tract should never exceed 2 per cent,¹² and this salt should not be given for more than 48 hours because it may promote severe acidosis.

A dosage of 1.5 Gm. per day (in three divided doses) is usually sufficient in young premature infants.

Other Calcium Salts. Oral treatment may be continued with calcium lactate or calcium gluconate 3 to 4 Gm. per day (in two or three divided doses) for approximately one week.

Treatment of Nonspecific Manifestations

Reports of the influence of treatment on premature infants with hypocalcemia accompanied by nonspecific clinical manifestations cannot be evaluated in the absence of controls.⁷ Until the results of properly controlled therapeutic trials are available this subject will continue to be controversial.

RICKETS

According to Follis and his co-workers "rickets is characterized by a failure of inorganic materials, particularly calcium and phosphorus, to be deposited in the organic matrices of cartilage and bone (osteoid)."²¹

In premature infants rickets tends to develop earlier, to progress more rapidly, and to be more severe than in those born at term.¹⁴ In addition, it has been considered more difficult to prevent rickets in premature infants.

Causes

The tendency for premature infants to develop rickets is due to a relatively small antenatal store of calcium and phosphorus (see Chap. 10), the rapid rate of postnatal growth and, perhaps, the defective absorption of vitamin D from the gastrointestinal tract.

Incidence

The incidence of rickets in premature infants is dependent upon the criteria chosen for the diagnosis as well as the degree of prematurity and the frequency

of occurrence of various precipitating factors. Eliot and Park considered that unless antirachitic treatment is begun soon after birth nearly all premature infants develop rickets, usually of a severe degree.

Clinical Studies. Von Sydow, examining a series of 118 premature infants with birth weights below 2000 Gm., found that roentgen signs of rickets appeared in more than half after the first month of life. The radiologic signs of rickets occurred more frequently in infants fed human milk. Calcium, phosphorus, and phosphatase values in the blood were also influenced by the type of milk fed and by supplements of vitamin D.

Eck and co-workers studied 69 premature infants with birth weights below 2000 Gm. who received human milk, cow's milk, or human milk supplemented with dried skimmed cow's milk, all received 800 units per day of a water-miscible vitamin D₂ preparation. Except for the fact that infants who received human milk exhibited craniotables relatively frequently, no clinical signs of rickets were found. Chemical investigations in this series showed frequent variations from normal values for older infants and changes that approximated those seen in cases of active rickets. Although the chemical variations were more pronounced in the group fed human milk than in the groups receiving cow's-milk mixtures, comparison of these slightly abnormal chemical findings with radiologic and clinical evidence of rickets revealed no correlation.

Postmortem Studies. Follis and co-workers²¹ determined the prevalence of rickets at necropsy in a series of 1303 children who died before they were 2 years old of a variety of conditions during the time period from 1926 through 1942 in Baltimore, Maryland. In the entire group the prevalence of moderate and severe rickets was high, but the incidence was not significantly higher in those born prematurely than in those born at term, being 60 per cent for the former and 56 per cent for the latter.

In an analysis of the prevalence of rickets by age at death, Follis' group²¹ noted only 2 cases in 360 infants who died in the first two weeks of life. After the age of two weeks the incidence rose sharply. No cases of congenital rickets were observed in 162 stillborn infants.

Ranström and von Sydow found a relatively high early incidence of histologic evidence of rickets in breast-fed premature infants who died during the period 1943 to 1945 in Gothenburg, Sweden. In 146 premature infants who died before they were 30 days old, 55 per cent were found to have rickets; a relatively high incidence was noted in infants who died within two days of birth. The mothers of infants in this series were not suffering from osteomalacia. The authors considered that the increase in the incidence of rickets immediately after birth among

the Swedish infants was caused by a deficiency of available minerals in human milk.

DIAGNOSIS

Clinical Signs

In premature infants clinical signs of rickets usually do not appear until the third month of life. A very early onset of rickets is usually considered to be related to maternal osteomalacia. There is conflicting evidence bearing on the question of whether early signs may appear in premature infants who are fed human milk^{13, 44, 53}

The development of rickets in premature infants is usually insidious. Craniotabes may be the first skeletal sign. Eliot and Park observed that the clinical signs of rickets become conspicuous in the skull of the premature because the head grows rapidly, and, in contrast to the term infant, the arms and legs are moved relatively little and as a result conspicuous deformities do not occur early. If the infants are untreated or inadequately treated, the disease progresses and the classical signs of rickets appear. These are enlargement of the cartilage-shaft junctions, particularly of the ribs and wrists, enlarged frontal bosses, delayed closure of the fontanelle and of the sutures of the skull, and a prominent abdomen.

Roentgenographic Signs

Early Rickets. The earliest changes in roentgenograms of the bones of premature infants that may be due to rickets are difficult to detect and to interpret. Pathologic appearances may be due to poor technique in taking the roentgenograms or to roentgenographic signs that result from rapid growth. In addition, none of the roentgenographic signs of early rickets is pathognomonic.

Figure 21-1 shows serial roentgenograms of the bones of the forearm of a premature infant. Park⁴¹ emphasized the importance of serial films because many times in his experience a doubtful diagnosis of rickets from an early film was confirmed by films taken after treatment had been given. Caffey considered that the roentgen film has limited value in the identification of early rickets because roentgen changes may appear several weeks after clinical and chemical signs are present. He noted that the greatest value of the roentgen examination is its accurate portrayal of the degree of healing.

Later Rickets. Eliot and Park listed the roentgenographic evidences of later rickets as cupping, spreading, spur formation, fringing, and stippling at the car-

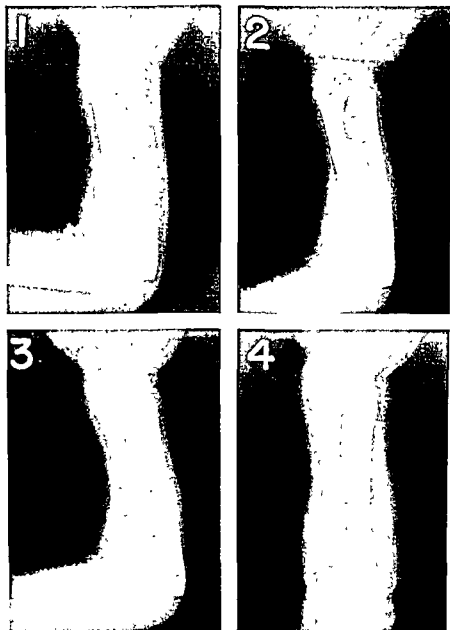


FIG. 21-1. Serial roentgenograms showing the development of rickets in a premature infant. (1) Age 60 days, slight demineralization of the shafts of the radius and ulna. (2) Age 75 days, spreading and fraying of the distal ends of ulna and radius, slight cupping of the ulna. (3) Age 83 days, progression of the signs seen earlier. (4) Age 106 days, healing rickets; calcium deposition at the diaphyseal-epiphyseal junction of the distal end of radius and ulna. A periosteal shadow is visible on the inner side of the shaft of the ulna and on both sides of the shaft of the radius. (Courtesy of John Caffey, M.D., Babies Hospital, New York.)

tilage-shaft junction. The evidences are the same in premature infants as in term infants and are described in detail, with explanation of the underlying pathology, in the monograph by these authors.

Biochemical Findings

Determination of the calcium, phosphorus, and phosphatase levels in the serum may at times be a more accurate method for early diagnosis of active rickets than are clinical and roentgenographic signs

Asymptomatic Premature Infants. Eek and others studied the chemical pattern of the serum in asymptomatic premature infants who received various types of feedings. Their findings are given in Table 21-2. The values for calcium were essentially the same in the groups who received human milk alone and those who

TABLE 21-2 VALUES FOR CALCIUM, PHOSPHORUS, AND PHOSPHATASE IN THE SERUM OF PREMATURE INFANTS ON DIFFERENT FEEDINGS

	Age (days)	Human milk			Cow's milk mixture ^a			Modified human milk ^b		
		No	Mean	S D	No	Mean	S D	No.	Mean	S D
Calcium (mg per 100 ml.)	0-14	9	10.6	±0.7	8	10.2	±0.9	12	9.0	±1.1
	15-30							17	9.8	
	31-45	18	10.3	±0.9	19	10.3	±0.4	16	9.6	±0.7
	46-60	12	10.4	±0.7	14	10.1	±0.8	18	10.0	±0.9
	61-75	16	10.4	±0.7	12	10.6	±0.7			
	76-100	10	10.7	±0.5	6	10.9	±0.3	14	10.3	±0.7
Phosphorus (mg per 100 ml)	0-14	15	4.0	±0.9	17	4.7	±0.9	12	4.4	±1.1
	15-30							17	4.7	
	31-45	18	3.8	±0.8	19	5.3	±0.8	16	5.0	±0.6
	46-60	13	4.0	±1.0	12	5.1	±0.9	18	4.8	±0.5
	61-75	16	3.8	±0.7	11	3.8	±0.9			
	76-100	10	4.0	±0.7	7	6.3	±0.7	14	4.9	±0.4
Phosphatase (King-Armstrong units)	0-14	6	13.6	±1.2	8	13.4	±2.1	9	19.3	±7.9
	15-30							17	21.4	
	31-45	13	18.3	±4.4	17	15.0	±2.8	16	19.6	±2.1
	46-60	9	17.3	±4.7	12	17.1	±4.6	18	22.3	±4.8
	61-75	13	20.1	±6.2	11	13.8	±4.2			
	76-100	10	21.3	±5.8	5	16.3	±5.9	13	17.2	±4.7

From Eek *et al.*¹³

All infants received 800 I.U. of a water miscible vitamin D₂ preparation daily

^a Equal parts of cow's milk and water with 7 per cent sugar for the first 8 weeks, later two parts of cow's milk and one part of water with 5 per cent sugar

^b Dried skimmed milk was added to human milk so that the calcium content of the mixture was 0.062 per cent and phosphorus 0.030 per cent.

received a cow's-milk mixture. Infants fed modified human milk showed the lowest concentrations of calcium. Phosphorus concentrations were lowest in the serum of infants fed human milk alone. The phosphatase values showed an increase from the neonatal levels in all groups; infants who received human milk alone and modified human milk had consistently higher values than those in the cow's-milk group.

Rickets. Eliot and Park noted that in premature infants with rickets it is common to find the concentration of inorganic phosphorus greatly reduced (below 4 mg. per 100 ml.) and the calcium moderately so (e.g., 6 mg. per 100 ml.).

The phosphatase activity in the serum is increased in rickets. Concentrations above 20 units (Bodansky) per 100 ml. are usually considered to be indicative of rickets in term infants.¹⁴ This is less certain in premature infants. Von Sydow found that when roentgen signs of rickets were present in premature infants most of the phosphatase values were higher than 30 units, and almost all exceeded 20 units.

Eliot and Park emphasized that rickets can develop in the presence of calcium and inorganic phosphorus concentrations which fall within the range regarded as normal for term infants. Eck's group, on the other hand, found variations from normal values, particularly in premature infants fed human milk, approximating those seen in cases of active rickets, yet they were unable to correlate abnormal serum values with an increased occurrence of the radiologic or clinical signs which they considered to be diagnostic of rickets.

TREATMENT OF ACTIVE RICKETS

When rickets is present Eliot and Park advised the use of vitamin D in amounts large enough to end the disease rapidly, followed by gradual lowering of the dose. Daily doses of 1500 to 5000 units are usually adequate to bring active rickets under control in several weeks. If larger doses are used in an attempt to effect a more rapid cure they should not be given for longer than 10 days.

PROPHYLAXIS

A daily prophylactic dose of 1000 units of vitamin D is often recommended¹⁴ to prevent rickets in premature infants, although there is evidence that a smaller dose is adequate.^{13, 25} We administer 1000 units per day in a water-miscible preparation (see Chap. 10).

Parenteral Vitamin D

In special cases in which adequate supervision of the premature infant is not

possible, single or repeated massive parenteral doses of vitamin D have been advised in place of daily oral prophylaxis throughout infancy.^{35, 36}

Hypervitaminosis D. Hallman and others suggested that large parenteral doses may produce hypervitaminosis D in some infants. The clinical signs and symptoms observed included lassitude, lack of appetite, thirst, polyuria, irritability, vomiting, loss of weight, hypercalcemia, and osteosclerosis.

TETANY DUE TO VITAMIN D DEFICIENCY

Although no longer a common cause of hypocalcemia in the United States, rickets caused by vitamin D deficiency may be associated with tetany. The association is especially likely during the healing phase of rickets.²⁷

Gribetz noted that the theories that have been advanced to explain the association include increased avidity of the bones for calcium and direct vitamin D-parathyroid antagonism. Guild observed that tetany due to vitamin D deficiency occurs infrequently during the first three months of life; the highest incidence is in the second half of the first year. She noted that premature infants show a special liability to tetany as they do to rickets.

DIAGNOSIS

In contrast to the uncertainty which often surrounds the diagnosis of tetany in the newborn period, a confident clinical diagnosis can usually be made in older infants. Clinical symptoms of manifest tetany are hypertonicity, muscular twitching, carpopedal spasm, laryngospasm, and generalized convulsions, these conditions occurring separately or in combination. The convulsions may occur in great numbers and are quite unique since children remain mentally alert and relatively active in the intervals between them.²⁸ A positive Chvostek's sign (facial phenomenon) in a term infant after one month of age is usually significant, but in premature infants neither Chvostek's sign nor Erb's sign (increased electrical excitability of motor nerves) can be depended upon for diagnosis up to two or three months of age. As Guild has stated, the ultimate confirmatory sign of tetany is a subnormal concentration of calcium in the blood.

Differential Diagnosis

Tetany due to vitamin D deficiency must be differentiated from tetany due to alkalosis, such as occurs in persistent vomiting, increased pulmonary ventilation, or following the administration of an excess of sodium bicarbonate. Tetany caused by this acid-base disturbance, while not associated with a decrease of total

serum calcium concentration, has been shown to be due to a decrease in the concentration of the ionizable calcium.²⁷

Hypocalcemia has been noted as a frequent complication of hypertonic dehydration in infancy, and convulsions are frequently observed during the course of this disturbance.^{17, 56} However, Finberg¹⁸ noted that while hypocalcemia may contribute to the manifestations related to the central nervous system in hypertonic dehydration, it is not always or even usually present in those with the most severe manifestations.

Other conditions associated with hypocalcemia in infancy and childhood are given in the accompanying tabulation.

PATHOGENESIS OF HYPOCALCEMIA:* CLASSIFICATION²⁷

A. Defects in intake 1 Dietary deficiency 2 Vitamin D-deficiency rickets 3 Ingestion of oxalates, citrates, etc 4 Postacidotic tetany 5 Hypertonic dehydration 6 Hypoproteinemia B. Defects in absorption 1 Congenital gastrointestinal malformation 2 Fibrocystic and celiac disease 3 Hepatic disease 4 Acute pancreatitis	C Defects in urinary excretion 1. Chronic nephritis 2 Tubular disease D Parathyroid disease 1. Temporary insufficiency (tetany of newborn) † 2 Postoperative tetany 3 Idiopathic 4. Pseudohypoparathyroidism ‡ E Unclassified 1. Neonatal hypocalcemia 2 Alkalosis 3. Unknown

TREATMENT

Treatment of tetany associated with rickets consists in the administration of calcium solutions by mouth or intravenously, depending on the severity of the symptoms. The calcium preparations that may be used and the precautions that must be observed are the same as those that were discussed under Neonatal Hypocalcemia. A dilute calcium chloride solution may be given by mouth to initiate therapy (1.5 to 3 Gm. daily, in three divided doses). Treatment may be continued with calcium lactate or with calcium gluconate in daily dosage of 3 to 6 Gm. (in

* Hypocalcemia refers to decrease of either total or ionized calcium concentration, the latter in certain instances existing without the former.

† It is not certain whether groups D₁ and E₁ are identical. Both should perhaps be cross-classified under category C.

‡ Pseudohypoparathyroidism may in reality be included in category C.

two or three divided doses). Guild advised that calcium salts be administered for at least two weeks and sometimes longer, while antirachitic treatment is getting under way.

ASCORBIC ACID (VITAMIN C) DEFICIENCY (SCURVY)

Earlier studies indicated that premature infants may have a relatively small supply of vitamin C in the liver at birth.³⁰ As this vitamin is not synthesized in the body, there is a rapid fall after birth. Although clinical manifestations of scurvy are rarely found in infants under 3 months of age, subclinical deficiency can occur much earlier if ascorbic acid is not supplied in adequate amounts.^{32, 33}

The practice of routinely administering vitamin C (see Chap. 10) has made scurvy a rare disease in infancy. However, Whelen and others have found that the condition cannot be completely eradicated without a continuing program of community education.

For a complete discussion of the subject of infantile scurvy the reader is referred to other sources.^{19, 20, 38, 42}

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Infants of Diabetic Mothers

UNRECOGNIZED PREMATUREITY

There has been increasing awareness that the large size of the newly born infants of a diabetic mother may often obscure actual prematurity.¹⁵ As a result, many of these infants are now admitted to nurseries for premature infants waiving the usual birth weight criteria for admission. A fair number of arguments can be presented to support this view. Cardell⁹ observed that a group of infants whose mothers had diabetes were heavier and longer than a control group of similar gestational age. He observed, in agreement with Warren and LeCompte, that a high proportion of the kidneys of these infants had immature glomeruli as compared with controls of a similar birth weight and concluded that gestational age should be considered a more accurate criterion than birth size in estimating the degree of maturity of the offspring of diabetic women.

Findings Suggestive of Prematurity

Other findings in these infants which are in contrast to those expected in infants of similar size, but expected in infants of similar gestational age, are a high incidence of respiratory distress,^{26, 29} extramedullary hematopoiesis,⁹ erythroblastemia,⁵ hypoglycemia,¹¹ hypocalcemia,⁴¹ hyperbilirubinemia,⁴² and unexplained episodes of apnea and cyanosis.¹¹ Skeletal maturation as judged by the centers of ossification has been found to be consistent with gestational age.⁹

The glycogen content of placentas from diabetic mothers at term was shown²⁰ to be higher than that of placentas of nondiabetic mothers. This finding in maternal diabetes resembles the condition expected earlier in pregnancy and has been interpreted to indicate retardation of placental development.

ANTENATAL CONSIDERATIONS

Fetal Deaths

The intrauterine existence of the infants of diabetic mothers is a hazardous one.²⁷ Hagbard, among others, has shown that the risk of intrauterine death is fairly high in the pregnancies of diabetic women and that this risk increases as the end of gestation approaches.

Role of Toxemia of Pregnancy. Most of the antenatal deaths occur before the onset of labor. A high incidence of toxemia of pregnancy in diabetic women has been cited in partial explanation for this increased risk of intrauterine death. Hagbard noted that the rates of occurrence of both toxemia of pregnancy and hydramnios rise considerably in these women during the last weeks of pregnancy.

Influence of the Severity and Duration of Maternal Diabetes. The influence of the severity of diabetes (duration of the diabetic state, calcified arteries, retinopathy, nephropathy) upon fetal loss has been considered at length by many authors. Evidence has been presented both for and against the argument that severity and duration of maternal diabetes influence fetal outcome.^{18, 30} However, there is general agreement that acidosis and coma are associated with increased fetal loss and that maternal hypoglycemia has no influence upon fetal outcome.¹⁸

Obstetric Management

Obstetric management of the pregnant diabetic is a controversial subject

Hormone Therapy. The hope that stilbestrol and progesterone regularly administered to the pregnant diabetic might minimize toxemia and reduce fetal mortality appears not to have been realized.²⁵ In this connection it should be noted that there is evidence that oral or intramuscular administration of progestins may occasionally cause partial masculinization of the female fetus (see Chap 6).

Medical Control and Planned Termination of Pregnancy. Most are agreed that the control of the diabetes should be strict and that the pregnancy should not be permitted to go to term. Pedersen³¹ has presented evidence from Denmark that fetal loss (both intrauterine and neonatal) was reduced by a program of strict medical care which included admission to the hospital eight weeks before calculated term and induction of labor five weeks later (at beginning of the thirty-eighth week) with drugs and artificial rupture of membranes. This regi-

men was associated with a reduction in fetal mortality as compared with earlier practices.

Type of Delivery. Vaginal delivery has been associated with a higher fetal loss in diabetic than in nondiabetic pregnancies, because the former patients have a

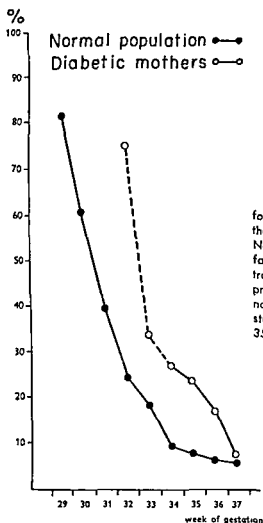


FIG. 22-1. Risk of neonatal death for live-born infants delivered before the thirty-eighth week of pregnancy. Neonatal death rates are higher in infants of diabetic mothers than in controls until the thirty-seventh week of pregnancy. (From Hagbard, L.: Pregnancy and diabetes mellitus: A clinical study. *Acta obst. et gynec. scandinav.* 35: Suppl. 1, 1956.)

higher incidence of dystocia due to uterine inertia, hydramnios, and fetal over-size Hagbard reported the results in a large series of diabetic women in whom a concerted effort was made to time delivery carefully in an attempt to avoid the double fetal risks that result from too early delivery (prematurity) and too late delivery (intrauterine death) (Fig. 22-1). The time chosen for terminating preg-

nancy was between the thirty-fifth and thirty-seventh weeks, usually by cesarean section (65 per cent of 249 cases). It is unfortunate that there is no valid way to compare the low perinatal mortality in this series that was conducted without concurrent controls and the good results in Pedersen's series³¹ (also without concurrent controls), since cesarean section was resorted to less frequently in the latter series (18 per cent of 130 cases).

NEONATAL CONSIDERATIONS

BODY SIZE

As has been noted above, the offspring of diabetic (and prediabetic^{14, 26}) women are heavier and longer than controls. However, Cardell⁹ found this to be true only for fetuses of gestational age more than 28 weeks. Fetuses of diabetic women less than 28 weeks of age were not heavier than controls, and Cardell⁹ suggested that the factor producing large infants might not be operative until after this time.

It is of interest that Hultquist produced giant fetuses in experimental animals by pancreatectomy.

Organ Weights. The organ weights of the infants of diabetic mothers have been compared with controls.^{9, 38} The brain weights of infants in the diabetic group were less than those of controls of similar body weight. Lung, liver, spleen, adrenal, and kidney weights were not considered by Cardell⁹ to be significantly different from controls of similar body weight, although these organs were heavier when the comparison was made on the basis of gestational age.

Although only a small proportion of infants of diabetic mothers in these studies had cardiomegaly, there is agreement that this finding occurs often enough to be considered significant.^{9, 38}

CLINICAL FINDINGS

General Appearance

The newborn infant of the diabetic mother can often be identified on inspection. Åkerrén has suggested the apt term "tomato face" to describe the round face with ballooning of the cheeks and markedly red skin.

The plump, well-rounded appearance presented by these infants has been attributed to edema;⁹ however, this point is in dispute.¹³ Osler and Pedersen presented evidence which indicated that the newborn infant of a diabetic mother is fat and nonedematous.

TABLE 22-1 RESPIRATORY SYMPTOMS IN INFANTS OF DIABETIC MOTHERS

<i>Respiratory symptoms</i>	<i>No</i>	<i>%</i>
Total viable infants	711	
Infants with respiratory distress clinically	216	31
I Time of onset		
0-6 hr.	175	81
6-24 hr	14	7
24 or more hr	12	6
Not recorded	15	7
II. Duration		
0-24 hr	85	39
24-48 hr	79	37
48 or more hr	25	12
Not recorded	27	13
III. Type		
Hoarseness and cough	195	90
Complaining cry	193	89
Retraction of chest wall	178	81
Cyanosis	119	55

From Gellis and Hsia.¹⁵

Respiratory Performance

The respiratory performance of these infants has assumed greater importance with the increasing conviction that the respiratory-distress syndrome is one of the most frequent conditions associated with neonatal death³⁹ (Table 22-1). Haddad *et al.* demonstrated that the neonatal respiratory rates of infants of diabetic mothers were significantly higher than either term or premature infants. They attributed this difference to the high incidence of respiratory distress in the maternal-diabetes group.

The infants who exhibit respiratory distress are noted to have very rapid respiratory rates (often exceeding 60 per minute), intercostal retractions, expiratory grunt, and cyanosis.²¹ These are indistinguishable from the signs manifested by the premature infant with respiratory distress (see Chap. 14).

Among infants of diabetic mothers there is a high incidence of unexplained episodes of apnea and cyanosis not related to signs of respiratory distress.¹⁸

Renal Vein Thrombosis

Avery *et al.* described two cases of renal vein thrombosis in infants of diabetic mothers and collected two more from the literature.^{4, 37} They suggested that

this diagnosis should be considered at the time of the sudden appearance of a mass in the flank, with or without such other findings as hematuria, fever, leukocytosis, thrombocytopenia, vomiting, diarrhea, and dehydration.

Congenital Malformations

There is no agreement concerning the interpretation of the incidence of congenital malformations among the offspring of diabetic mothers (from 6 to 37 per cent malformations in viable fetuses)¹⁸ This uncertainty reflects confusion about the definition of congenital abnormalities and lack of exact information about the normal population³³

LABORATORY STUDIES

Acid-Base Homeostasis

Cord-blood studies of 45 infants of diabetic mothers by Segal *et al.* revealed that an acidosis existed at the moment of birth, with an elevation of both carbon dioxide tension and lactate levels; lowered oxygen saturation was also found. Further studies of these infants in the first four hours of life revealed an uncompensated acidosis. Lowrey *et al.* reported similar findings. Both groups of investigators found high plasma carbon dioxide tensions, which indicated faulty gas exchange between mother and fetus and also suggested that ventilatory control of this factor was inadequate in the neonatal period. Similar findings have been described in premature infants (see Chap. 14).

Hemogram

The finding of numerous nucleated red blood cells in the peripheral blood of 9 out of 19 newborn infants of diabetic mothers was interpreted by Berglund and Zetterström as evidence that a high proportion of these infants had been subjected to serious intrauterine hypoxia.

Gellis and Hsia found that the hemoglobin concentration, red cell count, white cell count, and differential counts on the first day of life in a large number of infants of diabetic mothers did not differ significantly from the values seen in normal infants.

Urinary Excretion of Electrolytes

The increased excretion of electrolytes (sodium, potassium, and chloride) in the urine of babies born to diabetic mothers is similar to the pattern expected for premature infants.^{36, 40} Urine volume during the first 48 hours of life in a group

of thirsted infants of diabetic mothers was considerably greater than that of term infants who were fed during this period.¹² Again, this performance was similar to that expected in premature infants.¹⁹

Blood-Sugar Concentration

Blood-sugar concentration in the neonatal period and carbohydrate metabolism in infants of diabetic mothers have been the subjects of much study.^{11, 30} The present state of this controversial topic may be briefly summarized by the statement that almost all observers are agreed that the sugar content of the blood in the newborn infant of the diabetic mother falls more rapidly and reaches a lower value than that of normal term infants. A spontaneous rebound or return to values approaching those observed at birth has been observed by most investigators; the time for this return is estimated to be between six and twenty-four hours after delivery in fasting infants.

Pedersen³⁰ postulated that an elevated content of sugar in maternal blood stimulated the fetal output of insulin, he found that when the concentration of sugar in maternal blood was kept low the neonatal fall in the infant's blood was not greater than in normal term infants.

Gellis and Hsia determined the concentrations of sugar in the blood of approximately 100 infants of diabetic mothers and found that hypoglycemia occurred rarely. There have been many attempts to correlate blood-sugar levels and clinical symptoms (e.g., apnea, cyanosis, "twitchings"); most observers have failed to establish an association.²⁸ Cardell⁸ found no correlation between the lowest blood sugar recorded and the amount of islet tissue in the pancreas.

In a group of 40 infants born to diabetic mothers, 25 were given 2 Gm. of glucose orally during the first eight hours of life, the remaining 15 were fasted during this period.²³ There was no significant difference in the blood-sugar concentrations in these two groups. A controlled trial to compare the effects of glucose administration and fasting on neonatal mortality has not been reported (See also Chap. 21.)

Calcium and Phosphorus Homeostasis

Zetterstrom and Arnhold⁴¹ reported that hypocalcemia and hyperphosphatemia occur commonly in newborn infants born of diabetic mothers, particularly those delivered by cesarean section. They suggested that this is an additional expression of the resemblance of these subjects to premature infants and postulated that the manifestations of twitching, tremor, and attacks of cyanosis were related to these chemical deviations.

Gittleman *et al.* in an earlier study observed that the incidence of hypocalcemia on the first day of life was greater in infants whose mothers had abnormal pregnancies. Diabetes mellitus was included as one of the maternal conditions conducive to hypocalcemia in the infant. Craig observed a high incidence of hypocalcemic tetany in newly born infants of diabetic mothers. The clinical signs attributed to hypocalcemia appeared on the first day of life, and the initial manifestations were respiratory (tachypnea, retractions, apnea, and cyanosis). Following this the infants exhibited exaggerated responses to external stimuli, and in some the abnormal movements culminated in tetanic convulsions. All of Craig's patients were born prematurely; he suggested that the high incidence of hypocalcemia was favored by this circumstance.

Hyperbilirubinemia

Zetterström *et al.*⁴² found a high incidence of hyperbilirubinemia in infants of diabetic mothers. The usual timing of the peak level (fourth day) was somewhat later than expected for term infants and earlier than expected for premature infants.

An increased incidence of kernicterus among infants of diabetic mothers has not been reported. In this connection, Arnhold and Zetterström found that the concentrations of protein in the cerebrospinal fluid of infants of diabetic mothers were high and approximated the levels observed in premature infants.

Hormonal Studies

Hormonal imbalance has been frequently invoked to explain the difficulties of the newborn child of the diabetic mother. Farquhar¹² reviewed the arguments for and against the thesis of hyperadrenocorticism. The finding of a higher-than-normal urinary excretion of acid-stable formaldehydogenic steroids on the first day of life, together with many clinical arguments, were advanced by him as evidence of increased adrenocortical activity in these infants. A similar hypothesis had been presented earlier by Björklund,⁷ although the pattern of urinary excretion of steroids was not the same. Björklund⁸ obtained electrocardiograms of 15 children of diabetic mothers and discovered abnormalities in 11 which resembled those seen in hypokalemia. Increased pituitary activity and adrenocortical dysfunction was postulated.

Silver discovered abnormally low values of butanol-extractable iodine in 6 out of 7 newborns of diabetic mothers and suggested a temporary "physiologic hypothyroidism" in these infants.

POSTMORTEM FINDINGS

Reference has already been made to the larger-than-normal body and organ size of infants of diabetic mothers. In many of these infants who die in the neonatal period the microscopic appearance of the lungs is similar to that seen in premature infants who die after exhibiting signs of respiratory distress^{9, 38} (see Chap. 14).

Islet Hyperplasia

Hyperplasia of the islets of Langerhans of the pancreas has been found in a high proportion but not all of the infants of diabetic mothers. This finding has been considered to be caused by maternal hyperglycemia, which stimulates fetal insulin production. The clinical observation that the carbohydrate tolerance of the mother improves as pregnancy nears its end, only to return to its previous state following delivery, has been advanced as evidence for this hypothesis. However, the accuracy of this observation is disputed;¹⁸ moreover, hyperplasia of the islets has also been described²⁶ in prediabetic women and in erythroblastosis fetalis with normal maternal blood-sugar levels.

Cardell⁹ observed a close correlation between the amount of islet tissue and the body weight of the infant of the diabetic mother; this was not true of infants of nondiabetic mothers. He found a poor correlation between maturity and the amount of islet tissue in infants of diabetic mothers. In reviewing this subject he suggested that the increase of islet tissue might be due to overproduction of maternal growth hormone.

Ovarian Cysts

Luteinized follicular cysts described in many infants of diabetic mothers have been ascribed to a high concentration of chorionic gonadotropin and to extensive use of stilbestrol and ethisterone (ethynyltestosterone or pregnenolone) in these pregnancies.^{1, 9, 38}

Other Findings

A high incidence of active hematopoiesis in the liver and spleen has been thought by some³⁸ to be consistent with the degree of immaturity of these subjects and to be due to intrauterine hypoxia by others.⁵

Although an excess of glycogen has been described in the myocardium, Cardell⁹ expressed doubt that this could account for the examples of cardiomegaly in infants of diabetic mothers.

The implication of the common finding of immature renal glomeruli in these infants has already been discussed.

Present evidence indicates that there is no significant morphologic abnormality of the thyroid, pituitary, adrenals, brain (except for size), testes, and bones.⁵⁸

MANAGEMENT OF PREMATURE INFANTS OF DIABETIC MOTHERS

PREVENTION OF PREMATUREITY

Hagbard conducted an extensive inquiry in Sweden and concluded that the details of neonatal care were without demonstrable influence on survival rates among newborn infants of diabetic mothers. He found that the degree of maturity was the most important factor affecting their neonatal survival rate. To prevent the losses due to prematurity he advocated that the pregnancy be carried to the thirty-seventh week. After this time the pregnancy should be terminated, usually by cesarean section, to avoid the risk of intrauterine fetal death.¹⁸

NURSERY CARE

Environmental Conditions

Many have advocated that these infants be placed in incubators, despite their birth weight, with adequate heat and humidity to reduce heat loss. Hsia *et al.* demonstrated by a controlled clinical trial that the mortality rate among these newborn infants who were placed in environments supersaturated with water mist was not significantly different from that of controls in 50-70 per cent relative humidity. The conditions of the trial were terminated after 48 hours. Both groups were fasted during the trial, and the oxygen concentration in the incubators ranged from 40 to 60 per cent.

No studies are available of the development of the retinal vessels nor of the incidence of retrolental fibroplasia among the infants of diabetic mothers. However, since these infants have many stigmata of prematurity, a conservative policy of oxygen administration is well advised (see Chap. 7).

Feeding

The conflicting policies of withholding fluid and feedings from these infants during the first day or two after birth as opposed to early glucose administration, have not yet been subjected to a critical test with respect to their influence on neonatal mortality.

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Other Abnormal Conditions Associated with Prematurity

PROLONGED APNEA WITH CYANOSIS

DIAGNOSIS

Episodes characterized by sudden, inexplicable cessation of respiratory movement are familiar to all who care for premature infants. The duration of the period of respiratory arrest is usually more than half a minute. Miller¹⁵ commented that surprisingly good color is maintained for as long as the first 30 to 40 seconds of apnea, and cyanosis follows if respiratory movements do not resume. This has also been our experience. The attack of apnea usually occurs without warning, but Miller¹⁵ noted that slowing of the respiratory rate (below 30 per minute) may be a heralding sign. Although simple cutaneous stimulation may be sufficient to initiate respiration, these attacks are usually recurrent, and resumption of respirations is not spontaneous.

Differentiation From Periodic Breathing

These apneic episodes are different from the apnea which is a feature of periodic breathing commonly observed in premature infants.^{3, 6} In periodic breathing with apnea, the duration of respiratory arrest is more than 3 seconds but rarely more than 20 seconds.⁷ Recovery is spontaneous and the cycle is recurrent. Prolonged apneic episodes do not occur exclusively in premature infants who exhibit periodic breathing. However, both phenomena are seen more frequently in infants of low birth weight.^{3, 11, 15}

CLINICAL CONSIDERATIONS

Miller^{15, 16} reported that sudden, prolonged (60 seconds or more) apnea among newborn infants was encountered almost exclusively among those whose respiratory rates showed a significant increase after the first hour of life.

Illingworth collected a group of 170 newborn infants who had sudden attacks of cyanosis lasting from a few moments to half an hour; 103 of these were premature infants.

Age at Onset

Illingworth observed that 40 per cent of the attacks occurred in the first 24 hours and 72 per cent in the first three days. In 30 premature infants with severe apneic attacks reported by Miller *et al.*¹⁸ the initial episode appeared at some time during the first three days of life in 13 infants and beyond the third day in 17. The mortality rate among those with an early initial episode (12 of 13 infants) was greater than that among the infants who exhibited this sign later (6 of 17).

Relation to Respiratory Obstruction

Apneic episodes often occur immediately after a feeding, milk or tenacious mucus can be aspirated from the oropharynx and it appears that respiratory obstruction has been responsible. The number of apneic attacks can sometimes be reduced simply by relieving nasal obstruction.

In very small infants one can often induce apnea by flexing the head to produce oropharyngeal obstruction to the airway. When the head is extended respiratory movements commence. However, even elaborate efforts to maintain an adequate airway are not uniformly successful in eliminating apneic episodes.

Other Associations

Blystad classified the attacks of apnea observed in a series of 14 prematures in three categories. (1) those occurring during the course of neonatal dyspnea, (2) those which occurred during the first four days of life in infants whose respiratory performance before and between attacks was satisfactory, and (3) attacks occurring later than the fourth day of life. Blood-gas determinations disclosed that infants in the first group had marked acidosis, hypercapnea, and hypoxemia. All these infants died. Massive atelectasis and pulmonary hyaline membranes were found at necropsy and Blystad reasoned that the apneic episodes in these children were secondary to asphyxia.

In the second group the blood-gas analyses revealed no significant variation from values obtained in infants without apneic episodes. Four of the five infants in the second group survived, and no conclusions were drawn concerning the pathogenesis of these incidents.

In the third group respiratory acidosis and moderate hypoxemia were demonstrated; all of these infants survived. Moreover, the respiratory acidosis persisted long after the attacks of apnea had subsided. Blystad concluded that both pulmonary changes as well as central depression of respiration were involved in the pathogenesis of the observed respiratory acidosis in the last group.

Illingworth observed that a maternal history of toxemia, hypertension, and antepartum hemorrhage was obtained more frequently among newborn infants with cyanotic attacks than among unaffected infants. He found that these associations could not be explained on the basis of a common relationship with prematurity. The mortality rate among infants who had cyanotic attacks was higher than that of others of similar birth weight who did not suffer these attacks.

A high incidence of sudden attacks of respiratory arrest in infants of diabetic mothers has been ascribed to hypoglycemia by some and to hypocalcemia by others (see Chap. 22).

POSTMORTEM FINDINGS

In Illingworth's group the postmortem findings among 72 infants with cyanotic attacks, 84 per cent of whom were premature, were not different from those seen in 115 necropsies among controls. The incidence of atelectasis, cerebral hemorrhage, and congenital heart disease was similar in both groups. Miller *et al.*¹⁶ also found no difference in necropsy findings in apneic and non-apneic premature infants.

TREATMENT

Some apneic incidents can be terminated by simply rapping on the incubator. As many nurses have remarked, "They simply forget to breathe." However, the appearance of repeated prolonged apneic episodes in premature infants must always be taken seriously, in view of the high mortality associated with these manifestations. A detailed examination should be performed in an attempt to uncover a complication of prematurity. Lumbar puncture, blood culture, and other aids to diagnosis should be employed if the cause of the apneic episodes is not disclosed by physical examination.

Resuscitation

Careful suction of the oropharynx and the nose usually terminates the attack of apnea either by removing fluid and tenacious secretions or as the result of the sensory stimulation accompanying this maneuver. If simple aspiration does not result in the prompt resumption of respirations we have advocated that

the infant be intubated and ventilated until spontaneous respirations resume (see Chap. 6).

Oxygen Therapy

There is no evidence that the continuous administration of oxygen reduces the frequency of attacks of apnea, but short-term use of oxygen to relieve cyanosis is indicated

Other Measures

No firm recommendation concerning the administration of fluids, electrolytes, or glucose is possible in the present state of our knowledge

Nahas demonstrated that when an organic carbon dioxide buffer was infused into the veins of apneic experimental animals carbon dioxide was excreted by the kidney in sufficient amounts to maintain the acid-base balance of the blood within normal limits. Further reports on the influence of this organic buffer base in ameliorating the effects of respiratory failure will be awaited with interest by those who must deal with the problem of apnea in premature infants.

SCLEREMA NEONATORUM

There is little agreement upon a classification of disorders in which the skin of young infants becomes hard. For a full discussion of the varied terminology the reader is referred to a report by Hughes and Hammond. As noted by these authors it is difficult to compare the experience of different observers since their clinical categories do not coincide

CLINICAL FEATURES

Sclerema. *Sclerema* will be used here to describe a state in which there is induration of the skin and subcutaneous tissues which starts on the buttocks, thighs, or calves and spreads to other parts of the body, generally sparing the palms, soles, and genitalia. The skin is cold to the touch and cannot be picked up between the fingers, and movement of involved limbs is often limited.

The induration of sclerema neonatorum is generally considered to be the result of solidification of subcutaneous fat in association with low body temperature of seriously ill newborn infants. The low oleic acid content of fetal fat influences its melting point, and this is thought to be responsible for the predisposition to fat-hardening whenever there is chilling of the tissues.*

Hughes and Hammond summarized the details concerning 28 collected cases of sclerema. Only the minority were born prematurely. Since very small infants have little or no subcutaneous fat, the infrequent occurrence of a fat-solidifying syndrome among them would not appear to be surprising.

Scleredema. There is a clinical condition in which the subcutaneous tissues of premature infants become indurated in a manner and distribution identical to sclerema. This occurs in gravely ill premature infants usually on the second or third day of life when subcutaneous edema is still present. *Scleredema* was used in the past to denote the association of sclerema and edema.

Except for the fact that sclerema occurs principally in mature infants and in older premature infants, and scleredema in younger premature infants, the clinical features of these entities are virtually the same. Unless it is shown that they are the result of different pathologic processes (e.g., sclerema due to the solidification of fat, scleredema the result of some change in the physical state of the fluids of the subcutaneous tissue) sclerema should be used for both.

INCIDENCE

Gerlőczy observed that sclerema occurred principally among premature infants whose birth weight was between 1500 and 2000 Gm. Among 2100 premature infants in our nursery with a median birth weight of 1360 Gm 27 examples of sclerema were observed. More than half (18) of the affected infants weighed less than 1360 Gm. at birth. Twenty-five of the 27 infants died.

CAUSES

Sclerema is almost always associated with some other grave condition, such as enteritis, pneumonia, intracranial hemorrhage, etc. It occurs as an ominous and not uncommon complication in premature infants who undergo major surgery in the neonatal period.

Hughes and Hammond discussed the many theories of the cause of sclerema (chilling, hypothyroidism, dehydration, disordered lipid metabolism, maternal diet, etc.). They suggested that peripheral circulatory collapse, as a consequence of the accompanying serious disease, resulted in cooling of the subcutaneous tissues which enhanced fat-hardening.

The nature of the indurated material in the tissues of subjects with little or no subcutaneous fat has not been defined. Histologic examinations of the skin and subcutaneous tissue have generally disclosed no abnormality.

DIFFERENTIAL DIAGNOSIS

Subcutaneous Fat Necrosis. This condition is characterized by firm masses which are freely movable over the underlying subcutaneous tissue of cheeks, shoulders, and buttocks. Subcutaneous fat necrosis usually occurs in otherwise healthy mature infants.¹⁴

Other Conditions. The term "sclerema-like" has been applied to the plastic feel of the skin in severe dehydration, the doughy skin in hypernatremia, and to the boardlike muscles in kernicterus. However, the tissues in sclerema can be distinguished on the basis of the unique "skin-bound" quality as well as the distribution of induration at the onset.

TREATMENT

Warmth

External heat has been advocated for many years; however, this therapeutic measure has not been critically evaluated. In this connection it is of some interest to report observations made during the course of a clinical trial of the influence of two levels of ambient temperature on the survival of newly born premature infants. We noted that of three examples of sclerema encountered during the study, all occurred in infants who were assigned to the cool incubators (83–85° F [28.3–29.4° C.]).¹⁹

Vitamin E

Gerlóczy reported that vitamin E by mouth (5 mg per day) invariably induced a diuresis in 38 premature infants with "scleredema"; 36 of these infants survived. No concurrent controls were used, and for this reason it is difficult to interpret these results.

Steroids

In 1951 Kendig and Toone reported that they had successfully treated a 1700-Gm. infant with sclerema using cortisone (10 mg. every 8 hours for 3 doses and at 12-hour intervals for 5 subsequent doses). Since that time there have been several case reports of improvement following cortisone and adrenocorticotropin.^{1, 5, 21} In our nursery, however, three of the infants with sclerema were given cortisone with no apparent beneficial effect. No reports of extensive trials of the use of steroids are available that would justify the view that the outlook for sclerema has been improved by this treatment.¹⁴

MATERNAL NARCOTIC ADDICTION

Premature infants born of mothers who are addicted to narcotics (usually heroin) have been observed not infrequently in our nursery. Many of these infants have exhibited no abnormal symptoms in the neonatal period; however, others have displayed spectacular signs. Goodfriend *et al* reviewed the literature in 1956 and noted that varying degrees of clinical symptoms are manifested by the offspring, depending on the degree of addiction of the mother and the time of the last dose of narcotic before delivery. Since many addicts have no knowledge of the true dose of narcotic that they have been taking, no correlation exists between the reported dose and the severity of symptoms in the infant.

CLINICAL MANIFESTATIONS

The clinical symptoms reported by Goodfriend *et al*, by others,^{18, 20} and observed by us consist of extreme irritability, piercing cry, anorexia, and vomiting. These symptoms are not present at birth but develop in the first hours of life. More severe symptoms such as convulsions, fever, and cyanosis have also been reported. Deaths in the neonatal period¹³ have been observed following diarrhea and inanition.

TREATMENT

In our experience the symptoms have been mild, and sedation with phenobarbital has been used in only a few very irritable infants.

It is difficult to evaluate reports that claim the successful treatment of withdrawal symptoms with gradually diminishing doses of opium derivatives.¹³ Goodfriend *et al* reported a high mortality among infants who exhibited symptoms that went unrecognized and untreated.

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Part Three

PUBLIC-HEALTH CONSIDERATIONS

The Statistics of Deaths of Premature Infants

Available statistics dealing with deaths of premature infants are comprehensive for some countries, meager or unavailable for others. The chief sources of information are official national and local statistics, data from individual hospitals, and special reports based on clinical and pathologic studies.

STATISTICS ON DEATHS DUE TO PREMATUREITY IN THE UNITED STATES

SOURCES OF INFORMATION

Data Obtained from Death Certificates. The chief source of national information in regard to deaths from prematurity is the National Office of Vital Statistics, to which the various state health departments report the information obtained from death certificates. The data obtained are not always accurate, because in certifying births and deaths a clear distinction has not always been made between a live-born and a stillborn infant. Moreover, birth weight and period of gestation are not required report items on the death certificate; thus, premature infants cannot be identified unless prematurity is recorded as a factor contributing to death.

It should be pointed out that in tabulations based solely on death-certificate data, deaths that appear in the category "Immaturity unqualified"* are only those assigned to no other primary cause. In certifying causes of death included in the category "Certain diseases of early infancy," the physician is requested to indicate whether there was immaturity.³⁴ However, these categories do not include all of the deaths associated with premature birth.

Matching of Birth and Death Certificates. An item on birth weight was added to the birth certificates of all but one existing state in 1949† (see Chap.

* The terms "premature" and "immature" will be considered to be synonymous.

† On May 2, 1957, Massachusetts made reporting of birth weight on birth certificates obligatory. The newest states, Alaska and Hawaii, also report birth weight on birth certificates.

2); thus, by matching birth and death records and combining the data it became possible to obtain information on the total number of deaths among live-born infants by birth weight. Matching of birth and death records is not carried out routinely on a national basis; as a result, this information is available only from special studies.

Tabulation of Antenatal Deaths. Antenatal deaths associated with premature birth are not accounted for in tabulations from birth- and death-certificate data. Estimates of these deaths are available in reports which are based upon data collected on the Certificate of Fetal Death^{33, 36} Fetal deaths are usually tabulated by period of gestation. *Fetal death ratios* (fetal deaths per 1000 live births) and *fetal death rates* (fetal deaths per 1000 live births and fetal deaths combined) are also used in analyzing these data.

The recommendations of the World Health Organization for standardization of terms in the certification of birth and death are given in Appendix 1. The reader is also referred to other sources for terminology and recommended procedures.^{1, 34, 35}

DEATHS ATTRIBUTED TO PREMATUREITY AMONG ALL LIVE-BORN INFANTS

Premature birth takes a higher toll of infant life than any other condition, and it is one of the leading causes of death among the general population. Some idea of the extent of deaths attributed to prematurity among live-born infants can be gained from routine reports of deaths of infants under one year of age. In 1956 the total number of infant deaths in the United States was 108,183.³² The deaths of 64,515 infants, of whom almost all died in the first four weeks of life, were attributed to "certain diseases of early infancy"; in more than two-thirds of the individuals assigned to this category "immaturity" was noted on the death certificate.

Death Rates and Trends. Dunham¹² reviewed the trend of the neonatal mortality rate from premature birth in the United States, as determined from death-certificate data, between 1935 and 1948. The figures indicated that a marked decline had occurred during the thirteen-year period. In these computations, the numerator was the number of deaths in which the certificates stated no acceptable primary cause of death other than "premature birth." In 1948 revisions were adopted in the International List of Causes of Death which made it possible to identify a greater number of deaths associated with prematurity.²³ As a result of these changes in the classification, recent mortality rates from premature birth determined solely from death-certificate information cannot be compared with rates which date from the period before 1949.¹²

DEATHS AMONG LIVE-BORN PREMATURE INFANTS

The *total* number of neonatal deaths associated with prematurity (based on birth weight) in the United States was calculated for a three-month period (January 1 through March 31, 1950). In this study conducted by the National Office of Vital Statistics neonatal death records were matched with corresponding live-birth certificates. The results have been made available in a series of reports that will be referred to frequently in this chapter.

TABLE 24-1 LIVE BIRTHS, DEATHS OF INFANTS UNDER 28 DAYS, AND NEONATAL MORTALITY RATES BY BIRTH WEIGHT, SEX, AND COLOR
United States, Early 1950^a

	Birth weight (Gm)						Total
	1000 or less	1001- 1500	1501- 2000	2001- 2500	2500 or less	2501 or more	
No live births	3,928	5,081	11,388	41,240	61,637	776,149	837,786
White male	1,621	2,121	4,480	15,034	23,256	345,122	368,378
female	1,568	1,958	4,726	18,426	26,678	322,077	348,755
Nonwhite male	393	465	1,021	3,433	5,312	55,816	61,128
female	346	537	1,161	4,347	6,391	53,134	59,525
No neonatal deaths	3,424	2,801	2,403	2,078	10,706	6,035	16,741
White male	1,467	1,364	1,218	1,039	5,088	2,864	7,952
female	1,350	929	758	654	3,691	1,878	5,569
Nonwhite male	334	244	240	206	1,024	775	1,799
female	273	264	187	179	903	518	1,421
Neonatal mortality rates ^b (%)	87.2	55.1	21.1	5.0	17.4	0.8	2.0
White male	90.5	64.3	27.2	6.9	21.9	0.8	2.2
female	86.1	47.5	16.0	3.6	13.8	0.6	1.6
Nonwhite male	85.0	52.5	23.5	6.0	19.3	1.4	2.9
female	78.9	49.2	16.1	4.1	14.1	1.0	2.4

From U.S. National Office of Vital Statistics **

^a Excludes data for Massachusetts

^b Based on matched birth and death certificates. Neonatal deaths per 100 live births in each category

Among 837,786 live births in the United States early in 1950, 16,741 deaths occurred in infants under 28 days of age. The distribution of live births, deaths, and neonatal mortality rates by birth weight, sex, and color are presented in Table 24-1. More detailed tabulations of this material may be found in the reports of the National Office of Vital Statistics.^{26, 28, 29}

Birth weight-specific neonatal death rates for some states and other registration

areas are available in two reports of the National Office of Vital Statistics^{27, 30} (also see Appendix 4).

Trend of Mortality Rates by Birth Weight. An indication of the trend of neonatal mortality rates among premature infants in recent years is found in a study conducted by the New York State Department of Health^{20, 37} based

TABLE 24-2 CHANGE IN NEONATAL MORTALITY AND STILLBIRTH RATES
New York State Exclusive of New York City, 1945 to 1954

Year of birth	Neonatal mortality* (%) by birth-weight (Gm.) group						Stillbirth ^b	
	1000 or less	1001- 1500	1501- 2000	2001- 2500	2500 or less	2501 or more	Total ^c	rate
1945	94.6	69.7	25.7	7.4	22.8	1.0	2.5	2.3
1946	96.0	68.8	25.4	6.3	22.0	0.9	2.3	2.1
1947	95.4	67.8	25.5	5.5	21.4	0.9	2.3	1.9
1948	94.7	61.6	23.4	5.5	20.3	0.8	2.1	1.9
1949	94.8	60.7	19.9	5.2	19.3	0.8	2.0	1.8
1950	93.0	54.8	19.9	4.5	18.3	0.6	1.8	1.8
1951	94.2	52.4	18.0	3.7	17.2	0.6	1.7	1.7
1952	94.6	53.8	17.9	4.1	17.6	0.6	1.7	1.6
1953	96.7	51.8	17.8	4.1	17.6	0.6	1.7	1.6
1954	93.7	53.0	17.4	4.0	17.3	0.6	1.7	1.6
1945-49	95.1	65.6	23.8	5.9	21.1	0.9	2.2	2.0
1950-54	94.4	53.2	18.1	4.1	17.6	0.6	1.8	1.7
Per cent change in 1950-54 rate compared to 1945-49 rate	-0.7	-18.9	-23.9	-30.5	-16.6	-32.2	-21.9	-16.2

From Office of Vital Statistics and Bureau of Maternal and Child Health, New York State Department of Health.³⁰

* Neonatal deaths per 100 live births in each category

^b Adjusted to 1945-49 distribution of birth weight among live births in upstate New York. Based on matched birth and death certificates

^c Stillbirths per 100 reported total births.

on data from matched birth and death certificates. These rates are given in Table 24-2 and are shown graphically in Figure 24-1. During this ten-year period (1945-54) the over-all neonatal mortality rate declined by more than 30 per cent. However, the greatest reduction in mortality rate was in the group of large infants. Virtually no lowering occurred among infants weighing 1000 Gm. or less at birth. The rate of decline was directly proportional to the birth

weight in infants weighing 1001 to 2000 Gm. Baumgartner and co-workers reported similar results for New York City during the period 1947-57.

AGE AT DEATH

Almost all deaths attributed to premature birth occur in the first month of life. Among 47,621 deaths in infants under one year of age in 1956 in which there was mention of immaturity, 46,918 (98 per cent) occurred in infants under 28 days of age.³²

In the special tabulation of neonatal deaths under 28 days in the United States during the first three months of 1950 analyses were made by age and by

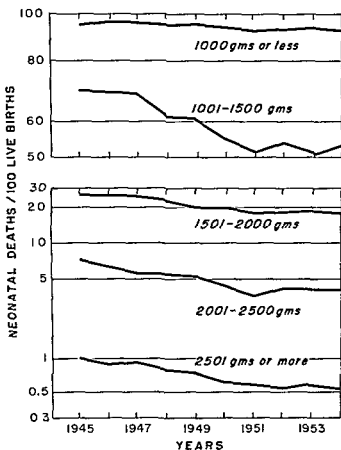


FIG. 24-1. Trends of neonatal death rates by birth weight in New York State exclusive of New York City, 1945-54. (Redrawn from Office of Vital Statistics and Bureau of Maternal and Child Health: Neonatal, Stillbirth and Perinatal Mortality and Operative Procedures for Delivery by Hospitals and Regions, New York State, Exclusive of New York City, 1950-1954. A pamphlet published by New York State Dept. of Health.)

TABLE 24-3. PERCENTAGE DISTRIBUTION OF NEONATAL DEATHS UNDER 28 DAYS BY AGE AND BIRTH WEIGHT
United States, Early 1950

<i>Age of infant at death</i>	<i>% of deaths by birth-weight (Gm.) groups</i>						<i>Total</i>
	<i>1000 or less</i>	<i>1001-1500</i>	<i>1501-2000</i>	<i>2001-2500</i>	<i>2500 or less</i>	<i>2501 or more</i>	
Under 1 day	75.2	55.3	47.0	37.8	56.3	34.1	48.4
1-6 days	23.0	35.2	41.2	46.0	34.5	42.6	37.6
Under 1 week	98.2	90.5	88.2	83.8	91.1	76.8	86.0
7-27 days	1.8	9.5	11.8	16.2	8.9	23.2	14.0

Adapted from U.S. National Office of Vital Statistics.²²

TABLE 24-4. MORTALITY RATES AT SPECIFIED AGES UNDER 28 DAYS BY BIRTH WEIGHT AND SEX
United States, Early 1950

	<i>Mortality Rates* (%) by birth-weight (Gm.) groups</i>					
	<i>1000 or less</i>	<i>1001-1500</i>	<i>1501-2000</i>	<i>2001-2500</i>	<i>2500 or less</i>	<i>2501 or more</i>
<i>Male</i>						
Under 1 day	69.8	35.4	12.5	2.6	12.2	0.3
Under 1 hour	16.7	4.1	1.4	0.5	2.1	0.1
1-23 hours	63.7	32.6	11.3	2.1	10.3	0.2
1 day	28.3	15.7	5.7	1.3	3.7	0.1
2 days	22.7	9.2	3.7	1.0	2.4	0.1
3-6 days	30.6	13.8	3.8	1.1	2.7	0.2
7-13 days	6.8	7.7	2.2	0.4	1.2	0.1
14-20 days	1.4	2.4	0.9	0.3	0.5	0.1
21-27 days	0.9	1.6	0.8	0.3	0.4	0.1
<i>Female</i>						
Under 1 day	61.0	25.5	7.5	1.4	7.7	0.2
Under 1 hour	13.6	4.4	1.5	0.3	1.6	0.1
1-23 hours	54.9	21.9	6.1	1.1	6.2	0.2
1 day	26.3	10.2	3.1	0.6	2.2	0.1
2 days	20.0	5.6	2.2	0.4	1.4	0.1
3-6 days	24.3	8.6	1.9	0.6	1.6	0.1
7-13 days	7.2	6.0	1.4	0.4	0.9	0.1
14-20 days	5.2	2.4	0.7	0.2	0.5	0.1
21-27 days	0.7	1.7	0.4	0.1	0.3	. .

From U.S. National Office of Vital Statistics.²²

* Rates per 100 children in each specified group alive at the beginning of each age interval.

birth weight.^{28, 29} More than half of the deaths of premature infants during the first 28 days of life occurred before the end of the first day (Table 24-3).

Relation to Birth Weight. The proportion of premature infants who died under one day of age varied with the weight of the infant. First-day mortality represented about three-fourths of all neonatal deaths among infants whose birth weight was 1000 Gm or less. The proportion diminished with increasing birth weight, somewhat more than a third (37.8 per cent) of the neonatal deaths occurred on the first day of life in infants whose birth weight was 2001-2500 Gm. Death rate decreased markedly for all weight groups after the first day. By the end of the first week more than nine-tenths of the neonatal deaths among premature infants had already taken place.

The risk of death by specified ages during the first month of life is shown

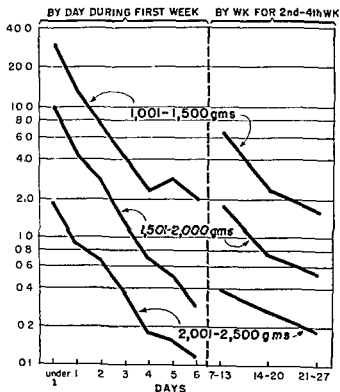


FIG. 24-2. Risk of mortality of premature infants with birth weights over 1000 Gm., at specified ages in the United States, early in 1950. Mortality rates are computed per 100 children in each specified group alive at the beginning of each age interval. (From U.S. National Office of Vital Statistics: Relation of weight at birth to cause of death and age at death in the neonatal period: United States, early 1950. *Vital Statistics—Special Reports* 39: [No. 6], 1956.)

for each birth-weight group and by sex in Table 24-4. These data are shown graphically in Figure 24-2. The rapid decline in risk among premature infants during the first week is striking; however, the remainder of the first month is still a hazardous one.

CAUSES OF NEONATAL DEATHS OF PREMATURE INFANTS

Tabulations of the causes of death of premature infants based on information reported on death certificates must be interpreted with considerable caution. Cause-of-death entries usually reflect clinical diagnoses, and even when entries are based on postmortem findings there may be disagreement between the pathologic causes and the causes recorded on the death certificates.¹⁶

When confronted with a neonatal death the certifying physician is beset with understandable confusion resulting from the fact that the cause of death may be related to some condition of the mother rather than to disease in the infant. The nosographic problem which is posed by the death of a premature infant is particularly difficult for both physicians and statisticians because of the use of "immaturity" (or "prematurity") as a cause of death. Recommended principles to be followed in certifying deaths are discussed in Appendix 2.

Certified Causes of Death by Age at Death. The distribution of infant mortality rates in the United States by cause and age may be found in routine reports of the National Office of Vital Statistics. As has been said, immaturity is included in the cause-of-death category entitled "Certain diseases of early infancy." The frequency distribution of causes for this group in the year 1956 is given in Table 24-5. In each category premature infants accounted for a substantial, but varying, proportion of the total infant deaths.

Certified Causes of Death by Birth Weight. An analysis of cause of death by birth weight among infants who died in the United States early in 1950 is also available.²⁸ A summary is presented in Table 24-6.

OTHER SOURCES OF DATA

Other sources of information in regard to deaths of premature infants are those from state and city health departments that have published death rates and other special information available in some health departments from matched birth and death certificates. Space does not permit inclusion of the results of all of these studies, but two examples based on relatively large numbers of infants will be cited here.

Chicago. Bundesen and his co-workers presented neonatal mortality rates by weight (maturity) based on 8905 neonatal deaths. In all of these cases "satisfac-

TABLE 24-5 DEATHS UNDER 28 DAYS AND UNDER 1 YEAR FROM SELECTED CAUSES
United States, 1956^a

<i>Cause of death</i>	<i>Under 28 days</i>		<i>Under 1 year</i>	
	<i>Total no.</i>	<i>No with mention of immaturity^b</i>	<i>Total no</i>	<i>No with mention of immaturity^b</i>
<i>Certain diseases of early infancy</i>				
Birth injuries	11,405	6,525	11,516	6,546
Postnatal asphyxia and atelectasis	17,820	12,841	18,075	12,914
Pneumonia of the newborn	3,400	1,023	3,400	1,023
Diarrhea of the newborn	526	103	527	103
Other infections of the newborn	675	221	686	222
Neonatal disorders arising from maternal toxemia	660	468	664	469
Hemolytic disease of newborn	2,319	483	2,361	485
Hemorrhagic disease of newborn	715	261	722	262
Ill-defined diseases peculiar to early infancy including nutritional mal-adjustment	3,354	2,791	3,870	2,903
<i>Immaturity</i>				
With mention of any other subsidiary condition	1,854		2,160	
Unqualified	20,348		20,534	
Total deaths due to certain diseases of early infancy	63,076	46,918	64,515	47,621

From U.S. National Office of Vital Statistics.³²^a Includes only deaths within the continental United States.^b With mention of immaturity on the death certificate.

tory" postmortem examinations were made. The results are shown in Figure 24-3. It can be seen that in this series of neonatal deaths the deaths of premature infants accounted for by far the largest proportion, 60 per cent.

The authors point out that the total neonatal mortality rate (all birth weights) for white infants was less than for nonwhite but the mortality rate for white premature infants was higher than that for nonwhite premature infants.

New York City. Baumgartner and co-workers reported the infant mortality among premature infants by birth weight and color in New York City for the year 1957 based on 15,237 premature live births. A greater proportion of nonwhite than white infants weighed 2000 Gm. or less at birth. As shown in Table 24-7, in each birth-weight category nonwhite infants had a lower mortality rate;

TABLE 24-6. CAUSES OF DEATH IN INFANTS UNDER 28 DAYS BY BIRTH WEIGHT
United States, Early 1950

<i>Cause of death</i>	<i>No. deaths by birth-weight (Gm.) groups</i>					
	<i>1000 or less</i>	<i>1001- 1500</i>	<i>1501- 2000</i>	<i>2001- 2500</i>	<i>2500 or less</i>	<i>2501 or more</i>
Congenital malformations	30	107	208	359	704	1,421
Certain diseases of early infancy	3,365	2,654	2,129	1,540	9,688	3,680
Birth injuries	479	350	329	277	1,435	1,317
Intracranial and spinal	56	71	124	150	401	810
Other birth injury	423	279	205	127	1,034	507
Postnatal asphyxia and atelectasis	476	493	586	514	2,069	934
Pneumonia of newborn	13	69	89	106	277	437
Diarrhea of newborn		10	27	24	61	90
Other infections of newborn	1	3	12	8	24	33
Neonatal disorders from toxemia	57	57	61	40	215	66
Hemolytic disease of newborn	17	32	55	89	193	350
Hemorrhagic disease of newborn	13	14	27	41	95	121
Ill-defined diseases of early infancy	182	148	100	84	514	152
Immaturity						
With mention of any other subsidiary condition	37	53	60	28	178	21
Unqualified	2,090	1,425	783	329	4,627	159
All other causes	29	40	66	179	314	934
Total no. deaths from all causes	3,424	2,801	2,403	2,078	10,706	6,035

From U.S. National Office of Vital Statistics **

Based on matched birth and death certificates, see Table 24-1

however, the difference in distribution of birth weights in the white and non-white groups was responsible for a paradoxical result in which the over-all non-white premature infant mortality rate was *higher* than that for white premature infants

STATISTICS ON DEATHS DUE TO PREMATUREITY IN COUNTRIES OTHER THAN THE UNITED STATES

Data from fourteen countries are given in Table 24-8 concerning the frequency of occurrence of deaths in the first week of life which were attributed to "immaturity" on death certificates.

Although a single international classification of causes of death was used in

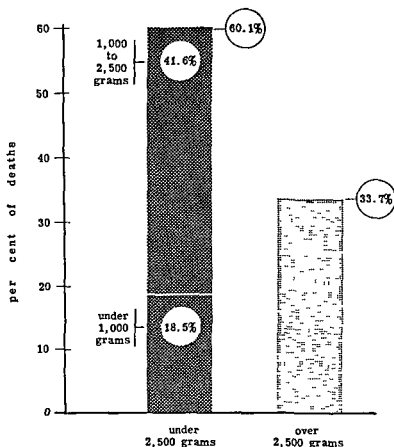


FIG. 24-3. Percentage distribution of neonatal deaths by birth weight in Chicago, 1936-49. These figures are based on 8905 deaths with satisfactory postmortem examinations and clinical investigations; in 6.2 per cent of the cases the weight at birth was unknown. (From Bundesen, H. N., Potter, E. L., Fishbein, W. I., Bauer, F. C., and Plotzke, G. V.: "Progress in the Prevention of Needless Neonatal Deaths." In *Annual Report of the Chicago Health Department, 1951.*)

these countries, it is possible that the wide differences in relative importance of prematurity in early neonatal deaths were the result of differences in registration practices rather than of inherent differences in experience. In the introductory note to the World Health Organization report³⁶ from which these figures were obtained, it was noted that in some countries a more or less high proportion of live-born infants who died shortly after birth were still reported to the registry office as having been born "lifeless." The imperfect nature of the data has a marked effect on early neonatal mortality rates.

The difficulties involved in the interpretation of death-certificate information have already been discussed, and it is clear that they are not resolved completely

TABLE 24-7. INFANT MORTALITY RATES AMONG LIVE-BORN PREMATURE
INFANTS BY COLOR AND BIRTH WEIGHT
New York City, 1957

	Birth weight (Gm.)				
	1000 or less	1001- 1500	1501- 2000	2001- 2500	2500 or less
White					
No live-born infants	660	695	1,791	7,408	10,554
No infant deaths	631	377	320	340	1,668
Specific death rate (%) ^a	95.6	54.2	17.9	4.6	15.8
Nonwhite					
No live-born infants	482	434	863	2,904	4,683
No. infant deaths	446	174	122	115	857
Specific death rate (%) ^a	92.5	40.1	14.1	4.0	18.3

Adapted from Baumgartner *et al.*^a, based on birth and death-certificate data.

^a Deaths of premature infants under 1 year per 100 live births in each category.

by a uniform system of classification of the causes of death. For this reason comparisons between countries should be avoided except for the purpose of indicating unsolved nosographic problems.

HOSPITAL DEATH-RATE STATISTICS

DEATH RATES

Hospital statistics in regard to deaths of premature infants are usually reported as *case-fatality rates* (deaths per 100 premature infants born on the maternity service or per 100 premature infants admitted to the nursery for premature infants). *Infant mortality rates* refer to deaths under one year of age per 1000 (or per 100) live-born infants, mature and premature.

Lack of Comparability of Data

Data from different hospitals vary widely and are usually not comparable because of (1) the use of different criteria for distinguishing between live-born and stillborn premature infants; (2) lack of uniformity in the definition of prematurity; (3) exclusion, from some reports, of infants of less than a specified period of gestation or weight; (4) failure to tabulate data in comparable birth-weight groups and by race, sex, and age at death; and (5) failure to consider, separately,

TABLE 24-8 EARLY NEONATAL MORTALITY^a ATTRIBUTED TO "IMMATURITY" ON DEATH CERTIFICATES

<i>Country</i>	<i>Death attributed to "immaturity"^b per 1000 live births</i>	<i>Relative importance of "immaturity" in early neonatal deaths (% of deaths)</i>
Australia (1953-55)	4.6	33.2
Belgium (1954-55)	8.1 ^c	47.7
Canada ^e (1953-55)	4.3	26.4
Denmark (1954-56)	3.1	19.8
England (1953-55)	4.5	30.7
Finland (1953-55)	6.4	41.2
Italy (1953-55)	6.4	33.6
Netherlands (1953-55)	2.2	17.4
New Zealand (1953-55)	3.4	28.2
Norway (1953-55)	3.0	28.3
Scotland (1953-55)	4.9	28.7
Sweden (1952-54)	3.0	24.2
Switzerland (1952-54)	1.0	5.8
United States (1953-55)	5.5	32.2
White	4.9	30.8
Nonwhite	8.6	38.0
New York City	6.4	38.5

Adapted from World Health Organization.⁵⁶

^a Deaths during the first week of life, except Belgium, per 1000 total live births

^b Deaths attributed to "Immaturity with mention of any other subsidiary condition" plus "Immaturity unqualified," 774 and 776 in the International Statistical Classification.

^c Proportion of deaths attributed to "immaturity" (774 and 776) among all deaths in the first week of life

^d Deaths under 5 days

^e Excluding Yukon, North West Territories, and Newfoundland.

premature infants born in a given hospital from those admitted after birth from other hospitals or from the home.

In addition, the populations of many nurseries are becoming highly selected because of efforts that are made to centralize the care of premature infants by transferring them from small hospitals to large premature infant centers. This form of selection, which results in the admission of infants of varying ages after birth, produces a distortion of the usual calculated mortality rate. The probability of dying diminishes with each passing hour after premature birth; therefore, the older the infant is upon admission to the premature infant center, the less likely he is to die after transfer.

In the case of death rates among premature infants errors introduced by differences in distribution of various characteristics produce greater distortion of the over-all rates than would ensue for the general population because the range of death risk is so great in the premature group. This is demonstrated by the experience reported in Table 24-7.

Validity of Specific Death Rates

One step in the right direction is the common practice of breaking down experiences into comparable birth-weight groupings (e.g., by 250- or 500-Gm. increments) and then to compare weight-specific categories. This often results in small numbers of infants in some of the classes, especially in the lower birth-weight groupings. In fact, it is necessary to subdivide the birth-weight groups even further to encompass other influential factors such as sex and race. Consequently, the various specific death rates have very little stability, since the presence or absence of only a few individuals in the category causes a large fluctuation in the calculated rate.

Reported Fatality Rates. Bain and her co-workers collected data from about half of the hospitals in the United States caring for 50 or more premature infants each year for the period 1945-47. Of 32,000 premature infants born in 323 hospitals during this period, 21.5 per cent died before discharge from the nursery. Birth weight-specific fatality rates were: 1000 Gm. or less, 89.6 per cent; 1001-1500 Gm., 54.4 per cent; 1501-2000 Gm., 22.8 per cent; and 2001-2500 Gm., 7.3 per cent.

Validity of Standardized Death Rates

It is possible to compensate for differences in distribution within the groups to be compared by the calculation of "standardized death rates." Such a method is used in death-rate studies of other population groups and has been helpful in permitting valid comparisons that could not be made from the crude rates. We proposed that a set of stable, specific Standard Mortality Rates for nurseries for premature infants be obtained.²¹ This would permit individual nursery rates to be adjusted with respect to differences in distribution of birth weight, gestational age, sex, color, place of birth, and duration of exposure to the risk of dying while under observation. The New York City Premature Nurseries Standard Mortality Rates which are given in Appendix 5 may be used for this purpose.

Considerable caution should still be exercised when specific mortality rates or even adjusted rates are compared from one year to another in the same nursery or between different nurseries. Crude nursery rates should not be compared.

TABLE 24-9 NEONATAL MORTALITY RATES BY BIRTH WEIGHT AND PLACE OF BIRTH
Upstate New York, 1950-54

Place of birth	Neonatal mortality (%) ^a by birth weight (Gm.) groups					Premature ^b	Total ^b
	1000 or less	1001- 1500	1501- 2000	2001- 2500	2501 or more		
Hospital ^c Annual average total birth volume—							
1000 or more	94.5	52.2	17.2	3.8	0.6	17.1	1.7
500-999	94.0	53.8	18.8	4.1	0.6	17.8	1.7
100-499	94.5	54.7	20.7	4.4	0.7	18.5	1.9
Less than 100	88.2	54.8	14.9	5.0	0.8	17.2	1.9
All hospital ^c deliveries	94.3	53.0	18.1	4.0	0.6	17.5	1.7
Home or nonmaternity service							
hospital	95.4	59.7	20.9	7.5	1.0	21.0	2.4
Total for all deliveries	94.4	53.2	18.2	4.1	0.6	17.6	1.7

From Office of Vital Statistics and Bureau of Maternal and Child Health (N.Y. State) ²⁰

^a Deaths under 28 days per 100 live births in each birth weight category. Prior to 1952 deaths under 1 month were considered "neonatal." However, the difference was so small that the neonatal rates were not significantly affected.

^b Adjusted to total birth-weight distribution of live births in 1945-59.

^c Includes only hospitals with maternity service.

Effect of Size of Hospital

Yankauer and Allaway²⁸ analyzed hospital neonatal mortality rates based upon matched birth and death certificates from upper New York State. This study involved 804,510 live births that occurred during the period 1950-54. The authors found that in hospitals with maternity services delivering 500 or more babies each year the total neonatal mortality rate was significantly lower than in hospitals with smaller maternity and newborn infant services (Table 24-9). This relationship was generally true for each individual birth weight group except the group weighing 1000 Gm. or less.

These figures were compared by Yankauer and Allaway²⁸ with similar data collected for the period 1945-49. They found that the greatest decline in neonatal mortality rates occurred in hospitals with a relatively large annual delivery volume.

CAUSES OF DEATHS

Limitations of Available Data

Even after careful clinical observation and complete pathologic examination there is often disagreement about which of several "terminal morbidity condi-

TABLE 24-10 DEATHS AMONG LIVE-BORN INFANTS DURING THE FIRST WEEK OF LIFE BY BIRTH WEIGHT AND BY CAUSE
University College Hospital, London, 1948-55

	<i>No. deaths by birth-weight (Gm) groups</i>					
	<i>1000 or less</i>	<i>1001- 1500</i>	<i>1501- 2000</i>	<i>2001- 2500</i>	<i>2500 or less</i>	<i>2501 or more</i>
No live births	52	89	203	449	793	9,251
No deaths in first week	49	46	35	27	157	64
Cause of death						
Pulmonary syndrome ^a	11	20	15	7	53	6
Intraventricular hemorrhage	6	7	7		20	
Pneumonia	9	2	1	4	16	11
Intracranial birth trauma	8	7	5	5	25	15
Congenital malformations	1	4	5	5	15	18
Other ^b	14	6	2	6	28	13

Adapted from Bound *et al.*,⁷ based on 221 neonatal deaths that occurred among 9250 term and 593 premature infants born in the Obstetric Hospital between 1948 and 1955, together with 1 term and 200 premature infants admitted from home or other hospitals after birth.

^a Resorption atelectasis together with one or more of the following features: hyaline membrane, intra-alveolar hemorrhage, pulmonary edema.

^b Including: Previability (birth weight under 1000 Gm, no lesion found), 11, erythroblastosis fetalis, 7, kernicterus of prematurity (without incompatibility), 6, meconium peritonitis, 2, septicemia, 2, inhalation of feed ing, 2, upper respiratory tract infection, 1, acute pulmonary edema, 1, renal vein thrombosis, 1, massive inhalation of blood, 1.

tions"²⁴ was the "specific cause of death." In addition to this, increasing interest and knowledge have produced changes in the frequency with which certain conditions are diagnosed. It is often difficult to decide whether increased incidence of a pathologic condition is the result of improved recognition or due to the operation of an unrecognized "cause" factor. Uncertainty of this kind was encountered, for example, in the experience with kernicterus caused by sulfisoxazole and vitamin K toxicity (see Chap. 13).

Another problem which has led to difficulty in the interpretation of cause-of-death data among premature infants stems from the practice of relating the number of morbid conditions found at necropsy to the number of consecutive necropsies performed rather than to the consecutive number of unselected live-born premature infants. A necropsy series very often includes infants transferred from other hospitals; these deaths are not necessarily representative of the deaths that would result from consecutive unselected live births. This difficulty is avoided in community studies of death certificates. However, as pointed out earlier, data based on death certificates have other and even greater limitations.

Another difficulty in interpretation of tabulations of cause of death is that antemortem diagnoses are often uncertain among premature infants. This adds to the confusion and has led to distortions concerning the incidence of disease (see Chap. 14) and to disagreement about the relative importance of various causes of death.

Principal Causes Reported

The causes of death among premature infants as judged by the findings revealed by postmortem examination have been studied in detail by several groups of investigators in recent years.^{2, 3, 7, 10, 18} The results of one of these surveys are given in Table 24-10

Although these studies are in general agreement on the "usual" causes of death in premature infants, there are differences in the details which probably can be explained on the basis of differences in terminology and classification. In general, postmortem examination shows that most of the deaths of premature infants are caused by a characteristic pulmonary syndrome (resorption atelectasis with or without pulmonary hyaline-membrane formation); and by intracranial bleeding, either asphyxial (intraventricular) hemorrhage or hemorrhage resulting from birth trauma. Infections and congenital malformations are also prominent "causes"

FACTORS INFLUENCING DEATH RATES OF PREMATURE INFANTS

The mortality rates of premature infants are, in general, affected by the same conditions that influence the incidence of prematurity (see Chaps 2 and 3).

INHERENT FACTORS IN THE INFANT

Body Size and Duration of Gestation

Birth Weight. It has been repeatedly demonstrated that the risk of death among newborn infants is closely related to the weight at birth. In the study conducted by the National Office of Vital Statistics,²⁸ mortality declined sharply with relatively small increases in birth weight even between 2500 Gm. and the mean birth weight.

Gestational Age. The duration of gestation as well as birth weight has a considerable influence on the survival of the newborn^{22, 28} (see Chap. 5). As is seen

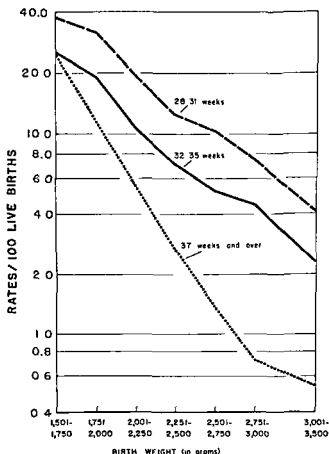


FIG 24-4. Neonatal mortality rates among single white births, by detailed birth weight and specified gestational age groups, United States, early in 1950. (From U.S. National Office of Vital Statistics: *Weight at birth and its effect on survival of the newborn in the United States, early 1950. Vital Statistics—Special Reports 39: [No. 1], 1954.*)

in Figure 24-4, the national study showed that the decrease in mortality with increasing birth weight was much more rapid among infants who were born after gestations of 37 weeks and more. This was particularly evident when the birth weight approached 2500 Gm., and the disparity continued well into the higher weight groups.

Birth Weight and Length and Gestational Age. A survey conducted in San Diego, California, explored the relationship between neonatal mortality and prematurity as judged by birth weight, birth length, and duration of gestation (Table 24-11). A larger proportion of live-born infants were considered to be premature on the basis of the gestational-age criterion than by either of the other criteria. Infants who were classified as premature by gestational age alone had the lowest neonatal mortality rate. The smallest proportion of live-born infants were premature by all three criteria; this group had the highest mortality rate in the neonatal period.

TABLE 24-11 NEONATAL MORTALITY OF WHITE, SINGLE LIVE BIRTHS
JUDGED PREMATURE BY THREE CRITERIA
San Diego, California, 1955

<i>Criteria of prematurity^a</i>	<i>Male</i>			<i>Female</i>		
	<i>No live births</i>	<i>No neonatal deaths</i>	<i>Mortality rates^b (%)</i>	<i>No live births</i>	<i>No neonatal deaths</i>	<i>Mortality rates^b (%)</i>
One criterion						
Gestation	788	145	18.4	622	89	14.3
Length	518	132	25.5	632	104	16.5
Weight	502	146	29.1	570	107	18.8
Two criteria						
Weight and length	332	126	38.0	383	102	26.6
Weight and gestation	323	132	40.9	286	86	30.1
Length and gestation	273	115	42.1	266	85	32.0
Three criteria						
Weight, length and gestation	238	114	47.9	230	84	36.5
TOTALS	9,348	202	2.2	8,649	141	1.6

Courtesy of Leslie Corsa, Jr., M.D., Chief, Bureau of Maternal and Child Health, State of California, Department of Public Health.

^a Criteria of prematurity: gestation, 36 completed weeks or less, length, less than 47 cm (18½ inches) crown heel, weight, 2500 Gm. or less at birth.

^b Deaths under 28 days per 100 live births in each category.

Color

Birth weight-specific neonatal mortality rates for the United States in the first three months of 1950 have been tabulated according to color, plurality, and sex of the infant.²⁶ The data indicated that for infants in all birth weight categories below 2500 Gm. the mortality rate was somewhat lower among nonwhite than white infants (Fig. 24-5). As mentioned earlier, Baumgartner's group reported similar results for New York City. It should be re-emphasized that a relatively high proportion of live-born nonwhite infants have low birth weights. This tends to distort the over-all mortality rate of this group (see Table 24-7).

Plurality of Birth

In the national study, the mortality rate of plural-born infants was lower than among the single-born who weighed between 1001 and 3000 Gm. (Fig. 24-6). At higher weights the plural-born infants had a relatively high mortality rate.

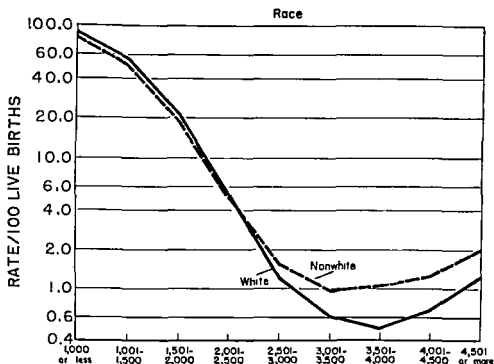


FIG. 24-5. Neonatal mortality rates by birth weight according to race, United States, early in 1950. (From U.S. National Office of Vital Statistics: Weight at birth and its effect on survival of the newborn in the United States, early 1950. *Vital Statistics—Special Reports 39*: [No. 1], 1954.)

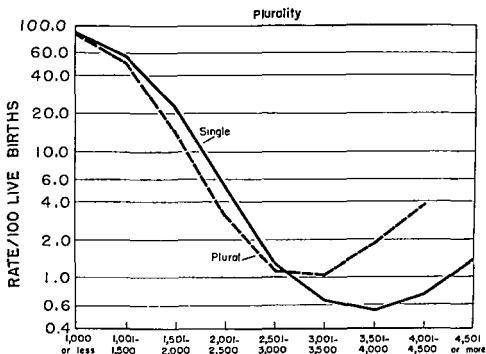


FIG. 24-6. Neonatal mortality rates by birth weight according to plurality, United States, early in 1950. (From U.S. National Office of Vital Statistics: Weight at birth and its effect on survival of the newborn in the United States, early 1950. *Vital Statistics—Special Reports 39*: [No. 1], 1954.)

First-Born vs. Second-Born Twins. Neonatal mortality rates are higher among second-born than among first-born twins.^{11, 14} Guttmacher and Kohl found that the increased risk of neonatal death in the second-born twin was largely confined to those weighing less than 2000 Gm. at birth, above that birth weight the outlook for a second-born twin was as optimistic as for the first.

Sex

Many studies have shown that neonatal mortality rates are considerably higher among prematurely born males than females at all levels of birth weight. The findings of the study conducted by the National Office of Vital Statistics are depicted in Figure 24-7. It was also found that after the first hour of life the mortality differentials between the sexes rose sharply and remained at a high level throughout most of the first week (see Table 24-4).

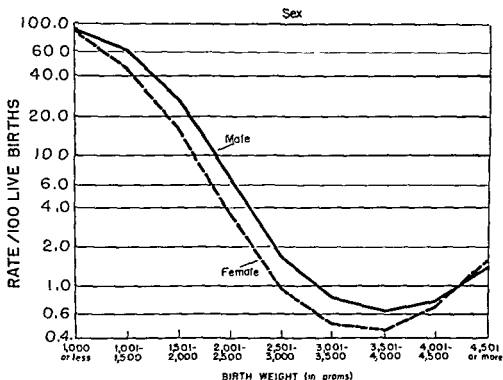


FIG. 24-7. Neonatal mortality rates by birth weight according to sex, United States, early in 1950. (From U.S. National Office of Vital Statistics: *Weight at birth and its effect on survival of the newborn in the United States, early 1950. Vital Statistics—Special Reports 39: [No. 1], 1954.*)

MATERNAL FACTORS

The maternal factors that have been studied in relation to deaths of premature infants are the mother's age and parity; complications of pregnancy, labor, and delivery; previous premature deliveries; certain nonobstetric complications during pregnancy; and socioeconomic status as it affects medical care.

The influence of anesthesia and analgesia on neonatal mortality has already been discussed (see Chap. 6). For other maternal factors see Chapters 19 and 22.

Birth Order and Maternal Age

The study conducted by the National Office of Vital Statistics showed that for premature infants the mortality rate was generally lower among first children than any of the succeeding total-birth orders.³¹ When both age of the mother and total-birth order were considered it was found that the mortality rate of premature infants decreased sharply from the youngest maternal group to ages 20–24 years for first births and to 25–29 years for later births (Fig. 24-8). The premature infant mortality rates varied erratically with birth order among women at ages over 29 years.

Previous Premature Deliveries

The relation of previous premature deliveries to the deaths of premature infants was studied by Bundesen and his co-workers. Among 2945 neonatal deaths of premature infants, a history of one or more previous premature deliveries was elicited in 27 per cent of the cases, in 1671 neonatal deaths among term infants a lower proportion of the mothers (19 per cent) gave this history.

Complications of Pregnancy and Delivery

The relationship between infection-caused deaths among premature infants and maternal complications of pregnancy and delivery such as infection, premature rupture of membranes, and prolonged labor has already been discussed (see Chap. 19). The association of other complications with neonatal death has been studied frequently and in detail.^{5, 7, 8, 10, 13, 15, 17, 18, 23} There is general agreement that certain conditions, including maternal toxemia, premature separation of the placenta, breech presentation, and delivery by cesarean section, are frequently associated with premature delivery. As noted by Kjessler, the conditions disposing toward premature birth often prove to be an important link in the sequence of events leading to death of the infant, and in this sense the com-

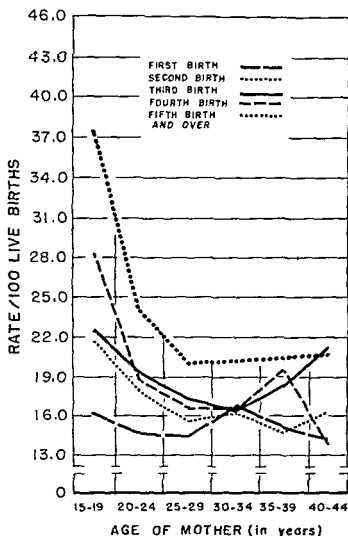


FIG. 24-8. Neonatal mortality rates of infants weighing 2500 Gm. or less, by age of mother for each total-birth order group, United States, early in 1950. (From U.S. National Office of Vital Statistics: *Weight at birth and survival of newborn, by age of mother and total-birth order: United States, early 1950. Vital Statistics—Special Reports 47: [No. 2], 1958.*)

plicating conditions are frequently considered to be responsible for many neonatal deaths.

Whether these complications are causally related to neonatal mortality except by a common association with prematurity remains a disputed point that cannot be settled on the basis of the evidence available at present.

Antenatal Care. It is clear from the discussion of maternal factors influencing

deaths of premature infants that early and adequate antenatal care may contribute to reduction of these deaths. For example, in New York City in 1957 infant mortality was highest in the group of infants whose mothers received no antenatal care (Table 24-12).

Place of Delivery. The study conducted by the National Office of Vital Statistics revealed that the neonatal mortality rates among premature infants were highest for nonmedically attended births, intermediate for the group handled by

TABLE 24-12 INFANT MORTALITY RATES BY BIRTH WEIGHT AND TIME OF MOTHER'S FIRST VISIT FOR ANTENATAL CARE
New York City, 1957

Trimester of first antenatal visit	No. deaths by birth-weight (Gm.) groups					
	2500 Gm. or less			2501 Gm. or more		
	No live births	No infant deaths	Infant mortality rate ^a (%)	No live births	No infant deaths	Infant mortality rate ^a (%)
First	5,506	813	14.8	65,446	548	0.8
Second	5,475	881	16.1	57,464	620	1.1
Third	2,496	261	10.5	21,907	342	1.6
No antenatal care	1,760	570	32.4	6,923	141	2.0
TOTAL	15,237	2,525	16.6	151,740	1,651	1.1

Courtesy of Jean Pakter, M.D., Maternity and Newborn Division, The City of New York Department of Health.

^a Deaths under 1 year of age per 100 live births

physicians at home, and lowest for hospital births.²⁹ The advantage for the hospital group was found to be most marked at birth weights above 2000 Gm. Similar observations were made by Brooks and others.

EXTRINSIC FACTORS

Other factors influencing the welfare of the infant at birth and in the later neonatal period also play an important role in the deaths of premature infants. The inverse relationship between socioeconomic status and infant mortality is well recognized.^{19, 37}

The infant's survival may be influenced by the quality of medical care received (i.e., the competence of medical and nursing personnel, and the availability of special equipment for the care of premature infants). Baumgartner and others reviewed the experience of ten years with specially equipped premature centers in New York City. They concluded that the mortality rates for premature infants

with birth weights above 1000 Gm. had been reduced by this intensified program for neonatal care.

For a discussion of the deaths of premature infants beyond the newborn period see Chapter 12.

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Programs for Premature Infant Care

The organization of programs for improving premature infant care has developed as a result of accumulated information in regard to the high mortality rates from prematurity, the causes of death, and the quality of care that must be provided to improve the outlook for the well-being and survival of these infants.

Programs have been initiated by individual hospitals or by official health agencies, state and city, with which hospital programs have been integrated. Some examples will be given to show the developments that have taken place over the years.

HOSPITAL PROGRAMS

The first "station" for the care of premature infants was established by Julius Hess in the Sarah Morris Hospital, Chicago, 1922. As the program developed it came to include, in addition to the special unit for care, ambulance service to convey infants born elsewhere in the city to the "station" for care, a specialized nursing service, and an outpatient clinic for follow-up care of the infants.¹¹ Later these services became integrated with the city health department program.

At about the time of the opening of the Sarah Morris Hospital station a few other hospitals in larger cities had special units for care of premature infants but had not developed programs to the extent of that in the Hess clinic.

In the early 1930s, Dunham made an informal survey of 105 hospitals in cities in various parts of the United States to determine the status of premature-infant care. It revealed that in the majority of these hospitals no special provisions were made for the care of premature infants and that in only four of them were fatality rates available. It is hardly necessary to point out the complete reversal of this situation that has ensued, so that at the present time it has become generally recognized that special provisions are needed in hos-

pitals for the care of these infants. More and more hospitals are meeting the requirements set up by special committees of the American Academy of Pediatrics and of the American Hospital Association, and thus are attempting to lower the fatality rates of prematurity. In addition, a number of organized centers for premature-infant care are now established in larger cities to serve the surrounding areas as a source of highly specialized care and as centers for reaching physicians and nurses the most recent methods for care of these infants.

CITY-WIDE PROGRAMS

In 1934 the Chicago City Health Department plan for care of premature infants came into effect. At first the program supplemented that of the Sarah Morris Hospital, but it was gradually expanded into a more complete program for the city as a whole. In six years the success of this city-wide plan was reflected in a decrease in the premature infant mortality rate.¹⁰

Another example of a city-wide program is that of the Department of Health of the City of New York. This program, initiated in 1938, is essentially one directed toward improved hospital care of premature infants.²⁴

It is obvious that the initiation and the success of such a program was made possible by the interest and cooperation of the medical profession, the hospitals, and the nursing and welfare organizations in the city. The Maternity and Newborn Division in the Bureau of Child Health of the New York City Department of Health has the responsibility for formulating plans and administering the program. The members of the division staff participating in this program include pediatric and obstetric medical and public-health-nursing consultants whose services are available to hospitals to advise on methods for improving care, to organize training programs in all aspects of premature infant care, to make studies of mortality and morbidity, and to evaluate methods for care.

Requirements have been drawn up by the city health department for hospital centers for premature infant care, and payments for care under the plan of the health department are made only to those hospital centers meeting the requirements (see *The Cost of Premature Infant Care* in this chapter).

Transportation services are provided to facilitate the hospitalization of infants born at home and the transfer to hospital centers of those born in hospitals that do not meet the health department requirements. In addition, a plan has been developed to coordinate hospital and home care so that continuous medical supervision will be assured.

The results of the New York City program were reviewed after 5 years and

more recently after 10 years of operation. Both reviews stressed the need for intensive follow-up care after discharge from the hospital.^{3, 15}

STATE-WIDE PROGRAMS

State health departments have also developed programs for premature infant care in cooperation with physicians and hospitals. These programs were initiated or extended when funds were made available to the U.S. Children's Bureau for grants to the State Health Departments, after the passage of the Federal Social Security Act of 1935.

Records of the U.S. Children's Bureau showed that as early as 1937 one state health department initiated an especially complete program directed by a staff pediatrician. Under a state law passed that year, reporting of premature birth to the local board of health, transportation of the baby by the department of health to a hospital especially equipped for this care, and hospitalization were provided. Postgraduate training in pediatric and nursing care of premature infants was an integral part of this program. Another state health department that had organized one of the earliest and most comprehensive of the special programs provided hospital care for mothers threatened with premature delivery as well as hospital care for premature infants. This same state as early as 1941 provided pediatric care, hospitalization and transportation for premature infants, and consultation and hospitalization for complicated obstetric cases referred by obstetric consultants. Training for nurses in the care of premature infants was offered under this plan also.

Within about five years after the passage of the Federal Social Security Act of 1935 over half the states made some provision in their plans for maternal and child health services for special care of premature infants or for improving the quality and availability of trained personnel to care for these infants. In the majority of these states emphasis was placed on one or more of the following: provision of incubators to local health departments, staff training through institutes, demonstrations and graduate courses for physicians and nurses, pediatric consultation to hospitals and physicians, and in a few states special studies on the scope and nature of the prematurity problem.

During the 1940s the programs were enlarged in many states, particularly in the direction of encouraging and assisting the organization of centers for premature infant care in hospitals. These centers, which were appropriately equipped and staffed with medical and nursing personnel specially trained in management of premature infants, often served also as demonstration, educational, and training centers for professional personnel in the state or from other

states. Gradually the areas within the states served by these centers have been extended, but state-wide coverage is still exceptional. By 1951 three-fourths of the states provided some special measures for care of premature infants under their maternal and child health programs; these programs included education and training of personnel, public-health nursing care, and payment of care either in individual hospitals or in special centers. Nineteen states had centers for premature infants in operation either on a demonstration and nurse-training basis in a single-hospital or in several hospitals which met standards for care of premature infants.

Three of these programs will be outlined briefly because they are among the best to be put into operation.

Colorado

The Colorado premature infant program was initiated in 1947 and is still continuing.^{17, 18} This program, as it has developed, has become an example of a very complete cooperative effort between the Colorado State Health Department and the University of Colorado. At the Medical Center of the University a Premature Infant Center was developed to give specialized hospital and follow-up care to premature infants born in the city and in the county of Denver. However, cases from anywhere in the state are eligible. Another activity of the Premature Infant Center is the teaching of the various aspects of premature infant care to members of the medical and nursing professions so that they may be qualified to organize similar projects in their own hospitals or communities.

Monthly discussions of stillbirths, neonatal deaths, and birth injuries are held for the medical and nursing staff and for social workers.

The Department of Obstetrics and Gynecology of the Medical Center cooperates fully with the Pediatrics Department in providing antenatal care with a view to preventing premature birth and to conducting labor in a manner favorable to the premature infant as well as to the mother. In addition, research into both the pediatric and obstetric aspects of prematurity is carried on and mortality rates are analyzed to assess the results of the program.¹⁸

North Carolina

In 1948 a program was initiated by the North Carolina State Board of Health,¹⁴ and five hospital centers for care of these infants were opened. The programs included facilities for transporting infants, the organization of refresher courses in premature infant care for nurses, a system for referral of cases to public-

health nurses for appraisal of the home, and provision of further public-health-nursing service in the home. In addition, through the state board of health, aid is given to hospitals other than the centers to supplement their equipment and to provide scholarships for nurses to study the specialized care of premature infants. In 1949 legislation was enacted which required reporting to the local health department, within 24 hours, the births of all infants weighing less than 2500 Gm.

Maryland

The Department of Health of the State of Maryland has also had a state-wide premature infant program for some time. Public-health nurses are instructed in the nursing care of premature infants born at home.⁸ When notified by the physician or midwife that a patient is in premature labor the nurse proceeds to the home with a premature infant carrier, oxygen equipment, and an emergency premature infant kit. Home-type incubators are provided by the county health departments for the care of the larger premature infants at home. Infants weighing less than 1800 Gm. and those requiring oxygen or showing signs of distress are transferred to centers for care.

PROGRAM OF THE U.S. CHILDREN'S BUREAU

The staff of the U.S. Children's Bureau is available for consultation to the states in the planning of programs for premature-infant care. On request, staff specialists in eight regional offices provide consultation and advice to state and local agencies regarding the development and extension of programs including prevention, care, and follow-up.

In the central office current information regarding research, new publications, and reprints on prematurity are collected for use of the staff in consultation to the states. The Bureau's *Statistical Series* presents data on operations of child health and welfare programs; statistics pertaining to prematurity are included. A pamphlet of information for parents who have a premature infant in the hospital was prepared under the sponsorship of the U.S. Children's Bureau. Copies of this booklet, entitled *Your Premature Baby*,⁶ may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C.

The Bureau administers, through its Division of Health Services, grants to state health agencies for use in maternal and child health programs. Special grants are made for specific demonstrations, conferences, and training.

The U.S. Children's Bureau is advised in its work by committees and conference groups called to consider special problems.

CENTERS FOR CARE OF PREMATURE INFANTS

It is obvious that the development of a hospital center for care of premature infants is basic to the development of a community program.²³ The hospitals which are to serve as centers must be chosen to meet the needs of a selected area and must be equipped and staffed to provide the highest type of care.

An outline of a plan for organization of such a center is presented.

ORGANIZATIONAL PLAN

1. STAFF

- a. A staff of physicians and nurses who are qualified by education and experience to care for premature infants.
- b. A medical social work consultant service.
- c. An obstetric staff that will provide antenatal, intrapartum, and postnatal care in the best interest of mother and infant.

2. EQUIPMENT AND FACILITIES

- a. A separate unit constructed and equipped to meet the standards for care of the American Academy of Pediatrics.¹
- b. Adequate space to meet the demands of the area to be served
- c. Equipment suitable for use with premature infants, such as incubators, bassinets, feeding equipment, and transfusion apparatus.
- d. Clinical records—medical and nursing.
- e. Laboratory services.
- f. Milk room planned and conducted in accordance with standards of the American Hospital Association.²
- g. Provisions for isolating infants suspected of having infections and for care of infected infants

3. EDUCATIONAL PROGRAM

- a. In-service programs for physicians, nurses, social workers, and auxiliary staff.
- b. Clinics, ward rounds, and seminars for physicians, nurses, and social workers in the community and for visiting physicians, nurses, and social workers.
- c. Special educational program for parents of premature infants and for the public in regard to the need for specialized care of premature infants and the facilities in the community for providing this care.

4. STATISTICAL SERVICES to make available morbidity and mortality data to permit evaluation of the methods of care.

5. **TRANSPORTATION SERVICES FOR INFANTS**
6. **FOLLOW-UP CLINIC** providing medical and psychologic examinations and counseling in regard to nursing, social, and economic problems
7. **COORDINATION OF HOSPITAL AND HOME CARE** through arrangements with public-health-nursing organizations for appraisal of the home as to its suitability for the infant's return and of the mother's ability to care for the infant. Arrangements for medical social-work consultation service to help with socioeconomic problems
8. **COOPERATIVE ARRANGEMENTS** with physicians, hospitals, and health and welfare agencies in the area to promote the complete functioning of the program. A medical consultation service to physicians and hospitals in the area in which the center is located

THE COST OF PREMATURE INFANT CARE

One of the problems in providing care of premature infants in hospitals is its relatively high cost. In 1959 Baumgartner and her co-workers estimated that the costs of care for a premature infant in New York City was \$25.00 per day.

To defray part of the expenditures on the part of the family and hospital, New York City introduced a program of reimbursement for premature infant care in approved centers.²² When the program began in 1950, the rate was \$12.00 per day; in 1956 it was increased to \$16.00 per day.³ A flexible plan of financial eligibility was devised to determine which families required assistance. In 1957, 83 per cent of families of premature infants cared for in "approved" centers required full financial assistance, and an additional 4.7 per cent were given partial assistance.

Wallace and co-workers²³ reported that the costs of construction and equipment for centers for premature infants in New York City in 1949 and 1951 averaged \$2914.00 per bassinets. Present-day costs are undoubtedly much higher.

POSTGRADUATE TRAINING OF PHYSICIANS AND NURSES

In 1949 the Committee for the Study of Child Health Services of the American Academy of Pediatrics pointed out that in some medical schools in the United States training in the care of newborn infants was the weakest feature in the pediatric course and that some hospitals approved for pediatric residency training provided very little experience in the care of premature infants.

During this same year the U.S. Children's Bureau recommended to the New

York State Department of Health that the Department of Pediatrics of the New York Hospital-Cornell Medical Center in New York City offer a series of institutes on premature infant care for physicians and nurses.

This program of postgraduate instruction has continued since 1949 and has been responsible for the instruction of physician-nurse teams from many parts of the United States and from other countries.²⁵ As a direct result of the Institutes in the Care of Premature Infants at New York Hospital-Cornell Medical Center, teaching programs in premature infant care have been initiated in other areas.

STANDARDS FOR CARE

The need for standards for hospital care of premature infants became apparent as the numbers of premature infants cared for in hospitals increased.

The U.S. Children's Bureau prepared the first *Standards and Recommendations for Hospital Care of Newborn Infants, Full-term and Premature*, which was approved by its medical advisory committee and by the American Academy of Pediatrics Committee on Fetus and Newborn, and published in 1943. Many state and local health departments as well as hospitals then accepted these standards for care. In 1947 the American Academy of Pediatrics arranged to take over the responsibility for publishing these standards and issued them with some changes and additions. Since then the Committee on Fetus and Newborn of the Academy has revised the *Standards* to meet changing concepts of the best methods for care; a new edition was published in 1957.¹

Certain of these standards that apply particularly to the premature infant will be found in Appendix 8. It should be pointed out that the reader should refer to the Academy manual for those standards for the term infant that apply to the premature infant also.

PROGRAMS FOR THE PREVENTION OF PREMATUREITY

PRECONCEPTIONAL STUDIES

A clinic was established in Syracuse, New York, for the purpose of studying couples with a pregnancy history of recurrent abortion, malformation, prematurity, or a combination of these conditions.¹² An attempt was made to reduce fetal loss in this group of patients by complete study before gestation and by careful management during subsequent pregnancies. Encouraging results in a small series was reported by Hughes.¹²

ANTENATAL CARE

The role of antenatal care in the prevention of premature birth has already been discussed (Chap. 3).

Standards

Standards of Prenatal Care, an Outline for the Use of Physicians, was first published by the U.S. Children's Bureau in 1925. It was revised in 1934 and again in 1939, with the assistance of the Bureau's advisory committee of obstetricians.²⁰ In general the standards point out the importance of visits to the physician for antenatal care early in pregnancy and for continuing the visits at regular intervals throughout pregnancy. At these visits consideration should be given to the mother's general health and her past pregnancy history as well as to the progress of her present pregnancy. On the basis of this history and of clinical and laboratory examinations, the physician will be able to diagnose any abnormalities in her condition and will also be able to calculate the probable date of confinement. (Nagele's rule is to add a year and seven days to the first day of the last menstrual period and subtract 3 months.)

There are certain general hygienic measures which the physician will discuss with the pregnant woman, such as:

1. Diet, exercise, work, sleep, rest, bathing, and sexual intercourse.
2. Avoidance of exposure to infections and communicable diseases.
3. Special precautions to avoid accidents, falls, and trauma.
4. Adjustment of daily routine of life to avoid undue fatigue and worry.
5. Help in regard to social and economic adjustments.

The diagnosis and treatment of puerperal and nonpuerperal complications of pregnancy that tend to bring about premature labor is outside the scope of this book. These conditions are briefly discussed in Chapter 3, since they play a role in causing premature birth.

The standards for antenatal care have been generally accepted, but the evaluation of antenatal care as a factor in preventing premature birth is complicated by the presence of other factors that play a role, such as economic status, failure on the part of some women to appreciate the value of antenatal care, inaccessibility of clinics, and sometimes the physician's failure to give adequate care.

Quality of Antenatal Care

The extent of application of the standards of antenatal care has been studied by Wallace.²¹ She found that, of the 14,599 visits to antepartum clinics in

New York City as reported in May, 1951, only 42 per cent of the visits and 34 per cent of the serologic tests for syphilis were made in the first trimester of pregnancy. Standards call for care beginning early in pregnancy and tests for syphilis made at the first visit.

In regard to the adequacy of medical staff for antenatal clinics Wallace²¹ stated: "In the antepartum clinics operated by the Department of Health, the standard of one obstetrician for every 12 patients seen per 3-hour session has been adopted and adhered to." In a survey of 75 hospitals in New York City, according to Wallace,²¹ antepartum clinics were found in 41 of them. Only 19 (46 per cent) of these 41 hospitals had enough clinic physicians to meet the obstetrician-patient ratio maintained in the clinics of the Department of Health.

SPECIFIC PROGRAM TO REDUCE THE INCIDENCE OF ECLAMPSIA

Another approach to the problem of prevention of premature birth is *organized* programs to lower the incidence of puerperal conditions with which premature labor is associated. An example is found in a report from the Women's Hospital, Sydney, Australia, of the efficacy of intensive antenatal-care programs in reducing the incidence of eclampsia. These measures were described by Hamlin under seven steps, as follows

1. Stimulation of Attendance at Antenatal Clinic

"Nursing sisters" were assigned the task of assuring that every expectant mother in their district made the required visits to the clinic.

2. Lectures

Two lectures were given to all new patients: one by the medical superintendent to allay fear, to explain the need for regular antenatal supervision and the dangers of excess weight gain during pregnancy, and to outline the basic principles of a high-protein, high-vitamin, low-carbohydrate diet, the other by the dietitian who elaborated in a practical way the details of the diet.

3. Increased Supervision of Patients in Country Districts

Every expectant mother living in a country district and booked for confinement at the Women's Hospital in Sydney was given on her first visit to the hospital a copy of her registration card. The woman was expected to make regular visits to a doctor in her locality, who was to record the visits on the

card. This card was to be brought back by the woman, filled out, upon her return late in pregnancy, to the hospital's outpatient clinic. The physician caring for her in the interval between the first and last visit was asked to report regularly to the hospital her weight and blood pressure.

4. Coordination with Antenatal Clinics

The Women's Hospital sought and obtained good coordination with those physicians in the government antenatal clinics who supervised the hospital's patients living in Sydney's outlying districts.

5. Blood Pressure

Any patient who, after the twentieth week, had a diastolic blood pressure of 85 or more, or a systolic blood pressure of 130 or more, where original readings had been less, was seen more frequently and admitted to the hospital early in pregnancy.

6. Edema and Diet

Digital edema sufficient to cause a ring to be uncomfortably tight at the thirty-first week, especially in young primiparas, was considered a warning sign. If not controlled, the patient "will almost certainly have hypertension by the thirty-seventh or thirty-eighth week or in labour." Such patients were referred to the dietitian for precise instructions about a high-protein, high-vitamin, low-carbohydrate diet in which salt was restricted. If the excess weight and edema did not respond, or if there was a rise in blood pressure, patients with digital edema were admitted to the hospital.

7. Diet

Increasing control was exercised over the women's rate of weight gain between the twentieth and thirtieth weeks of pregnancy, because a gain of more than 8 pounds during that period was considered as "evidence that pathological processes are already disturbing the milieu intérieur."

The incidence of eclampsia among booked* patients at the Women's Hospital, Sydney, had been 2.8 per 1000 patients in 1935-47 and 1.2 and 2.1 per 1000 patients in 1945 and 1947, respectively. Following the introduction of the new standards for care in 1948 there was a rapid reduction in eclampsia,

*"Booked" patients are those who have attended the outpatient department once before being admitted to the hospital.

which Hamlin attributed to the control of diet from early pregnancy and particularly between the twentieth and thirtieth weeks. Another member of the staff of the Women's Hospital, Sydney, wrote¹³ that from March 15, 1950, to October 31, 1951, there had been no case of eclampsia among 6600 "booked" patients in that hospital. Hamlin added that "extremely few of the graver types of pre-eclampsia have been encountered. Not one cesarean section was performed during the year ending March, 1951, for pre-eclampsia in a booked patient."

RECOMMENDED ACTION FOR STATE ORGANIZATIONS

In the United States, although the importance of concerted efforts to reduce the incidence of prematurity has been recognized, plans for such a purpose on a state-wide basis have only very recently been made.

The California State Health Department, recognizing the importance of this problem, held two "working conferences" on prevention of prematurity in May, 1952. A plan for a preventive program was developed¹⁹ and recommendations were made as follows

RECOMMENDATIONS OF THE CALIFORNIA CONFERENCE ON PREVENTION OF PREMATURITY

1. Studies

Conference of Local Health Officers. It was recommended that the conference might study county hospital policies and legal restrictions on admission of pregnant women for outpatient and inpatient care and make recommendations to the County Supervisors Association.

Another recommendation was that, in cooperation with other professional groups, the conference might study and develop standards for antenatal care for the guidance of health departments and other community agencies.

State Department of Public Health. The state department was asked to explore with other appropriate agencies, such as schools of medicine and public health, the feasibility of initiating research in the prevention of prematurity. Other working groups reported the need for studies in the following fields:

- a. A study to determine if there is a difference in the physical, emotional and social factors present in pregnancies which terminate prematurely as compared with those which go to term. One group recommended that such a study be made on a current, continuous basis, and two other groups recommended retroactive studies.
- b. A demonstration study to develop effective ways of providing services for the

prevention of prematurity in a rural area removed from medical centers where there are few local resources and facilities despite problems of distance and transportation.

- c. A study of the nutritional habits of women who have had premature babies
- d. A study of the antenatal care of women in industry
- e. An administrative study of ways in which small health jurisdictions can share the services of the medical social worker, nutritionist, health educator and record analyst

2. Professional Education

The Conference of Local Health Officers was asked to consider, through its liaison committee with the California Medical Association, the need for placing special emphasis on postgraduate education in antenatal and obstetric care and their relation to premature birth

Medical Schools. It was suggested that medical school curricula might include courses which would assist the student in becoming aware of his responsibility in community problems, such as the prevention of prematurity, and that postgraduate courses in obstetrics and obstetric consultation services should be offered to general practitioners.

The State Department of Public Health was asked to supply continuing information on research and program development. It was suggested that the State department could also be helpful in in-service education of staff and in assisting local departments in community organization for study and action in the prevention of prematurity

3. Records

The State Department of Public Health was asked to consider the following changes in the birth certificate form:

- a. Add an item to obtain information regarding previous premature deliveries, and another asking for the length of the baby
- b. Substitute for the item asking for the number of weeks of gestation one asking for the date of the last known menstruation.
- c. Provide a checklist of the complications of pregnancy.

It was suggested that the Division of Laboratories and the Bureaus of Maternal and Child Health and Venereal Diseases might explore the practicality of having included on the antenatal blood test laboratory form a notation as to the period of gestation so that local departments might have this information as a guide for follow-up on antenatal care.

4. Committees

The State Department of Public Health. It was recommended that a standing advisory committee to the state department on the prevention of prematurity be appointed with

representation from the California Medical Association, the specialty societies in obstetrics and gynecology and from medical schools.

The department was also asked to appoint a follow-up committee to assess the influence of the working conferences and to consider calling other meetings on this problem at a later date.

Conference, Medical Association, State Department. Another recommendation was made for the appointment of a State Committee on the Prevention of Prematurity with representation of the California Conference of Local Health Officers, California Medical Association and State Department of Public Health. It was suggested that in each local public health jurisdiction a committee also be appointed with wide representation which might make recommendations on general and specific needs to the state committee.

IMPLEMENTATION OF THE RECOMMENDATIONS

Since that time there has been considerable progress in carrying out the specific recommendations which were made during the conference in 1952.⁵ For example, a state-wide survey of the quantity, quality, and eligibility of public antenatal care in California was conducted during 1954-56.¹⁶

The birth-certificate changes were adopted and the present certificate in California asks for the date of the first day of the last normal menstrual period, the month in pregnancy when antenatal care was begun, and the length of the infant at birth.

The suggestion concerning the appointment of a standing advisory committee on the prevention of prematurity was adopted and the scope of its interest was expanded to include the entire field of maternal and child health. This committee with wide representation meets periodically to make appropriate recommendations to the State Department of Health.

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Appendixes

appendix 1. Recommendations for the Improvement and Standardization of Vital Statistics,* Particularly As They Are Related to Prematurely Born Infants

PRINCIPLES FOR LEGAL REGISTRATION OF VITAL EVENTS IN SO FAR AS THEY RELATE TO VITAL STATISTICS

* * *

202. Definition for Statistical Purposes of Each Event on Which Data May Be Collected by the Registration Method

* * *

(c) *The recommended statistical definitions are as follows*

(1) *Live birth* is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live-born

All live-born infants should be registered and counted as such irrespective of the period of gestation or whether alive or dead at time of registration, and if they die at any time following birth they should also be registered and counted as deaths.

(2) *Death* is the permanent disappearance of all evidence of life at any time after live birth has taken place (post-natal cessation of vital functions without capability of resuscitation) This definition therefore excludes foetal deaths.

(3) *Foetal death* is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the foetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.

(4) *Stillbirth* is defined as synonymous with late foetal death, that is, one of twenty-eight completed weeks of gestation or over, subject to considerations mentioned in the footnote to this definition †

* Excerpts from Statistical Office of the United Nations *Principles for a Vital Statistics System* New York, United Nations, 1953, ST/STAT/SER/M/19

† Countries which prefer to continue to use the term "stillbirth" in statistical publications instead of the term "foetal death" should, in such publications, define stillbirths as early, intermediate, and late foetal deaths, as the case may be. The Statistical Commission has in mind the possibility that the use of the term "foetal death" in statistical publications may cause confusion in some cases and may lead to impairment of the clear distinctions at present drawn in recording and compiling statistics of live births and deaths

(5) *Marriage* is the legal union of persons of opposite sex. The legality of the union may be established by civil, religious, or other means as recognized by the laws of each country; and irrespective of the type of marriage, each should be reported for vital statistics purposes

* * *

(8) *Legitimation* is the formal investing of a person with the status and rights of legitimacy, according to the laws of each country.

(9) *Recognition* is the legal acknowledgment, either voluntarily or compulsorily, of the paternity of an illegitimate child

* * *

PRINCIPLES FOR THE RECORDING, REPORTING, AND COLLECTING OF DATA FOR STATISTICAL PURPOSES

* * *

308. Content of the Statistical Report on a Vital Event

* * *

(a) Items suggested for each of five statistical reports are given below, arranged in alphabetical order by event and participants, with an indication of first (*) and second priority rating. Some countries at the early stages in the development of their vital statistics systems may wish to subdivide the first priority group in order to establish immediate and more advanced goals.

(1) Live-birth statistical report items

(i) *Characteristics of the event or child*

- *Attendant at birth
- *Date of occurrence
- *Date of registration
- Hospitalization
- *Legitimacy
- Period of gestation
- *Place of occurrence
- *Sex
- *Type of birth, i.e., single or plural issue
- Weight at birth

(ii) *Characteristics of parents*

- Date of birth of father; if not available, age
- *Date of birth of mother; if not available, age
- Date of marriage (for legitimate births)
- Industry
- Literacy or level of formal education

*Number of children born to this mother

Occupation

*Place of usual residence (of mother)

Status (as employer, employee, etc.)

(2) Death statistical report items

(i) *Characteristics of event*

*Cause of death

*Certifier

*Date of occurrence

*Date of registration

*Place of occurrence

(ii) *Characteristics of decedent*

Age of surviving spouse (for married)

*Date of birth, if not available, age

Hospitalization

Industry

Legitimacy (for under one year of age)

Literacy or level of formal education

Marital status

Number of children born (for females of child-bearing age or over)

Occupation

*Place of usual residence

*Sex

Status (as employer, employee, etc.)

(3) Foetal-death statistical report items

(i) *Characteristics of event or product*

Cause of foetal death

Certifier or attendant

*Date of occurrence (of foetal delivery)

*Date of registration

Hospitalization

*Legitimacy

*Period of gestation

*Place of occurrence

*Sex

*Type of birth, i.e., single or plural issue

Weight at delivery

(ii) *Characteristics of parents*

Date of birth of father; if not available, age

*Date of birth of mother; if not available, age

Date of marriage (for legitimate pregnancies)

Industry

- Literacy or level of formal education
- *Number of children born to this mother
- Occupation
- *Place of usual residence (of mother)
- Status (as employer, employee, etc)

* * *

309 Definition of Each Item on the Statistical Report

(a) Each item on the statistical report should be accompanied by a clear, explicit, and simple definition for the guidance of the person recording the information

(b) In order to achieve international comparability, definitions adopted should be in accordance with established international standards and, in so far as possible, with current population census practice in each country

(c) Definitions which may operate to improve international comparability in connexion with the items suggested for inclusion in the statistical reports (Principle 308) are given below. Except where otherwise indicated, the characteristics should be reported as of the date of occurrence of the event

(1) *Age* (duration of life at death, at birth of child, at delivery of foetus, at marriage, at divorce) is the estimated or calculated interval between the date of birth and the date of occurrence of the event, expressed in the largest possible completed units of time, such as years, months, weeks, days or hours of life, as appropriate.

(2) *Attendant at birth* is the physician, midwife, nurse, or other person who delivered the mother

(3) *Birth order* is a tabulation concept based on item (19), "Number of children born to this mother". For definitions, see Principle 410 (e) (5) and (20).

(4) *Cause of death* is the morbid condition or disease process, abnormality, injury or poisoning leading directly, or indirectly, to death. Symptoms or modes of dying such as heart failure, asthenia, etc., are not considered to be causes of death for statistical purposes. The *underlying cause of death*, which, rather than the direct or intermediate antecedent cause, is the one to be adopted as the main cause for tabulation of mortality statistics may be defined as (a) the disease or injury which initiated the train of morbid events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury

* * *

(6) *Date of birth* (of parents, of deceased, of bride and groom, of divorcees) should be expressed as year, month, and day of birth, that is, in detail equivalent to that given for "date of occurrence of event" in order that exact interval between the two dates may be determined in completed years, months, weeks, days, or hours of life, as required. If it is not possible to establish date of birth, give "age" as defined in (1) above.

* * *

(8) *Date of occurrence* (of live birth, death, delivery of dead foetus, marriage or divorce) is the exact date when the event occurred, and should be expressed in terms of day, month, and year, and hour if appropriate.

* * *

(13) *Legitimacy* is the status of the child or dead foetus with respect to being legitimate, that is, considered as the lawful issue of a couple.

* * *

(16) *Live-birth order* is a tabulation concept based on "Number of children born to this mother", item (19). For definition, see Principle 410 (e) (5)

(17) *Marital status* should be expressed in such categories as are required for national purposes but in a manner which will be in conformity with the following concepts as applied to the event being reported: married; in stable *de facto* unions (consensually married); widowed, not remarried, divorced, not remarried, single—that is, *not married, widowed, or divorced in the sense stated above. Should it be impossible to obtain information on consensual unions separately, they should be recorded as "married"*

(18) *Marriage birth order* is a tabulation concept based on "Number of children born to this mother", item (19). For definitions, see Principle 410 (e) (5) and (20).

(19) *Number of children born to this mother* is defined as "total issue", that is, all children (including this one in the case of the live-birth or foetal-death report) born alive or born dead during the lifetime of this mother, and expressed in such a way as to distinguish (a) children now living, (b) children born alive and now dead, and (c) children born dead. In the case of plural issue, each child or foetus resulting from a confinement should be counted separately. For legitimate births, provision may be made to obtain information on how many children in (a), (b), and (c) above were issue of the current and, in some instances, of the previous marriages. If the distinction between (a), (b), and (c) above is not practicable, the country should endeavour to obtain information on "total live births to the mother", or nearest approximation.

* * *

(23) *Period of gestation* is the number of completed weeks which have elapsed between the first day of the last menstrual period and the date of delivery, irrespective of whether the product of conception was live-born or born without evidence of life.

* * *

(27) *Total birth order* is a tabulation concept based on "Number of children born to this mother", item (19). For definitions, see Principle 410 (e) (20).

(28) *Type of birth* refers to the single or plural nature of the issue of the pregnancy to which the statistical report relates. Each live-born infant or dead foetus should be characterized as single, twin, triplet, and so forth, and, for each member of a plural

birth, provision should be made to indicate the condition of the other member(s) (mates) with respect to being born alive or dead (foetal death), and, if desired, sex.

* * *

(31) *Weight* of a live-born child at birth or of a dead-born foetus at delivery should be the weight determined immediately after delivery, and should be expressed in grammes to a degree of significance which will allow a classification of 500-gramme intervals to be made

* * *

PRINCIPLES FOR COMPILATION OF VITAL STATISTICS

* * *

409. Tabulation by Place of Occurrence and Place of Residence

* * *

(b) Determination of "place of residence" for purposes of tabulation should be made as follows

Live births Foetal deaths Infant deaths	}	Place of residence of mother

* * *

410 Annual Tabulation Programme for National and International Purposes

* * *

(e) An annual tabulation programme based on the first priority (*) statistical items listed in Principle 308 and defined in Principle 309 is given in this paragraph. Unless otherwise specified and as applicable, it is suggested that the tabulations outlined below be made for the following geographic areas (1) the country as a whole; (2) each major civil division; and (3) each very important city. "Residence" is determined as set forth in Principle 409.

(1) *Live births classified by place of occurrence*

(Tabulate also for each geographic unit smaller than the major civil division.)

Classification

Place of occurrence: each major civil division, each geographic unit smaller than the major civil division, each very important city in the country.

(2) *Resident live births classified by attendant at birth*

(Tabulate also for each geographic unit smaller than the major civil division.)

Classification

Attendant: physician, midwife, nurse, other, not stated

(3) *Resident live births classified by month of occurrence*

Classification

Month of occurrence: calendar month

- (4) Resident live births cross-classified by sex and legitimacy

Classifications

Sex: male, female.

Legitimacy: legitimate, illegitimate, not stated

- (5) Resident live births cross-classified by age of mother and live-birth order*

Classifications

Age under 15 years, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50 and over, not stated.

Live-birth order. 1st, 2nd, 3rd, 4th . . . 10th and over, not stated.

- (6) Deaths classified by place of occurrence

(Tabulate also for each geographic unit smaller than the major civil division.)

Classification

Place of occurrence: each major civil division, each geographic unit smaller than the major civil division, each very important city in the country.

- (7) Deaths classified by place of residence of decedent

(Tabulate also for each geographic unit smaller than the major civil division)

Classification

Place of residence. each major civil division, each geographic unit smaller than the major civil division, each very important city in the country.

- (8) Resident deaths cross-classified by month of occurrence and selected causes of death

Classifications

Month of occurrence. calendar month.

Causes of death: selected underlying causes†

- (9) Deaths cross-classified by sex, age, and cause

(Tabulate only for the country as a whole.)

Classifications

Sex: male, female.

Age: under 1 year, 1, 2, 3, 4, 5-9, 10-14, 15-19, 20-24, 25-29 . . . 85 and over, not stated.

* Live birth order is the numerical order of the child (the report of whose birth is being tabulated) in relation to all previous live-born issue of the mother, irrespective of whether pregnancies were nuptial or extra-nuptial. It is computed on the basis of information given under item (19) of Principle 309, that is, "Number of children born to this mother" (a) now living, and (b) born alive and now dead. Should it be desirable to compute live-birth order solely on nuptial or legitimate issue, it is suggested that the term "marriage live-birth order" be adopted for this modified index.

† Causes of death to be selected are those which are not only important to the country as leading causes of death but which also have significant seasonal variation. Categories should be selected from the "Detailed List" of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* Sixth Revision of the International Lists of Diseases and Causes of Death, Adopted 1948, Volume 1 (Bulletin of the World Health Organization, Supplement 1, Geneva, Switzerland, 1948), pp 1-42

Cause of death: Intermediate List of 150 Causes.*

- (10) Resident deaths cross-classified by sex, age, and cause

Classifications

Sex: male, female.

Age: under 1 year, 1-4, 5-14, 15-24, 25-34 . . . 65-74, 75 and over, not stated

Cause: Abbreviated List of 50 Causes.†

- (11) Resident deaths cross-classified by type of certification and cause

Classifications

Type of certification: ‡ medical, other, not stated.

Cause: Intermediate List of 150 Causes *

- (12) Infant deaths (under 1 year of age) classified by place of occurrence

(Tabulate also for each geographic unit smaller than the major civil division.)

Classification

Place of occurrence: each major civil division, each geographic unit smaller than the major civil division, each very important city in the country.

- (13) Infant deaths (under 1 year of age) classified by place of residence of mother

(Tabulate also for each geographic unit smaller than the major civil division.)

Classification

Place of residence: each major civil division, each geographic unit smaller than the major civil division, each very important city in the country.

- (14) Resident infant deaths (under 1 year of age) cross-classified by age and month of occurrence

Classifications

Age: under 28 days, under 1 year, not stated

Month of occurrence: calendar month

- (15) Resident infant deaths (under 1 year of age) cross-classified by sex and age

Classifications

Sex: male, female

Age: under 1 day, 1, 2, 3, 4, 5, 6 days; 7-13, 14-20, 21-27, 28 days to under 2 months; 2, 3, 4 . . . 11 months, not stated

- (16) Resident infant deaths (under 1 year of age) classified by cause of death

Classification

Causes of death: selected underlying causes §

* *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, op cit, pp 355-360.

† *Ibid*, pp 361-2

‡ In order to give some indication of the specific type of medical certification, it is suggested that, if possible, a distinction be made between certification by the physician or surgeon who attended the deceased at the last illness and certification by a medical practitioner who only examined the body after death

§ Causes of death to be selected are those which are important as causes of infant mortality. Categories should be selected from the "Detailed List" of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, op cit, pp. 1-42.

(17) Foetal deaths classified by place of occurrence

Classification

Place of occurrence: each major civil division, each very important city in the country.

(18) Resident foetal deaths classified by sex and period of gestation

Classification

Period of gestation: under 20 completed weeks, 20-27 completed weeks, 28-36 completed weeks, 37 completed weeks and over, not stated.

(19) Resident late* foetal deaths cross-classified by sex and legitimacy

Classifications

Sex: male, female, not stated.

Legitimacy: legitimate, illegitimate, not stated

(20) Resident late* foetal deaths cross-classified by age of mother and total birth order†

Classifications

Age: under 15 years, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50 and over, not stated.

Total birth order: 1st, 2nd, 3rd, 4th . . . 10th and over, not stated

(21) Confinements‡ cross-classified by type of birth and status of issue with respect to being born alive or dead

Classifications

Type of birth: single, twin, triplet, quadruplet, etc., and not stated

Status of issue:

Single — live birth,
foetal death,

Twin — 2 live births,
1 live birth and 1 foetal death,
2 foetal deaths,

Triplet — 3 live births,
2 live births and 1 foetal death,
1 live birth and 2 foetal deaths,
3 foetal deaths;

and so forth.

* "Late foetal deaths" refer to those of 28 completed weeks of gestation and over

† "Total birth order" is the numerical order of the foetus (the report of whose death is being tabulated) in relation to all previous issue of the mother, irrespective of whether the issue were live-born or dead foetuses, or whether pregnancies were nuptial or extranuptial. It is computed on information given in item (19) of Principle 309, that is "Number of children born to this mother", or "total issue". Should it be desirable to restrict "total birth order" to nuptial or legitimate issue only, it is suggested that the term "marriage total birth order" be adopted for this modified index.

‡ "Confinements", as used here, is synonymous with "deliveries", "maternities", or "total cases of birth". The number of confinements is the same as the number of individuals (live-born or still born) in the case of single births, but is of course less than the total number of live births plus foetal deaths in the case of plural issue, inasmuch as the term refers to the "sets" of twins or triplets

For further recommendations see also:

Recommendations for Developing Comparable Statistics on Prematurely Born Infants and Neonatal Mortality. Joint Statement of Public Health Conference on Records and Statistics, Association of Maternal and Child Health and Crippled Children Directors, and Federal Security Agency (Children's Bureau and National Office of Vital Statistics), December, 1950

Report of the Working Group on Natality and Fetal Death. Sixth National Meeting of the Public Health Conference on Records and Statistics. Reproduced by the U.S. National Office of Vital Statistics. Document No. 398, 1956.

U.S. National Committee on Vital and Health Statistics: Recommendations for the improvement of fetal death statistics *Pub Health Rep.* 70:1049, 1955.

appendix 2. Certification of Live Birth, Fetal Death, and Death

CERTIFICATION OF LIVE BIRTH AND FETAL DEATH

In order to certify a birth as premature the physician must enter in items 22a and 22b of the Standard Certificate of Live Birth (Fig. A2-1) the number of completed weeks of pregnancy and weight at birth. He must adhere closely to the official definition of *live birth* as distinguished from *fetal death* which has been adopted by the World Health Assembly and is recommended for use in the United States (see Appendix 1)

Fetal death irrespective of the duration of pregnancy is registered in most states on the Standard Certificate of Fetal Death (Fig. A2-2). In states that do not provide this form both a birth and death certificate must be prepared and filed. The medical portion includes items on the length of pregnancy (18a), weight at birth (18b), legitimacy (19), and information concerning causes of fetal death (22). The instructions for reporting causes of fetal death are given in the *Physicians' Handbook on Death and Birth Registration*.

A check list of supplementary items which are recommended for inclusion on the certificates of live birth and fetal death is given in Figure A2-3. These items are not a part of the standard certificates but can be of considerable value to health agencies and research groups concerned with antenatal and postnatal care and with the outcome of pregnancies.

Form approved
Federal Bureau No. 94-5245-1

CERTIFICATE OF LIVE BIRTH

STATE OF _____ BIRTH NO. _____

1. PLACE OF BIRTH a. COUNTY		2. USUAL RESIDENCE OF MOTHER (If any, date mother lived) a. STATE	
3. CITY, TOWN, OR LOCATION		4. CITY, TOWN, OR LOCATION	
5. NAME OF HOSPITAL OR INSTITUTION (If not in hospital, give street address)		6. STREET ADDRESS	
7. IS PLACE OF BIRTH INSIDE CITY LIMITS? YES ☐ NO ☐		8. IS RESIDENCE INSIDE CITY LIMITS? YES ☐ NO ☐	
9. IS RESIDENCE ON A FARM? YES ☐ NO ☐			

CHILD

1. NAME (Type or print) First Middle Last		2. SEX Male ☐ Female ☐	
3. AGE (At time of birth) Years		4. BIRTHPLACE (State or foreign country)	
5. USUAL OCCUPATION		6. KIND OF BUSINESS OR INDUSTRY	
7. COLOR OR RACE		8. COLOR OR RACE	
9. PREVIOUS DELIVERIES TO MOTHER (Do not include live births) a. How many OTHER children born alive and are now living? b. How many OTHER children born dead or stillborn? c. How many stillborn children born dead or stillborn after resuscitation?		10. PREVIOUS DELIVERIES TO MOTHER (Do not include live births) a. How many OTHER children born alive and are now living? b. How many OTHER children born dead or stillborn? c. How many stillborn children born dead or stillborn after resuscitation?	

MOTHER

11. NAME (Type or print) First Middle Last		12. AGE (At time of birth) Years	
13. BIRTHPLACE (State or foreign country)		14. USUAL OCCUPATION	
15. KIND OF BUSINESS OR INDUSTRY		16. COLOR OR RACE	
17. PREVIOUS DELIVERIES TO MOTHER (Do not include live births) a. How many OTHER children born alive and are now living? b. How many OTHER children born dead or stillborn? c. How many stillborn children born dead or stillborn after resuscitation?		18. PREVIOUS DELIVERIES TO MOTHER (Do not include live births) a. How many OTHER children born alive and are now living? b. How many OTHER children born dead or stillborn? c. How many stillborn children born dead or stillborn after resuscitation?	

19. INFORMANT

20. NAME (Type or print) First Middle Last		21. ADDRESS	
22. DATE RECEIVED BY LOCAL REG.		23. REGISTRAR'S SIGNATURE	
24. DATE ON WHICH GIVEN NAME ADDED		25. BY (Signature)	

FOR MEDICAL AND HEALTH USE ONLY
(This section will not be filed out)

26. LENGTH OF PREGNANCY Completed weeks		27. WEIGHT AT BIRTH LB. OZ.	
28. LEGITIMATE YES ☐ NO ☐			

(SPACE FOR ADDITION OF MEDICAL AND HEALTH ITEMS BY INDIVIDUAL STATES)

FIG. A2-1. Standard Certificate of Live Birth. (Courtesy of U.S. National Office of Vital Statistics.)

CERTIFICATION OF DEATH

Principles to be followed in certifying cause of death are given in the *Physicians' Handbook on Death and Birth Registration* and were discussed by Erhardt. On the Standard Certificate of Death (Fig. A2-4) the medical certification (item 18) consists of two parts for entry of the causes of death. The first part includes several lines (1a, b, c) for the physician to state either a single condition or a pathologically or etiologically related sequence of conditions which led directly to death. The most recent manifestation is stated first, the *underlying cause* is stated last. For example:

I (a) Pulmonary hemorrhage,
due to (b) kernicterus,
due to (c) hemolytic disease of the newborn.

The *underlying cause* is the disease or injury which initiated the train of morbid

CERTIFICATE OF FETAL DEATH¹

Form approved,
Public Health No.

STATE OF _____ STATE FILE NO. _____

1. PLACE OF DELIVERY a. COUNTY _____ b. CITY, TOWN, OR LOCATION _____ c. NAME OF HOSPITAL OR INSTITUTION _____ d. IS PLACE OF DELIVERY IN CITY LIMITS? YES ☐ NO ☐		2. USUAL RESIDENCE OF MOTHER (If born does mother live?) a. STATE _____ b. CITY, TOWN, OR LOCATION _____ c. STREET ADDRESS _____ d. IS RESIDENCE INSIDE CITY LIMITS? YES ☐ NO ☐	
3. NAME OF FETUS (if given) _____ 4. SEX OF FETUS MALE ☐ FEMALE ☐ UNDETERMINED ☐		5. DATE OF DELIVERY (Day) _____ (Year) _____	
6. THIS DELIVERY SINGLE ☐ TWIN ☐ TRIPLET ☐ 1ST ☐ 2D ☐ 3D ☐		7. IF TWIN OR TRIPLET WAS THIS FETUS DELIVERED FIRST ☐ MIDDLE ☐ LAST ☐	
8. FATHER a. NAME (Last, first, middle, last) _____ b. AGE (At time of delivery) YEARS _____ c. BIRTHPLACE (State or foreign country) _____ d. USUAL OCCUPATION _____		9. COLOR OR RACE _____ 10. KIND OF BUSINESS OR INDUSTRY _____	
11. MOTHER a. NAME (Last, first, middle, last) _____ b. AGE (At time of delivery) YEARS _____ c. BIRTHPLACE (State or foreign country) _____ d. PREVIOUS DELIVERIES TO MOTHER (Do not include this fetus) a. How many children born alive after this one? _____ b. How many children born dead after this one? _____ c. How many previous fetal deaths (stillborn born dead or any time after conception)? _____		12. COLOR OR RACE _____	
13. INFORMANT a. LENGTH OF PREGNANCY (Completed weeks) _____ b. WEIGHT OF FETUS (LB) _____ (OZ) _____ c. LEGITIMATE YES ☐ NO ☐			
14. WHEN DID FETUS DIE? BEFORE LABOR ☐ DURING LABOR ☐ AFTER LABOR ☐ UNKNOWN ☐			
15. WAS AUTOPSY PERFORMED? YES ☐ NO ☐			
16. CAUSE OF FETAL DEATH PART I: FETAL DEATH WAS CAUSED BY: Fetal or maternal condition directly causing fetal death (do not use such terms as stillbirth or prematurity) Fetal and/or maternal conditions, if any, giving rise to this above cause (e.g. placenta previa, uterine rupture) PART II: OTHER SIGNIFICANT CONDITIONS of fetus or mother which may have contributed to fetal death, but, in no way due to, or caused by, any of the above (e.g. congenital anomalies) I hereby certify that the delivery occurred on the date stated above and the fetus was born dead.			
17. ATTENDING PHYSICIAN'S SIGNATURE (Specify M.D., D.O., midwife or other) _____ 18. DATE SIGNED _____		19. ATTENDING PHYSICIAN'S ADDRESS _____ 20. SIGNATURE OF AUTHORIZED OFFICIAL _____ TITLE _____	
21. BURIAL, CREMATION, REMOVAL (Specify) _____ 22. DATE _____ 23. NAME OF CEMETERY OR CREMATORY _____ 24. LOCATION (City, town, or county) _____ (State) _____		25. FUNERAL DIRECTOR _____ DATE REC'D BY LOCAL REG. _____ REGISTRAR'S SIGNATURE _____	

¹Optional Inclusion—Certificate of Fetal Death (Stillborn)

FIG. A2-2. Standard Certificate of Fetal Death. (Courtesy of U.S. National Office of Vital Statistics.)

events leading to death. Every effort should be made to avoid the term "prematurity" in part I, which is reserved for specific pathologic entities.

Part II allows for the reporting of other significant conditions contributing to the death but not related to the disease last named in part I. For example:

II Prematurity

Physicians should be aware of the need for reporting prematurity in part II. In the International Lists⁴ each of the cause groups in the general category "Certain diseases of early infancy" (Section XV) has two subcategories to indicate whether "immaturity" was or was not reported. Although the cause-of-death data do not include all deaths that involve prematurely born children, complete reporting of prematurity will improve existing estimates from death certificate tabulations.

To the right of the cause-of-death statements in both part I and part II of item 18, space is left for the physician to enter the approximate interval between onset of the condition and death. This should be given as accurately as possible and the unit of time should be specified, e.g. 2 hours, 1 day, etc.

**SUPPLEMENTARY ITEMS FOR MEDICAL AND HEALTH
SECTIONS OF LIVE-BIRTH AND FETAL-DEATH CERTIFICATES**

OPTIONAL ITEMS RELATED TO PREGNANCY LABOR, AND DELIVERY

(Enter one or more checks in each section)

Conditions present during pregnancy <i>(Check one or more items)</i>	Conditions of labor <i>(Check one or more items)</i>	Methods of delivery <i>(Check one or more items)</i>
☐ None known ☐ Pre-eclampsia ☐ Eclampsia ☐ Hypertensive disease ☐ Uterine bleeding, not associated with labor ☐ Pyelitis ☐ Nephritis ☐ Heart disease ☐ Diabetes ☐ Syphilis ☐ Tuberculosis ☐ German measles ☐ Other viral infection <i>(specify)</i> _____ ☐ Anemia ☐ Malignant neoplasms or related conditions ☐ Injury or operation ☐ Other <i>(specify)</i> _____ _____ _____	☐ Normal labor ☐ Placenta praevia ☐ Abruptio placentae ☐ Other hemorrhage ☐ Prolapse of cord ☐ Breech presentation ☐ Other malpresentation ☐ Labor, 30 hours or more ☐ Other <i>(specify)</i> _____ _____ ☐ No labor*	☐ Spontaneous ☐ Low forceps ☐ Mid forceps ☐ High forceps ☐ Low cervical cesarean section ☐ Classical cesarean section ☐ Other cesarean section ☐ Breech extraction ☐ Internal version and extraction ☐ Other <i>(specify)</i> _____ _____ ☐ Laparotomy for ectopic* ☐ Curettage, therapeutic termination* ☐ Curettage for incomplete termination*

*For inclusion only on fetal-death certificates in areas where regulations call for reporting all fetal deaths

Was mother's blood tested for Rh factor?

No ☐ Yes, Rh negative, sensitized ☐ Yes, other ☐

Congenital malformation? No ☐ Yes ☐ If Yes, describe _____

Birth injury to fetus? ** No ☐ Yes ☐ If Yes, describe _____

**Use "infant" in place of "fetus" on live-birth certificate

FIG. A2-3. Supplementary items for medical and health sections of live birth and fetal death certificates. (Courtesy of U.S. National Office of Vital Statistics.)

CERTIFICATE OF DEATH

Form approved
Federal Bureau No. 46-38742

BIRTH NO.		STATE OF		STATE FILE NO.	
1. PLACE OF BIRTH a. COUNTY			2. USUAL RESIDENCE (Where deceased lived) a. STATE		
b. CITY, TOWN, OR LOCATION			c. CITY, TOWN, OR LOCATION		
d. NAME OF HOSPITAL OR INSTITUTION			e. STREET ADDRESS		
f. PLACE OF DEATH WAS DE CITY, TOWN, OR VILLAGE			g. IS RESIDENCE INSIDE CITY LIMITS?		
h. IS RESIDENCE ON A FARM?			i. IS RESIDENCE ON A FARM?		
3. NAME OF DECEASED (Type in print)			4. DATE OF DEATH		
5. SEX			6. DATE OF BIRTH		
7. COLOR OR RACE			8. AGE (In years last birthday)		
9. USUAL OCCUPATION (Give kind of work done during last 12 months if retired)			10. KIND OF BUSINESS OR INDUSTRY		
11. FATHER'S NAME			12. MOTHER'S MAIDEN NAME		
13. WAS DECEASED EVER IN U. S. ARMED FORCES? (If yes, in or out of service)			14. SOCIAL SECURITY NO.		
15. CAUSE OF DEATH (State only one cause per Part I and Part II)			16. INTERNAL BETWEEN ONSET AND DEATH		
PART I. DEATH WAS CAUSED BY IMMEDIATE CAUSE (a)			PART II. OTHER SIGNIFICANT CONDITIONS CONTRIBUTING TO DEATH BUT NOT RELATED TO THE TERMINAL DISEASE COMBINED UNDER IN PART I (a)		
b. ACCIDENT			c. SUICIDE		
d. NON-ACCIDENT			e. NON-SUICIDE		
f. TIME OF DEATH (Hour, Month, Day, Year)			g. PLACE OF DEATH (City, Town, or Village)		
h. INJURY OCCURRED WHILE AT WORK			i. PLACE OF INJURY (If in or about house, give address)		
j. CITY, TOWN, OR LOCATION			k. COUNTY		
l. STATE			m. DATE SIGNED		
n. SIGNATURE (Type in print)			o. ADDRESS		
p. DATE			q. NAME OF CLERGY OR CREMATOR		
r. LOCATION (City, Town, or Village)			s. STATE		
t. FUNERAL DIRECTOR			u. DATE RECEIVED BY LOCAL REG.		
v. ADDRESS			w. REGISTRAR'S SIGNATURE		

FIG. A2-4. Standard Certificate of Death. (Courtesy of U.S. National Office of Vital Statistics)

In all cases the item on whether an autopsy was performed should be answered "Yes" or "No" (item 19).

In certifying causes of death, the disease or condition should be reported in specific terms, if possible. It is recommended that the approved terms listed in the *Standard Nomenclature of Diseases*¹ be used.

REFERENCES

1. American Medical Association: *Standard Nomenclature of Diseases and Operations*. New York, Blakiston, 1952.
2. ERHARDT, C. L. What is "The cause of death"? *J A M A*. 168:161, 1958.
3. *Physicians' Handbook on Death and Birth Registration* (ed 11). Washington, D C, U.S. Department of Health, Education, and Welfare, 1958, Public Health Service Publication No. 593.
4. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* (7th rev.). Geneva, Switzerland, World Health Organization, 1957.

appendix 3. Birth-Weight Distributions in the United States, 1956

TABLE A3-1 DISTRIBUTION OF REGISTERED LIVE BIRTHS BY BIRTH WEIGHT AND COLOR FOR THE UNITED STATES AND FOR ITS GEOGRAPHIC DIVISIONS AND BY SEX FOR THE UNITED STATES, 1956

Area and color	Median weight (Gm.)	Per cent distribution by birth weight					
		1000 Gm. or less	1001-1500 Gm.	1501-2000 Gm.	2001-2500 Gm.	2500 Gm. or less	2501 Gm. or more
United States*	3,310	0.6	0.6	1.4	5.0	7.6	92.4
White	3,330	0.5	0.6	1.3	4.5	6.8	93.2
Nonwhite	3,180	0.9	1.1	2.3	7.8	12.1	87.9
Male	3,370	0.6	0.6	1.4	4.4	7.0	93.0
White	3,400	0.5	0.6	1.2	4.0	6.3	93.7
Nonwhite	3,240	1.0	1.1	2.1	6.9	11.0	89.0
Female	3,250	0.5	0.6	1.5	5.7	8.3	91.7
White	3,270	0.5	0.6	1.3	5.1	7.4	92.6
Nonwhite	3,130	0.9	1.1	2.4	8.8	13.2	86.8
New England*	3,310	0.5	0.6	1.3	5.0	7.4	92.6
White	3,320	0.5	0.5	1.2	4.8	7.1	92.9
Nonwhite	3,110	1.6	2.1	3.9	10.4	18.0	82.0
Middle Atlantic	3,280	0.6	0.6	1.4	5.1	7.7	92.3
White	3,300	0.5	0.5	1.3	4.7	7.0	93.0
Nonwhite	3,110	1.5	1.3	2.5	8.7	13.9	86.1
East North Central	3,330	0.6	0.6	1.4	4.7	7.3	92.7
White	3,350	0.5	0.5	1.2	4.3	6.5	93.5
Nonwhite	3,140	1.2	1.2	2.5	8.5	13.3	86.7
West North Central	3,360	0.5	0.6	1.3	4.1	6.4	93.6
White	3,380	0.4	0.5	1.2	3.9	6.0	94.0
Nonwhite	3,160	1.1	1.2	2.6	8.2	13.1	86.9
South Atlantic	3,290	0.6	0.8	1.6	5.7	8.6	91.4
White	3,320	0.5	0.6	1.3	4.8	7.2	92.8
Nonwhite	3,210	0.7	1.1	2.3	7.7	11.8	88.2
East South Central	3,320	0.5	0.7	1.5	5.5	8.1	91.9
White	3,350	0.4	0.6	1.3	4.7	6.9	93.1
Nonwhite	3,230	0.6	0.9	1.9	7.4	10.8	89.2

(Continued on page 476)

TABLE A3-1. DISTRIBUTION OF REGISTERED LIVE BIRTHS BY BIRTH WEIGHT AND COLOR FOR THE UNITED STATES AND FOR ITS GEOGRAPHIC DIVISIONS AND BY SEX FOR THE UNITED STATES, 1956 (Continued)

Area and color	Median weight (Gm.)	Per cent distribution by birth weight					
		1000 Gm. or less	1001- 1500 Gm.	1501- 2000 Gm.	2001- 2500 Gm.	2500 Gm. or less	2501 Gm. or more
West South Central	3,310	0.5	0.7	1.5	5.1	7.8	92.2
White	3,340	0.4	0.6	1.3	4.5	6.8	93.2
Nonwhite	3,220	0.9	1.1	2.1	7.4	11.5	88.5
Mountain	3,240	0.5	0.7	1.4	5.9	8.4	91.6
White	3,250	0.5	0.6	1.4	5.8	8.3	91.7
Nonwhite	3,170	0.8	0.8	1.7	6.9	10.3	89.7
Pacific	3,320	0.6	0.6	1.3	4.6	7.2	92.8
White	3,330	0.6	0.6	1.3	4.4	6.8	93.2
Nonwhite	3,170	1.2	1.0	2.2	7.1	11.4	88.6

Adapted from U.S. National Office of Vital Statistics. Natality, United States and each state, and Alaska, Hawaii, Puerto Rico, and the Virgin Islands (U.S.), 1956. *Vital Statistics—Special Reports 48*: (No. 14), 1958.

* Excludes births to residents of Massachusetts, since birth weight data were not available for births that occurred in this state.

appendix 4. Mortality Rates for States

Matching of birth and death records is not carried out routinely on a national basis. In the period 1952-54 data on neonatal deaths and births for certain states and other registration areas were matched according to an agreed-upon plan to permit the tabulation of comparative statistics on neonatal mortality by birth weight. These rates for infants with a birth weight of 2500 Gm. or less are presented in Table A4-1.

The National Office of Vital Statistics noted that data in this report are derived from registered events. In 1953 it was estimated that 99.0 per cent of the white and 94.8 per cent of the nonwhite births were registered. No definitive information is available on the completeness of neonatal-death registration, but it is thought to vary generally, as does birth-registration completeness. A number of infants who die immediately after birth may be reported as fetal deaths, while others may not be reported at all. This situation is undoubtedly of relatively greater importance at the very low birth weights and might lead to an understatement of mortality rates among these children.

TABLE A4-1. NEONATAL MORTALITY RATES (PER 100) BY BIRTH WEIGHT AND COLOR

<i>Reporting area and period</i>	<i>Birth weight (Gm.)</i>				
	<i>1000 or less</i>	<i>1001- 1500</i>	<i>1501- 2000</i>	<i>2001- 2500</i>	<i>2500- or less</i>
Arkansas, 1952-54, total	70.7	44.6	18.8	4.9	14.8
White	74.9	52.7	19.3	5.4	16.4
Nonwhite	62.0	28.9	18.0	4.1	11.8
Colorado, 1952-54, total	—*	—	—	—	13.9
White	—	—	—	—	13.8
Nonwhite	—	—	—	—	15.1
Connecticut, 1952-54, total	91.9	55.4	16.8	3.9	16.6
White	92.4	56.5	17.3	4.0	16.5
Nonwhite	88.0	45.2	12.2	2.8	17.9
Georgia, 1952-54, total	80.8	48.5	18.9	4.8	15.7
White	86.5	53.6	19.7	5.0	16.8
Nonwhite	72.9	43.2	17.9	4.5	14.4
Illinois, 1952 and 1953, total	93.2	52.1	17.9	4.1	17.5
White	93.9	54.4	18.5	4.3	18.1
Nonwhite	90.0	43.7	15.4	3.3	15.3
Indiana, 1954, total	—	51.5	21.8	5.1	18.9
White	—	54.0	21.6	5.1	19.1
Nonwhite	—	37.1	22.9	4.8	18.0
Iowa, 1952-54, total	89.2	62.7	22.0	4.9	18.7
Kansas, 1953, total	88.0	59.0	19.5	5.2	18.3
White	88.4	60.1	19.8	5.5	18.6
Nonwhite	84.0	51.5	17.4	..*	15.9
Kentucky, 1952-54, total	83.9	55.7	20.3	5.4	17.6
White	84.3	56.9	21.2	5.7	17.8
Nonwhite	81.6	47.8	13.9	3.5	15.6
Maryland (excl. Baltimore), 1953-54, total	74.7	53.9	16.8	4.2	15.8
White	76.9	53.7	16.8	4.3	15.9
Nonwhite	68.0	54.8	16.8	3.9	15.7

(Continued on page 478)

TABLE A4-1. NEONATAL MORTALITY RATES (PER 100) BY BIRTH WEIGHT AND COLOR (Continued)

<i>Reporting area and period</i>	<i>Birth weight (Gm.)</i>				
	<i>1000 or less</i>	<i>1001- 1500</i>	<i>1501- 2000</i>	<i>2001- 2500</i>	<i>2500- or less</i>
Baltimore, Md., 1952-54, total	87.1	44.0	16.8	3.3	15.4
White	89.8	47.5	20.8	3.5	15.8
Nonwhite	84.5	40.8	12.4	3.1	14.9
Michigan, 1953, total	91.1	55.2	17.1	4.5	17.9
White	94.5	57.1	18.0	4.5	18.1
Nonwhite	76.5	47.7	13.0	4.7	16.5
Mississippi, 1952, total	85.7	56.1	23.7	6.1	17.9
White	91.1	58.9	24.7	6.0	20.1
Nonwhite	81.9	54.5	23.1	6.2	16.8
Missouri, 1954, total	91.4	54.4	17.5	5.2	18.3
White	94.3	57.3	18.1	5.7	18.9
Nonwhite	82.1	44.8	15.4	3.5	16.0
Montana, 1953, total	87.8	52.5	21.4	3.9	17.4
White	86.8	50.0	22.0	4.0	17.0
Nonwhite			..	..	25.7
New Hampshire, 1952-54, total	91.1	55.4	16.3	4.7	16.3
New York (excl. N.Y.C.), 1952-54, total	93.9	54.8	17.9	4.0	17.1
New York City, total	89.4	46.0	14.2	3.2	14.4
White	90.4	48.3	14.8	3.4	13.8
Nonwhite	87.5	40.2	12.2	2.4	16.2
North Carolina, 1952-54, total	78.4	48.6	18.6	4.9	15.8
White	80.8	50.3	17.8	4.5	15.5
Nonwhite	75.0	46.2	19.7	5.4	16.2
Oregon, 1952-54, total	95.5	54.2	21.3	4.4	17.9
White	95.8	54.9	21.4	4.5	18.0
Nonwhite	89.3	38.5	19.2	.	16.4

TABLE A4-1. NEONATAL MORTALITY RATES (PER 100) BY BIRTH WEIGHT AND COLOR (*Continued*)

Reporting area and period	Birth weight (Gm.)				
	1000 or less	1001-1500	1501-2000	2001-2500	2500- or less
Rhode Island, 1952 and 1953, total	92.7	66.7	17.7	3.8	17.0
White	93.3	64.2	17.9	3.9	16.7
Nonwhite	87.5	—		0	23.0
Tennessee, 1952-54, total	88.8	54.7	20.8	5.3	17.8
White	91.3	58.1	22.5	5.8	18.7
Nonwhite	83.4	47.3	16.8	4.1	15.9
Vermont, 1953 and 1954, total	93.2	64.8	21.2	5.2	18.1
White	93.2	64.5	21.4	5.2	18.1
Nonwhite	—	..	0	—	..
Virginia, 1953 and 1954, total	92.1	57.4	21.0	4.8	18.2
White	93.3	58.6	20.9	4.8	18.3
Nonwhite	89.6	55.3	21.4	4.8	18.1
West Virginia, 1954, total	64.3	49.5	16.7	4.8	14.4
White	66.5	50.5	17.5	4.9	14.4
Nonwhite	54.4	40.0		.	13.7
Wisconsin, 1952 and 1953, total	95.9	62.4	22.0	5.2	19.6
White	96.3	61.9	22.2	5.3	19.7
Nonwhite	89.2	87.5	19.1	3.2	16.4
Hawaii, 1952-54, total	90.8	56.6	15.4	3.5	14.4
White	91.6	49.0	14.1	5.5	17.5
Nonwhite	90.6	58.9	15.9	3.0	13.6
Virgin Islands, 1952-54, total	..	71.4	27.5	..	17.0
White	—	—	..	0	..
Nonwhite	..	71.4	25.5	..	16.8

From U.S. National Office of Vital Statistics: Births and neonatal deaths by birth weight: Reporting areas, 1952-54, *Vital Statistics—Special Reports 47*: (No. 1), 1957.

Data for Florida were made available for neonatal deaths among single live births in 1953. Neonatal mortality rates per 100 single live births in birth-weight category 2500 Gm. or less were: white, 18.1 per cent; nonwhite, 17.3 per cent.

* Two dots (..) indicate rate not computed where number of deaths was less than 10, a dash (—) indicates rate not computed for other reasons.

appendix 5. Life Tables for Ten Premature Centers in New York City

During a three-year period (1955-57) 7530 premature infants were admitted to ten premature centers in New York City. The characteristics and fate of this population of infants were determined and tabulated biweekly by a peripatetic clerk. The experience was subdivided into specific categories as follows (Table A5-1):

(a) Place of birth (intramural—within the reporting hospital; extramural—admitted from all other sources, other hospitals, home delivery, etc.)

TABLE A5-1. PREMATURE INFANTS ADMITTED TO TEN PREMATURE CENTERS IN NEW YORK CITY DURING A THREE-YEAR PERIOD, 1955-57

	<i>No entries</i>	<i>No. discharges*</i>	<i>No deaths^b</i>
All infants	7,530	2,439	2,075
Intramural	5,167	1,997	1,535
Extramural	2,363	442	540
White	4,075	1,453	1,023
Nonwhite	3,455	986	1,052
High gestational age	2,732	1,164	501
Other (low & unknown) gestational age	4,798	1,275	1,574
Male	3,689	1,139	1,158
Female	3,841	1,300	917
Birth weight (Gm)			
500 or less	289	0	289
501-750	335	1	328 ^c
751-1000	492	4	383
1001-1250	694	12	332
1251-1500	992	28	282
1501-1750	1,357	163	202
1751-2000	1,611	797	148
2001-2250	1,399	1,121	78
2251-2500	361	313	33

* Discharged from nursery alive before 28 days of age.

^b Deaths before 28 days of age

^c The difference between the number of entries and the sum of discharges and deaths gives the size of the population in each birth-weight category remaining in the nursery longer than 28 days.

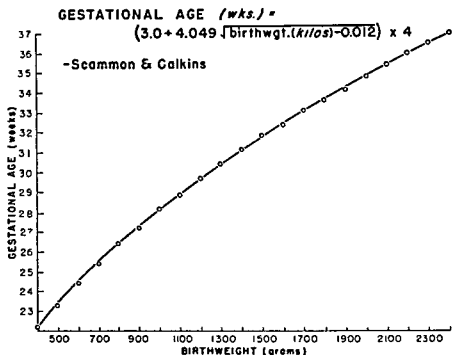


FIG. A5-1. The relation between gestational age and birth weight calculated from Scammon and Calkins' regression equation.¹ The graph is entered with a given value for birth weight. If the infant's gestational age (number of completed weeks from the first day of the mother's last menstrual period) is found to be on or above the curve, this infant is characterized as having a "high gestational age," below the curve, "low gestational age."

(b) Color (white or nonwhite on the basis of the mother's answer to the question "Nationality and race?" on the hospital admission forms)

(c) A valuation of gestational age (Fig. A5-1) No differences were demonstrable in the death rates of infants with "low gestational age" and of others whose gestational age was unknown when the other factors here considered were held constant. Therefore, these two categories were considered together as "other gestational age"

(d) Sex.

(e) Birth weight.

Within each of these mutually exclusive categories the age-specific death rates were summarized by the life-table method. The life tables are presented in this section of the Appendix (Tables A5-2 through A5-9, pages 484-499).

The column labeled n_x records the number of infants who were admitted to the nursery alive during the age intervals. Infants who were admitted before 15 minutes of age are placed in the l_x column at 15 minutes of age.

w_x records the number of infants discharged alive during the age intervals

d_x refers to the number of deaths which occurred in the nursery during the age interval.

l_x notes the number of individuals present in the nursery at the *beginning* of the age interval. The life tables begin at 15 minutes of age. Therefore, all individuals who were admitted to the nursery before the age of 15 minutes are placed in the "15-29 minute" l_x column. Actually, most of these entered just prior to 15 minutes. Each succeeding l_x entry is determined by summing the number of infants present alive at the beginning of the age interval and the number admitted alive during this same period, and subtracting the discharges either dead or alive from this total.* For example (intramural, white, high gestational age, male 1501-1750 Gm) 10 infants were present at 15 minutes of age, 21 were admitted during the interval "15-29 minutes," and 1 death occurred during the interval. Thus 30 infants ($10 + 21 - 1$) were present at the beginning of the "30-59 minute" interval.

The q_x values are the specific probabilities of dying which are computed for each age interval of the life tables. It should be noted that the admissions (n_x) may have arrived at various times within the age interval, some at the very first moment of the interval, others at the very last moment, and still be credited with having been admitted within that time of life. It is assumed that the admissions occurred uniformly throughout the intervals so that, on the average, they were all exposed for one-half the time interval (i.e., n_x admissions yield $\frac{1}{2} n_x$ full exposures). Similarly, those infants who were discharged alive during the age interval are assumed to represent $\frac{1}{2} w_x$ full exposures. Thus, the individuals present alive at the beginning of the interval plus one-half of those admitted during the interval, less one-half of those discharged alive form the denominator for the deaths which occurred during the period.† For example (intramural, white, high gestational age, male, 1501-1750 Gm) q_x for the interval "15-29 minutes" was calculated as:

$$\frac{1}{10 + \frac{1}{2}(21)} = 0.049$$

For each table the probabilities of dying are also given for the broad intervals "15 minutes up to 7 days" and "15 minutes up to 28 days." These values (Q_x) are cumulative death rates and represent one minus the product of the complements of the specific rates (q_x). For example (intramural, white, high gestational age, male, 1501-1750 Gm) the "15 minute up to 7 days" cumulative death rate was calculated as follows:

$$Q_x = 1 - (1 - 0.049) \times (1 - 0.014) \times (1 - 0.017) = 1 - 0.745 = 0.255$$

The median age at entry and median age at discharge alive (before 28 days) for each life table are given.

$$*l_{x+1} = (l_x + n_x) - (d_x + w_x) \quad \dagger q_x = \frac{d_x}{l_x + \frac{1}{2}(n_x - w_x)}$$

In Table A5-10 the median age at the time of admission to the nursery and the cumulative 7-day death rate for each specific category are summarized (see pages 500 and 501)

The values of q_x in each life table may be utilized as a set of standard rates to adjust individual nursery death rates, as we proposed in 1955.² The reader is referred to that report for a statement of the proposal and for the details of the calculations.

ACKNOWLEDGMENTS

Compilation of the data in these life tables was made possible by a grant from the United States Public Health Service (RG 4277) Mrs Lois Mark and Mrs Ethne Marengo faithfully visited the premature centers and recorded the details of each admission Mrs Molly Park collated the data and performed the statistical computations under the supervision of Dr. John W. Fertig, School of Public Health and Administrative Medicine, Columbia University. The cooperating premature centers were located in Babies Hospital, Bellevue Hospital, Flushing Hospital, Harlem Hospital, Kings County Hospital, Lincoln Hospital, Mount Sinai Hospital, New York Hospital, Queens General Hospital, and St. Vincent's Hospital

Dr. Harold Jacobziner and Mr. Carl L. Erhardt provided supplementary information from the records of the New York City Department of Health

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- 1 SCAMMON, R. E., and CALKINS, L. A. *The Development and Growth of the External Dimensions of the Human Body in the Fetal Period*. Minneapolis, Minn., Univ. Minnesota Press, 1929.
- 2 SILVERMAN, W. A., FERTIG, J. W., and KRAUSS, A. A proposed method of computing standardized death rates for premature nurseries. *Pediatrics* 15:467, 1955

TABLE A5-2. INTRAMURAL, WHITE, HIGH GESTATIONAL AGE

Age	Birth weight (Gm)																			
	500 or less					501-750					751-1000					1001-1250				
	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x
MALE																				
15-29 min	1		1			4		1			2		2			6		8		
30-59			1	2	0.500	5		1	5	0.133	5		4			11		14		
1 hour(s)			1					1	9	0.111			2	9	0.222	1		1	25	0.039
2-5			1	1	1.000			6	8	0.750			2	7	0.286			6	25	0.240
6-11								2			1		5					1	19	0.053
12-17								2					3	6	0.500			2	18	0.111
18-23								2					3							16
1 day(s)								1	2	0.500			1	3	0.333			1	16	0.062
2								1					2					1	15	0.067
3								1					2							14
4								1	1	1.000			2					2	14	0.143
5													1	2	0.500			1	12	0.083
6													1							11
15 minutes up to 7 days SUBTOTAL	2*	0	2		<i>Q</i> _x =1.000 ^b	10*	0	10		<i>Q</i> _x =1.000 ^b	10*	0	9		<i>Q</i> _x =0.908 ^b	26*	0	15		<i>Q</i> _x =0.578 ^b
7-13 days													1					2	11	0.182
14-20													1							9
21-27													1							9
15 minutes up to 28 days TOTAL	2*	0	2		<i>Q</i> _x =1.000 ^b	10*	0	10		<i>Q</i> _x =1.000 ^b	10*	0	9		<i>Q</i> _x =0.908 ^b	26*	0	17		<i>Q</i> _x =0.655 ^b
Median age at entry ^a					—					30 min					36 min					27.5 min
Median age at discharge (alive) ^a					—					—					—					—
FEMALE																				
15-29 min.	1					4		1			7		6			6		4		
30-59	1		1			2		2	5	0.333	4		13			7		10		
1 hour(s)			2			1		5			1		17						17	
2-5			2			1		3	6	0.462			4	18	0.222			1	17	0.118
6-11			2					1	4	0.250			2	14	0.143			1	15	0.067
12-17			1	2	0.500			1	3	0.333			12					2	14	0.143
18-23			1	1	1.000			2					1	12	0.083					12
1 day(s)								2					3	11	0.273			1	12	0.083
2								2	2	1.000			1	8	0.125					11
3													1	7	0.143					11
4													1	6	0.167					11
5													1	5	0.200					11
6													1	4	0.250					11
15 minutes up to 7 days SUBTOTAL	2*	0	2		<i>Q</i> _x =1.000 ^b	9*	0	9		<i>Q</i> _x =1.000 ^b	15*	0	15		<i>Q</i> _x =0.834 ^b	17*	0	6		<i>Q</i> _x =0.354 ^b
7-13 days													1	3	0.333					11
14-20													2							11
21-27													2							11
15 minutes up to 28 days TOTAL	2*	0	2		<i>Q</i> _x =1.000 ^b	9*	0	9		<i>Q</i> _x =1.000 ^b	15*	0	16		<i>Q</i> _x =0.945 ^b	17*	0	6		<i>Q</i> _x =0.354 ^b
Median age at entry ^a					—					28.1 min					21.4 min					26.2 min
Median age at discharge (alive) ^a					—					—					—					—

* Includes admissions up to 15 minutes of age

^b *Q*_x death rate equals one minus the product of the complements of *q*_x^a Median not computed for a total number of entries (*n*_x) or discharges (*w*_x) of five or less

TABLE A5-2. INTRAMURAL, WHITE, HIGH GESTATIONAL AGE (continued)

Bulk weight (Gm)

1251-1500					1501-1750					1751-2000					2001-2250					2251-2500				
n_x	u_x	d_x	l_x	q_x	n_x	u_x	d_x	l_x	q_x	n_x	u_x	d_x	l_x	q_x	n_x	u_x	d_x	l_x	q_x	n_x	u_x	d_x	l_x	q_x
MALE																								
13		6			21		1 10	0 049		15		17			20		25			6		11		
14		19			31		30			48		32			51		45			13		17		
4		33			13		61			20		1 80	0 011		35		96			14		1 30	0 027	
2		2 37	0 053				1 74	0 014		5		99			13	1 1	131	0 007		6	1 1	43	0 025	
		1 37	0 027				4 73	0 055				104			1		142					47		
		1 36	0 028				1 69	0 014		1	1 1	104	0 010		1		143					47		
		35					2 68	0 029		1		102			2		144			2		1 47	0 021	
		6 35	0 171				5 66	0 076				4 103	0 039		1		4 146	0 027				1 48	0 021	
		2 29	0 069				2 61	0 033				1 99	0 010		2		143			1	1 1	47	0 022	
		1 27	0 037				59					1 98	0 010		1	1 1	141	0 007				45		
		26					1 59	0 017		1	1 1	97	0 010				139					45		
		26					58					95			1		139					2 45		
		26					58					95					140			4		43		
39 ^a	0	13	$Q_x=0.335^b$		75 ^a	0	17	$Q_x=0.255^b$		106 ^a	2	9	$Q_x=0.086^b$		150 ^a	4	6	$Q_x=0.041^b$		52 ^a	8	5	$Q_x=0.111^b$	
	1	26				3	58				3	95				37	2 140	0 016		1	19	39		
		1 25	0 040			4	55				19	92				68	1 101	0 015			14	1 21	0 071	
	2	24				6	51				42	73				22	32				6	6		
39 ^a	3	14	$Q_x=0.362^b$		75 ^a	13	17	$Q_x=0.255^b$		106 ^a	66	9	$Q_x=0.086^b$		150 ^a	131	9	$Q_x=0.071^b$		53 ^a	47	6	$Q_x=0.174^b$	
		31 1 min					36 3 min					43 1 min					47 6 min					51 9 min		
		—					20 1 days					22.5 days					23 5 days					12 7 days		

FEMALE

15	7	19	8	23	19	36	37	13	26
17	22	21	27	40	42	52	73	8	39
3	1 39 0.025	6	48	24	82	48	125	16	47
	1 41 0.024	3	54	9	106	10	1 173 0.006	5	1 63
			57	1	1 115 0.009	2	182	3	1 67 0.014
1	2 40 0.049		57	1	1 115 0.009	2	182		69
	1 39 0.026		57		115	1	184		1 69 0.014
1	2 38 0.052		1 57 0.018		1 115 0.009	1	2 185 0.011	1	1 68
	37		2 56 0.036		114	2	1 3 184 0.016		1 68
	1 37 0.027		54		114	2	2 182		2 67
	2 36 0.056		54		114		2 182	1	3 65
	34	1	54	1	114		180		2 63
	34		53	1	113		2 180		61
44*	0 10 $Q_x=0.233^b$	57*	1 3 $Q_x=0.053^b$	118*	1 3 $Q_x=0.027^b$	193*	9 6 $Q_x=0.033^b$	73*	10 2 $Q_x=0.028^b$
	1 34 0.029		53		3 114		49 178	1	36 61
	33		53		27 111		77 1 129 0.011		18 1 26 0.059
	1 33		10 51		48 84		35 51		5 7
44*	1 11 $Q_x=0.255^b$	57*	13 3 $Q_x=0.053^b$	118*	79 3 $Q_x=0.027^b$	193*	170 7 $Q_x=0.044^b$	74*	69 3 $Q_x=0.085^b$
	30.0 min		32.1 min		42.8 min		43.6 min		27.7 min.
	—		23.4 days		22.2 days		16.4 days		11.8 days

TABLE A5-3. INTRAMURAL, WHITE, OTHER (LOW AND UNKNOWN) GESTATIONAL AGE

Age	Birth weight (Gm.)																				
	500 or less					501-750					751-1000					1001-1250					
	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	
MALE																					
15-29 min	4		13			9		5			24		12			24		9			
30-59	7		17			8		4	14	0.222	13		2	36	0.047	15		1	33	0.025	
1 hour(s)	1		5	24	0.204	4		2	18	0.100	3		4	47	0.082	7		2	47	0.040	
2-5	2		17	20	0.810	1		14	20	0.683	1		16	46	0.344	1		7	52	0.135	
6-11			2	5	0.400			2	7	0.286			6	31	0.194	1		10	46	0.215	
12-17			1	3	0.333			2	5	0.400	1		4	25	0.157			9	37	0.243	
18-23			1	2	0.500			1	3	0.333			5	22	0.227			2	28	0.071	
1 day(s)			1	1	1.000	1		1	2	0.400			5	17	0.294			8	26	0.308	
2								2	2	1.000			5	12	0.417			4	18	0.222	
3													3	7	0.428					14	
4													1	4	0.250					24	
5													2	3	0.667					14	
6													1							14	
15 minutes up to 7 days SUBTOTAL	27*	0	27	$Q_x=1.000^b$		28*	0	28	$Q_x=1.000^b$		54*	0	53	$Q_x=0.983^b$		57*	0	45	$Q_x=0.755^b$		
7-13 days													1					5	14	0.357	
14-20													1						9		
21-27													1				1		9		
15 minutes up to 28 days TOTAL	27*	0	27	$Q_x=1.000^b$		28*	0	28	$Q_x=1.000^b$		54*		53	$Q_x=0.983^b$		57*	1	48	$Q_x=0.845^b$		
Median age at entry*					16	9 min				30	0 min				24	4 min.				27	2 min.
Median age at discharge (alive)*					—					—					—					—	
FEMALE																					
15-29 min	8		6			8		2	9	0.154	16		14			17		11			
30-59	6		2	14	0.118	9		1	15	0.051	11		30			13		28			
1 hour(s)	2		7	18	0.368	3		2	23	0.082	2		4	41	0.095	1		1	41	0.024	
2-5	3		11	13	0.759	4		11	24	0.423	1		6	39	0.152			5	41	0.122	
6-11	3		3	5	0.462			8	17	0.470			8	34	0.235			2	36	0.056	
12-17			3	5	0.600			3	9	0.333			4	26	0.154			3	34	0.089	
18-23			2	2	1.000	1		1	6	0.154			5	22	0.227			1	31	0.032	
1 day(s)								6	6	1.000			3	17	0.176			11	30	0.367	
2													2	14	0.143			1	19	0.053	
3													12						18		
4													12					1	18	0.056	
5													2	12	0.167				17		
6													1	10	0.100				17		
15 minutes up to 7 days SUBTOTAL	28*	0	28	$Q_x=1.000^b$		34*	0	34	$Q_x=1.000^b$		44*	0	35	$Q_x=0.797^b$		42*	0	25	$Q_x=0.596^b$		
7-13 days													1	9	0.111				2	17	0.118
14-20													8					1	15		
21-27													8						14		
15 minutes up to 28 days TOTAL	28*	0	28	$Q_x=1.000^b$		34*	0	34	$Q_x=1.000^b$		44*	0	36	$Q_x=0.820^b$		42*	1	27	$Q_x=0.644^b$		
Median age at entry*					30	0 min				30	0 min				22	5 min				23	8 min.
Median age at discharge (alive)*					—					—					—					—	

* Includes admissions up to 15 minutes of age ^b Q_x death rate equals one minus the product of the complements of q_x * Median not computed for a total number of entries (n_x) or discharges (w_x) of five or less

TABLE A5-3. INTRAMURAL, WHITE, OTHER (LOW AND UNKNOWN)
GESTATIONAL AGE (continued)

Birth weight (Gm.)

1251-1520					1521-1750					1751-2000					2001-2250					2251-2500				
<i>n</i> _x	<i>n</i> _y	<i>d</i> _x	<i>d</i> _y	<i>q</i> _x	<i>n</i> _x	<i>n</i> _y	<i>d</i> _x	<i>d</i> _y	<i>q</i> _x	<i>n</i> _x	<i>n</i> _y	<i>d</i> _x	<i>d</i> _y	<i>q</i> _x	<i>n</i> _x	<i>n</i> _y	<i>d</i> _x	<i>d</i> _y	<i>q</i> _x	<i>n</i> _x	<i>n</i> _y	<i>d</i> _x	<i>d</i> _y	<i>q</i> _x
MALE																								
26	11				31	18				44	26				35	34				17	22			
19	37				48	1 49	0 014			57	70				64	69				10	39			
4	1 56	0 017			9	1 96	0 010			27	1 127	0 007			27	133				19	49			
2	6 59	0 100			3	9 104	0 085			4	4 153	0 026			7	1 1 160	0 006			7	3 65	0 042		
	6 55	0 109			2	6 98	0 061			1	5 153	0 032				2 165	0 012			1	72			
	7 49	0 143				4 94	0 042				5 149	0 034			1	2 1 163	0 006			1	1 71	0 014		
	2 42	0 048				2 90	0 022				2 144	0 014			1	161				1	2 71	0 028		
	8 40	0 200			1	10 88	0 113				9 142	0 063			1	8 162	0 049			1	3 70	0 042		
	32					3 79	0 038			1	4 133	0 030			1	1 155	0 006			2	2 68	0 029		
	1 32	0 031				2 76	0 008				1 130	0 008				155					1 68	0 015		
	31					74				1	129				2	155				1	67			
	2 31	0 064				1 74	0 014				1 128	0 008				153				3	1 68			
	1 29	0 034				73					127				1	153				1	1 70	0 014		
62*	0	34	$Q_x=0.550^b$		112*	0	39	$Q_x=0.357^b$		160*	1	32	$Q_x=0.202^b$		172*	5	13	$Q_x=0.078^b$		85*	2	13	$Q_x=0.171^b$	
	28					1	2 73	0 028			4	3 127	0 024		2	12	154			3	19	70		
	1 28	0 036				70					15	120				51	144				33	54		
	1	1 27	0 038			4	70				37	1 105	0 012			57	93				18	21		
62*	1	36	$Q_x=0.583^b$		112*	5	41	$Q_x=0.375^b$		160*	57	36	$Q_x=0.231^b$		174*	125	13	$Q_x=0.078^b$		88*	72	13	$Q_x=0.171^b$	
	26 5 min					34 4 min					35 3 min					38 4 min					45 0 min			
	—					—					22 8 days					20 2 days					17 2 days			
FEMALE																								
21	11				19	20				38	14				52	23				14	14			
21	32				32	39				50	52				58	75				20	28			
10	53				10	71				29	102				31	133				18	1 48	0 018		
2	2 63	0 031				3 81	0 037			2	1	131			16	164				3	1 1 65	0 015		
	7 63	0 111			1	3 78	0 038			1	2 132	0 013			1	1 180	0 006				1 66	0 015		
	3 56	0 045				1 76	0 013				1 131	0 008				1 180	0 006			2	65			
	2 53	0 038				2 75	0 027				130				1	179					67			
	4 51	0 078				6 73	0 082				7 130	0 054			2	3 180	0 016			1	1	67		
	47					1 67	0 015				2 123	0 016			1	1 179	0 006				67			
	1 47	0 021				66					2 121	0 016			2	1	179			2	1	67		
	46					66					119					179				2	1 4 67	0 015 ^b		
	1 46	0 022				66					119				1	179					67			
	45					66				1	119					1	180			1	67			
65*	0	20	$Q_x=0.309^b$		82*	0	16	$Q_x=0.196^b$		134*	2	14	$Q_x=0.106^b$		187*	2	6	$Q_x=0.034^b$		75*	5	4	$Q_x=0.062$	
	2 45	0 044				66				2	1	118				19	1 179	0 006			18	1 66	0 018	
	1	43				1	1 66	0 015			20	119			3	67	1 159	0 008			32	1 47	0 032	
	1	42				4	1 64	0 016			40	99				61	94				12	14		
65*	2	22	$Q_x=0.340^b$		82*	5	18	$Q_x=0.221^b$		136*	63	14	$Q_x=0.106^b$		190*	149	8	$Q_x=0.048^b$		75*	67	6	$Q_x=0.109^b$	
	30 7 min					31 9 min.					39 6 min					40 3 min					44 2 min.			
	—					—					22 5 days					19 6 days					16 3 days			

TABLE A5-4 INTRAMURAL, NON-WHITE, HIGH GESTATIONAL AGE

Age	Birth weight (Gm)																				
	500 or less					501-750					751-1000					1001-1250					
	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	
MALE																					
15-29 min	2		1			8		1	7	0.091	8		1			15		1			
30-59	2		3			11		14			13		9			12		16			
1 hour(s)	1		2	5	0.364	4		2	25	0.074	1		3	22	0.133	2		28			
2-5			2	4	0.500			13	27	0.481	1		3	20	0.146			2	30	0.067	
6-11			2	2	1.000	1		4	14	0.276			6	18	0.333			2	28	0.071	
12-17								2	11	0.182			12					3	26	0.115	
18-23								1	9	0.111			1	12	0.083			3	23	0.130	
1 day(s)								6	8	0.750			3	11	0.273			3	20	0.150	
2								2					2	8	0.250			2	17	0.118	
3								2					6					1	15	0.067	
4								2					1	6	0.167			14			
5								1	2	0.500			5					14			
6								1					5					1	14	0.071	
15 minutes up to 7 days SUBTOTAL	6*	0	6		<i>Q</i> _x =1.000 ^b	31*	0	30		<i>Q</i> _x =0.972 ^b	24*	0	19		<i>Q</i> _x =0.795 ^b	30*	0	17		<i>Q</i> _x =0.567 ^b	
7-13 days								1					1	5	0.200			1	13	0.077	
14-20								1					1	4	0.250			1	12		
21-27								1					3					11			
15 minutes up to 28 days TOTAL	6*	0	6		<i>Q</i> _x =1.000 ^b	31*	0	30		<i>Q</i> _x =0.972 ^b	24*	0	21		<i>Q</i> _x =0.877 ^b	30*	1	18		<i>Q</i> _x =0.600 ^b	
Median age at entry*					30.0 min					31.4 min					36.9 min					29.0 min	
Median age at discharge (alive)*					—					—					—					—	
FEMALE																					
15-29 min	4		1	3	0.200	12		3			10		5			18		3			
30-59	2			6		3		2	15	0.121	8		15			14		21			
1 hour(s)				8		1		2	16	0.121	3		2	23	0.085			35			
2-5				4	8	0.500	1		8	15	0.516			3	22	0.136		35			
6-11				1	4	0.250			1	8	0.125			19				1	35	0.028	
12-17				3				1	7	0.143			2	19	0.105			34			
18-23				1	3	0.333			6				1	17	0.059			1	34	0.029	
1 day(s)				2	2	1.000			3	6	0.500			3	16	0.188		1	3	33	0.092
2									3					1	13	0.077		29			
3									3					1	12	0.083		1	29	0.034	
4									2	3	0.667			11				28			
5									1					11				28			
6									1					1	11	0.091		1	28	0.036	
15 minutes up to 7 days SUBTOTAL	9*	0	9		<i>Q</i> _x =1.000 ^b	20*	0	19		<i>Q</i> _x =0.953 ^b	24*	0	14		<i>Q</i> _x =0.585 ^b	35*	1	7		<i>Q</i> _x =0.203 ^b	
7-13 days									1					1	10	0.100		3	27	0.111	
14-20									1					1	9	0.111		24			
21-27									1					8				1	24		
15 minutes up to 28 days TOTAL	9*	0	9		<i>Q</i> _x =1.000 ^b	20*	0	19		<i>Q</i> _x =0.953 ^b	24*	0	16		<i>Q</i> _x =0.668 ^b	35*	2	10		<i>Q</i> _x =0.292 ^b	
Median age at entry*					20.6 min					23.8 min					25.5 min					27.1 min	
Median age at discharge (alive)*					—					—					—					—	

* Includes admissions up to 15 minutes of age

^b *Q*_x death rate equals one minus the product of the complements of *q*_x* Median not computed for a total number of entries (*n*_x) or discharges (*w*_x) of five or less

TABLE A5-4. INTRAMURAL, NON-WHITE, HIGH GESTATIONAL AGE (continued)

Birth weight (Gm)

1251-1500					1501-1750					1751-2000					2001-2250					2251-2500				
<i>n</i> _x	<i>n</i> _z	<i>d</i> _x	<i>d</i> _z	<i>q</i> _x	<i>n</i> _x	<i>n</i> _z	<i>d</i> _x	<i>d</i> _z	<i>q</i> _x	<i>n</i> _x	<i>n</i> _z	<i>d</i> _x	<i>d</i> _z	<i>q</i> _x	<i>n</i> _x	<i>n</i> _z	<i>d</i> _x	<i>d</i> _z	<i>q</i> _x	<i>n</i> _x	<i>n</i> _z	<i>d</i> _x	<i>d</i> _z	<i>q</i> _x
MALE																								
14	4				24	4				24	8				10	7				3	4			
23	18				26	28				48	32				52	17				1	7			
4	1 41	0 023			5	54				13	80				12	69				1	8			
	2 44	0 045			1	1 59	0 017			2	1 93	0 011			5	81					9			
	42				1	59				1	94					86					9			
	2 42	0 048			1	60					95				2	1 86	0 011				9			
	1 40	0 025				61					1 95	0 010				1	87				9			
	1 39	0 026				1 61	0 016				3 94	0 032				86					9			
	2 38	0 053				60				1	2 91	0 022			1	4 86	0 046				9			
	56					1 60	0 017				1 90	0 011				2 83	0 024				9			
	36					59					89					1 81	0 012				1	9		
	1 36	0 028				59					89					80					8			
	35					59					89					80					1	8		
45*	0 10	Q _x =0.224 ^b			62*	0 3	Q _x =0.050 ^b			97*	0 8	Q _x =0.083 ^b			89*	1 8	Q _x =0.090 ^b			9*	2 0	Q _x =0.000 ^b		
	35					59					3 89	0 034			2	18	80				1	1 7	0 154	
	35					4 59				24	86				40	64					4	5		
	1 1 35	0 029				7 55				30	62				20	24					1	1		
45*	1 11	Q _x =0.247 ^b			62*	11 3	Q _x =0.050 ^b			97*	54 11	Q _x =0.114 ^b			91*	79 8	Q _x =0.090 ^b			9*	8 1	Q _x =0.154 ^b		
	35 9 min					33 5 min					40 3 min					46 4 min						17 5 min		
	—					22 5 days					21 7 days					17 6 days						15 8 days		
FEMALE																								
26	1 5	0 056			36	7				32	5				15	7				2	1			
26	30				40	23				73	37				57	22				1	3			
6	1 56	0 017			6	2 63	0 030			20	110				23	79					4			
	3 61	0 049				1 67	0 015			4	1 130	0 008			3	102					4			
	1 58	0 017				66				1	1 133	0 007				105				1	3			
	1 57	0 018				66					1 133	0 008			1	1 105	0 009				4			
	1 56	0 018				66					132					105					4			
	2 55	0 036				66					1 132	0 008				105					4			
	2 53	0 038				1 66	0 015			1	3 131	0 023				105					4			
	1 51	0 020				65					1 127	0 008				1 105	0 010				4			
	50					65					126				1	104					1	4		
	50					65					126					105					3			
	50					65					126					105					3			
63*	0 13	Q _x =0.240 ^b			69*	0 4	Q _x =0.059 ^b			135*	1 8	Q _x =0.061 ^b			107*	0 2	Q _x =0.019 ^b			5*	2 0	Q _x =0.000 ^b		
	3 1 50	0 021				65					5 1 126	0 008			1	25	105					3		
	3 46					65				32	120				49	81					2	3		
	43					10 65				46	88				22	32					1	1		
63*	6 14	Q _x =0.256 ^b			69*	10 4	Q _x =0.059 ^b			135*	84 9	Q _x =0.069 ^b			108*	96 2	Q _x =0.019 ^b			5*	5 0	Q _x =0.000 ^b		
	30 6 min					31 1 min					42 5 min					46 8 min						—		
	14 0 days					24 5 days					21 6 days					17 3 days						—		

TABLE A5-5. INTRAMURAL, NON-WHITE, OTHER (LOW AND UNKNOWN) GESTATIONAL AGE

Age	Birth weight (Gm)																			
	500 or less					501-750					751-1000					1001-1250				
	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x
MALE																				
15-29 min	38		1	37	0.018	38		15			37		14			43		12		
30-59	28		10	74	0.114	14		2	53	0.033	31		3	51	0.045	32		1	55	0.014
1 hour(s)	6		8	92	0.084	5		12	65	0.178	3		6	79	0.074	4		3	86	0.034
2-5	1		64	90	0.707	1		27	58	0.462			25	76	0.329			14	87	0.161
6-11			23	27	0.852			14	32	0.438			13	51	0.255			13	73	0.178
12-17			1	4	0.250			5	18	0.278			6	38	0.158			2	60	0.033
18-23			2	3	0.667			3	15	0.231			5	51	0.156			1	58	0.017
1 day(s)			1	1	1.000			8	10	0.800			3	27	0.111			11	57	0.193
2								2					1	24	0.042			46		
3								2					23					5	46	0.109
4								2	2	1.000			3	23	0.130			1	41	0.024
5													1	20	0.050			40		
6													19					40		
15 minutes up to 7 days SUBTOTAL	110*	0	110	$Q_x=1.000^b$		73*	0	73	$Q_x=1.000^b$		85*	0	66	$Q_x=0.780^b$		91*	0	51	$Q_x=0.559^b$	
7-13 days													5	19	0.263			1	40	0.025
14-20													1	2	0.148			1	40	
21-27														11				1	39	
15 minutes up to 28 days TOTAL	110*	0	110	$Q_x=1.000^b$		73*	0	73	$Q_x=1.000^b$		85*	1	73	$Q_x=0.862^b$		92*	2	52	$Q_x=0.570^b$	
Median age at entry*			22.1 min					23.5 min					26.6 min					26.9 min		
Median age at discharge (alive)*			—					—					—					—		
FEMALE																				
15-29 min	33		1	32	0.021	30		20			23		15			25		7		
30-59	23		4	64	0.053	16		4	50	0.069	37		1	38	0.018	38		1	32	0.020
1 hour(s)	6		16	83	0.186	7		9	62	0.137	6		3	74	0.039	3		1	69	0.014
2-5			63	73	0.863			23	60	0.383			9	77	0.217			4	71	0.096
6-11	1		7	10	0.667			8	37	0.216			10	68	0.147			6	67	0.090
12-17			2	4	0.500			5	29	0.172			7	58	0.121			3	61	0.049
18-23			2					2	24	0.083			51					7	58	0.121
1 day(s)			2	2	1.000			10	22	0.454			6	51	0.118			3	51	0.059
2								2	12	0.167			5	45	0.111			1	48	0.021
3								1	10	0.100			40					1	47	0.021
4								6	9	0.667			2	40	0.050			1	46	0.022
5								1	3	0.333			1	38	0.026			1	45	0.022
6								2					1	37	0.027			1	43	0.023
15 minutes up to 7 days SUBTOTAL	95*	0	95	$Q_x=1.000^b$		73*	0	71	$Q_x=0.973^b$		81*	0	45	$Q_x=0.558^b$		73*	1	30	$Q_x=0.416^b$	
7-13 days								2					5	36	0.239			2	42	0.048
14-20								2					1	31	0.032			40		
21-27								1	1				1	30	0.033			40		
15 minutes up to 28 days TOTAL	95*	0	95	$Q_x=1.000^b$		73*	1	71	$Q_x=0.973^b$		81*	0	52	$Q_x=0.644^b$		73*	1	32	$Q_x=0.444^b$	
Median age at entry*			22.0 min					23.2 min					32.0 min					33.6 min		
Median age at discharge (alive)*			—					—					—					—		

* Includes admissions up to 15 minutes of age. ^b Q_x death rate equals one minus the product of the complements of q_x * Median not computed for a total number of entries (n_x) or discharges (w_x) of five or less

TABLE A5-5. INTRAMURAL, NON-WHITE, OTHER (LOW AND UNKNOWN) GESTATIONAL AGE
(continued)

Birth weight (Gm)																									
1251-1500					1501-1750					1751-2000					2001-2250					2251-2500					
<i>n_x</i>	<i>n_x</i>	<i>d_x</i>	<i>L_x</i>	<i>g_x</i>	<i>n_x</i>	<i>n_x</i>	<i>d_x</i>	<i>L_x</i>	<i>g_x</i>	<i>n_x</i>	<i>n_x</i>	<i>d_x</i>	<i>L_x</i>	<i>g_x</i>	<i>n_x</i>	<i>n_x</i>	<i>d_x</i>	<i>L_x</i>	<i>g_x</i>	<i>n_x</i>	<i>n_x</i>	<i>d_x</i>	<i>L_x</i>	<i>g_x</i>	
MALE																									
42	1	10	0.032		47		4			54		12			42		9			3		2			
36		51			64		1	51	0.012	83		66			80		51			9		5			
8	4	87	0.044		13		114			22		149			24		1	131	0.007	2	1	14			
	4	91	0.044		1		6127	0.047		3		4171	0.023		4		154			2		1	15	0.062	
	7	87	0.080				4122	0.033		1		3170	0.018				1	158	0.006				16		
	4	80	0.050				1118	0.008		1		168					157						16		
	2	76	0.026				4117	0.034				1169	0.006		1		2	157	0.013	1		1	16	0.061	
	8	74	0.108				6113	0.053				1168	0.006		1		156			1			16		
	3	66	0.045				3107	0.028				167					1	157	0.006	1			17		
	63						104					2167	0.012				156				1		18		
	63						104					165			2		156						17		
	63						104					1165	0.006				158						17		
	63						1104	0.010				164					158				1		17		
96*	0	33	$Q_x=0.359^a$		129*	0	26	$Q_x=0.207^b$		176*	0	12	$Q_x=0.070^b$		163*	0	5	$Q_x=0.032^b$		21*	3	2	$Q_x=0.119^b$		
	63					2	1103	0.010			1	2164	0.012		2	10	2	158	0.013		4	1	16	0.071	
	1	63	0.016			3	100				18	1261	0.006				80	148			5		21		
	62					7	97				74	142					45	1	68	0.022		4	1	6	0.250
96*	0	34	$Q_x=0.369^a$		129*	12	27	$Q_x=0.215^b$		176*	93	15	$Q_x=0.087^b$		165*	135	8	$Q_x=0.066^b$		21*	16	4	$Q_x=0.386^b$		
	28.6 min						36.3 min					38.0 min					41.8 min						45.3 min.		
	—						22.0 days					23.6 days					19.0 days						15.4 days		
FEMALE																									
32		17			35		10			57		8			22		5			5		4			
48	1	49	0.014		61		45			89		65			79		1	27	0.015	4			9		
9		96			14		1106	0.009		22		1154	0.006		26		1	105	0.008	1			13		
	3	105	0.028		3		2119	0.016		4		4175	0.022		7		130						14		
	4	102	0.039				4120	0.033				175					1	137	0.007		1		14		
	3	98	0.031				2116	0.017				175			1		136						13		
	95						114					1175	0.006				1	137	0.007				13		
	7	95	0.074				4114	0.035		1		2174	0.011		2		2	136	0.014				13		
	1	88	0.011				110					1173	0.006		1		136						13		
	87						110			1		172					1	137	0.007				13		
	1	88	0.011		1		110			1	1	173					136				1		13		
	2	87	0.023			3	111					173					136						12		
	1	85	0.012				110					173			1		136				1		11		
107*	0	23	$Q_x=0.229^a$		124*	1	13	$Q_x=0.106^b$		183*	1	9	$Q_x=0.051^b$		144*	0	7	$Q_x=0.057^b$		14*	4	0	$Q_x=0.000^b$		
	1	84	0.012				1	110			2	1	1173	0.006		13	1	137	0.008		2		10		
	3	83					2	109				25	173				61	123			4		6		
	2	1	80	0.013			10	107				68	145				36	62			2		4		
107*	5	25	$Q_x=0.240^b$		124*	14	13	$Q_x=0.106^b$		185*	95	10	$Q_x=0.057^b$		144*	110	8	$Q_x=0.065^b$		14*	12	0	$Q_x=0.000^b$		
	32.8 min						38.4 min					39.3 min					47.1 min						24.0 min.		
	—						23.1 days					22.0 days					18.8 days						10.5 days		

TABLE A5-6. EXTRAMURAL, WHITE, HIGH GESTATIONAL AGE

Age	Birth weight (Gm.)																			
	500 or less					501-750					751-1000					1001-1250				
	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>	<i>n_x</i>	<i>w_x</i>	<i>d_x</i>	<i>l_x</i>	<i>q_x</i>
MALE																				
15-29 min																				
30-59																				
1 hour(s)																				
2-5						1					2					4				
6-11						1	1				1	2				3	1	4	0.182	
12-17						3	2				3					6			6	
18-23							1	5	0.200		1	3	0.286			5			12	
1 day(s)						1	2	4	0.444		8	3	0.428			9			2.17	0.093
2							2	3	0.667		1	1	0.118			3			2.24	0.078
3							1	1	1.000			1	0.125			1			2.25	0.078
4												7						1.24	0.042	
5												7						1.23	0.043	
6												1	7	0.143				22		
15 minutes up to 7 days						6	0	6	$Q_x=1.000^b$		13	0	7	$Q_x=0.730^b$		31	0	9	$Q_x=0.421^b$	
SUBTOTAL																				
7-13 day												2	6	0.333				2.22	0.091	
14-20												4						20		
21-27												4					1	20		
15 minutes up to 28 days						6	0	6	$Q_x=1.000^b$		13	0	9	$Q_x=0.820^b$		31	1	11	$Q_x=0.475^b$	
TOTAL																				
Median age at entry ^a					—				14.0 hrs					1.3 days				21.0 hrs.		
Median age at discharge (alive) ^c					—				—					—				—		
FEMALE																				
15-29 min						1										1			1	
30-59																1			1	
1 hour(s)																1			2	
2-5											4					9			3	
6-11						1	1				4	4				7			12	
12-17						1	2				2	8				6			19	
18-23							3				4	1	10	0.083		9			1.25	0.034
1 day(s)						1	2	3	0.286		6	7	13	0.438		11			5.33	0.078
2							2	3	0.667		2	1	12	0.083		4			2.47	0.046
3							1					12				1	4	4.3	0.094	
4							1					1	12	0.083		2			1.38	0.026
5							1					1	11	0.091				2.39	0.051	
6							1					10						1.37	0.027	
15 minutes up to 7 days						4	0	3	$Q_x=0.762^b$		22	1	11	$Q_x=0.605^b$		31*	1	14	$Q_x=0.307^b$	
SUBTOTAL																				
7-13 days												2	10	0.200				2.36	0.056	
14-20												8						1.34	0.029	
21-27												1	8	0.125		1		33		
15 minutes up to 28 days						4	0	3	$Q_x=0.762^b$		22	1	14	$Q_x=0.714^b$		31*	2	17	$Q_x=0.365^b$	
TOTAL																				
Median age at entry ^a					—				—					19.5 hrs.				18.3 hrs.		
Median age at discharge (alive) ^c					—				—					—				—		

* Includes admissions up to 15 minutes of age. ^b Q_x death rate equals one minus the product of the complements of q_x .^c Median not computed for a total number of entries (n_x) or discharges (w_x) of five or less.

TABLE A5-6. EXTRAMURAL, WHITE, HIGH GESTATIONAL AGE (continued)

Birth weight (Gm)																									
1251-1500					1501-1750					1751-2000					2001-2250					2251-2500					
<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	
MALE																									
										1															
													1												
										1															
6					6					4			2												
10	1	6	0.091		11		6			4		1	6	0.125	1					1					
5		15			8		17			9			9		2		1						1		
4		2	20	0.091	13		25			3		1	18	0.051			3						1		
12		3	22	0.107	27		7	38	0.136	19		1	20	0.034	5		3						1		
5	1	2	31	0.061	8		58			8	1		38				8						1		
		33			4		1	66	0.015	3			45				8						1		
		33			4		4	69	0.056	2	1	1	48	0.021	1		8						1		
		33			3			69		1		1	48	0.021	1		9						1		
		33						72		1			48		2		10						1		
42	1	8	$Q_x=0.307^b$		84	0	12	$Q_x=0.194^b$		56	2	5	$Q_x=0.232^b$		12	0	0	$Q_x=0.000^b$		1	0	0	$Q_x=0.000^b$		
		33					1	72					49		1	2	2	12	0.174				1		
		34					3	71		1	10		49				9				1		1		
	2	34					18	68			20		40				6	7							
43	3	8	$Q_x=0.307^b$		84	22	12	$Q_x=0.194^b$		57	32	5	$Q_x=0.132^b$		13	10	2	$Q_x=0.174^b$		1	1	0	$Q_x=0.000^b$		
		18	8 hrs					1	1 days				1.3 days					1	7 days				—		
	—								23	7 days			22	4 days				22	2 days				—		
FEMALE																									
										2													1		
2		1			1																		1		
		1						1															1		
3		3			3			1		1			2										1		
10		1	6	0.091	8			4		5			3		1					1			1		
12		15			21			12		14			8		2		1						2		
11		1	27	0.031	19			33		11			22		4		3						2		
9		1	37	0.024	15		1	52	0.017	4		1	33	0.028	4		7						2		
16		4	45	0.075	25		2	66	0.025	18		1	36	0.022	2		11						2		
4		2	57	0.034	13		2	89	0.021	8	1	1	53	0.018	1		13						2		
1		2	59	0.034				1	100	0.010	9		1	59	0.016			14					2		
1		1	58	0.017	5			99		6			67		1		14						2		
1		1	58	0.017	2		1	104	0.010	2		1	73	0.014			1	15	0.067				3		
		58						105					74				14						3		
71*	0	13	$Q_x=0.282^b$		112	0	7	$Q_x=0.080^b$		80	1	5	$Q_x=0.094^b$		15	0	1	$Q_x=0.067^b$		3	0	0	$Q_x=0.000^b$		
		58						1	105	0.010	3		1	74		1	2	14					3		
		1	57	0.018				104		11	1	76	0.014				6	13			3		3		
		2	56				19	104		37			64				3	1	7	0.182					
71*	3	14	$Q_x=0.295^b$		112	19	8	$Q_x=0.089^b$		83	50	6	$Q_x=0.107^b$		16	11	2	$Q_x=0.217^b$		3	3	0	$Q_x=0.000^b$		
		22	1 hrs					19	6 hrs				1.2 days					19	5 hrs				—		
	—								24	5 days			23	3 days				18	1 days				—		

TABLE A5-7. EXTRAMURAL, WHITE, OTHER (LOW AND UNKNOWN) GESTATIONAL AGE

Age	Birth weight (Gm)																			
	500 or less					501-750					751-1000					1001-1250				
	<i>n</i> _e	<i>w</i> _e	<i>d</i> _e	<i>l</i> _e	<i>q</i> _e	<i>n</i> _e	<i>w</i> _e	<i>d</i> _e	<i>l</i> _e	<i>q</i> _e	<i>n</i> _e	<i>w</i> _e	<i>d</i> _e	<i>l</i> _e	<i>q</i> _e	<i>n</i> _e	<i>w</i> _e	<i>d</i> _e	<i>l</i> _e	<i>q</i> _e
MALE																				
15-29 min						1					1									
30-59						2	1				1	1	1	0.667		2				
1 hour(s)						3	1	5	0.222		3	1	1	0.400		2	1	2	0.333	
2-5	2		1	1.000		2	2	5	0.333		5	1	3	0.182		5	1	3	0.182	
6-11			1				3	5	0.600		1		7			5	3	7	0.316	
12-17			1	1	1.000			2			3	2	8	0.210		7	1	9	0.080	
18-23						2	1	2	0.333		5	2	9	0.174		10	1	15		
1 day(s)							3	3	1.000		5	11	12	0.759		17	8	24	0.246	
2						1	1	1.000				6				3	4	33	0.116	
3												2	6	0.333		1	32			
4												4					1	33	0.030	
5											1	4				1	32			
6												5					33			
15 minutes up to 7 days SUBTOTAL	2	0	2	$Q_e=1.000^b$		11	0	11	$Q_e=1.000^b$		25	0	20	$Q_e=0.983^b$		53	1	19	$Q_e=0.778^b$	
7-13 days												1	5	0.200			2	33	0.061	
14-20												1	4	0.250			31			
21-27												3					1	31	0.032	
15 minutes up to 28 days TOTAL	2	0	2	$Q_e=1.000^b$		11	0	11	$Q_e=1.000^b$		25	0	22	$Q_e=0.990^b$		53	1	22	$Q_e=0.798^b$	
Median age at entry*									1.8 hrs					15.0 hrs				21.3 hrs		
Median age at discharge (alive)*																				
FEMALE																				
15-29 min.						2					2									
30-59						2	1					1	2	0.500		1				
1 hour(s)							1	3	0.333		7	1				5	1	1	0.286	
2-5						1	1	2	0.400		3		8			9		5		
6-11							1	2	0.500		5	3	11	0.222		10	2	14	0.105	
12-17							2	2	1.000		5	13				15	4	22	0.136	
18-23						3					4	3	18	0.150		11	1	33	0.026	
1 day(s)						3	1	3	0.222		10	3	19	0.125		16	10	43	0.196	
2							2	5	0.400		1	4	26	0.151		7	8	49	0.152	
3							1	3	0.333			4	23	0.174		2	1	48	0.020	
4								2				19				1	49			
5								2				4	19	0.210			2	50	0.040	
6								2				1	15	0.067			1	48	0.021	
15 minutes up to 7 days SUBTOTAL						10	0	8	$Q_e=1.000^b$		37*	0	23	$Q_e=0.851^b$		77	0	30	$Q_e=0.662^b$	
7-13 days							2	2	1.000			2	14	0.143			5	47	0.106	
14-20												12					42			
21-27												12					42			
15 minutes up to 28 days TOTAL						10	0	10	$Q_e=1.000^b$		37*	0	25	$Q_e=0.872^b$		77	0	35	$Q_e=0.693^b$	
Median age at entry*									20.0 hrs					13.8 hrs				17.4 hrs		
Median age at discharge (alive)*																				

* Includes admissions up to 15 minutes of age.

* Q_e death rate equals one minus the product of the complements of q_e .* Median not computed for a total number of entries (n_e) or discharges (w_e) of five or less.

TABLE A5-7. EXTRAMURAL, WHITE, OTHER (LOW AND UNKNOWN)
GESTATIONAL AGE (continued)

Birth weight (Gm)

1251-1500					1501-1750					1751-2000					2001-2250					2251-2500					
<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	
MALE																									
3		1			1					2					1		1								
1		1	4	0.222	1		1								2		2								
2		4			4		2			5		2			3		4			3					
14		6			12		1	6	0.083	9		7			9		7			3			3		
24		4	20	0.125	16		1	17	0.040	13		1	16	0.044	6		2	16	0.105	1	1		6		
18		40			15		1	32	0.025	15		1	28	0.028	5		20						6		
7		8	58	0.130	12		1	46	0.019	13		42			6		25						6		
38		8	57	0.105	39		6	57	0.078	26		7	55	0.103	8		3	31	0.086	2			6		
8		4	87	0.044	21		3	90	0.050	17		1	74	0.012	2		36						8		
6		1	91	0.011	4		108			9		1	90	0.020	2		1	38	0.026				8		
1		4	95	0.041	3		3	112	0.026	7		2	98	0.020	2		39						8		
1	1	2	93	0.022	1		112			1		103			1		41						8		
1		1	91	0.011		1	2	113	0.018	1	1	104			1		42						8		
125 ^a	1	33	<i>Q</i> _x =0.536 ^b		129	1	18	<i>Q</i> _x =0.280 ^b		118	1	13	<i>Q</i> _x =0.201 ^b		49 ^a	0	6	<i>Q</i> _x =0.203 ^b		9	1	0	<i>Q</i> _x =0.000 ^b		
		3	91	0.033	1		2	110	0.018	7	1	104			2	1	43			1	1		8		
1		4	88	0.045	1		1	109	0.009	8		1	110	0.009		8	1	44	0.025		5		8		
1		85			7		1	107	0.010	24		101				19	35			1			3		
126 ^a	2	40	<i>Q</i> _x =0.572 ^b		130	9	22	<i>Q</i> _x =0.307 ^b		125	34	14	<i>Q</i> _x =0.208 ^b		51 ^a	28	7	<i>Q</i> _x =0.223 ^b		10	8	0	<i>Q</i> _x =0.000 ^b		
		18	0 hrs				1	1 days				1	2 days				16	2 hrs					4	7 hrs	
		—					23	5 days				23	0 days				22	8 days					18	2 days	
FEMALE																									
1					1										1										
1		1			1		1																		
2		2			3		2			2					1		1			1					
13		2	4	0.190	11		5			8		2			7		2			2			1		
10		2	15	0.100	15		16			6		10			4		9						3		
10		1	23	0.036	12		2	31	0.054	9		16			4		13						3		
11		1	32	0.027	18		41			9		1	25	0.034	4		17						3		
32		7	42	0.121	33		7	59	0.093	26		33			4		21			1			3		
8		5	67	0.070	14		3	85	0.033	13		59			3		25						4		
3		2	70	0.028	1		5	96	0.052	10		72			3		1	28	0.034				4		
1		4	71	0.056	2	1	92			4		1	82	0.012	4		30						4		
		2	68	0.029			2	95	0.012	2		1	85	0.012			34			1			4		
1		66					91			1		86					34						5		
93	0	26	<i>Q</i> _x =0.502 ^b		111	1	19	<i>Q</i> _x =0.230 ^b		90	0	3	<i>Q</i> _x =0.058 ^b		35	0	1	<i>Q</i> _x =0.034 ^b		5	0	0	<i>Q</i> _x =0.000 ^b		
		1	67	0.015	3	1	1	91	0.011	6	2	1	87	0.011	2	4	34						5		
1	1	1	66	0.015	3		92			5		1	90	0.011	1	11	1	32	0.037		2		5		
		65			6		89			22		84				14	21			1			3		
94	2	28	<i>Q</i> _x =0.517 ^b		114	11	20	<i>Q</i> _x =0.238 ^b		96	29	5	<i>Q</i> _x =0.079 ^b		38	29	2	<i>Q</i> _x =0.070 ^b		5	3	0	<i>Q</i> _x =0.000 ^b		
		23	4 hrs				22	7 hrs				1	5 days				21	0 hrs					—		
		—					22	8 days				23	4 days				14	3 days					—		

TABLE A5-8. EXTRAMURAL, NON-WHITE, HIGH GESTATIONAL AGE

Age	Birth weight (Gm)																			
	500 or less					501-750					751-1000					1001-1250				
	n_x	w_x	d_x	l_x	q_x	n_x	w_x	d_x	l_x	q_x	n_x	w_x	d_x	l_x	q_x	n_x	w_x	d_x	l_x	q_x
MALE																				
15-29 min																				
30-59																1				
1 hour(s)																			1	
2-5																			1	
6-11										1									1	
12-17											1		1		1				1	
18-23										1		1			3				2	
1 day(s)						1							2		2				5	
2								1		1			2		3				7	
3								1	1	1.000			3		1				10	
4												1	3	0.333					11	
5													2						11	
6													2						11	
15 minutes up to 7 days																				
SUBTOTAL						1	0	1	$Q_x=1.000^b$		3	0	1	$Q_x=0.333^b$		11	0	0	$Q_x=0.000^b$	
7-13 days													2						11	
14-20													2						11	
21-27													2					1	11	0.091
15 minutes up to 28 days																				
TOTAL						1	0	1	$Q_x=1.000^b$		3	0	1	$Q_x=0.333^b$		11	0	1	$Q_x=0.091^b$	
Median age at entry ^a					—					—					—				1.2 days	
Median age at discharge (alive) ^a					—					—					—				—	
FEMALE																				
15-29 min																				1
30-59																				1
1 hour(s)																				
2-5																				
6-11																				
12-17																				
18-23																				
1 day(s)						1														
2																				
3																				
4																				
5																				
6																				
15 minutes up to 7 days																				
SUBTOTAL						7	0	6	$Q_x=0.994^b$		11	0	6	$Q_x=0.694^b$		21*	0	4	$Q_x=0.514^b$	
7-13 days																				
14-20																				
21-27																				
15 minutes up to 28 days																				
TOTAL						7	0	6	$Q_x=0.994^b$		12	2	7	$Q_x=0.755^b$		21*	0	9	$Q_x=0.657^b$	
Median age at entry ^a					—				1.5 hrs.					18.0 hrs					1.3 days	
Median age at discharge (alive) ^a					—				—					—					—	

^a Includes admissions up to 15 minutes of age.^b Q_x death rate equals one minus the product of the complements of q_x .^c Median not computed for a total number of entries (n_x) or discharges (w_x) of five or less.

TABLE A5-8 EXTRAMURAL, NON-WHITE, HIGH GESTATIONAL AGE (continued)

Barb weight (Gm)

1251-1500	1501-1750	1751-2000	2001-2250	2251-2500
$n_x \quad w_x \quad d_x \quad l_x \quad q_x$	$n_x \quad w_x \quad d_x \quad l_x \quad q_x$	$n_x \quad w_x \quad d_x \quad l_x \quad q_x$	$n_x \quad w_x \quad d_x \quad l_x \quad q_x$	$n_x \quad w_x \quad d_x \quad l_x \quad q_x$

MALE

		1	1	2	1				
			1		3				
1		2	1	1	3	1			
2	1	1	3	3	1 4 0.182	1	1		
5	3	4	4	1	6		2		
1	1 8 0.118	2	8		7		2		
6	8	15	1 10 0.057	7	7		2		
2	1 14 0.067	4	24	3	14	4	2		
1	15	2	28	2	17		6		
	16		30		19		6		
	16	1	30		19		6		
	16		31		19		6		
18 0 2 $Q_x=0.177^b$		32 0 1 $Q_x=0.057^b$		20 ^a 0 1 $Q_x=0.182^b$		6 0 0 $Q_x=0.000^b$			
	16		31		19		1 6		
	16		31		3 19		2 5		
	16	1 4	31		6 1 16 0.077		3 5		
18 0 2 $Q_x=0.177^b$		33 4 1 $Q_x=0.057^b$		20 ^a 9 2 $Q_x=0.245^b$		6 6 0 $Q_x=0.000^b$			
	10 days		14 days		1.3 days		22 days		
					22.8 days		21.0 days		

FEMALE

[illegible]

TABLE A5-9. EXTRAMURAL, NON-WHITE, OTHER (LOW AND UNKNOWN) GESTATIONAL AGE

Age	Birth weight (Gm.)																				
	500 or less					501-750					751-1000					1001-1250					
	<i>n_e</i>	<i>n_d</i>	<i>d_e</i>	<i>l_e</i>	<i>q_e</i>	<i>n_e</i>	<i>n_d</i>	<i>d_e</i>	<i>l_e</i>	<i>q_e</i>	<i>n_e</i>	<i>n_d</i>	<i>d_e</i>	<i>l_e</i>	<i>q_e</i>	<i>n_e</i>	<i>n_d</i>	<i>d_e</i>	<i>l_e</i>	<i>q_e</i>	
MALE																					
15-29 min						1					1		1			1		2			
30-59						1		1			1		2			4		1	3	0.200	
1 hour(s)	3					5		2	2	0.571			1	3	0.333	6		6			
2-5			3	3	1.000	1		1	3	0.286	2		2			2		3	12	0.231	
6-11						1		3	3	0.857	1		1	4	0.222	2		2	11	0.167	
12-17								1			1		1	4	0.222	4		2	11	0.154	
18-23								1			2		4			3		13			
1 day(s)								1			4		3	6	0.375	9		2	16	0.098	
2						1		1					1	7	0.143	5		1	23	0.039	
3								1	2	0.500			6					27			
4								1	1	1.000			2	6	0.333			2	27	0.074	
5													4					25			
6													4					2	25	0.080	
15 minutes up to 7 days																					
SUBTOTAL	3	0	3	$Q_4=1.000^b$		8	0	8	$Q_4=1.000^b$		13*	0	9	$Q_4=0.856^b$		38*	0	15	$Q_4=0.681^b$		
7-13 days													2	4	0.500			23			
14-20													2			1		23			
21-27													2					1	24	0.042	
15 minutes up to 28 days																					
TOTAL	3	0	3	$Q_4=1.000^b$		8	0	8	$Q_4=1.000^b$		13*	0	11	$Q_4=0.928^b$		39*	0	16	$Q_4=0.694$		
Median age at entry*									1	7 hrs					15	0 hrs.			15	8 hrs	
Median age at discharge (alive)*																					
FEMALE																					
15-29 min	1					1					1					1					
30-59	3		1					1			3		1			8		1			
1 hour(s)	1		4			2		1			6		4			7		3	9	0.240	
2-5			3	5	0.600			2	3	0.667	2		4	10	0.364	3		1	13	0.069	
6-11			2			3		1	1	0.400	3		2	8	0.210	2		15			
12-17			2	2	1.000			3			5		9			5		17			
18-23						2		1	3	0.250	4		1	14	0.062	3		22			
1 day(s)						1		2	4	0.444	3		7	17	0.378	7		2	25	0.070	
2								3					2	13	0.154	1		1	30	0.033	
3								1	3	0.333			11			1		1	30	0.033	
4								2					31					2	30	0.067	
5								2					1	11	0.091	1		1	28	0.035	
6								1	2	0.500			10					28			
15 minutes up to 7 days																					
SUBTOTAL	3	0	5	$Q_4=1.000^b$		9	0	8	$Q_4=0.922^b$		27	0	17	$Q_4=0.775^b$		39	0	11	$Q_4=0.446^b$		
7-13 days								1					10					28			
14-20								1	1	1.000			10					28			
21-27						1							1	10	0.100			28			
15 minutes up to 28 days																					
TOTAL	3	0	5	$Q_4=1.000^b$		10	0	9	$Q_4=1.000^b$		27	0	18	$Q_4=0.795^b$		39	0	11	$Q_4=0.446^b$		
Median age at entry*										10	0 hrs				9	0 hrs			7	5 hrs	
Median age at discharge (alive)*																					

* Includes admissions up to 15 minutes of age. * Q_4 death rate equals one minus the product of the complements of q_e .* Median not computed for a total number of entries (n_e) or discharges (n_d) of five or less.

TABLE A5-9. EXTRAMURAL, NON-WHITE, OTHER (LOW AND UNKNOWN)
GESTATIONAL AGE (*continued*)

Birth weight (Gm)																			
1251-1500					1501-1750					1751-2000					2001-2250				
<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x	<i>n</i> _x	<i>w</i> _x	<i>d</i> _x	<i>l</i> _x	<i>q</i> _x
MALE																			
3	1				4	1				1	1				1	1			
2	4				3	5				4	1				3	1			
3	1 6 0.133				4	8				8	5				6	4			
7	1 8 0.087				9	1 12 0.061				1	13				1	10			
6	14				5	20				5	14					11			1
7	1 20 0.042				5	1 25 0.036				6	19					11			1
14	5 26 0.152				16	3 29 0.081				11	1 25 0.033				2	11			1
6	2 35 0.053				5	42				1	35					13			1
1	1 39 0.025				3	47				4	1 36 0.026					13			1
	39					50				2	39				1	1 13 0.074			1
	1 39 0.026				1	50					41					13			1
1	38					51					41					13			1
31 ^a	0 12 <i>Q</i> _x =0.420 ^b				56	0 5 <i>Q</i> _x =0.168 ^b				43	0 2 <i>Q</i> _x =0.053 ^b				14	0 1 <i>Q</i> _x =0.074 ^b			1 0 0 <i>Q</i> _x =0.000 ^b
	3 39 0.077				3	51				2	1 1 41 0.024				1	2 13			1
	36				2	54				1	7 1 41 0.026				2	4 1 12 0.100			1 1 2
	36				3	56				1	12 34					5 9			1
31 ^a	0 15 <i>Q</i> _x =0.465 ^b				61	3 5 <i>Q</i> _x =0.168 ^b				47	20 4 <i>Q</i> _x =0.104 ^b				17	11 2 <i>Q</i> _x =0.167 ^b			2 1 0 <i>Q</i> _x =0.000 ^b
	21 0 hrs.					23 4 hrs.					22 5 hrs					5 0 hrs			—
—	—				—	—					22 2 days					20 1 days			—
FEMALE																			
1					1					1					3				
1	1				3	1				2	1				3				
3	2				6	4				3	3				6	3			
3	5				7	10				8	6				3	9			
9	1 8 0.080				2	17				3	14				3	12			
3	2 16 0.114				6	1 19 0.045				3	1 17 0.054					15			
3	17				7	24				2	19				3	15			
9	20				18	1 31 0.025				4	21				4	18			
2	29				6	1 48 0.020				3	25					22			
1	1 31 0.052				2	53				5	28				3	22			
	31				2	1 55 0.018				1	33				3	25			
	31				2	1 56 0.018					1 34 0.029					28			
	31				1	56				1	33					28			
35	0 4 <i>Q</i> _x =0.211 ^b				63	1 5 <i>Q</i> _x =0.136 ^b				36	0 2 <i>Q</i> _x =0.082 ^b				28	0 0 <i>Q</i> _x =0.000 ^b			
	31				2	1 57				1	1 34 0.029				1	28			
2	31					58					1 34					11 29			
	33				3	58				2	12 33				1	8 18			
37	0 4 <i>Q</i> _x =0.211 ^b				65	5 5 <i>Q</i> _x =0.136 ^b				39	13 3 <i>Q</i> _x =0.109 ^b				33	19 0 <i>Q</i> _x =0.000 ^b			
	15 0 hrs					1 0 days					17 0 hrs					11 0 hrs			—
—	—				—	—					24 2 days					20 1 days			—

TABLE A5-10. SUMMARY: MEDIAN AGE AT ENTRY INTO PREMATURE

Birth weight (Gm.)	High gestational age							
	White				Nonwhite			
	Male		Female		Male		Female	
	Median x^a	Q_z^b	Median x^a	Q_z^b	Median x^a	Q_z^b	Median x^a	Q_z^b
INTRAMURAL								
500 or less	—	1.000	—	1.000	30.0 min.	1.000	20.6 min.	1.000
501-750	30.0 min.	1.000	28.1 min.	1.000	31.4 min.	0.972	23.8 min.	0.953
751-1000	36.0 min.	0.908	21.4 min.	0.834	36.9 min.	0.795	25.5 min.	0.585
1001-1250	27.5 min.	0.578	26.2 min.	0.354	29.0 min.	0.567	27.1 min.	0.203
1251-1500	31.1 min.	0.335	30.0 min.	0.233	35.9 min.	0.224	30.6 min.	0.240
1501-1750	36.3 min.	0.255	32.1 min.	0.053	33.5 min.	0.050	31.1 min.	0.059
1751-2000	43.1 min.	0.086	42.8 min.	0.027	40.3 min.	0.083	42.5 min.	0.061
2001-2250	47.6 min.	0.041	43.6 min.	0.033	46.4 min.	0.090	46.8 min.	0.019
2251-2500	51.9 min.	0.111	27.7 min.	0.028	17.5 min.	0.000	—	0.000
EXTRAMURAL								
500 or less	—	—	—	—	—	—	—	—
501-750	14.0 hours	1.000	—	0.762	—	1.000	1.5 hours	0.994
751-1000	1.3 days	0.730	19.5 hours	0.605	—	0.333	18.0 hours	0.694
1001-1250	21.0 hours	0.422	18.3 hours	0.307	1.2 days	0.000	1.3 days	0.514
1251-1500	18.8 hours	0.307	22.1 hours	0.282	1.0 days	0.177	1.3 days	0.359
1501-1750	1.1 days	0.194	19.6 hours	0.080	1.4 days	0.057	1.2 days	0.021
1751-2000	1.3 days	0.232	1.2 days	0.094	1.3 days	0.182	1.1 days	0.038
2001-2250	1.7 days	0.000	19.5 hours	0.067	2.2 days	0.000	21.0 hours	0.000
2251-2500	—	0.000	—	0.000	—	0.000	—	0.000

^a Median age at entry into premature nursery.^b Q_z = death rate up to seven days.

NURSERY AND CUMULATIVE 7-DAY DEATH RATE FOR SPECIFIC CATEGORIES

<i>Other (low and unknown) gestational age</i>							
<i>White</i>				<i>Nonwhite</i>			
<i>Male</i>		<i>Female</i>		<i>Male</i>		<i>Female</i>	
<i>Median x^a</i>	<i>Q₃^b</i>	<i>Median x^a</i>	<i>Q₃^b</i>	<i>Median x^a</i>	<i>Q₃^b</i>	<i>Median x^a</i>	<i>Q₃^b</i>
INTRAMURAL							
16.9 min.	1.000	30.0 min.	1.000	22.1 min.	1.000	22.0 min.	1.000
30.0 min.	1.000	30.0 min.	1.000	23.5 min.	1.000	23.2 min.	0.973
24.4 min.	0.983	22.5 min.	0.797	26.6 min.	0.780	32.0 min.	0.558
27.2 min.	0.759	23.8 min.	0.596	26.9 min.	0.559	33.6 min.	0.416
26.5 min.	0.550	30.7 min.	0.309	28.6 min.	0.359	32.8 min.	0.220
34.4 min.	0.357	31.9 min.	0.196	36.3 min.	0.207	38.4 min.	0.106
33.3 min.	0.202	39.6 min.	0.106	38.0 min.	0.070	39.3 min.	0.051
38.4 min.	0.078	40.3 min.	0.034	41.8 min.	0.032	47.1 min.	0.057
43.0 min.	0.171	44.2 min.	0.062	48.3 min.	0.119	24.0 min.	0.000
EXTRAMURAL							
—	1.000	—	—	—	1.000	—	1.000
1.8 hours	1.000	20.0 hours	1.000	1.7 hours	1.000	10.0 hours	0.972
15.0 hours	0.983	13.8 hours	0.851	15.0 hours	0.856	9.0 hours	0.775
21.3 hours	0.778	17.4 hours	0.662	15.8 hours	0.681	7.5 hours	0.446
18.0 hours	0.536	23.4 hours	0.502	21.0 hours	0.420	15.0 hours	0.211
1.1 days	0.280	22.7 hours	0.230	23.4 hours	0.168	1.0 day	0.136
1.2 days	0.201	1.5 days	0.058	22.5 hours	0.058	17.0 hours	0.082
16.2 hours	0.203	21.0 hours	0.034	5.0 hours	0.074	12.0 hours	0.000
4.7 hours	0.000	—	0.000	—	0.000	—	0.000

appendix 6. Recommended Daily Dietary Allowances for the Nonpregnant and Pregnant Woman

The Food and Nutrition Board of the National Research Council has presented a consideration of other nutrients not listed in Table A6-1. These are carbohydrates, fat, water, sodium, potassium, magnesium, phosphorus, copper, iodine, fluorine, trace elements, vitamin B₁₂ (cyanocobalamin), folic acid, pantothenic acid, biotin, vitamin E, and vitamin K. From this material only those sections are given below that mention specifically the needs of women during pregnancy and lactation.

TABLE A6-1. RECOMMENDED DAILY ALLOWANCES* OF NUTRIENTS FOR WOMEN

	Calories ^b	Protein (Gm)	Calcium (Gm)	Iron (mg)	Vit A (I U)	Thia- mine (mg)	Ribof- lavin (mg)	Niacin equi- (mg)	Ascorbic acid (mg)	Vit D (L U)
Woman ^c	1500	58	0.8	11	5000	1.2	1.5	17	70	
Pregnant (second half)	+ 300	+20	1.5	15	6000	1.3	2.0	+ 3	100	400
Lactating (850 ml daily)	+1000	+10	2.0	15	8000	1.7	2.5	+ 2	150	400

From *A Report of the Food and Nutrition Board: Recommended Dietary Allowances* Washington, D. C., National Academy of Sciences-National Research Council, 1958, Publication 589.

* The recommended allowances can be attained with a variety of common foods, providing other nutrients for which human requirements have been less well defined.

^b Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others engaged in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.

^c 25 years of age, 163 cm (64 in.) tall, weighing 58 kg (128 lb)

Phosphorus. All evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of women during the latter part of pregnancy or in lactation periods.

Iodine. Analyses of urinary excretion of iodine indicate that intake averages about 150 μg per day. The need for iodine is increased in pregnancy. Ingestion of iodized table salt will provide an adequate iodine intake.

Vitamin B₆ Group. Pregnant women with apparently normal vitamin B₆ stores have alterations of tryptophan metabolism which can be eliminated by added vitamin B₆.

Vitamin K. On the basis of laboratory evidence, the routine maternal administration of vitamin K has been advocated for the prevention of hemorrhage of the newborn. This practice is now questioned on a number of grounds.

In the absence of liver disease, there seems to be no reason to supplement maternal diets in this country with vitamin K. The Food and Nutrition Board stated that vitamin K may be administered to the mother in dosages of 2 to 5 mg. in situations conducive to neonatal hemorrhage (e.g., prematurity, anoxia, erythroblastosis). For a full discussion of this controversial matter see Chapters 6 and 20.

appendix 7. Techniques of Feeding

GAVAGE

[The technique of gavage described here is from the manual of the Pediatrics Department of The New York Hospital²]

When indicated, feedings are given through a rubber catheter (#8F) which has been passed through the *mouth* into the stomach. The safe use of gavage feedings depends primarily upon avoidance of overfeeding and aspiration. The following steps are taken in carrying out a gavage feeding:

- a. The infant is properly positioned by slightly elevating head and shoulders.
- b. The length of catheter to be inserted is carefully measured. (A good approximation of the correct length is obtained by measuring the distance from the bridge of the nose to the xiphoid process of the sternum.) A Kelly clamp is used to mark off the measurement.
- c. A diaper restraint and a bib are applied to the infant and he is turned on his right side.
- d. The catheter, with clamp still in place, is inserted into the stomach.
- e. To rule out endotracheal placement of the catheter, the clamp is temporarily re-

- leased and the open end of the catheter is placed under sterile water in a medicine glass. If bubbles are not evident, the clamp is replaced.
- f. *The funnel and connecting tubing are attached by means of a glass adapter*
 - g. The feeding is introduced into the funnel and residual air is expressed from the tubing by "milking" the tube.
 - h. The clamp is again released and the feeding is allowed to flow slowly with the funnel elevated about 12 inches above the level of the mattress.
 - i. When the last of the feeding has reached the lower end of the glass adapter, the clamp is reapplied and the tube is *quickly* withdrawn from the infant's stomach.
 - j. The tubing is next rinsed through with the water used in testing the position of the catheter earlier in the procedure
 - k. The infant is then elevated to a sitting position and "bubbled," after which his position is changed to the opposite side.

INDWELLING NASOGASTRIC TUBE

The feeding techniques described for use of the indwelling nasogastric tube are those practiced at Babies Hospital, Columbia-Presbyterian Medical Center, New York City.

The early indwelling tubes were made of polyethylene and had the advantage of a small caliber (P.E. 50). However, the fact that the distal end of each tube must be carefully and individually blunted^{1, 4} makes it impractical to use polyethylene tubes routinely. These small handmade tubes are now used only rarely and for very small infants.

Sterile polyvinyl tubes are now available from a number of manufacturers; they are prepared with a closed rounded distal end and two lateral openings.⁵ Some models are made with an attached stopper on the proximal end. The smallest polyvinyl feeding tube (#5F, length 15 inches) is suitable for most premature infants.

The insertion of the tube is the responsibility of the physician; the administration of the feeding is the responsibility of the nurse. Before inserting the tube the distance from the xiphoid process to the tip of the ear lobe and thence to the nostril is measured and this point is marked on the tube with a piece of adhesive tape. The tube is then gently inserted into the nostril until this marker is reached. A stopper is then placed in the proximal end of the tube. The tube is attached to the infant's face (i.e., upper lip and cheek) with adhesive to prevent displacement.

The following criteria are used to indicate that the tube has not entered the trachea: (1) The infant tolerates the tube without respiratory difficulty. (2) When the bell of a stethoscope is over the stomach area, air injected with a syringe can be heard to bubble into the stomach. (3) Saline solution (0.5 ml.) can be injected without causing respiratory disturbance.

A new tube is inserted every five days; the alternate nostril is used for every new tube.

Nursing Technique for Nasogastric Feeding

The nursing techniques used at Babies Hospital are described by Parke as follows:

"Equipment needed for feeding by this method is: a formula bottle, a small bottle of sterile saline solution, and a sterile container with a 30 ml. medicine glass, a 20 ml. syringe, a 2 ml. syringe and a No. 23 needle." To give the feeding the procedure is as follows:

"The baby is placed on his side, covered with a light diaper restraint, with a pad roll at his back. The stopper is removed from the tube. Then 0.4 ml. of sterile saline is drawn into the 2 ml. syringe. The formula is poured into the medicine glass and the correct amount is drawn into the 20 ml. syringe. The tip of the syringe is inserted into the plastic tube. The formula is pushed slowly into the tube, with special care to keep the tip of the syringe connected during the entire feeding process. Next, the 2 ml. syringe is attached to the mouth of the tube and the saline solution is injected to clear the tube of milk and to prevent curds in the tube. This done, the stopper is replaced, and the restraint removed from the baby."

DROPPER FEEDING

[The following technique for dropper feeding is described in the manual of the Pediatrics Department of The New York Hospital²]

All droppers are fitted with protective rubber tubing which extends $\frac{1}{4}$ inch beyond the glass tip.

- a The medicine glass containing the feeding is placed in a small basin of warm water throughout the procedure.
- b The infant is held in the same position as for bottle feeding.
- c The dropper tip is placed on the infant's tongue well back in the mouth.
- d As the bulb is released, pressure is exerted on the back of the tongue with the tip of the dropper to stimulate swallowing.
- e. The flow of milk is directed toward the side of the mouth and the pharynx is inspected after each dropperful to ensure that feeding has been swallowed.
- f. The baby is "bubbled" twice during the feeding.
- g The infant is replaced in the bassinet according to the procedure outlined for infants fed by nipple.

BOTTLE FEEDING

[The following technique for bottle feeding is described in the manual of the Pediatrics Department of The New York Hospital]

A 4-ounce bottle with soft rubber nipple* is used. The nipple holes should be of such size and number that the feeding mixture drops slowly when the bottle is in-

*Petr nipples. Seamless Rubber Co., New Haven, Conn.

verted. All nipples are tested in this fashion before each feeding and those permitting a faster flow are discarded. *Propping bottles is not permitted*

- a. The nurse is seated during the feeding, holding the infant in a semi-upright position in her arm.
- b. After the nipple cover is removed, the nipple is touched to the infant's lips. Usually the infant will open his mouth and the nipple can then be placed on top of the tongue. If the tongue is elevated against the palate, it may be brought down into feeding position by manipulation of the nipple and gentle pressure against the cheeks
- c. Half of the feeding is given and, after covering the nipple, the infant is "bubbled"
- d. The remainder of the feeding is given and the baby is again "bubbled"
- e. The infant is returned to the bassinet and placed on his side
- f. The head of the bassinet is elevated about 6 inches for the next 15 minutes

FEEDING PRECAUTIONS

The following safety measures are of primary importance in feeding all premature infants who commonly have poor swallowing and gag reflexes, weak sucking ability, relaxed tongue, and small stomach capacity. Furthermore, these infants are seldom able to indicate by refusal when they are being fed too rapidly or too much food. *Of necessity, therefore, the nurse has a special responsibility to exercise good and conservative judgment in the feeding procedure.*

1. Small, frequent feedings, given at regular intervals, must be so planned that they do not overtax the infant's capacity to retain them. Feedings must be individualized. Overfeeding, leading to distention and regurgitation, is to be avoided. Initial feedings should be small and subsequent increases in volume should be on the order of no more than 1-2 ml. per feeding per day. Many small infants being fed by gavage will not tolerate increases in volume of more than 1 ml. per feeding every 2 days. Greater increases (up to 3 ml. per feeding per day) are permitted in premature infants who are fed by bottle and who need and are capable of handling larger intakes.

2. The nurse must be ready to interrupt the administration of the feeding promptly and to change the position of the infant should signs of distress become evident. This implies close observation of the infant's color, respiration, and feeding behavior throughout the feeding period

3. The nurse is given discretion in situations where individual feedings may need to be interrupted or omitted entirely. Decisions concerning subsequent feedings are made by the physician after examining the infant and reviewing his feeding history.

4. Infants fed by nipple should be allowed to rest occasionally during the feeding.

5. Ample time for "bubbling" is necessary to insure against loss of feeding or aspiration through uncontrolled eructation

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appendix 8. Special Standards and Recommendations for Hospital Care of Premature Infants

[The following material is reproduced from *Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature*. Evanston, Ill., American Academy of Pediatrics, 1957.]

INTRODUCTION

A premature infant is defined as any infant born alive weighing at birth 2500 grams (5 lb 8 oz) or less.

Premature infants require special care in respect to equipment and experience of personnel. Whether such special care is given separately from or together with the care of full-term infants is a practical question of hospital design and operation that depends on the size of the service, type of hospital, and other available services in or near the community.

Large obstetrical and children's hospitals, and large general hospitals with pediatric services which care for premature infants, should meet the standards described later in the special sections on premature infants. Smaller services which would not expect to keep a 5-infant unit fairly well occupied, should aim at meeting the same objectives in premature infant care by transfer to another institution if possible, or by appropriate adaptations within their own regular services for newborn infants, as specified later. A maternity service that has 1500 or more live births per year can expect to draw from those births enough of the smaller and weaker premature infants to warrant setting up a special unit as described below.

Many of the larger premature infants, such as those above 5 lb, may receive simi-

lar hospital care as is provided for normal full-term infants and be placed in regular nurseries *

In large general hospitals the Premature Infant Unit preferably should be located in proximity to the delivery service to minimize problems of transportation and relationship of mother to child. Careful planning is necessary to coordinate activities of pediatric and obstetric staffs. Under no circumstances should infants in a special premature unit be cared for together with or in exposure to infectious patients.

When special services for premature infants are available in the community, as would be recommended, reporting of premature births to the health department is desirable.

For infants born prematurely at home, local conditions govern the requirement and procedure for transfer to hospitals. Admission of such infants to a special unit depends upon the size and condition of the infant and the situation in the home. When indicated, immediate transfer to a hospital meeting the standards set forth in the following pages should be made by means described under "Techniques of care," unless the locality maintains an active public health program for home care of such infants.

The following pages describe the personnel, facilities, and routines of care for premature infant units receiving infants either by birth in the same hospital or by transfer from outside. Thus, they apply whether the nursery is in a general, maternity, or children's hospital.

MEDICAL SERVICE FOR PREMATURE INFANT CARE

[The directives in boldface type in this Appendix are considered by the American Academy of Pediatrics as obligatory: " (They) must be fulfilled by every hospital . . . that care for newborn infants. . . They cannot be compromised "]

The care of premature infants should be the responsibility of the pediatric medical staff. A physician (preferably a certified pediatrician) with special interest and training in the care of such infants should be clearly designated **Physician-in-Charge of Premature Infants**, whether a separate unit is set up for prematures or, as under certain circumstances described above, premature infants are not cared for in a separate unit.

To achieve smooth and efficient operation, it is strongly recommended that in large obstetric and general hospitals the **Physician-in-Charge of Premature Infants** be made

* Under certain circumstances individualization of admission policies by the following rules is more satisfactory than an arbitrary weight limit

- 1 All infants who weigh less than 2250 gm. (5 lb.) at birth must be admitted to the Premature Infant Unit.
- 2 Upon the birth of an infant weighing between 2250 and 2500 gm. (5-5½ lb.) the physician will be notified immediately and will decide whether the infant will be admitted to the Premature Infant Unit.
- 3 Any infant weighing more than 2500 gm. (5½ lb.) at birth may be admitted to the Premature Infant Unit if the physician believes the infant actually to be premature.

a member of a joint Committee on the Premature Unit, with representatives from the obstetrical, administrative, and nursing divisions of the hospital

The physician-in-charge should supervise and be responsible for

- routines
- visits
- staff conferences
- records and forms
- examination schedules

Routines

Although not necessarily in direct charge of each individual infant, the Physician-in-Charge of Premature Infants should formulate policies and procedures as written standing orders for all premature infants under staff and private care, and be given full authority to see that these are carried out.

The policies thus agreed upon as standing orders should include not only those of daily routine but also those covering extraordinary circumstances such as *an outbreak of infection*.

Visits

Each infant should be under the continuous care of a pediatrician (whether or not he be the physician-in-charge). Moreover, a qualified physician, preferably a resident assigned to that service, must visit the nursery at least once daily and be on call day and night.

Staff Conferences

Periodic conferences upon policies and procedures should be arranged by the physician-in-charge for the medical, anesthesia, nursing, and social service personnel. In any hospital maintaining a premature infant unit, joint obstetric-pediatric-pathologic conferences should be conducted monthly to discuss morbidity and mortality.

If infants born outside the hospital are admitted for care, the referring private physician should be invited to observe the infant during his course in the nursery, and to attend such conferences.

Records and Forms

A medical evaluation (see "Techniques of care") of each premature infant should be recorded by his pediatrician immediately after admission.

The physician-in-charge should be responsible for the compilation of annual statistics on the incidence, morbidity, and mortality of all premature infants in the institution.

Forms for such statistics are included in the [American Academy of Pediatrics] manual. Thus tabulated, comparison of results in different hospitals and for different years in the same hospital, is a powerful stimulus for improvement in care.

Examination Schedules

A complete physical examination should be performed and recorded as soon as the infant's condition allows, weekly thereafter, and at discharge. The discharge examination should include funduscopy.

NURSING SERVICE FOR PREMATURE INFANT CARE

In planning the nursing service to provide good care for the premature infant, consideration should be given to the weight of the infant, the condition of the infant, the medical policy of the institution regarding the weight group cared for in the premature nursery, the education program for parents, the education program for medical and nursing students, and the total in-service education carried out in the department.

To date, there has been no study on which to base the amount of nursing care required for infants of varying weights and conditions and the types of personnel (graduate nurse, student nurse, practical nurse, or auxiliary worker) required to give such care. Such studies are now planned. Until their completion the following standards and recommendations are made from observation and experience in premature infant centers throughout the country.

Of special importance are

- supervision

- ratio of nursing personnel to premature infants

- auxiliary workers

- student nurses

- infants in observation or isolation units

Supervision

The nursing service of the premature infant nursery should be under the direction of a supervising nurse who is a registered professional nurse with advanced training and experience in the care of premature infants.

In addition to the supervising nurse, there should be at least one registered professional nurse with advanced training and experience in the care of pre-

mature infants for supervision of the unit for each 8-hour period of the 24 hours.

Ratio of Nursing Personnel to Premature Infants

The weight and condition of the premature infant are factors in determining the ratio of nurses to premature infants. In general and pending further studies, it is suggested that a reasonable ratio should be one nurse to every 5 infants. This would provide approximately 5 hours of nursing care per infant.

If it is the medical policy of the hospital to accept only infants in the small-weight groups, the skilled nursing care required for these infants would necessarily be higher than indicated above. Clinical research programs involving nursing care and time necessitate an increased nursing staff.

The nursing care of all premature infants should be assigned by the supervising nurse, according to the condition of the infants and the ability of the personnel.

Auxiliary Workers

There has been a marked revision in thinking as to greater use of subprofessional workers (aides and assistants) in premature infant nurseries. Definite statements concerning desirable practices in that regard must await further investigation.

Student Nurses

It is desirable for student nurses to have training in the premature infant nursery. For the protection of the infants, and to assure that this education is adequate, student nurses should always work under the immediate supervision of a registered professional nurse.

In such a program it would be desirable for student nurses to be assigned first to the care of the larger premature infants of 2000-2500 grams (4½ to 5½ lb.) and then gradually assigned to the smaller infants. Opportunity should be provided for the student nurse to participate in the teaching program for parents.

Infants in Observation or Isolation Units

If premature infants are removed from the premature infant unit to an observation unit or isolation nursery in another part of the hospital, these infants should be under the care of graduate nurses who have satisfactorily completed a period of training in the care of premature infants.

Nurses assigned to the care of premature infants should not care for sick patients elsewhere.

PHYSICAL FACILITIES FOR THE CARE OF PREMATURE INFANTS

Many of the standards and recommendations for physical facilities for the full-term newborn nursery also apply to units for premature infant care. However, due to the types of services performed in the premature units, additional requirements must be met in regard to space allocation, environmental conditions, and equipment.

The techniques employed in observation and isolation units or with the individual incubators provided for premature infant care must also reflect the nature of the treatment being performed, in that special measures which emphasize limitation of contacts and personnel cleanliness must be observed.

Therefore, these requirements are more specifically treated in regard to

- premature infant nurseries
- special measures for prevention of infection
- accessory rooms

Premature Infant Nurseries

Space allocation. The U.S. Public Health Service requires that, in new construction, units designed for premature infants shall have no more than six bassinets per room, and shall provide thirty square feet per bassinet. The use of incubators may safely permit up to 12 infants per room, but the floor space per incubator or bassinet should remain 30 square feet.

Environmental conditions. If satisfactory atmospheric conditions are provided by incubators, air-conditioning of the nursery is not necessary, except for the comfort of nurses and for the use of certain types of incubators which cannot function properly except with room air-conditioning.

Construction of walls, ceilings, and floors should be as described . . . for full-term infant nurseries. The greatest possible utilization of glass walls to allow constant observation of infants is strongly recommended.

Equipment. The premature nursery must be well illuminated. Nurses' desks, chart rack, sterilizer, work space, supply cupboards, and utility room must be provided outside the nursery proper. Within it there must be supply cupboards, receptacles for soiled linen and separate closed containers for soiled diapers, bottle warmers, conveniently located lavatory facilities with hot and cold running water under elbow, foot, or knee control, etc., as previously described. . . .

In most premature infant nurseries from 50 to 75% of the infants will be in incubators. The number of incubators will be determined by the usual number of patients, birth weight, distribution of infants born in the hospital, and admission policies regarding ones born outside. All incubators must be free from fire and electrical

hazards as shown by approval of the Underwriters' Laboratories. If not equipped with a compartment for individual supplies, each incubator should have its own bedside table. Besides this equipment the following items must be included:

Accurate scales

A suction device, with individual catheters for individual infants

Oxygen, preferably piped along walls by a manifold system, and apparatus for its administration and control of its concentration

An electric outlet for each incubator and bassinet

Individual equipment and supplies for 24 hours for each infant

Medicine droppers with rubber tips, gavage tubes, and other special feeding equipment

Special needles, tubing, and glassware in sterile packages ready for infusions, transfusions, lumbar punctures, etc.

Special Measures for Prevention of Infection

Prevention of infections requires consideration before all other aspects of nursery planning and construction. Either of two plans may be used, in accordance with local public health regulations, the situation and type of the hospital, and the number and sources of the premature infants for whom it cares.

Plan 1 provides for observation and isolation in separate nurseries. Plan 2 utilizes individual air-conditioned incubators for isolation purposes. The plan to be used should be chosen and enforced by the Physician-in-Charge of Premature Infants.

Observation and isolation units—Plan 1. Besides the room or rooms for premature infants considered to be noninfected, an observation nursery may be provided for infants whose place of birth, history, or physical signs suggest potential infection. Premature infants born outside the hospital should be directly admitted to such a nursery. Those developing suspicious symptoms in the premature nursery or nurseries should be removed to it immediately. Infants suspected of different types of infection may, with proper technique, occupy the same observation nursery unit. Occasionally it may be necessary to improvise an extra nursery to meet such an emergency.

An isolation nursery should also be provided, to which infants in whom suspicion of infection has become fact must be immediately removed. The pediatric division of the same or of another hospital (if available nearby) may be the best possible isolation nursery. Where possible, separate nursing staffs should be provided for these three nurseries.

Individual incubators—Plan 2. Individual air-conditioned incubators in which strict isolation is maintained at all times may be utilized for either the nonsuspect or the suspect infants, without the construction of a separate observation nursery. It may even be possible to omit an isolation nursery under this plan and to care for actually infected infants in separate atmospheres in the same nursery with infants con-

sidered to be noninfected, *but only if personnel are suitably trained and observe scrupulous technique.*

Closing of nursery. If, under either of these plans, diarrheal infection develops, it may be advisable to employ the drastic procedure of removing any infected infant to another ward or hospital and closing the nursery where the infection arose to further admissions. A nursery thus closed must not be reopened until the discharge of the last exposed infant from it. It then should be thoroughly aired and washed before its re-use.

Limitation of contacts. Entry to any unit or room containing any premature infant should be strictly limited to the essential personnel; and, to these only when they are free from illness. In teaching hospitals, medical students may be considered essential personnel, depending upon the ruling of the Physician-in-Charge of Premature Infants.

The best safeguard against entrance by infected personnel is voluntary reporting of illness. To encourage this, plans should exist for assignment to work elsewhere in the hospital of personnel with minor illnesses. Such a policy will reduce hesitation to report illness because of fear of salary loss.

Cleanliness of personnel. Rigidly enforced regulations should govern the apparel of physicians, nurses, and workers entering any nursery containing a premature infant. Clean gowns, changed daily, are essential. The hands of all personnel should be washed on entry to the nursery, before handling a premature infant, and after examining or diapering him. The newer detergents containing synthetic bacteriostatic or germicidal agents have shown superiority to soap and may be used.

The care and examination of the premature infant should be conducted in his crib or incubator. Separate instruments for examination must be kept in the nursery and cleansed between use for different infants. Cubicles and ultraviolet light are not recommended. Dry-sweeping of floors is contraindicated.

Accessory Rooms

The feedings for the premature infant nursery may be prepared in the regular formula room. The premature nursery unit should have its own utility room.

Premature infants should not be taken from their nursery to any examining room or treatment room. However, in large premature centers there should be a room where mothers can feed and attend their infants as a preliminary to discharge.

TECHNIQUES OF CARE

The care given to premature infants must meet even more closely the requirements established in this manual or by the individual hospital than the care given the full-term infant.

Many of the techniques employed in the full-term newborn nursery are applicable to the care of the premature infant. However, the techniques treated here reflect the more specialized care necessary for the premature infant:

- immediate care in preparation and delivery
- continuing nursery care.

Immediate Care in Preparation and Delivery

When a premature birth is anticipated, the nursery personnel should be warned by the delivery room sufficiently early so that preparation for the infant can be made, and the physician who will care for him can be present at his birth.

Maternal analgesia, anesthesia, and type of delivery should be considered in terms of the special handicaps of the premature infant. Even for the smallest prematures, two or three minutes can be safely and advantageously used for drainage of the trachea and bronchi and aspiration by gentle suction with a soft, blunt catheter of any fluid in the nose, throat, and oropharynx.

Transfer to nursery If the infant is delivered in the hospital where he is to be cared for, he should be moved in a heated and oxygenated incubator from the delivery room to the nursery. The importance of heat, oxygen, and gentle suction probably outweighs the need for great haste in his transfer to the nursery.

If the infant must be transferred from home or from another hospital to a premature infant unit, special equipment should be provided. This should be in the form of a clean and electrically safe portable incubator provided with a supply of oxygen, gauge to determine amount and flow of oxygen, and a device for suction. It must be so constructed that the infant may be constantly observed. No infant should be thus transported without the attendance of a specially trained nurse or physician.

Continuing Nursery Care

The nursing supervisor or the graduate nurse on duty for premature infants must be in immediate attendance upon every premature infant at his arrival in the nursery. The pediatric house officer or private pediatrician should see the infant immediately on admission.

Examinations. Although the general condition of a premature infant may not permit a complete examination upon admission, his temperature should be taken and as complete an inspection as is safe should be carried out at once without removal of the infant from the incubator. This inspection and the necessary constant observation dictate the absence of wrappings and blankets unless no other means of temperature control is available.

A more detailed examination can usually be performed, preferably in the incubator, during the first 24 hours.

Treatment. Treatments for the premature infant, although rarely necessary, should be spaced so as to avoid fatigue or undue exposure.

Determinations of hemoglobin concentrations should be made at least once during hospital stay and repeated as indicated. Transfusions are rarely indicated for the anemia of prematurity.

Incubator care. The decision as to which premature infants are to be placed in incubators on admission rests upon the experience and judgment of the physician and nurse, but every small infant, and many larger ones, requires incubator care.

Whether in an incubator or not, placing the baby on his abdomen or turning him from side to side will tend to prevent amniotic fluid or mucus from reaching or remaining in the lungs. To assure removal of such liquids, the nose and throat should be suctioned gently as often as any fluid seems to accumulate there.

Oxygen. The accumulated evidence definitely incriminates the excessive use of oxygen as a major factor in the cause of retrolental fibroplasia in premature infants. "Excessive use" implies concentrations of more than 40% or the prolongation of administration after the indication for its use has passed. It is possible that even short periods of administration of higher concentration may be harmful.

On the other hand, the intelligent use of oxygen can be the means of saving the lives of hypoxic, dyspneic, and cyanotic babies. It would be unwise to arbitrarily deny adequate oxygen (and perhaps life) to those babies because of possible injury to the eyes of some.

Accordingly, the following recommendations are made:

1. Oxygen should be prescribed only on medical order the same as any drug or treatment. (Except in emergency.)
2. Oxygen should not be administered routinely but only upon specific medical indication.
3. Oxygen concentration should be kept at the lowest possible level that will relieve the symptoms for which it is given, if possible not over 40%.
4. Oxygen therapy should be discontinued as soon as the indication for it has passed.
5. Ordinarily, the indications for supplemental oxygen are general cyanosis (not acrocyanosis) and dyspnea. The urgency of treating these symptoms must rest with the clinical judgment of the attending physician.
6. Oxygen concentration must be determined by means of an oxygen analyzer as often as necessary to keep it properly stabilized but at least every four hours.
7. A source which does not contain or deliver more than 40% oxygen will insure against exceeding that concentration but may not be adequate in those occasional instances where higher concentration is desired. If such a restricted source of oxygen is employed, additional oxygen should be available for those special instances where it is indicated.

8. There are no apparent contraindications to the use of supplemental oxygen in infants weighing more than five pounds.

Changes in condition. Close observation should be maintained for changes in condition of the premature infant, and such changes reported promptly to the physician-in-charge. Of particular significance are:

- change in general activity (depression or twitching)
- change in skin color (cyanosis or pallor)
- change in character of respiration
- change in temperature
- watery stools
- bleeding
- vomiting
- early jaundice

Drugs. Vitamin K (2.5 mg.) should be given once to all premature infants. Excessive dosage of Vitamin K may be harmful.

There is little justification for the use of the so-called "respiratory stimulants" lobeline, coramine®, metrazol®, etc. Moreover, these drugs may act as poisons if given in excess. In rare instances very weak premature infants may benefit from the general stimulant effect of caffeine in single or repeated dosages of 3 mg. ($\frac{1}{20}$ grain) per pound of body weight, I.M.

The physical stimulus of frequent change of position, gentle massage of the infant, or gentle snapping of the feet is as useful as any medication for the somnolent and depressed infant whose life may largely depend on keeping him awake.

GENERAL CARE

Good medical care, expert nursing, and prevention of infection save more prematurely born infants than do the other factors to be considered below. Therefore, details of the following aspects of care may be varied to some extent for local circumstances:

- care of skin
- clothing
- temperature
- weighing
- feeding

Care of Skin

The skin of the premature infant requires no bathing or oiling if care is exercised so that the body folds do not become irritated and the diaper is changed as soon as wet or soiled. Any skin irritation should be reported to the physician promptly.

Clothing

Clothing is preferably not used for small infants in properly air-conditioned incubators, as it interferes with easy movement and constant observation. Clothing of larger premature infants may under suitable environment be similar to that of full-term newborn infants.

All linen used for the premature infant should be autoclaved or laundered separately from the regular hospital laundry and with special care.

Temperature

The axillary temperature of the infant should be taken on admission, hourly for the first 4 hours, and every 4 hours thereafter, unless wide variation or other circumstances require a shorter interval or until satisfactory status of infant indicates a longer interval as for full-term babies. . . . The thermometer should be held in place by pressing the infant's arm gently against it for 1 1/2 minutes. Each infant must have his own thermometer. The temperature of the infant and of his immediate environment should be determined and recorded simultaneously.

Temperature and relative humidity of the environment should be adjusted according to the individual infant's requirements. Most small infants require relatively high temperature and humidity, but constancy is of more importance than any arbitrary level of either. The infant's axillary temperature should not vary more than 2 degrees per day, but this stabilization may be at any level between 94 and 99 degrees. This may require incubator temperature from as high as 94 degrees for smaller infants to 85 degrees for larger ones. Relative humidity should be approximately 65% in incubators.

As the infant grows and his temperature becomes stabilized, the temperature and humidity of the incubator should be changed gradually toward 85 degrees and room humidity. After these conditions are reached the infant may be dressed and removed to an unheated bed at room conditions of temperature and humidity.

Weighing

Weight should be taken as soon as possible after birth, but the first weighing may be postponed if the condition is precarious. Thereafter, except in unusual circumstances, it is unnecessary to weigh the infant oftener than every third or fourth day.

Feeding

Opinion varies as to the proper time of first feeding. In general, more than half the deaths of premature infants occur within the first 24 hours; about 70% within the

first 48 hours. That such deaths are not due to starvation or dehydration has been amply demonstrated by mortality and autopsy records of infants in nurseries in which no fluid is given during the first two days. It has also been demonstrated that feeding of the smaller and more edematous infants may be delayed as long as 4 days. If the infant's condition is precarious, early feeding introduces extra hazards of vomiting and/or aspiration. Therefore a delay of at least 24 hours is justifiable and, by present knowledge, longer delays appear to be safe. During this period the administration of parenteral fluid is rarely indicated.

The first feedings may best consist of sterile water or a 5% sugar or glucose solution. These and subsequent feedings may be given either by gavage or from a medicine dropper with a rubber tip. The choice depends upon the experience of the nurse.

Brecht feeders, which force food into the baby's mouth, are dangerous and should never be used. Gavage feeding should be given only by a nurse who is trained and experienced in its use. The utilization of a polyethylene catheter of 0.05 cm. internal diameter, rounded at its tip to avoid sharp edges, inserted through the nose into the lower esophagus by the pediatrician, and left there 3-7 days for feeding by glass syringe, may prove advantageous. A small soft nipple may be used when the infant demonstrates ability to suck.

Feeding techniques. The infant should be supported or held in a semi-reclining position during each feeding period, and if fed by bottle, the bottle must always be held and never propped. Infants in oxygen should be fed in the incubator. No bottle feeding should exceed 20 minutes.

Occasionally a larger premature infant is vigorous enough to be put to the mother's breast, and if the circumstances allow it, advantage should be taken of this situation. If it seems likely that the infant's stay in the hospital is to be relatively short, the mother should be taught to express the milk from her breast manually or to remove it by hand pump to maintain her supply for the earliest possible transfer of the child to the breast.

Milk mixtures. In general, the type of food does not determine whether the premature infant will survive, but to some extent influences the rate and composition of his growth. Long experience and laboratory studies have shown that easy digestion, satisfactory growth, and reduction of excretory load occur with the relatively low electrolyte and nitrogen content of human milk. Cow's milk mixtures, which provide higher retentions of nitrogen, calcium, phosphorus, and presumably other electrolytes, may increase weight gain per calorie fed, but introduce a larger renal load.

Vitamin mixtures. The vitamin requirements for the premature infant cannot be stated exactly. In the light of present knowledge the supply will be adequate if the infant receives ascorbic acid, Vitamin A, and Vitamin D according to the following simple routine.

Addition of water-soluble mixtures of Vitamins A, C, and D to the milk before terminal sterilization, avoids the danger of contamination when vitamins are introduced

just before feeding. When the sterilization is carried out in closed containers, either by autoclaving under pressure or by streaming steam, the loss of Vitamin C is approximately 10%

In some large institutions, as a time-saving device, the vitamin mixture is added to a large batch of formula, using one concentration for infants under 1500 grams and another for those between 1500 and 2500. Water-soluble mixtures of Vitamins A, C, and D are available commercially in a concentration of 1800 units of Vitamin D, 9000 units of Vitamin A, and 90 milligrams of Vitamin C per cc. For infants under 1500 grams, addition of 3 cc. of this mixture to each quart of a formula containing 20 calories per ounce (0.67 cal/cc.) will provide, per 100 calories or per 150 cc. (5 oz.) of fluid intake, 800 units of Vitamin D, 4000 units of Vitamin A, and 40 milligrams of Vitamin C. For infants over 1500 grams, the amount of this mixture may be halved.

The use of medicinal iron is of no value in preventing the anemia of prematurity. However, prophylactic administration of iron (5-10 mgm. per day) beginning at 2 to 3 months of life and continuing for 3 to 6 months is of value in preventing later iron deficiency anemia.

Amounts and caloric requirement. The amount of food will vary with the age, weight, and condition of the infant. In general more mistakes are made by feeding too much and too early than too little and too late. Excessively large feedings even if given by gavage may lead to aspiration.

Caloric requirements are usually met if the infant receives 40 calories per pound (80/kilo) per day by the end of the first week and 60 calories per pound (125/kilo) before the end of the second week. The fluid requirements after the first week will be satisfied with approximately 2-2½ oz. per pound (125-140 cc./kilo) per 24 hours.

Frequency of feeding. To avoid over-distention the interval between feedings should usually be shortened in the smaller infants. As a rough rule, infants within a few ounces (+ or -) of 2 lb. (about 1000 gm.) may be fed every 2 hours; those of about 3 lb. (1350 gm.), every 3 hours, and those of about 4 lb. (1800 gm.) and above, every 4 hours.

Feeding records. Records of infant's diet and progress should be kept daily. The items to be covered are shown on the sample forms in the appendix [to the manual].

PREPARATION FOR DISCHARGE

Agencies available for participation in care after discharge will obviously vary greatly in various locations. The principle nevertheless remains that by every available means, especially by planning with the parent and physician before and after the infant's discharge, the good care begun in the hospital should be continued at home.

No infant should be discharged until he has demonstrated an ability to thrive in air conditions similar to those of his home. While a discharge weight of

5 ½ lb. (2.5 kg.) is a desirable standard, the condition of the individual infant, the home conditions, maternal ability, breast milk supply, etc., may permit an earlier discharge or dictate a later one.

Besides establishing conditions for discharge, the hospital should prepare the mother for the responsibilities she will encounter in caring for her baby at home by giving instructions and arranging for:

home care

follow-up by private physician or public health agency

Home Care

For all nonprivate patients and those private patients where the physician so requests, cooperative arrangements should be made with the local public health nursing agencies [see Fig. A8-1], for sample of form that can be used for this purpose so that a nurse may visit the home before the discharge and report the suitability of the home and the family's ability to provide adequate care for the infant. She should determine that there is no illness present in the household, and that the necessary equipment for the infant is provided.

The nurse should instruct the mother regarding preparations for the infant. She should be available to demonstrate to the mother the actual care of the infant in the home as directed by the infant's physician. The number of her visits may vary with the circumstances in each case.

The parents should receive instruction in the hospital, regarding care of their infant, by demonstration, by participation, and in writing. A copy of specific recommendations for the individual infant should be available for the public health nursing agency. At the time of discharge, the infant should be dressed outside of the premature infant nursery proper.

Follow-up by Private Physician or Public Health Agency

A plan for follow-up should be formulated by the physician who has been in charge of the infant in the hospital and by the public health nurse. Continuing medical supervision for the care of the premature infant should be provided by the private pediatrician, family doctor, or clinic to whom a copy of the hospital record should be transmitted promptly.

PREMATURE INFANT NURSERY OPERATING PROCEDURES

The following operating procedures will govern the care of all infants admitted to the premature infant nursery.

**PREMATURE INFANT SERVICE
REQUEST FOR HOME VISIT**

TO: _____ Address: _____	FROM: _____ Hospital Premature Station Address: _____

REQUEST FOR HOME VISIT

Premature Infant _____ Hospital No. _____

(Surname)

(Given Name)

(1) Parents: Father: _____ Mother: _____

(Surname) (Given Name)

(Surname) (Maiden Name) (Given Name)

Father's Occupation: _____

Address: _____

(Street)

(City)

(Parish)

(Telephone Number)

Directions for locating home: _____

(2) Medical Data:

Infant's Birth Date: _____ Birth Weight: _____ Race: _____ Sex: _____

Type of Delivery: _____

Maternal Complications: _____

S.T.S.: Mother: _____

Abnormalities in Infant: _____

Remarks: _____

(3) Social Data Known to Hospital

Marital Status of Parents: _____

Economic Status: _____

Attitude towards Infant: _____

SERVICES REQUESTED OF PUBLIC HEALTH NURSE OR OTHER WORKER:

A visit to evaluate the home is requested because advance information about home conditions will assist all concerned to plan for this infant's care following discharge. Best possible conditions should exist in the home if the infant is to develop properly and if readmissions to the hospital are to be avoided. If the home is adequate it will not be necessary to report information in detail in No 2 on the other side. In noting supplies in No 3 put "yes" and "no." In No 4 under "attitude of mother and family towards infant" check word or words most descriptive of attitude. Under "Medical Supervision" write name of private doctor or hospital. Check if under supervision of Parish Health Unit. Under No 5 "Situation Found" write your evaluation of this visit. Section No. 6 "Plans for correction of problems you have found" has been provided so you may indicate your plans for referral to appropriate agency if indicated. There are situations which you may plan to handle yourself. If so, indicate. Ask the mother to let you know if any problems arise in regard to health or the social and economic situation in the family. If changes develop notify the Premature Station immediately. Return form to Hospital Premature Station within 7 days.

Name—Premature Nursery Supervisor

Date: _____

Name—Medical Social Supervisor

FIG. A8-1. Suggested form for request for home visit. (From American Academy of Pediatrics: *Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature*. Evanston, Ill., American Academy of Pediatrics, 1957.)

Admissions

1 All infants who weigh less than 2250 gm. (5 lb.) at birth will be admitted to the premature nursery automatically.

2 Upon birth in the hospital of an infant weighing between 2250 gm and 2500 gm (5½ lb.) the resident on call will be notified immediately and he will decide whether the infant will be admitted to the premature nursery.

3 Any infant weighing more than 2500 gm (5½ lb.) at birth may be admitted to the premature unit, if the pediatric resident in charge believes the infant actually needs premature care.

Nursery Environment

For the benefit of those infants who are not in incubators, the room temperature should be 75° to 80° F; room humidity 55-65%. The room temperature and humidity (dry and wet bulb reading) should be recorded at 7:00 A.M., 3:00 P.M. and 11:00 P.M. The supervising nurse will be responsible for reporting any deviations to the engineering department. In her absence, she should delegate this responsibility to another individual.

Wearing Apparel

Nurses and nurses' aides should wear a scrub dress which must be changed daily. If this uniform is worn elsewhere than on the nursery floor a covering gown should be used.

Physicians, technicians, and housekeeping personnel should wear a gown and mask when on duty in the nursery.

Hand Technique

All personnel handling infants will wash hands before and after handling each infant, using technique recommended by the American Academy of Pediatrics.

Premature Infant Care

Notification of nursery. When the birth of a premature infant is anticipated, the nurse in charge of the delivery rooms will notify the Premature Nursery Supervisor or nurse in charge (in order that preparations for care on arrival may be completed). She will also notify the resident assigned to the premature nursery, and, if a private service infant, also the physician named by the obstetrician or otherwise chosen to be in charge of the infant (so that he or they can be present at the infant's birth).

Preparation for infant. On receiving word of the expected admission of a premature infant, the Premature Nursery Supervisor will

a. Warm an incubator to 90° F. temperature and have a supply of oxygen available. Relative humidity should be about 65%. These conditions may need to be modified as soon as the state of the infant is ascertained.

b. Have suction apparatus and an individual soft blunt catheter available for gentle suction.

Transfer of infant. The premature infant should be transported from the place of his birth, whether it be the delivery room, home, or another hospital, in a heated and oxygenated incubator. A specially trained nurse or physician should accompany the infant.

Admission form. An admission form is to accompany each infant from the delivery room as in the case of full term infants [see Fig A8-2]

Supervision. The Premature Nursery Supervisor or another graduate nurse on duty must be in immediate attendance upon each premature infant as soon as he arrives in the nursery. The resident should see the infant immediately on admission.

Nursery care upon admission. On admission of the infant, the supervisor or graduate nurse in charge of the premature nursery will

a. Notify the Pediatric House Officer, unless it is clear that he was present at the delivery

b. In the case of private service infants, notify the private pediatrician, if one has been arranged for. If no orders have been received, the infant will be treated in the same manner as the staff service infants.

c. Place all infants on the "Dangerously Ill List" on their arrival in the premature nursery. (The physician is responsible for explaining the meaning of this to the parents)

d. See that identification has been attached to the infant.

Clothing Except for small infants kept in incubators with controlled humidity and heat, all will be clothed in diaper and cotton shirt. Small infants in such controlled incubators need have no clothing

Change in condition. The Premature Nursery Supervisor or graduate nurse in charge shall at once notify the Pediatric House Officer, who will notify the private physician in the case of a private infant, of any marked change in their charges' condition. Examples are: change in skin color (cyanosis or pallor), change in general activity (depression or twitching), change in character of respiration, change in temperature, watery stools, bleeding, vomiting, early jaundice. (In cases of apparent death, oxygen should not be discontinued until a physician has pronounced the patient dead.)

Records. The data pertaining to the infant's temperature, food, vitamins, weight, vomiting, refusal, stools, general condition, and special circumstances of environment, such as incubator temperature and oxygen concentration, etc., should be recorded.

Written orders. All orders for the care and feeding of infants in the premature nur-

Hospital Name—Newborn Nursery Record

Hosp. No. _____ Male
 _____ Female infant of _____
 Mother's Rec. No. _____ White Birth _____ A.M.
 _____ Colored Date _____ Time _____ P.M.

MATERNAL HISTORY:

Previous Preg. _____ Born alive _____ Now living _____ Mother's age _____ Blood type _____ Rh _____

Maternal Disease _____

Complications of this pregnancy _____

Maternal S.T.S.: Prenatal: Date _____ Neg _____ Pos _____ Unknown _____

Note: If mother's S.T.S. ever positive, summary of treatment should be entered in progress notes.

Maternal Chest X-Ray Date _____ Result _____

PRESENT DELIVERY:

Duration of gestation _____ Prenatal care no _____ yes _____ Fetal age _____
 E.D.D. _____

Duration of labor, 1st and 2nd stage: _____

Membrane ruptured: Spont. _____ Arnf. _____ Hrs. before del. _____

Presentation _____ Position _____ Type Del. _____

Reasons if operative _____

Analgesia (Type and time before del.) _____

Anaesthesia _____

Complications of del. _____

INFANT RECORD:

_____ 1% AgNO₃ instilled in each eye _____
 (Signature of nurse and time)

Breathed: Spont. _____ With stim. _____ min. after del. Type of stim. _____

Suction _____

 (Signature of Delivery Nurse)

Identif. and sex
 Checked by

 (Signature of Nursery Nurse)

Birth Weight: _____

FIG. A8-2. Suggested form to accompany each infant from the delivery room to the premature nursery. (From American Academy of Pediatrics: *Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature*. Evanston, Ill., American Academy of Pediatrics, 1957.)

sery are to be given in writing by a physician. In the absence of such orders the nursery supervisor shall call and request them from the Pediatric House Officer for staff service patients or from the physician in charge of the private patient.

Feeding

Written orders. Feeding orders will be written only by a staff physician so authorized by the hospital. He will prescribe in writing

- a. Composition of the feeding mixture, e g , 5% glucose, breast milk, cow's milk mixture, etc.

- b. Amount to be offered at each feeding and subsequent increases

- c. Time of initiation, and intervals between feedings.

Techniques. How the infant is fed is more important than what he is fed. Technique takes precedence over the best calculations. The choice of technique will often depend upon the experience of the nurses.

Prefeeding testing. Before feeding, the bottle should be placed in the bottle warmer provided in the nursery. Test the heat of the milk for proper warmth by allowing a few drops to fall on the inner surface of the wrist

Postfeeding cleansing. After the feeding, before the milk dries in the nipple, the nipple, bottle, and accessories should be washed thoroughly in cold water, forcing water through the nipple. Place them in the rack for used bottles and in the containers for used accessories. If droppers or gavage tubes are used, these should be promptly washed by forcing cold water through them

Return of bottles. Return clean bottles, nipples, and other bottle equipment (caps, etc.) to the milk laboratory wash room before going off duty

Physicians

Assignment of resident. A resident will be assigned to the premature infant nursery. He will work under the immediate supervision of the chief pediatric resident and the attending physician assigned to be in charge of the premature nursery and the private physician in private cases.

Assistance at delivery. The resident assigned to the premature nursery will try to be present at the delivery of the premature infant and render such assistance as is requested.

Immediate care. He will take charge as soon as the obstetrician directs and accompany the infant to the premature nursery or see it as soon after its arrival as possible.

Assignment of nursery space. The resident will direct the placing of infants in clean observation or isolation nurseries

Examination of infant. A medical evaluation will be recorded by the resident immediately after admission. The completeness of this first examination will depend upon

his judgment of the infant's general condition. It should certainly include careful inspection of color, activity and respiration. Look carefully for any sign of bleeding.

The complete physical examination, including measurements of body length and head circumference, is to be done at the earliest safe opportunity, weekly thereafter, and at discharge. All examinations of infants in incubators should be carried out without removal from the incubator. *Examining equipment provided by the nursery will be used in place of the physician's personal equipment.*

Supervision of temperature and oxygen. The infant's axillary temperature should not vary more than 2 degrees per day, but the stabilization may be at any level between 94° and 99° F. This may require incubator temperature from as high as 94° F for smaller infants to 85° F. for larger ones. Relative humidity should be approximately 65% for infants in incubators.

[For details for the use of oxygen, see above.]

As the infant grows and his temperature becomes stabilized, the temperature and humidity of the incubator should be changed gradually toward 85° F and room humidity. Finally, the infant should be removed to an unheated bassinet under room air conditions in preparation for discharge.

Daily rounds. The physician in charge or another staff physician on service with him should visit the nursery daily. The resident on duty should make rounds in the nursery each morning and visit at least once again in the afternoon. A designated house officer will be on call at all hours.

Information for Inquiring Relatives

All information for parents, relatives or friends as to the condition of the infants in the premature nursery is to be given by a physician, with the exception that nurses may state whether the infant's condition is "satisfactory," "unchanged," or "poor." Requests for information concerning private service infants are to be referred to the private physician in charge. Requests for information concerning staff service infants will be answered by the Pediatric House Officer personally or by telephone at the nursery on week days from 8:30 A.M. to 9:00 P.M. or at another regularly designated time.

The Pediatric House Officer should regard the questions of parents of ward infants in his charge as opportunities for valuable parental education and should constantly endeavor to prepare mothers for effective home care of infants after discharge. This is considered to be one of his more valuable experiences and an important duty.

Supplies

The supervising nurse or person delegated by her will be responsible for the following:

Milk requisitions These should be sent to the milk laboratory by 8:00 A.M., if possible, for a 24-hour supply of milk mixtures.

Milk storage. She should check to see that milk mixtures are received in proper condition and are properly labeled before being stored in the refrigerator

Linen. A 24-hour supply of infant linen is to be ordered daily. Linen should be stored in designated cabinet drawers in the treatment room. A procedure for disposal of soiled linen should be maintained

Drugs are to be ordered daily before 10:00 A.M.

Cleansing of supplies and equipment. This is necessary after their use in examination or treatment of each infant.

Cooperative Arrangements for Home Visits and Discharge

Home visit. When a staff service infant (and in private service cases at the request of the physician) reaches the age of 3 to 10 days the hospital Social Service Department should be officially notified. The Social Service Department will request the appropriate public health and/or social service agency to make a home visit and submit a report of its findings [see Fig. A8-1]. This report is entered as a part of the infant's hospital record.

Instruction visit Another visit should be requested at least a week before the expected day of discharge. The purpose of this visit is to instruct the mother in regard to preparations to receive the infant and to determine the presence of infection in the home or other factors that might make the infant's homecoming hazardous. The report of this visit should be forwarded to the hospital and placed in the record as soon as possible.

Discharge notice. The hospital, through its Social Service Department or through the Premature Nursery Supervisor, should notify the public health and/or social service agency when the infant is within a day of expected discharge.

Discharge permission Before dressing an infant for discharge, the Auditing Office must be notified. When this office gives its "O.K.," dress the infant in the ante-room, not in the nursery proper. Notify the house officer that the infant is ready for discharge.

PREMATURE INFANT NURSERY STANDING ORDERS

The following standing orders will govern the care of all infants admitted to the premature infant nursery unless they are specifically changed by the physician in charge of the nursery or the physician of the individual private service infant

Standing Operating Procedures are to be followed

Admission Orders—Immediate Care

1 Place infant on his side, on a slanted mattress so that his head is below the chest in the incubator. The incubator should be heated so that the infant's axillary temperature does not vary more than 2 degrees per day between 94 and 99° F. For small infants this may require an incubator temperature as high as 94° F and for larger infants the incubator temperature may need to be only 85° F

2 Oxygen should be given only upon orders by a physician

3. See that the cord has been tied securely

4 Take the infant's axillary temperature by holding the thermometer in axilla with infant's arm pressed against it for 1½ minutes

5. See that silver nitrate eye treatment has been completed

6. Administer 25 mgm of vitamin K intramuscularly unless already given Excessive dosage may be harmful

7 Weigh the infant. (This may be deferred if the condition of the infant makes it inadvisable.)

8. Give no bath

General Orders—Continuing Care

1. *Skin care.* On admission, excess blood or excess vernix caseosa may be gently removed with sterile cotton, either dry or moistened with warm tap water. Buttocks are to be cleaned in similar manner. Use as little rubbing as possible. No other care is to be given except that a gentle shampoo with soap and water is sometimes needed for infants at one to two week intervals Any skin irritation should be reported to the physician promptly.

2. *Temperature of infants* is to be taken by axilla (using infant's individual thermometer) on admission and hourly for the first 4 hours, then every 4 hours thereafter unless wide variation or other circumstances require a shorter interval or until stabilized (i.e., when it does not vary more than 2 degrees per day between 94° and 99° F.).

The axillary temperature should be taken by holding the thermometer in place by pressing the infant's arm gently against it for 1½ minutes The temperature of the infant and of his immediate environment should be determined and recorded simultaneously.

3. Weigh the infant as soon after birth as condition permits and thereafter every third day. Weigh on discharge.

4. *Blood test.* When the discharge order is written, it is routine to obtain a test of blood hemoglobin.

Emergencies

In sufficient emergency, in the absence of a physician, the nurse in charge may give temporary treatment in the following instances to ward or private patients:

Respiratory distress characterized by cyanosis or apnea, with or without aspiration of food or liquid, may be alleviated by clearing the air passages by postural drainage with or without suction and administering oxygen.

Low body temperature can be treated by increasing the incubator temperature, providing extra wrappings, or transferring the infant from a bassinet to an incubator.

appendix 9. Growth Data

Serial body weights were obtained of 235 apparently healthy surviving premature infants in the premature nursery of Babies Hospital, New York City. All infants received half-skim cow's-milk mixtures (see Chap. 10). No significant sex and color differences were observed. The weights and increments of weight gain of this group of infants during their stay in the premature nursery are given in Tables A9-1 and A9-2.

Cherry and her co-workers obtained serial measurements of 417 apparently normal Negro infants having birth weights of 1001 through 2000 Gm. During the nursery stay all infants received cow's-milk mixtures consisting of 1 part evaporated milk, 2 parts water, and sufficient carbohydrate to bring the caloric value to 67 calories per 100 ml. Approximately three months after discharge from the nursery the mothers were advised to change the milk mixture to equal parts of evaporated milk and water without added carbohydrate. Data obtained in this study are presented in Tables A9-3 through A9-8.

REFERENCE

CHERRY, F. F., BANCROFT, H., and NEWSOM, W. T. Growth of Negro premature infants. *Pediatrics* 24:13, 1959

TABLE A9-1. MEAN WEIGHTS OF PREMATURE INFANTS BY AGE AND BIRTH WEIGHT

Age (days)	1000 Gm and under			1001-1500 Gm.			1501-2000 Gm.		
	No	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Birth	36	913	± 81	100	1303	±141	100	1716	±130
3	36	801	± 73	99	1201	±161	100	1625	±141
6	36	790	± 93	99	1214	±176	98	1657	±171
9	35	798	±100	100	1239	±185	100	1702	±181
12	35	826	±107	100	1292	±197	99	1768	±201
15	35	872	±114	100	1353	±216	97	1850	±216
18	36	923	±125	100	1428	±233	95	1930	±223
21	36	965	±140	99	1509	±249	93	2018	±219
24	36	1019	±156	100	1599	±270	.	.	.
27	36	1093	±171	98	1675	±266	.	.	.
30	36	1150	±194	99	1774	±282	..	..	..
33	34	1219	±191	97	1853	±280	..	.	.
36	36	1281	±204	95	1928	±272	.	..	..
39	36	1347	±212	93	2008	±275	.	..	..
42	36	1426	±234	.	..	..	..	..	..
45	36	1500	±245	..	..	.	..	..	..
48	35	1590	±259	.	..	..	..	..	.
51	36	1688	±273	..	..	..	..	..	.
54	35	1769	±272	..	..	..	..	..	..
57	35	1854	±279	.	..	..	..	..	.
60	35	1931	±293	..	..	..	..	..	..
63	32	1981	±288	..	..	..	..	..	..
66	32	2063	±294	.	..	..	..	..	..

S.D. = standard deviation.

TABLE A9-2. MEAN INCREMENTS OF WEIGHT GAIN BY THREE-DAY INTERVALS AND BIRTH WEIGHT

Age interval (days)	1000 Gm. and under			1001-1500 Gm.			1501-2000 Gm.		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Birth-3	36	-111	±58	99	-102	±68	100	-91	±66
3-6	36	- 11	±41	98	14	±47	98	32	±56
6-9	35	- 3	±32	99	24	±38	98	46	±47
9-12	34	35	±25	100	53	±39	99	65	±44
12-15	34	46	±28	100	61	±43	96	88	±41
15-18	35	51	±29	100	75	±36	94	91	±42
18-21	36	42	±30	99	84	±39	91	97	±61
21-24	36	54	±30	99	85	±39	..	..	..
24-27	36	74	±33	98	84	±39	..	..	..
27-30	36	57	±45	98	99	±45	..	..	..
30-33	34	60	±38	97	90	±42	..	..	..
33-36	34	71	±35	95	86	±45	..	..	..
36-39	36	66	±44	93	89	±43	..	..	..
39-42	36	80	±41	..	..	..	..	..	..
42-45	36	74	±35	..	..	..	..	..	..
45-48	35	98	±41	..	..	..	..	..	..
48-51	35	89	±38	..	..	..	..	..	..
51-54	35	98	±43	..	..	..	..	..	..
54-57	35	85	±36	..	..	..	..	..	..
57-60	35	77	±83	..	..	..	..	..	..
60-63	32	92	±45	..	..	..	..	..	..
63-66	32	82	±53	..	..	..	..	..	..

TABLE A9-3. WEIGHTS OF NEGRO INFANTS HAVING BIRTH WEIGHTS
OF 1001-1500 GM.

Age (wks)	Males				Females			
	No.	Weight (Gm.)			No.	Weight (Gm.)		
		Q ₁	Q ₂	Q ₃		Q ₁	Q ₂	Q ₃
Birth	42	1235	1350	1430	62	1170	1310	1420
1	41	1080	1150	1295	62	1010	1168	1290
2	41	1082	1205	1276	59	1010	1250	1370
3	40	1175	1309	1400	56	1070	1380	1500
4	38	1292	1420	1513	55	1140	1500	1635
5	37	1420	1580	1700	52	1220	1665	1805
6	36	1520	1680	1840	51	1275	1785	1970
8	33	1755	1940	2170	38	1540	2075	2268
10	22	2100	2400	2844	37	1845	2523	2693
15	17	3138	3396	3820	29	2874	3345	3742
20	13	3931	4423	5202	26	3884	4253	4706
25	12	4589	5226	5756	23	4509	5188	5415
30	12	4990	5574	6312	21	4791	5557	6039
35	10	5038	6080	6898	20	5415	6010	6322
10 mo.	8	6612	7944	8496	14	6237	6634	7201
12 mo.	7	7066	8508	9416	11	7031	7399	7881

From Cherry *et al.*¹Q₁=25th, Q₂=50th, or median, Q₃=75th percentile.

TABLE A9-4. WEIGHTS OF NEGRO INFANTS HAVING BIRTH WEIGHTS OF 1501-2000 GM.

Age (wks.)	Males				Females			
	No.	Weight (Gm.)			No.	Weight (Gm.)		
		Q ₁	Q ₂	Q ₃		Q ₁	Q ₂	Q ₃
Birth	150	1724	1822	1911	163	1655	1792	1902
1	140	1596	1716	1822	161	1550	1683	1809
2	136	1579	1789	1943	153	1627	1784	1906
3	124	1783	1918	2079	141	1761	1926	2078
4	90	1955	2110	2275	120	1871	2155	2353
5	76	2039	2326	2633	99	2041	2353	2552
6	69	2326	2605	2832	87	2382	2665	2835
8	69	2832	3090	3317	78	2778	3090	3317
10	73	3232	3629	3799	79	3175	3572	3742
15	63	4224	4593	4876	77	3969	4451	4848
20	53	4933	5557	5868	73	4763	5188	5613
25	42	5727	6265	6804	58	5443	5783	6294
30	36	6209	6861	7343	55	6010	6464	7003
35	32	6634	7059	7910	52	6662	7031	7655
10 mo.	25	7428	7825	8959	37	7201	7683	8165
12 mo.	18	7938	8675	9752	27	7626	8278	8874

From Cherry *et al.*¹Q₁=25th, Q₂=50th, or median, Q₃=75th percentile.

TABLE A9-5. CROWN-HEEL LENGTHS OF NEGRO INFANTS HAVING BIRTH WEIGHTS OF 1001-1500 GM.

Age (wks.)	Males			Females		
	No.	Mean	S.D.	No.	Mean	S.D.
Birth	24	39.5	± 1.37	43	39.4	± 1.60
1	22	39.5	± 1.56	35	39.3	± 1.85
2	20	40.0	± 1.22	39	39.6	± 2.09
3	20	40.4	± 1.78	36	40.2	± 2.31
4	19	40.8	± 2.09	38	40.9	± 2.28
5	22	41.3	± 1.85	39	41.6	± 2.61
6	22	42.0	± 1.67	35	41.9	± 2.57
8	20	43.0	± 1.71	23	43.3	± 2.57
10	14	45.3	± 2.60	25	44.8	± 3.16
15	8	50.5	± 3.59	19	48.9	± 3.30
20	4	55.6	± 3.57	19	52.8	± 3.15
25	5	57.9	± 4.03	18	56.0	± 3.28
30	8	60.9	± 3.00	17	58.5	± 3.26
35	8	62.4	± 2.92	17	60.4	± 3.66
10 mo.	7	66.3	± 2.62	14	65.4	± 2.18
12 mo.	6	69.2	± 3.64	10	68.8	± 2.31

From Chetty *et al.*¹

TABLE A9-6. CROWN-HEEL LENGTHS OF NEGRO INFANTS HAVING BIRTH WEIGHTS OF 1501-2000 GM.

Age (wks.)	Males			Females		
	No.	Mean	S.D.	No.	Mean	S.D.
Birth	96	43.9	± 1.38	100	42.9	± 2.13
1	76	43.5	± 1.32	80	43.8	± 1.50
2	73	43.8	± 1.75	74	43.9	± 1.48
3	63	44.4	± 1.52	73	44.4	± 1.48
4	48	44.9	± 1.57	54	45.3	± 1.56
5	38	46.0	± 1.85	49	46.1	± 1.59
6	46	47.0	± 2.89	54	47.1	± 1.88
8	52	48.9	± 1.97	59	48.8	± 1.97
10	58	50.5	± 1.75	63	50.8	± 1.86
15	50	54.4	± 1.55	65	54.7	± 2.06
20	38	57.8	± 2.03	65	58.3	± 2.01
25	30	61.2	± 2.54	49	61.0	± 2.15
30	27	63.6	± 2.32	46	63.2	± 1.97
35	27	65.6	± 2.13	46	65.4	± 1.98
10 mo.	22	69.0	± 2.06	36	68.0	± 1.67
12 mo.	16	71.3	± 2.34	26	70.7	± 1.55

From Cherry *et al.*¹

TABLE A9-7. HEAD CIRCUMFERENCES* OF NEGRO INFANTS HAVING BIRTH WEIGHTS OF 1001-1500 GM.

Age (wks)	Males †			Females		
	No.	Mean	S D.	No.	Mean	S D.
Birth	24	28.1	±2.01	43	27.5	±1.31
1	22	27.6	±1.27	35	27.2	±1.57
2	19	28.2	±1.16	39	27.7	±1.64
3	20	28.7	±1.28	36	28.6	±1.75
4	19	29.4	±1.26	38	29.4	±1.80
5	21	30.4	±1.12	39	30.1	±1.86
6	23	31.2	±1.09	35	30.8	±2.10
8	21	32.4	±1.03	23	31.9	±1.94
10	15	33.9	±1.50	25	33.1	±1.77
15	8	36.5	±1.85	19	35.4	±1.70
20	4	39.1	±.99	19	37.5	±1.68
25	5	40.2	±1.11	18	39.1	±1.79
30	8	41.4	±1.04	17	40.3	±1.70
35	7	42.3	±.86	17	41.2	±1.76
10 mo.	7	43.5	±1.10	14	42.8	±.88
12 mo.	6	44.8	±1.16	10	43.8	±1.00

From Cherry *et al.*¹

* Largest occipitofrontal circumference.

TABLE A9-8. HEAD CIRCUMFERENCES* OF NEGRO INFANTS HAVING BIRTH WEIGHTS OF 1501-2000 GM.

Age (wks.)	Males			Females		
	No	Mean	S.D.	No.	Mean	S.D.
Birth	97	30.4	± 1.37	100	30.1	± 1.48
1	75	30.4	± 1.14	80	30.5	± 1.22
2	73	30.9	± 1.19	74	31.0	± 1.18
3	64	31.6	± 1.19	73	31.6	± 1.22
4	49	32.2	± 1.89	54	32.3	± 1.09
5	39	33.1	± 1.52	49	33.0	± 1.17
6	45	34.0	± 1.37	54	33.7	± 1.24
8	53	35.2	± 1.17	59	34.8	± 1.22
10	59	36.1	± 1.18	63	36.0	± 1.23
15	51	38.2	± 1.13	65	37.8	± 1.22
20	39	40.0	± 1.20	65	39.5	± 1.24
25	29	41.4	± 1.14	49	40.7	± 1.20
30	27	42.1	± 1.08	46	41.9	± 1.20
35	27	43.1	± 1.23	46	42.9	± 1.25
10 mo.	22	44.3	± 1.17	36	44.0	± 1.31
12 mo.	16	45.4	± 1.27	26	45.1	± 1.44

From Cherry *et al.*¹

* Largest occipitofrontal circumference.

appendix 10. Tables of Normal Values for Various Tests

It is difficult to interpret the results of various tests that are performed on premature infants. Much of the uncertainty results from the paucity of comparative data from "normal" premature infants

In this appendix an attempt has been made to assemble data concerning values for tests made on asymptomatic premature infants. These data are supplementary to the "normal values" given earlier in appropriate chapters of the book.

The reader is cautioned to note that in some categories the number of individuals studied was much too small to expect that the probable limits of the normal range are accurately predicted. Nevertheless, these observations should provide a rough estimate of the expected range of values until the results of larger studies become available. See pages 540-547 for Tables A10-1 through A10-6.

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TABLE A10-1. HEMATOLOGIC VALUES AT VARIOUS

Birth weight	1-3	4-7	2	3	4
	← Days →		← Weeks →		
1501-2000 Gm.					
Hemoglobin	17.8 ± 1.3		17.8	15.8	13.8
Erythrocytes	4.7 ± 0.5		4.9	4.6	4.2
Reticulocytes	3.9 ± 2.5		1.7	1.3	2.0
Platelets	144 ± 69	148 ± 54	169.0	174.0	180.0
Leukocytes	11.7 ± 5.2	9.9 ± 4.5	13.1	13.2	13.1
Segmented neutrophils	45 ± 9	34 ± 11	36.0	32.0	28.0
Eosinophils	1.0	2.1	2.3	2.4	3.1
Band forms	6.1	4.7	3.3	3.1	3.0
Young neutrophils	2.1	3.4	1.5	0.9	1.3
Lymphocytes	42.0 ± 9.9	51.0 ± 12.9	52.0	58.0	61.0
Monocytes	2.0 ± 1.7	3.0 ± 2.3	4.0	4.0	4.0
Nucleated red blood cells	6.4	0.5	0.0	0.0	1.6
1201-1500 Gm					
Hemoglobin	20.2 ± 3.1	18.0 ± 1.9	17.1	14.5	12.0
Erythrocytes	5.2 ± 1.3	4.5 ± 1.0	4.3	3.8	3.4
Reticulocytes	2.7 ± 1.6	1.2 ± 0.7	0.9	0.9	1.0
Platelets	151 ± 35	134 ± 49	153.0	191.0	189.0
Leukocytes	10.8 ± 4.0	8.9 ± 2.9	14.3	13.6	11.0
Segmented neutrophils	47.0 ± 16.9	31 ± 9	33.0	42.0	26.0
Eosinophils	1.3	2.2	2.5	3.3	5.1
Band forms	11.9	10.5	5.9	4.3	3.0
Young neutrophils	5.1	2.4	2.7	2.2	1.8
Lymphocytes	34.0 ± 10.3	48.0 ± 13.9	52.0	45.0	59.0
Monocytes	3.0 ± 2.5	6.0 ± 4.4	3.0	4.0	4.0
Nucleated red blood cells	19.8	0.8	0.0	0.2	0.4
1200 Gm. and Less					
Hemoglobin	15.6 ± 1.0	16.4 ± 1.9	15.5	12.8	11.3
Erythrocytes	3.4 ± 1.3	3.7 ± 0.5	4.0	3.8	3.2
Reticulocytes	8.4 ± 3.9	3.9 ± 2.1	1.9	2.7	4.1
Platelets	148 ± 61	163 ± 69	162.0	167.0	158.0
Leukocytes	14.8 ± 10.2	12.2 ± 7.0	15.8	14.0	13.2
Segmented neutrophils	46.0 ± 7.1	32.0 ± 10.9	41.0	34.0	28.0
Eosinophils	0.4	6.2	1.0	1.9	3.7
Band forms	10.7	9.7	8.0	8.0	5.9
Young neutrophils	2.0	3.9	5.3	4.1	3.6
Lymphocytes	32.0 ± 11.2	43.0 ± 12.8	39.0	48.0	55.0
Monocytes	5.0 ± 4.3	7.0 ± 4.9	5.0	4.0	4.0
Nucleated red blood cells	16.7	1.1	0.1	0.1	1.0

Values for hemoglobin are expressed as Gm./100 ml., erythrocytes as millions/mm.³, reticulocytes per 100 RBC; platelets and leukocytes are expressed as thousands/mm.³; nucleated erythrocytes as the average number encountered while counting 100 leukocytes; and other values as percentage of leukocytes.

With additions from Wolff, J. A., and Goodfellow, A. M.²

For other data see Hadley and Chinnock¹ and Sisson and Whalen.³

AGES IN THREE BIRTH WEIGHT GROUPS

5	6	7	8	9	10	11	12	Average Number Cases	Average Standard Deviation (2-12 wks.)
←—————Weeks————→									
11.3	9.0	9.0	9.5	9.0	12.0	9.0	10.3	3	± 1.6
3.5	3.2		2.9	3.2	2.9	4.0	2.9	3	± 0.6
1.0	1.8		1.9	6.1		4.8	2.3	3	± 1.1
187.0	204.0	200.0	199.0	236.0	256.0	193.0	263.0	11	± 56.0
11.5	11.9	9.3	9.8	10.3	8.9	9.6	11.0	10	± 3.2
20.0	26.0	16.0	20.0	15.0	31.0	23.0	16.0	8	± 10.4
2.2	3.6	2.7	2.4	2.0	3.3	3.6	1.8	8	
1.3	3.1	0.5	3.6	4.0	0.3	2.8	3.2	8	
1.1	1.1	0.7	1.8	0.3	0.0	1.6	0.6	8	
70.0	57.0	75.0	68.0	76.0	64.0	65.0	73.0	8	± 11.4
5.0	8.0	4.0	4.0	2.0	1.0	5.0	4.0	8	± 3.6
0.8	0.6	0.0	5.6	0.0	0.0	0.0	0.0	8	
10.7	9.1	8.7	8.3					10	± 1.7
3.1	2.9	2.5	2.6					10	± 0.5
1.5	2.2	2.9	2.7					10	± 0.7
214.0	212.0	254.0	244.0	189.0			183.0	13	± 70.0
9.9	10.5	10.4	9.1	9.0				13	± 3.1
26.0	20.0	22.0	25.0	27.0				9	± 9.9
3.9	2.6	2.3	2.3	4.8	3.5	1.5	2.3	9	
3.0	1.4	2.9	2.1	3.4	1.0	2.0	3.3	9	
0.9	1.7	0.6	1.6	0.0	0.3	1.0	0.3	9	
61.0	69.0	68.0	64.0	63.0				9	± 13.7
5.0	5.0	5.0	5.0	2.0				9	± 2.6
0.7	1.4	1.3	1.0	10.0	0.5	0.0	0.7	9	
9.5	8.5	7.5	7.8	7.4	8.1		7.7	10	± 1.4
2.8	2.6	2.5	2.3	2.4	2.4		2.8	10	± 0.6
4.3	5.4	5.3	6.1	5.3	4.0		3.4	10	± 2.2
180.0	210.0	171.0	212.0	214.0	218.0	252.0	218.0	13	± 64.0
11.0	10.8	10.2	9.9	9.9	11.1	10.2	9.7	13	± 4.0
22.0	23.0	21.0	23.0	20.0	21.0	24.0	19.0	9	± 10.0
3.7	2.0	2.2	3.8	5.0	5.1	5.7	5.6	9	
7.0	5.8	4.4	4.4	2.2	2.4	3.5	6.0	9	
4.4	2.6	3.4	2.0	1.5	0.8	1.3	2.0	9	
59.0	61.0	66.0	65.0	70.0	68.0	62.0	59.0	9	± 12.0
5.0	6.0	3.0	3.0	2.0	3.0	4.0	7.0	9	± 2.8
1.7	2.7	1.3	2.0	1.3	1.6	1.7	0.4	9	

TABLE A10-2. HEMATOCRIT VALUES IN PREMATURE INFANTS
BY AGE AND BIRTH WEIGHT

<i>Birth weight</i> (Gm.)	<i>Age</i> (hrs)			
	0-5	6-23	24-47	48-71
1501-2000				
No.	25	25	23	11
Mean	65	65	57	62
S.D.	± 9	±10	± 9	± 9
1001-1500				
No.	5	19	23	9
Mean	62	63	62	60
S.D.	± 6	± 8	± 8	±10
1000 or less				
No.	1	2	7	3
Mean	60	52	61	57
S.D.	..		± 6	

Courtesy of W. A. Blanc, M.D., and T. Lermontoff, Babies Hospital, N.Y.C.

TABLE A10-3. SUMMARY OF VARIOUS CHEMICAL CONSTITUENTS OF PLASMA ON THE FIRST DAY OF LIFE IN PREMATURE INFANTS BY BIRTH WEIGHT

Plasma ^a constituent		Birth weight (Gm.)			
		1000 or less (4 infants)	1001-1500 (17 infants)	1501-2000 (29 infants)	2001-2500 (26 infants)
pH	Mean	7.3	7.3	7.3	7.4
	S.D.	±0.1	±0.1	±0.1	±0.1
Total CO ₂ ^b (mEq./L.)	Mean	19	20 (16)	20	21
	S.D.	±4	±4	±3	±3
pCO ₂ (mm. Hg)	Mean	37	38 (16)	37	36
	S.D.	±9	±10	±9	±7
Protein base-binding power (mEq./L.)	Mean	11.7	11.7	12.6	12.8
	S.D.	±1.4	±1.5	±1.4	±1.3
Chloride (mEq./L.)	Mean	100	101	105	104
	S.D.	±6	±5	±4	±5
Sodium (mEq./L.)	Mean	138	133 (16)	135	134
	S.D.	±2	±2	±3	±3
Potassium (mEq./L.)	Mean	6.4	6.0	5.4	5.6
	S.D.	±1.2	±0.8	±0.5	±0.9
Urea (mg./100 ml.)	Mean	22	21	16	16
	S.D.	±6	±12	±6	±7
Sugar (mg./100 ml.)	Mean	43	40	46	48
	S.D.	±22	±15	±18	±13
Total protein (Gm./100 ml.)	Mean	4.8	4.8	5.2	5.3
	S.D.	±0.6	±0.6	±0.6	±0.5

From Pincus *et al.*¹ and Saito *et al.*²

^a Capillary blood obtained by heel puncture.

^b Measured as bicarbonate.

For other data see Reardon *et al.*³ and Crump *et al.*⁴

TABLE A10-4 CEREBROSPINAL FLUID FINDINGS IN PREMATURE INFANTS BY POSTNATAL AGE

Age (mo.)	No. observations	Color		Cell count		Total protein ^a	
		Colorless	Yellow	Mean	Observed range	Mean	Observed range
0-1/4	21	0	21	9	4-18	100	50-138
1/4-1/2	15	1	14	13	3-44	128	50-269
1/2-3/4	14	5	9	9	1-31	75	31-131
3/4-1	16	10	6				
1-1 1/2	31	22	9	8	1-39	66	25-138
1 1/2-2	25	23	2	7	2-32	62	25-138
2-3	39		.	6	0-13	54	25-94
3-6							
Birth wt. (Gm)							
1500 or less	12		.	5	2-10	50	25-69
1501-2000	6	..	..	3	1-8	45	25-69
2001-2500	5			2	0-2	34	19-63

From Oula.⁴^a Colorimetric method of Leikola—mg. per 100 ml.

TABLE A10-5. CEREBROSPINAL-FLUID SUGAR COMPARED WITH BLOOD-SUGAR CONCENTRATION IN PREMATURE INFANTS

<i>Age (mo)</i>	<i>No. cases</i>	<i>Mean sugar concentration (mg /100 ml)*</i>		<i>No. cases CSF > blood</i>
		<i>CSF</i>	<i>Blood</i>	
0-1	16	81.1	77.7	9
1-2	5	77.6	85.8	2
2-3	5	72.0	72.8	2

From Otula.⁴

* Crecelius-Seifert method.

TABLE A10-6. BLOOD PRESSURE IN NEWBORN INFANTS^a

	TWO CUFF METHOD ^b (SYSTOLIC PRESSURE)				
	Age				
<i>Term infants</i>	< 5 min.	5-15 min	15-30 min.	½-1 hr	1-4 hr
No.	37	37	37	37	37
Mean	84	78	70	70	61
Mean $\pm$ 2 S.D.	56-112	50-106	47-92	47-92	43-79
<i>Premature infants</i>	< 5 min.	5-15 min	15-30 min.	½-1 hr	1-4 hr
2001-2500 Gm. b.w.					
No.		1	1	2	4
Mean		64	52	48	48
Observed range			.	36-60	42-60
Mean $\pm$ 2 S D			.		
1501-2000 Gm. b.w.					
No.	4	4	5	8	7
Mean	61	56	57	55	53
Observed range	54-68	48-66	46-64	46-68	46-60
Mean $\pm$ 2 S D					
1001-1500 Gm. b.w.					
No.	1	1	1	1	1
Mean					.
Observed value or range	54	46	46	48	48
1000 Gm. or less b.w.					
No.					
Mean					
Observed range					

Courtesy of Gerald A. Neligan, D.M., King's College, Newcastle-upon-Tyne, England.

^a Apparently normal infants with no respiratory distress or other gross disease; all survived.

^b This method is described by Ashworth *et al.*¹

^c Courtesy of Robert H. Usher, M.D., Royal Victoria Hospital, Montreal, Canada.

BY BIRTH WEIGHT AND AGE: TWO METHODS

			FLUSH METHOD ^c (MEAN PRESSURE)			
			<i>Age</i>			
<i>4-24 hr</i>	<i>1-4 days</i>	<i>4-7 days</i>	<i>0-6 hr.</i>	<i>6-48 hr</i>	<i>2-4 days</i>	<i>4-90 days</i>
37	37	37	14	18	2	12
64	73	78	62	68	82	85
47-81	54-92	63-92	38-86	50-86		59-111
<i>4-48 hr.</i>	<i>2-4 days</i>	<i>4-6 days</i>				
6	5	5	12	14	11	12
60	67	71	53	60	68	81
48-64	56-72	62-70				
			26-80	41-80	37-99	40-121
8	6	6	17	19	14	16
57	63	65	41	52	66	76
48-64	46-74	60-76				
..			10-73	28-76	42-90	46-106
1	1	1	2	3	1	4
.	.		43	46	78	57
53	70	72	32-60	30-74	70-85	42-86
			2	2	2	2
			44	43	52	72
			40-48	30-48	46-59	66-78

appendix 11. Forms Used by the Premature Transport Service of the Department of Health of the City of New York

HOSPITAL DELIVERY PREMATURE INFANT TRANSPORTATION RECORD

Name of Infant _____		Sex _____	Color _____	Religion _____	Baptized _____
Address _____		Floor or Apt. _____		Telephone Number _____	
Borough _____		(If none, neighbor's)			
Place of Birth _____		Date of Birth _____			Am Pm
Weight at Birth _____		grams or _____	lbs _____	or If multiple birth give details _____	
Condition at Birth _____					
Specify preventative for ophthalmia neonatorum used _____ Tracheal catheter used? _____					
How soon after birth was oxygen started? _____ Whole blood (if given, how much) _____					
Stimulants (if given, name and dosage) _____					
Vitamin K dosage _____ Parenteral fluids _____					
MOTHER'S HEALTH DURING THIS PREGNANCY (Including Prenatal Care)					
History including operations, injuries, complications, and other facts contributing to premature delivery _____					
Blood pressure Systolic _____ Diastolic _____					
Last menstruation Date _____		Fetal age by history _____			
Did mother have serological test for syphilis during pregnancy or at delivery? _____					
If so, date _____		Result _____		If no test, reason _____	
Were any Rh, Rh antibody, or related types of determinations done on fetus or family? _____					
Describe _____					
LABOR AND DELIVERY. Duration, 1st stage _____ hrs. 2nd stage _____ hrs. 3rd stage _____ hrs. _____ mins					
Precipitate _____		Spontaneous _____		Induced _____ If induced, method _____	
Were any manual, instrumental, or operative procedures used at delivery? (Include episiotomy and repair of tears) _____					
Specify _____					
Indications for procedures _____					
Position a) at onset of labor _____ b) at delivery _____					
Medications, drugs and anesthetic _____					
Ambulance delivery? _____ Attendant at Birth Dr. _____ Private patient _____					
General Service Patient _____		Address _____		Telephone Number _____	
FAMILY HISTORY (Parents of baby)					
NAME (For Mother Maiden Name)		AGE OR AGE AT DEATH	LIVING OR DEAD	HEALTH CONDITION OR CAUSE OF DEATH	
Father _____		_____	_____	_____	
Mother _____		_____	_____	_____	
HISTORY OF PREVIOUS PREGNANCIES (List chronologically giving earliest pregnancy first)					
YEAR	LIVE BIRTH OR FETAL DEATH	PREMATURE OR FULL TERM	AGE OR AGE AT DEATH	LIVING OR DEAD	HEALTH CONDITION OR CAUSE OF DEATH
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
MOTHER'S SIGNATURE _____			WITNESSED BY _____		
		ARRIVAL	DEPARTURE	TIME OF INCUB.	CONDITION OF BABY
Station _____		_____	a.m. p.m.	_____	_____
Hospital of Birth _____		a.m. p.m.	a.m. p.m.	_____	_____
Premature Center _____		a.m. p.m.	a.m. p.m.	_____	_____
Station _____		a.m. p.m.	_____	_____	_____
Oxygen administered. Started _____ a.m. p.m. Discontinued _____ a.m. p.m.					
Signed _____ Date _____					

Maternity and Newborn Division
Bureau of Child Health—Department of Health—City of New York

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Fig. A11-1. Premature-infant transportation record (Courtesy of Department of Health, City of New York.)

PREVENTION OF RETROLENTAL FIBROPLASIA

NAME OF INFANT _____

HOME ADDRESS _____

PLACE OF _____ DATE OF

BIRTH _____ BIRTH _____

INSTRUCTIONS: FILL OUT THIS FORM IN DUPLICATE FOR EVERY INFANT TRANSPORTED BY THE PREMATURE TRANSPORT SERVICE. FORMS SHOULD BE READY AT TIME OF TRANSPORT.

	DELIVERY ROOM	NURSERY
WAS INCUBATOR USED? (ANSWER "YES" OR "NO")		
TYPE INCUBATOR USED?		
WAS OXYGEN ADMINISTERED? ("YES" OR "NO")		
Time Started		
Time Stopped		
OXYGEN CONCENTRATION		
How Was Concentration Controlled?		
How Was Concentration Analyzed?		
CONCENTRATION READINGS		
When Were Readings Taken?		
By Whom Were Readings Taken?		
TOTAL DURATION OF OXYGEN ADMINISTERED (IN HOURS AND MINUTES)		
REASONS FOR ADMINISTRATION OF OXYGEN		
SIGNATURE OF HOSPITAL REPRESENTATIVE SUBMITTING THIS INFORMATION	TITLE OF HOSPITAL REPRESENTATIVE	

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MATERNITY AND NEWBORN DIVISION

BUREAU OF CHILD HEALTH DEPARTMENT OF HEALTH CITY OF NEW YORK
 FIG. A11-2. Oxygen administration record. (Courtesy of Department of Health, City of New York.)

MOTHER'S NAME _____			
RACE _____	SEX _____	DATE OF BIRTH _____	TIME _____ A.M. P.M.
IF MULTIPLE BIRTH, LIST ORDER OF BIRTH _____			
LEFT FOOT IMPRESSION		RIGHT FOOT IMPRESSION	
		MOTHER'S & BIRTH INDEX FINGER IMPRESSION	

FIG. A11-3. Newborn footprint record. (Some blank space has been deleted from lower portion of form in order to meet size limitations of reproduction.) Equipment to take footprints may be obtained from Frank C. Hollister Company, Chicago, Ill. (See also American Hospital Association: *Principles and Recommended Procedure as a Guide for the Identification of the Newborn in Hospitals*. Chicago, American Hospital Association, 1957.)

appendix 12. Notes on Postmortem Examination of Premature Infants*

The technique for performing autopsies on premature infants does not differ from that used in other newborn infants. This method has been adequately described by Potter and Adair, by Potter, and by Stowens. Since so little is known about the pathogenesis of many of the commonest conditions which occur in premature infants, it is advisable to collect precise and exact descriptive data at every opportunity.

In a number of premature infants no adequate primary cause of death can be detected. The pathologic diagnosis may turn out to be an enumeration of gross and microscopic findings. The difficult task of the pathologist consists of the interpretation of these data; this may be unsatisfactory even with all available information from the obstetrician, anesthesiologist, and pediatrician and a comprehensive understanding of present concepts of fetal and neonatal physiology.

* Dr. William A. Blanc, Babies Hospital, New York, prepared these notes and has kindly given permission for their reproduction.

ARTIFACTS

Emphysema, interstitial emphysema, and pneumothorax may result from attempts at resuscitation.

Intracardiac injection or postmortem puncture of heart or lungs for bacteriologic sampling may produce hemothorax, hemopericardium, or hemoperitoneum. In the last case, laceration of the liver may be very difficult to detect.

Ventricular taps, performed after death, may also produce blood effusion. The amount of cerebrospinal fluid removed by the clinician, its appearance and hematocrit, if bloody, should be recorded to permit an evaluation of the severity of intracranial hemorrhage.

All the indwelling catheters (nasogastric, umbilical vein, etc.) should be left in place so that the location of the tip and a possible traumatic lesion can be properly evaluated.

PLACENTA

This organ should be available with every autopsy of a newborn infant.

If twin placentas are submitted, the cords should be properly identified and marked (e.g., twin A, twin B). Vascular connections should be explored by injection of all vessels; mere examination is misleading. In addition to routine specimens a sample of the dividing membrane should be obtained, as this will indicate if the twins are mono- or dichorial.

The fetal, maternal, and cut surfaces should be examined by a trained observer for anomalies and for traumatic, degenerative, and inflammatory lesions. The dull, opaque, grayish appearance of the fetal surface characteristic of inflammation is quite common. Vernix granulomata ("amnion nodosum") are characteristic of oligohydramnios and may be associated with fetal anuria or oliguria, resorption of amniotic fluid (as in intrauterine death), or prolonged leaking of amniotic fluid. Attention should be given to any morphologic expressions of placental dysfunction (e.g., placenta-to-fetus weight ratio,* extensive infarction, extensive fibrosis, thrombosis of chorionic vessels, yellow staining of amnion, etc.). The following sections should be taken: umbilical cord, a roll of membranes including the margin of rupture (which may be wrapped around a marginal fragment of placenta); and a central fragment of placenta (whole thickness), including some chorionic vessels.

BODY

The external examination should be elaborate; all anomalies should be photographed, since word descriptions are rarely adequate. Roentgenograms should also be obtained in all infants so that bone and muscular defects may be detected. Anom-

* Placental weight after trimming of cord and membranes

alies of facies and pinnae often provide clues to the presence of visceral abnormalities (especially genitourinary).

If ophthalmologic anomalies (especially microphthalmia and cataract) are present, the skull should be examined by transillumination and roentgenography, and a sterile sample of cerebrospinal fluid should be collected for inoculation into mice. Heart blood and a lung swab should be taken and sent to the bacteriology laboratory. If viral infection is suspected or was present in the mother, fragments of heart, liver, spinal cord and a loop of intestine may be deep-frozen in separate containers for viral study; these specimens may also be useful for fungal studies. Material kept in a refrigerator is adequate for culture of *Listeria monocytogenes*; this should be attempted if small pustules are present in the skin and disseminated areas of necrosis are found on gross or microscopic examination of the liver, gastrointestinal tract, and lungs.

THORAX

The presence of extrapulmonary air should be checked

The pulmonary veins and the branches of the superior vena cava should be dissected in situ. A search should be made for a left superior vena cava. The innominate artery should be followed to ascertain the presence of the right subclavian artery. If absent in the usual site, this branch may be found stemming from the descending aorta and coursing behind the esophagus. The inferior surface of the lungs should be examined for accessory vessels reaching them through the diaphragm.

ABDOMEN

Umbilical arteries must be counted. The umbilical vein should be checked for traumatic lesions (e.g., catheterization).

Stomach and intestine should be examined for ulcers, perforation, or muscular defect. Bile ducts and portal vein should be dissected.

Care must be taken to differentiate multiple spleens from accessory spleens.

The inferior vena cava, renal veins, and femoral veins should be examined for thrombi.

CENTRAL NERVOUS SYSTEM

It is important to use a technique which will permit sampling of the cerebrospinal fluid, and evaluation of the amount and extension of intracranial hemorrhage. What we call the "vertebral window" technique is adequate for these purposes. After the viscera have been removed the vertebral canal is entered anteriorly. The intervertebral discs between L-3 and L-4, L-4 and L-5, and L-5 and S-1 are carefully cut through and the vertebral bodies of L-4 and L-5 removed without entering the dural sac. The head is flexed forward and this movement fills the dural sac with

cerebrospinal fluid. The sac can then be drained and its contents measured and examined. The remainder of the vertebral column is then removed.

The brain may be removed after a modified Beneke technique, as described by Stowens, with the following addition. After one of the parietal flaps is reflected, the meningeal veins running into the longitudinal sinus are examined and the head is tilted forward, the occipital lobe is gently retracted laterally, and the vein of Galen and the tentorium inspected. The maneuver is repeated on the opposite side. After fixation and sectioning the volume of the blood clot can be measured.

HEART

The heart should be kept attached to lungs until all cardiac cavities and vessels have been examined. The aorta and the ductus arteriosus may be opened anteriorly. The widest circumference of the ductus should be compared to the wider of the circumferences of the left carotid and left subclavian. The mean ratio is about 1.25.

The fossa ovalis should be measured. The extent to which the septum primum covers the foramen should be described (i.e., complete covering, extent of overlapping, or anterior defect which should be measured). The diameter of the foramen should also be measured by inserting a probe of known size. This method will help to detect otherwise unsuspected "premature closure" or stenosis of the foramen ovale.

LUNGS

Dark red, meaty, firm lungs that are associated with hyaline membranes show in addition a clear net of dilated, pale-gray subpleural lymphatics and the changes are uniform throughout all lobes.

Hemorrhage in lymphatics accompanies hemorrhagic pneumonia and idiopathic pulmonary hemorrhage. Areas of pneumonia may appear as firm, dull red, or gray-red, slightly granular areas.

A crude evaluation of the amount of air (in milliliters) contained in lungs may be obtained by attaching small weights to lungs immersed in water and determining the weight (in grams) necessary to sink the lungs.

PANCREAS

The gross diagnosis of cystic fibrosis of pancreas can be made in cases of meconium ileus and in some cases of antenatal volvulus.

LIVER

The umbilical vein and portal branches should be opened and the ductus venosus probed. A small number of ducti will be found closed or actually stenotic, a finding

which could explain difficulties in passing a catheter or abnormalities in the recorded values of venous pressure.

The biliary passages should be carefully dissected, probed and examined for patency. The gallbladder may be compressed after the duodenum has been opened and the free flow of bile noted as well as its amount and color.

Close inspection of the liver may reveal multiple tiny whitish dull patches of necrosis. In such cases, material should be obtained for viral studies (herpes, Coxsackie virus). Infections with *Listeria monocytogenes* may produce similar lesions. Usually, however, no causal agent is found and the necroses are considered anoxic.

STOMACH

The organ should be opened, flattened and examined in transmitted light for erosions, ulcers and possible muscular defects.

GENITOURINARY TRACT

The organs of the genitourinary tract should be retained as a unit without severing individual connections. If the bladder is large and thick-walled, the entire urethra should be removed for examination.

NECK ORGANS

The esophagus should be opened posteriorly and the trachea anteriorly; this facilitates exposure of fistulae.

TISSUES FOR MICROSCOPIC EXAMINATION

Sections from each organ or organ segments should be prepared. A section from each lung should be obtained and identified by a system of shape or notching. If Coxsackie infection is suspected, multiple sections of heart should be taken. Both right and left lobe of liver should be sampled.

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appendix 13. Postmortem Organ Weights

TABLE A13-1. ORGAN WEIGHTS OF PREMATURE INFANTS* AT NECROPSY BY BODY WEIGHT AT BIRTH

		<i>Birth weight groups^b (Gm)</i>							
		500	750	1000	1250	1500	1750	2000	2250
No. cases		317	311	295	217	167	148	140	124
Body length, (cm)	Mean	29.4	32.9	35.6	38.4	41.0	42.6	44.9	46.3
	S.D.	± 2.5	± 3.0	± 3.1	± 3.0	± 2.7	± 3.1	± 2.8	± 2.9
<i>Organ weights (Gm.)</i>									
Heart	Mean	5.0	6.3	7.7	9.6	11.5	12.8	14.9	16.0
	S.D.	± 1.6	± 1.8	± 2.0	± 3.3	± 3.3	± 3.2	± 4.2	± 4.3
Lungs (com- bined)	Mean	12	19	24	30	34	40	44	48
	S.D.	± 5	± 6	± 8	± 9	± 11	± 13	± 13	± 15
Spleen	Mean	1.3	2.0	2.6	3.4	4.3	5.0	6.0	7.0
	S.D.	± 0.8	± 1.2	± 1.5	± 1.8	± 2.0	± 2.5	2.7	± 3.3
Liver	Mean	26	39	47	56	65	74	82	88
	S.D.	± 10	± 12	± 12	± 21	± 18	± 20	± 23	± 24
Adrenals (com- bined)	Mean	2.6	3.2	3.5	4.0	4.5	5.3	5.3	6.0
	S.D.	± 1.7	± 1.5	± 1.6	± 1.7	± 1.8	± 2.0	± 2.0	± 2.3
Kidneys (com- bined)	Mean	5.4	7.8	10.4	12.9	14.9	17.4	18.8	20.2
	S.D.	± 2.1	± 2.6	3.4	± 3.9	± 4.2	± 4.7	± 5.0	± 4.9
Thymus	Mean	2.2	2.8	3.7	4.9	6.1	6.8	7.9	8.2
	S.D.	± 0.8	± 1.3	± 2.0	± 2.1	± 2.7	± 3.0	± 3.4	± 3.4
Brain	Mean	70	107	143	174	219	247	281	308
	S.D.	± 18	± 27	± 34	± 38	± 52	± 51	± 56	± 49
Placenta	Mean	161	175	222	253	256	319	354	358
	S.D.	± 44	± 23	± 51	± 58	± 63	± 56	± 71	± 66

Courtesy of P. Gruenwald, M.D., and H. N. Minh, M.D., Department of Obstetrics and Gynecology, The Johns Hopkins University, Baltimore, Md.

* Premature infants who were stillborn (nonmacerated) or who died during the first 3 days of life (isoimmunization and diabetic pregnancies and infants with gross malformations were excluded).

^b250-Gm. birth-weight groups, i.e., 500 = 376-625, 750 = 626-875, etc.

TABLE A13-2. ORGAN WEIGHTS OF PREMATURE INFANTS* AT NECROPSY BY GESTATIONAL AGE

		<i>Gestational age, completed weeks^b</i>							
		21-22	23-24	25-26	27-28	29-30	31-32	33-34	35-36
No. cases		85	108	143	139	148	150	104	87
Body weight (Gm.)	Mean	597	638	845	1020	1230	1488	1838	2165
	S.D.	±229	±240	±246	±340	±340	±335	±530	±600
Body length (cm.)	Mean	30.0	31.3	33.3	36.0	37.8	40.5	42.8	45.0
	S.D.	± 4.0	± 3.7	± 3.6	± 4.2	± 3.7	± 4.5	± 4.5	± 4.6
<i>Organ weights (Gm.)</i>									
Heart	Mean	4.9	4.9	6.4	7.6	9.3	11.0	13.4	15.1
	S.D.	± 1.6	± 1.6	± 2.0	± 2.3	± 3.3	± 3.7	± 3.9	± 4.8
Lungs (combined)	Mean	15	17	18	23	28	34	40	46
	S.D.	± 5	± 6	± 6	± 7	± 11	± 11	± 13	± 16
Spleen	Mean	1.6	1.7	2.2	2.6	3.4	4.1	5.2	6.7
	S.D.	± 1.0	± 1.1	± 1.5	± 1.4	± 2.0	± 2.1	± 2.1	± 3.0
Liver	Mean	31	32	39	46	53	65	74	87
	S.D.	± 13	± 15	± 15	± 16	± 19	± 22	± 27	± 33
Adrenals (combined)	Mean	2.6	2.9	3.4	3.7	4.2	4.3	5.5	6.4
	S.D.	± 1.1	± 1.4	± 1.5	± 1.7	± 2.2	± 2.3	± 2.3	± 3.0
Kidneys (combined)	Mean	5.9	6.4	7.9	10.4	12.3	14.5	17.7	21.6
	S.D.	± 2.4	± 2.6	± 2.9	± 3.6	± 3.9	± 4.8	± 5.3	± 6.7
Thymus	Mean	2.4	2.7	3.0	3.8	4.6	5.5	7.5	8.1
	S.D.	± 1.1	± 1.4	± 2.3	± 2.1	± 2.3	± 2.3	± 3.8	± 4.2
Brain	Mean	81	92	111	139	166	209	246	288
	S.D.	± 30	± 31	± 39	± 48	± 55	± 44	± 58	± 62

Courtesy of P. Gruenwald, M.D., and H. N. Minh, M.D., Department of Obstetrics and Gynecology, The Johns Hopkins University, Baltimore, Md.

* See Table A13-1, footnote a. ^b Completed weeks from the first day of the last menstrual period.

appendix 14. Conversion Tables

TABLE A14-1 CONVERSION OF POUNDS AND OUNCES TO GRAMS

Ounces	1 lb	2 lb	3 lb.	4 lb	5 lb.	6 lb.	7 lb.	8 lb.
	GRAMS							
0	454	907	1,361	1,814	2,268	2,722	3,175	3,629
1	482	936	1,389	1,843	2,296	2,750	3,204	3,657
2	510	964	1,418	1,871	2,325	2,778	3,232	3,686
3	539	992	1,446	1,899	2,353	2,807	3,260	3,714
4	567	1,021	1,474	1,928	2,381	2,835	3,289	3,742
5	595	1,049	1,503	1,956	2,410	2,863	3,317	3,771
6	624	1,077	1,531	1,985	2,438	2,892	3,345	3,799
7	652	1,106	1,559	2,013	2,466	2,920	3,374	3,827
8	680	1,134	1,588	2,041	2,495	2,948	3,402	3,856
9	709	1,162	1,616	2,070	2,523	2,977	3,430	3,884
10	737	1,191	1,644	2,098	2,552	3,005	3,459	3,912
11	765	1,219	1,673	2,126	2,580	3,033	3,487	3,941
12	794	1,247	1,701	2,155	2,608	3,062	3,515	3,969
13	822	1,276	1,729	2,183	2,637	3,090	3,544	3,997
14	851	1,304	1,758	2,211	2,665	3,119	3,572	4,026
15	879	1,332	1,786	2,240	2,693	3,147	3,600	4,054

Prepared by U. S. Children's Bureau

The table provides a convenient method of converting pounds and ounces into grams. The conversion can be done by multiplying the number of pounds by 453.6 and the number of ounces by 28.4 and adding the two products. For example, to convert 3 pounds 14 ounces, 3 multiplied by 453.6 = 1,360.8; 14 multiplied by 28.4 = 397.6, 1,360.8 + 397.6 = 1,758.4 Gm.

To convert into pounds and ounces a weight in grams not shown in the table, multiply the number of grams by .002205. For example, 2,000 Gm. multiplied by .002205 = 4.41 lb., or 4 lb. 6½ oz., 1,260 Gm. multiplied by .002205 = 2.77830, or 2.78 lb., or 2 lb. 12½ oz.

TABLE A14-2 CONVERSION OF INCHES TO CENTIMETERS

<i>Inches</i>	<i>Centimeters</i>	<i>Inches</i>	<i>Centimeters</i>	<i>Inches</i>	<i>Centimeters</i>
10	25.40	15	38.10	20	50.80
10½	26.67	15½	39.37	20½	52.07
11	27.94	16	40.64	21	53.34
11½	29.21	16½	41.91	21½	54.61
12	30.48	17	43.18	22	55.88
12½	31.75	17½	44.45	22½	57.15
13	33.02	18	45.72	23	58.42
13½	34.29	18½	46.99	23½	59.69
14	35.56	19	48.26	24	60.96
14½	36.83	19½	49.53		

Prepared by U.S. Children's Bureau.

The table shows the equivalents of inches in centimeters, by half-inch intervals from 10 to 24 inches. Since 1 inch is equal to 2.54 cm, all other values (below, between, and above) may be obtained by multiplying the number of inches by 2.54. To convert centimeters into inches, divide the number of centimeters by 2.54 and round to full or half inches.

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